ISSN: 0300-0729

INTERNATIONAL RHINOLOGIC SOCIETY

RHINOLOGY

Official Journal of the European and International Societies

VOLUME 50 | SUPPLEMENT 23 | MARCH 2012

VOLUME 50 | SUPPLEMENT 23 | EPOS2012 | MARCH 2012

European Position Paper on Rhinosinusitis and Nasal Polyps 2012

Fokkens W.J., Lund V.J., Mullol J., Bachert C., et al.

EPOS2012

European Position Paper on Rhinosinusitis and Nasal Polyps 2012

Wytske J. Fokkens, chair [a], Valerie J. Lund, co-chair [b], Joachim Mullol, co-chair [c], Claus Bachert, co-chair [d], Isam Alobid [c], Fuad Baroody [e], Noam Cohen [f], Anders Cervin [g], Richard Douglas [h], Philippe Gevaert [d], Christos Georgalas [a], Herman Goossens [i], Richard Harvey [j], Peter Hellings [k], Claire Hopkins [l], Nick Jones [m], Guy Joos [n], Livije Kalogjera [o], Bob Kern [p], Marek Kowalski [q], David Price [r], Herbert Riechelmann [s], Rodney Schlosser [t], Brent Senior [u], Mike Thomas [v], Elina Toskala[w], Richard Voegels [x], De Yun Wang [y], Peter John Wormald [z]

Rhinology supplement 23 : 1-298, 2012

a Department of Otorhinolaryngology, Academic Medical Center, Amsterdam, the Netherlands
b Royal National Throat, Nose and Ear Hospital, London, United Kingdom
c Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic – IDIBAPS, Barcelona, Catalonia, Spain
d Upper Airway Research Laboratory, Department of Otorhinolaryngology, Ghent University Hospital, Ghent, Belgium
e Section of Otolaryngology-Head and Neck Surgery, University of Chicago Medical Center, and the Pritzker School of Medicine, University of Chicago, Chicago, IL, USA
f Department of Otorhinolaryngology-Head and Neck Surgery, University of Pennsylvania Health System, Philadelphia, Pennsylvania, PA, USA
g Department of Otorhinolaryngology, Head and Neck Surgery, Lund University, Helsingborg Hospital, Helsingborg, Sweden
h Department of Otolaryngology-Head and Neck Surgery, Auckland City Hospital, Auckland, New Zealand
i Department of Microbiology, University Hospital Antwerp, Edegem, Belgium
j Rhinology and Skull Base Surgery, Department of Otolaryngology/Skull Base Surgery, St Vincents Hospital, University of New South Wales & Macquarie University, Sydney, Australia
k Department of Otorhinolaryngology, Head and Neck Surgery, University Hospitals Leuven, Leuven Belgium
l ENT Department, Guy's and St Thomas' Hospital, London, United Kingdom
m Department of Otorhinolaryngology, Head and Neck Surgery, Queens Medical Centre, Nottingham, United Kingdom
n Department of Respiratory Medicine, Ghent University, Gent, Belgium
o Department of Otorhinolaryngology/Head and Neck Surgery, Zagreb School of Medicine, University Hospital "Sestre milosrdnice", Zagreb, Croatia
p Department of Otolaryngology-Head and Neck Surgery Northwestern University Feinberg School of Medicine, Northwestern Memorial Hospital, Chicago, IL, USA
q Department of Immunology, Rheumatology and Allergy, Medical University of Łódź, Łódź, Poland
r Academic Centre of Primary Care, University of Aberdeen, Foresterhill Health Centre, United Kingdom
s Department of Otorhinolaryngology, Medicial University Innsbruck, Innbruck, Austria
t Department of Otolaryngology - Head and Neck Surgery, Medical University of South Carolina, Charleston, SC, USA
u Department of Otolaryngology-Head and Neck Surgery, Division of Rhinology, University of North Carolina at Chapel Hill, NC, USA
v Primary Care Research, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton, Southampton, United Kingdom
w Center for Applied Genomics, Children's Hospital of Philadelphia, PA, USA
x Division of Otorhinolaryngological Clinic at Clinical Hospital of the University of São Paulo, Brazil
y Department of Otolaryngology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
z Department of Surgery-Otolaryngology, Head and Neck Surgery, Adelaide and Flinders Universities, The Queen Elizabeth Hospital, Woodville, South Australia, Australia

Consultants

Surayie H.M. Al Dousary [1], Wilma Anselmo-Lima [2], Tomislav Baudoin [3,] Roxanna Cobo [4], Jiannis Constantinidis [5], Hun-Jong Dhong [6], Javier Dibildox [7], Nguyen Dung [8], Jan Gosepath [9], Mats Holmström [10], Maija Hytönen [11], Roger Jankowski [12], Mark Jorissen [13], Reda Kamel [14], Hideyuki Kawauchi [15], David Kennedy [16], Jean Michel Klossek [17], Vladimir Kozlov [18], Heung-Man Lee [19], Donald Leopold [20], Andrey Lopatin [21], Bradley Marple [22], Eli Meltzer [23],Hiroshi Moriyama[24], Bob Naclerio [25], Kimihiro Okubo[47], Metin Onerci [26], Nobuyoshi Otori [24], Muge Ozcan [27], Jim Palmer [28], Enrique Pasquini [29], Desiderio Passali [30], Chae-Seo Rhee [31], Claudia Rudack [32], Glenis Scadding [33], Elie Serrano [34], Erika Sims [35], Heinz Stammberger [36], Sverre Steinsvåg [37], Pongsakorn Tantilipikorn [38], Sanguansak Thanaviratananich [39], De Hui Wang [40], Retno Wardani [41], Geng Xu [42], Jiannis Yiotakis [43], Mario Zernotti [44], Yamei Zhang [45], Bing Zhou [46]

[1]ENT Department, King Abdulaziz University Hospital, Riyad, Faculty of Medicine, King Saud , Saudi Arabia; [2]Department of Ophthalmology, Otorhinolaryngology and HNS, Faculty of Medicine of Ribeirão Preto- University of São paulo, Paulo, Brasil; [3]Department of Otolaryngology-Head and Neck Surgery, Sestre Milosrdnice University Hospital, Zagreb, Croatia; [4]Depeartment of Otolaryngology, Centro Medico Imbanaco, Cali, Colombia; [5]2nd Department of Otorhinolaryngology, Aristotle University, Thessaloniki, Greece; [6]Department of Otorhinolaryngology, Sungkyunkwan University, Samsung Medical Center, Korea; [7]Service of Otolaryngology. Faculty of Medicine, Autonomus University of San Luis Potosi, and Hospital Central "Dr. I. Morones Prieto", San Luis Potosi, México; [8]ENT hospital, medical University HCM ville, Ho Chi Minh City, Vietnam; [9]Department of Otolaryngology, Head and Neck Surgery, HSK, Dr. Horst Schmidt Kliniken, Academic Hospital University of Mainz ,Wiesbaden, Germany; [10]Department of Otorhinolaryngology, Karolinska University Hospital, Stockholm, Sweden; [11]Department of Otorhinolaryngology,Helsinki University Central Hospital, Helsinki, Finland; [12]ORL Dept, Université de Lorraine, Hôpital Central, Nancy, France; [13]Dienst NKO-GH, UZLeuven, Leuven, Belgium; [14]Department of Rhinology, Cairo University, Cairo, Egypt; [15]Department of Otorhinolaryngology, Shimane University, Faculty of Medicine, Izumo, Japan; [16]Department of Rhinology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [17]ENT and Head and Neck Department, University Hospital Jean Bernard Service, ORL, Poitiers Cedex, France; [18]Department of Otorhinolaryngology, Central Clinical Hospital under the President of Russian Federation, Moscow, Russian Federation; [19]Department of Otorhinolaryngology-Head and Neck Surgery, Korera University College of Medicine, Seoul, Korea; [20]Department of Otorhinolaryngology, University of Vermont, Burlington, VM, USA; [21]ENT clinic, the First Moscow State Medical University, Moscow, Russian Federation; [22]Department of Otolaryngology, University of Texas Southwestern Medical School, Dallas, TX, USA; [23]Allergy & Asthma Medical Group & Research Center, University of California, San Diego, San Diego, CA, USA; [24]Department of Otorhinolaryngology, Jikei University School of Medicine, Tokyo, Japan; [25]Department of Otolaryngology Head and Neck Surgery, University of Chicago, IL, USA; [26]Department of Otorhinolaryngology, Hacettepe University, Ankara, Turkey; [27]Department of Otorhinolaryngology, Ankara Numune Education and Research Hospital Otorhinolaryngology Clinic, Ankara, Turkey; [28]Division of Rhinology, Dept of ORL:HNS, University of Pennsylvania, Philadelphia, PA, USA; [29]ENT department, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy ; [30]University of Siena, Italy; [31]Department of Otorhinolaryngology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Korea; [32]Department Otorhinolaryngology, University Hospital Münster, Münster, Germany; [33]Department of Allergy & Medical Rhinology , Royal National Throat, Nose and Ear Hospital, London, United Kingdom; [34]Department of Otorhinolaryngology Head and Neck Surgery, Larrey University Hospital, Toulouse, France; [35]Research in Real Life Ltd, Oakington, Cambridge, UK and Norwich Medical School, University of East Anglia, Norwich, Norfolk, UK; [36]Department of General Otorhinolaryngology-Head and Neck Surgery, Medical University Graz, Austria; [37]Department. of ORL, Sørlandet Hospital, Kristiansand and Haukeland University Hospital, Bergen, Norway; [38]Rhinology and Allergy Division, Mahidol University, Siriraj Hospital, Bangkok, Thailand; [39]Department of Otorhinolaryngology, Khon Kaen University, Khon Kaen, Thailand; [40]Department of Otorhinolaryngology, Eye and ENT Hospital, Fudan University, Shanghai, China; [41]Rhinology Division - ENT Department, Faculty of Medicine University of Indonesia, Dr. Cipto Mangunkusumo Hospital, Jakarta; [42]Otorhinolaryngology Hospital of The first Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; [43]Otorhinolaryngology Department, Athens University, Ippokration General Hospital, Athens, Greece; [44]ENT Department, School of Medicine, Catholic University of Córdoba, Cordoba, Argentina; [45]Department of ENT, Beijing Children's Hospital Affiliate of Capital Medical University, Beijing, China; [46]Department of Otolaryngology-Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University, Beijing, China; [47] Department of Otolaryngology, Nippon Medical School, Tokyo, Japan.

.

Aknowledgements

The EPOS2012 group express their gratitude to Marjolein Cornet, Tanja van Ingen, Judith Kosman en Christine Segboer for helping with the preparation of this document and they thank Bionorica, the European Academy of Allergy and Clinical Immunology, the European Rhinologic Society, Grupo Uriach, Hartington, Medtronic, Neilmed, Sanofi and Regeneron for their unrestricted support.

Contents

Abbreviations

12-LO	12-Lipoxygenase
15-HETE	15-Hydroxyeicosatetraenoic acid
AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery
ABRS	Acute bacterial rhinosinusitis
AE	Adverse event
AERD	Aspirin Exacerbate Respiratory Disease
AFRS	Allergic fungal rhinosinusitis
AFS	Allergic fungal sinusitis
AIDS	Acquired Immunodeficiency Syndrome
AIFRS	Acute invasive fungal rhinosinusitis
AMCase	Acid mammalian chitinase
AML	Acute myeloid leukemia
AOAH	Acyloxyacyl hydrolase
APC	Antigen presenting cell
AR.	Allergic Rhinitis
ARS	Acute Rhinosinusitis
ASA-sensitive	Aspirin sensitive
ATA	Aspirin tolerant
BAFF	B-cell activating factor
BAL	Bbronchoalveolar lavages
BD	Twice daily
BUD	Budesonide
CBCT	Cone beam CT
CCL	CC chemokine ligand
CCR3	C-C chemokine receptor type 3
CF	Cystic fibrosis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CH	Cluster headache
CI	Confidence interval
cNOS	Constitutive Nitric oxide
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclooxygenase enzyme
CpG	—C—phosphate—G—
CPH	Chronic Paroxysmal Hemicrania
CRP	C-Reactive Protein
CRS	Chronic rhinosinusitis
CRSsNP	Chronic Rhinosinusitis without nasal polyps
CRSwNP	Chronic Rhinosinusitis with nasal polyps
CSS	Chronic Sinusitus Survey
CT	Computed tomography
CTLs	Cytotoxic lymphocytes
CVID	Common variable immune deficiency
CXCL	CXC chemokine ligand
DAMP	Damage-associated molecular pattern
DBPC	Double-blind placebo-controlled
DC	Dendritic cell
DM	Diabetes mellitus
DMBT1	Malignant brain tumor
ECM	Extracellular matrix
ECP	Eosinophil cationic protein
ECs	Epithelial cells
EMMA	Endoscopic maxillary mega-antrostomy
EMMPRIN	Extracellular matrix metalloproteinase inducer
EMTU	Epithelial-mesenchymal unit
eNOS	Endothelial NOS
ENT	Ear Nose and Throat
ES	Effect Size
ESR	Erythrocyte sedimentation rate
ESS	Endoscopic sinus surgery
ESSAL	Endoscopic surgery with serial antimicrobial lavage
FEE	Functional endoscopic ethmoidectomy
FESS	Functional Endoscopic Sinus Surgery
FEV1	Forced expiratory volume in one second
FOXP3	Forkhead box P3
FP	Fluticasone propionate
G-CSF	Granulocyte colony-stimulating factor
GA(2) LEN	Global Allergy and Asthma European Network
GAR	Glucocorticoid receptor
GB	Goblet cells
GERD	Gastroesophageal reflux disease
GM-CSF	Granulocyte macrophage colony-stimulating factor
GP	General Practitioners
GVHD	Graft versus host disease
GWAS	Genome wide association studies
HC	Hemicrania continua
HIF	Hypoxia-inducible factor
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRQL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
i.v.	Intravenous
ICAM-1	Inflammatory adhesion molecule
ICD-9	International Classification of Diseases-9
ICU	Intensive care unit
IFN	Interferon
Ig	Immunoglobulin
IHC	Immunohistochemistry
IHS	International Headache Society
IL	Interleukin
IL-22R	Interleukin-22 Receptor
INCS	Intranasal corticosteroid
iNOS	Inducible Nitric oxide
IVIG	Intravenous immunoglobulin
KCN	Key cytokine negative
LO	Lipoxygenase
LPS	Lipopolysaccharides
LT	Leukotriene
MCP	Monocyte chemotactic protein
MDC	Myeloid dendritic cells
MF	Mometasone furoate

MHC-II	Major histocompatibility complex II
MMP	Matrix metalloproteinase
MMR	Macrophage mannose receptor
MPO	Myeloperoxidase
MRA	Magnetic resonance angiography
mRNA	Messenger Ribonucleic acid
MRSA	Methicillin-resistant Staphylococcus aureus
MSCT	Multislice CT
MT	Middle Turbinate
MUC	Mucin
NAMCS	National Ambulatory Medical Care Survey
NANC	Non-cholinergic system
NF-κB	Nuclear factor kappaB
NK	Natural Killer
NKT	Natural killer T cell
NLR	NOD-like receptor
NMDA	N-methyl-D-aspartate
nNOS	Neural NOS
NO	Nitric oxide
NOD	Nucleotide Oligomerization Domain
NOS	Nitric oxide synthase
NP	Nasal polyps
NPV	Negative predictive value
NSAIDs	Non steroidal anti inflammatory drugs
OCS	Oral corticosteroid
OD	Once daily
OM-85 BV	Oral bacterial lysate Broncho Vaxom
OMC	Ostio-meatal complex
OPN	Osteopontin
OR	Odds ratio
PAI-1	Plasminogen activator inhibitor
PAMP	Pathogen associated molecular patterns
PAR	Protease-activated receptor
PBMCs	Peripheral blood mononuclear cells
PCD	Primary cilia dyskinesia
PCV7	7-valent Pneumococcal conjugate vaccine
PDC	Plasmacytoid dendritic cells
PDGF	Platelet-derived growth factor
PEF	Pulmonary expiratory flow
PEFR	Peak expiratory flow rate
PET	Positron emission tomography
PGE2	Prostaglandin E2
PGI2	Prostacyclin
PGP	N-acetyl Pro-Gly-Pro
PH	Paroxysmal Hemicrania
PID	Primary immunodeficiencies
PIP	Prolactin-induced protein
PKC	Protein kinase C
PLUNC	Palate Lung Nasal Epithelial Clone
PMN	Polymorphonuclear neutrophils
PNIF	Peak nasal inspiratory flow
POSTN	Periostin
PPV	Positive predictive value
PROMS	Patient Reported Outcome Measures
PRR	Pattern Recognition Receptor
PSP	Paranasal sinus pneumatization
QOL	Quality of Life
RANTES	Regulated upon Activation, Normal T-cell Expressed, and Secreted
RAST test	Radioallergosorbent test
RCT	Randomised controlled trial
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RR	Relative Risk
RSDI	Rhinosinusitis Disability Index
RSTF	Rhinosinusitis Task Force
RSV	Respiratory syncytial virus
RT-PCR	Staphylococcal enterotoxins
SAEs	Serious adverse events
SAg	Staphylococcal superantigenic toxins
SCF	Stem cell factor
SCIT	Subcutaneous Immunotherapy
SD	Standard deviation
SF-36	Short Form (36) Health Survey
sLe(x)	Sialylated Lewis X
SMD	Standardised mean difference
SMG	Submucosal gland
SN-5 survey	Sinus and Nasal Quality of Life Survey
SNOT	Sino-Nasal Outcome Test
SNP	Single nucleotide polymorphisms
SP-A	Surfactant protein A
SPD	Surfactant protein D
SPT	Skin Prick Test
SRSA	Slow reacting substance of anaphylaxis
STAT	Signal transducer and activator of transcription
SUNCT	Short-lasting neuralgiform pain with conjunctival injection and tearing
TARC	Thymus and activation-regulated chemokine
TBP	Temporal bone pneumatization
TCR	T cell receptor
TDS	Three times daily
TEPD	Sinus transepithelial potential difference
tgAAVCF	Adeno-associated cystic fibrosis transmembrane conductance regulator (CFTR) viral vector/gene construct
TGF	Transforming growth factor
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptor
TNF	Tumor necrosis factor
TSLP	Thymic stromal lymphopoietin
TXA2	Thromboxane
URTI	Upper respiratory tract infection
VAS	Visual analogue scale
VCAM	Vascular cell adhesion protein
VEGF	Vascular endothelial growth factor

1. Introduction

Rhinosinusitis is a significant health problem which seems to mirror the increasing frequency of allergic rhinitis and which results in a large financial burden on society [1] .
The last decade has seen the development of a number of guidelines, consensus documents and position papers on the epidemiology, diagnosis and treatment of rhinosinusitis and nasal polyposis [1-6]. In 2005 the first European Position Paper on Rhinosinusitis and Nasal Polyps (EP^{3}OS) was published [4, 7]. This first evidence based position paper was initiated by the European Academy of Allergology and Clinical Immunology (EAACI) to consider what was known about rhinosinusitis and nasal polyps, to offer evidence based recommendations on diagnosis and treatment, and to consider how we could make progress with research in this area. The paper was endorsed by the European Rhinologic Society. Such was the interest in the topic and the increasing number of publications that by 2007 we felt it necessary to update the document: EP^{3}OS2007 [1, 5]. These new publications included some important randomized controlled trials and filled in some of the gaps in our knowledge, which has significantly altered our approach. In particular it has played an important role in the understanding of the management of ARS and has helped to minimize unnecessary use of radiological investigations, overuse of antibiotics, and improve the under utilisation of nasal corticosteroids [8]. EP^{3}OS2007 has had a considerable impact all over the world but as expected with time, many people have requested that we revise it, as once again a wealth of new data has become available in the intervening period. Indeed one of its most important roles has been in the identification of the gaps in the evidence and stimulating colleagues to fill these with high quality studies.

The methodology for EPOS2012 has been the same as for the other two productions. Leaders in the field were invited to critically appraise the literature and write a report on a subject assigned to them. All contributions were distributed before the meeting in November when the group came together in Amsterdam and during the 4 days of the meeting every report was discussed in detail. In addition general discussions on important dilemmas and controversies took place. Finally the management schemes were revised significantly in the light of any new data which was available. Finally we decided to remove the "3" out of EPOS2012 title (EPOS212 instead of EP^{3}OS2012) to make it more easy to reproduce.
Evidence based medicine is an important method of preparing guidelines. In 1998 the Centre for Evidence Based Medicine (CEBM) published its levels of evidence, which were designed to help clinicians and decision makers to make the most out of the available literature. Recently the levels of evidence were revised in the light of new concepts and data (Table 1). Moreover a number of other systems which grade the quality of evidence and strength of recommendation have been proposed. The most important of these is probably the GRADE initiative [9]. For the EPOS2012 we have chosen to collect the evidence using the orginal CEBM format but we plan to update the EPOS2012 clinical recommendations subsequently, following the approach suggested by the GRADE working group.

Table 1.1. Category of evidence [10].

Ia	Evidence from meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
IIa	Evidence from at least one controlled study without randomisation
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Table 1.2. Strength of recommendation.

A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

This EPOS 2012 revision is intended to be a state-of-the art review for the specialist as well as for the general practitioner:

- to update their knowledge of rhinosinusitis and nasal poly-posis;
- to provide an evidence based review of the diagnostic methods;
- to provide an evidence-based review of the available treatments;
- to propose a stepwise approach to the management of the disease;
- to propose guidance for definitions and outcome measurements in research in different settings.

Overall the document has been made more consistent, some chapters are significantly extended and others are added. Last but not least contributions from many other part of the world have increased our knowledge and understanding.
One of the important new data acquired in the last year is that on the prevalence of CRS in Europe. Previously we had relied on estimates from the USA pointing at a prevalence of 14%. Firstly the EPOS epidemiological criteria for CRS from the 2007 document were validated. We have shown that the EPOS symptom-based definition of CRS for epidemiological research has a moderate reliability over time, is stable between study centres, is not influenced by the presence of allergic rhinitis, and is suitable for the assessment of geographic variation in prevalence of CRS [11]. Secondly, a large epidemiological study was performed within the GA(2)LEN network of excellence in 19 centres in 12 countries, encompassing more than 50.000 respondents, in which the EPOS criteria were applied to estimate variation in the prevalence of Chronic rhinosinusitis for Europe. The overall prevalence of CRS was 10.9% with marked geographical variation (range 6.9-27.1) [12]. There was a strong association of asthma with CRS at all ages and this association with asthma was stronger in those reporting both CRS and allergic rhinitis (adjusted OR: 11.85). CRS in the absence of nasal allergies was positively associated with late-onset asthma [13].

In the EPOS2012 we have made a stricter division between CRS with (CRSwNP) and without nasal polyps (CRSsNP) [14]. Although there is a considerable overlap between these two forms of CRS in inflammatory profile, clinical presentation and effect of treatment [1, 15-20] there are recent papers pointing to differences in the respective inflammatory profiles [21-26] and treatment outcome [27]. For that reason management chapters are now divided in ARS, CRSsNP and CRSwNP. In addition the chapters on acute and chronic paediatric rhinosinusitis are totally revised and all the new evidence is implemented.

We sincerely hope that EPOS will continue to act as a stimulus for continued high quality clinical management and research in this common but difficult range of inflammatory conditions.

2. CLASSIFICATION AND DEFINITION OF RHINOSINUSITIS

2.1. Introduction

Rhinitis and sinusitis usually coexist and are concurrent in most individuals; thus, the correct terminology is now rhinosinusitis. Most guidelines and expert panel documents now have adopted the term rhinosinusitis instead of sinusitis [1, 2, 6, 28, 29]. The diagnosis of rhinosinusitis is made by a wide variety of practitioners, including allergologists, otolaryngologists, pulmonologists, primary care physicians, paediatricians, and many others. Therefore, an accurate, efficient, and accessible definition of rhinosinusitis is required.

Due to the large differences in technical possibilities to diagnose and treat rhinosinusitis with or withouw nasal polyps by various disciplines, the need to differentiate between subgroups varies. On the one hand the epidemiologist wants a workable definition that does not impose too many restrictions to study larger populations. On the other hand researchers in a clinical setting are in need of a set of clearly defined items that describes their patient population (phenotypes) accurately and avoids the comparison of 'apples and oranges' in studies that relate to diagnosis and treatment. The taskforce tried to accommodate these different needs by offering definitions that can be applied in different circumstances. In this way the taskforce hopes to improve the comparability of studies, thereby enhancing the evidence based diagnosis and treatment of patients with rhinosinusitis and nasal polyps.

2.2. Clinical definition of rhinosinusitis

2.2.1. Clinical definition of rhinosinusitis in adults

Rhinosinusitis in adults is defined as:

- inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
  - ± facial pain/pressure
  - ± reduction or loss of smell

and either

- endoscopic signs of:
  - nasal polyps, and/or
  - mucopurulent discharge primarily from middle meatus and/or
  - oedema/mucosal obstruction primarily in middle meatus

and/or

- CT changes:
  - mucosal changes within the ostiomeatal complex and/or sinuses

2.2.2. Clinical definition of rhinosinusitis in children

Paediatric rhinosinusitis is defined as:
inflammation of the nose and the paranasal sinuses characterised by two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- ± facial pain/pressure
- ± cough
-

and either

- endoscopic signs of:
  - nasal polyps, and/or
  - mucopurulent discharge primarily from middle meatus and/or
  - oedema/mucosal obstruction primarily in middle meatus

and/or

- CT changes:
  - mucosal changes within the ostiomeatal complex and/or sinuses

2.2.3. Severity of the disease in adult and children*

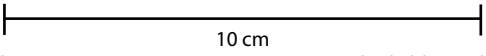
The disease can be divided into MILD, MODERATE and SEVERE based on total severity visual analogue scale (VAS) score (0 10 cm):

- MILD = VAS 0-3
- MODERATE = VAS >3-7
- SEVERE = VAS >7-10

To evaluate the total severity, the patient is asked to indicate on a VAS the answer to the question:
A VAS > 5 affects the patient QOL

- only validated in adult CRS to date

How troublesome are your symptoms of rhinosinusitis?



2.2.4. Duration of the disease in adults and children

Acute:
< 12 weeks
complete resolution of symptoms.
Chronic:
≥12 weeks symptoms
without complete resolution of symptoms.

Chronic rhinosinusitis may also be subject to exacerbations

2.2.5. Control of disease

The goal of CRS treatment is to achieve and maintain clinical control. Control is defined as a disease state in which the patients do not have symptoms or the symptoms are not bothersome, if possible combined with a healthy or almost healthy mucosa and only the need for local medication. We do not know what percentage of patients with CRS actually can achieve control of disease and further studies are necessary. We here propose an assessment of current clinical control of CRS (see Table 2.1.). Further validation of this table is necessary.

2.2.6. Definition of difficult-to-treat rhinosinusitis

Patients who have persistent symptoms of rhinosinusitis despite appropriate treatment (recommended medication and surgery). Although the majority of CRS patients can obtain control, some patients will not do so even with the maximal medical therapy and surgery.
Patients who do not reach an acceptable level of control despite adequate surgery, intranasal corticosteroid treatment and up to 2 short courses of antibiotics or systemic corticosteroids in the last year can be considered to have difficult-to-treat rhinosinusitis.

2.3. Definition for use in epidemiology studies/General Practice

For epidemiological studies the definition is based on symptomatology without ENT examination or radiology.

2.3.1. Definition of acute rhinosinusitis

2.3.1.1. Acute rhinosinusitis (ARS) in adults

Acute rhinosinusitis in adults is defined as:
sudden onset of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- ± facial pain/pressure,
- ± reduction or loss of smell

for <12 weeks;
with symptom free intervals if the problem is recurrent,
with validation by telephone or interview.

2.3.1.2. Acute rhinosinusitis in children

Acute rhinosinusitis in children is defined as:
sudden onset of two or more of the symptoms:

- nasal blockage/obstruction/congestion
- or discoloured nasal discharge
- or cough (daytime and night-time)

for < 12 weeks;
with symptom free intervals if the problem is recurrent;
with validation by telephone or interview.

Questions on allergic symptoms (i.e. sneezing, watery rhinorrhea, nasal itching, and itchy watery eyes) should be included.
ARS can occur once or more than once in a defined time period. This is usually expressed as episodes/year but there must be

Table 2.1. Assessment of current clinical control of CRS.

Assessment of current clinical control of CRS (in the last month)			
Characteristic	**Controlled (all of the following)**	**Partly Controlled (at least one present)**	**Uncontrolled**
Nasal blockage	Not present or not bothersome	Present on most days of the week	Three or more features of partly controlled CRS
Rhinorrhea/ Postnasal drip	Little and mucous	Mucopurulent on most days of the week	
Facial pain/headachec	Not present or not bothersome	Present	
Smell	Normal or only slightly impaired	Impaired	
Sleep disturbance or fatigue	Not impaired	Impaired	
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa (nasal polyps, mucopurulent secretions, inflamed mucosa)	
Systemic medication needed to control disease	Not needed	Need of a course of antibiotics or systemic corticosteroids **in the last three months**	Need of long term antibiotics or systemic corticosteroids **in the last month**

complete resolution of symptoms between episodes for it to constitute genuine recurrent ARS.
We recognise that in general acute rhinosinusitis will usually last a maximum of a few weeks. In the literature a number of different classifications have been proposed. In the past the term 'subacute' was sometimes used to fill the gap between acute and chronic rhinosinusitis. However the EPOS group felt that a separate term to describe patients with prolonged acute rhinosinusitis was not necessary because the number of patients who have such a prolonged course is small and there are very little data on which to offer evidence based recommendations on how to manage these patients.
Also in the literature the term 'acute on chronic' can be found. The EPOS group felt that the term 'exacerbation of CRS' was more appropriate and also consistent with the term used in other respiratory diseases such as asthma.

2.3.1.3. Classification of ARS in adults and children

ARS comprises of viral ARS (common cold) and post-viral ARS. In the EPOS 2007 the term non-viral ARS was chosen to indicate that most cases of ARS are not bacterial. However this term apparently led to confusion and for that reason we have decided to choose the term post-viral ARS to express the same phenomenon. A small percentage of the patients with post-viral ARS will have bacterial ARS.

Common cold/ acute viral rhinosinusits is defined as: duration of symptoms for less than 10 days.

Acute post-viral rhinosinusitis is defined as:
increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration.

Acute bacterial rhinosinusitis (ABRS)
Acute bacterial rhinosinusitis is suggested by the presence of at least 3 symptoms/signs of [236, 247]:

- Discoloured discharge (with unilateral predominance) and purulent secretion in cavum nasi,
- Severe local pain (with unilateral predominance)
- Fever (>38ºC)
- Elevated ESR/CRP
- 'Double sickening' (i.e. a deterioration after an initial milder phase of illness). (for more details see chapter 3.3.2.1.5)

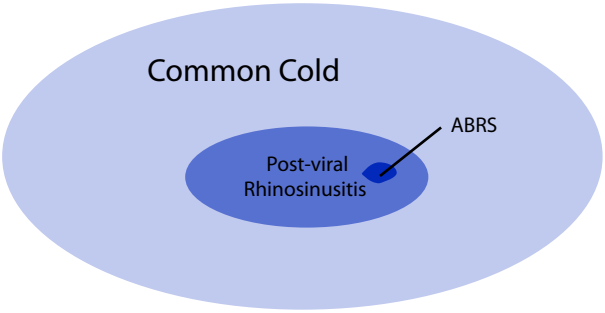


Figure 2.1. Acute rhinosinusitis can be divided into Common Cold and post- viral rhinosinusitis. A small subgroup of the post-viral rhinosinusitis is caused by bacteria (ABRS).

2.3.2. Definition of Chronic rhinosinusitis

2.3.2.1. Definition of Chronic rhinosinusitis in adults

Chronic rhinosinusitis (with or without nasal polyps) in adults is defined as:
presence of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- ± facial pain/pressure;
- ± reduction or loss of smell;

for ≥12 weeks;
with validation by telephone or interview.

Questions on allergic symptoms (i.e. sneezing, watery rhinorrhea, nasal itching, and itchy watery eyes) should be included (see Figure 2.2).

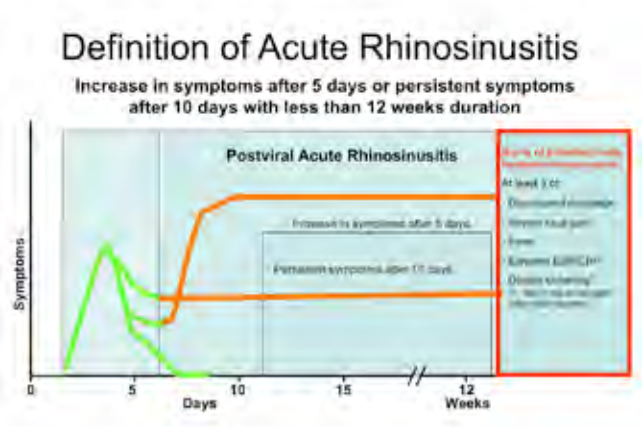


Figure 2.2 Definition of ARS

2.3.2.2. Definition of Chronic rhinosinusitis in children

Chronic rhinosinusitis (with or without nasal polyps) in children is defined as:
presence of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- ± facial pain/pressure;
- ± cough;

for ≥12 weeks;
with validation by telephone or interview.

2.4. Definition for research

For research purposes acute rhinosinusitis is defined as above. Bacteriology (antral tap, middle meatal culture) and/or radiology (X-ray, CT) are advised, but not obligatory.
For research purposes chronic rhinosinusitis (CRS) is defined as per the clinical definition. For the purpose of a study, the differentiation between CRSsNP and CRSwNP must be based on endoscopy.

2.4.1. Definition of chronic rhinosinusitis when no earlier sinus surgery has been performed

Chronic rhinosinusitis with nasal polyps (CRSwNP): bilateral, endoscopically visualised in middle meatus.
Chronic rhinosinusitis without nasal polyps (CRSsNP): no visible polyps in middle meatus, if necessary following decongestant.

This definition accepts that there is a spectrum of disease in CRS which includes polypoid change in the sinuses and/or middle meatus but excludes those with polypoid disease presenting in the nasal cavity to avoid overlap.

2.4.2. Definition of chronic rhinosinusitis when sinus surgery has been performed

Once surgery has altered the anatomy of the lateral wall, the presence of polyps is defined as bilateral pedunculated lesions as opposed to cobblestoned mucosa > 6 months after surgery on endoscopic examination. Any mucosal disease without overt polyps should be regarded as CRS.

2.4.3. Conditions for sub-analysis

The following conditions should be considered for sub-analysis:

1. aspirin sensitivity based on positive oral, bronchial, or nasal provocation or an obvious history;
2. asthma / bronchial hyper-reactivity / COPD / bronchiectasies based on symptoms, respiratory function tests;
3. allergy based on specific serum specific IgE or Skin Prick Test (SPT).
4. total IgE in serum (treatment effects may be influenced by IgE level)

2.4.4. Exclusion from general studies

Patients with the following diseases should be excluded from general studies, but may be the subject of a specific study on chronic rhinosinusitis with or without nasal polyps:

1. cystic fibrosis based on positive sweat test or DNA alleles;
2. gross immunodeficiency (congenital or acquired);
3. congenital mucociliary problems (eg. primary ciliary dyskinesia (PCD));
4. non-invasive fungal balls and invasive fungal disease;
5. systemic vasculitis and granulomatous diseases;
6. cocaine abuse;
7. neoplasia.

3. Acute Rhinosinusitis

3.1. Epidemiology and predisposing factors of ARS

Summary

ARS is a very common condition that is primarily managed in primary care. Prevalence rates vary from 6-15% depending on the study parameters, although studies specifying ARS report 6-12%, with a prevalence of recurrent ARS estimated at 0.035%. The primary cause of ARS are viruses with 0.5-2.0% of patients developing acute bacterial rhinosinusitis secondary to a viral infection. Prevalence of ARS varies with season (higher in the winter months) and climatic variations, and increasing with a damp environment and air pollution.

There appears to be overwhelming bodies of evidence to support the hypotheses that on-going allergic inflammation and cigarette smoke exposure predispose patients to ARS possibly via changes to ciliary motility and function. However, the role of laryngopharyngeal reflux in ARS is unclear. Chronic concomitant disease in children, poor mental health, and anatomical variations have been associated with an increased likelihood of ARS. Although ciliary function is altered in ARS, there is little evidence to support a role for ARS in primary cilia dyskinesia progression.

Further research is required to elucidate the underlying mechanisms by which on-going allergy and cigarette smoke exposure increases susceptibility to ARS is urgently needed. This review found that there is a paucity of studies characterising patients with ARS and concomitant diseases. Characterisation studies are required to identify possible co-existing or predisposing diseases beyond allergy, smoking, and possibly laryngopharyngeal reflux.

3.1.1. Epidemiology of ARS

ARS is highly prevalent, affecting 6-15% of the population.

The incidence of acute sinusitis or rhinosinusitis (ARS) is very high, as previously described [8] and as summarised in Table 3.1.1. It has been estimated that adults suffer two to five episodes of viral ARS (or colds) per year and school children may suffer seven to ten colds per year [8, 30]. Approximately 0.5-2% of viral upper respiratory tract infections are complicated by bacteria infection [8, 31]. In a recent analysis of ENT problems in children using data from Dutch general practices participating in the Netherlands Information Network of General Practice from 2002 to 2008, Uijen et al. [32] reported stable incident rates of 18 cases of sinusitis per 1000 children aged 12-17 years per year and 2 cases per 1000 children in those aged 0-4 years. In children aged 5-11, Uijen et al. observed a decreasing incidence from 7 cases per 1000 children in 2002 down to 4/1000 in 2008 ($p<0.001$). In contrast, using the data for 240,447 consultations for a respiratory tract infection obtained from the EPR system Swedestar database, Neumark et al. [33] reported only a 2.5% decrease in consultations for sinusitis over the period from 1999 to 2005. In a small study, Oskarsson and Halldórsson [34] reported an incidence of 3.4 cases per 100 inhabitants per year of acute sinusitis across a population derived from three health care centres in Iceland.

In Germany, from July 2000 to June 2001, 6.3 million separate diagnoses of ARS were identified resulting in 8.3 million prescriptions [30]. In a three-year case-control study of the Dutch population, van Gageldonk-Lafeber estimated that annually, 900,000 individual patients consulted their primary care physician for acute respiratory tract infection [35].

In the USA, upper respiratory tract infection is the third most common reason for a primary care provider consultation, with approximately a third of these attributed to ARS [36]. Reported in 2009 and using data from the US National Health Interview Survey for years 1997 through to 2006, Bhattacharyya reported a 1-year disease prevalence of 15.2%, although the author discusses that this is likely to include both ARS and CRS. USA guidelines suggest that rhinosinusitis affects a reported 1 in 7 adults [37-39]. Specifically focusing on ARS, an average of 8.4% of the Dutch population reported at least one episode of ARS per year in 1999 [8], while during January to March 2002, 9% (23 of 266 patients) of previously healthy patients presented with ARS at a Medical Centre Clinic in San Francisco, USA [40]. In the Finnish MIKSTRA study conducted during 1998 and 1999, 12% (1601 of 13740) of patients were diagnosed with acute maxillary sinusitis [41]. Using the same database, Rautakorpi [42] reported that 12% of consultations for infection were attributed to sinusitis. In Asia, an estimated 6-10% of patients seen at GP, otolaryngologist, and

paediatrician outpatient practices present with ARS [9]. Recurrent ARS may be considered distinct from ARS and CRS. Using data from a medical claims database for 13.1 million patients from 2003 to 2008, the point prevalence of recurrent ARS has been reported to be 0.035%, and considerably lower than that of ARS [43]. Whether recurrent ARS should be considered a form of acute or CRS requires further discussion.

A number of studies have described patients attending secondary care facilities for acute rhinosinusitis as summarised in Table 3.1.2. In North-western Nigeria, 195 of 1661 patients seen in a secondary care ENT facility presented with rhinosinusitis, of which 16.4% had ARS [44]. The proportion of patients with acute rhinitis was considerably higher than had been previously reported by Ogunleye et al. in 1999 [45]. In a retrospective review of 90 patients attending a secondary care clinic in Ibadan, Nigeria, they reported that only 7% of the 90 patients were identified as having ARS [45]. A prevalence of ARS of 1.4% was reported in a 292 patient study of upper respiratory tract infections presenting at Siriraj Hospital, Thailand, between April and October 2004 [46]. This low prevalence may be due to the majority of patients with ARS presenting to their primary care provider rather than hospital. An increasing prevalence of sinusitis has been reported in Turku in south-western Finland, in which a 3.14 fold increase in the number of patients presenting with acute frontal sinusitis at a secondary care facility was observed between 1977-81 (134 patients) and 1982-1986 (421 patients) [47]. While this may be as a result of increasing diagnosis

Table 3.1.1. Acute Rhinosinusitis (ARS) incidence and prevalence primary care studies.

Author, year, ref.	Evidence	Type of study
Uijen 2011 [32]	Incidence of ARS during 2002 to 2008: 0-4 years: 2/1000 per year in all years 5-14 years: 7/1000 in 2002 reducing to 4/1000 in 2008 (p<0.001 12-17 years: 18/1000 per year in all years.	Retrospective, population study
Oskarsson 2011 [34]	Incidence of ARS is 3.4 cases per 100 inhabitants per year, or 1 in 29.4 patients visits their GP due to ARS.	Retrospective population study
Wang 2011 [9]	6-10% of patients present at GP, otolaryngologist or paediatric out-patient practices with ARS	Multi-national questionnaire survey
Bhattacharyya 2011 [43]	Point prevalence of 0.035% for recurrent ARS during 2003-2008.	Retrospective cohort study
Meltzer, Kaliner, Kaliner 2011, 1997, 1997 [2, 38, 39]	1 in 7 adults affected by rhinosinusitis in USA	Guidelines
Neumark 2009 [33]	7.5% of consultations for respiratory tract infections (or 1 in every 13.3) were attributable to sinusitis. Expanding to all primary care consultations, 19.3 consultations/1000 patients were attributable to sinusitis.	Prospective population study
Bhattacharyya 2009 [37, 48]	For 1997-2006, 1 year prevalence of sinusitis (all forms) was 15.2%	Retrospective cohort study
Fokkens 2007 [8]	For 1999, 8.4% of the Dutch population reported at least one episode of ARS	Guideline
van Gageldonk-Lafeber 2005 [35]	Incidence of acute respiratory tract infection (including ARS) during 2000-2003 was 54.5 cases /1000 patient-years, or 1 in every 18.3 consultations	Prospective case-control study
Cherry 2005 [36]	In the USA, upper respiratory tract infection is third most common cause of a primary care consultation, of which a third is attributable to ARS.	National Survey
Louie 2005 [40]	In US study conducted during January to March 2002, 9% of previously healthy patients presented with ARS.	Prospective study
Varonen, Rautakorpi 2004, 2001 [41, 42]	During 1998-1999, 12% of patients were diagnosed with ARS. 12% of consultations for infection (all cause) over this time period were attributable to ARS	Cross-sectional multi-centre epidemiological survey
Bachert 2003 [30]	Between July 2000 and June 2001 6.3 million separate diagnoses of ARS were identified in Germany, resulting in 8.3 million prescription	Review

and willingness to refer to secondary care, Suonpaa and Antila [47] suggest that increasing air pollution in the city area of Turku may be partly responsible.

3.1.2. Factors associated with ARS

Identifying factors predictive of ARS and/or acute respiratory tract infections could aid resource availability.

3.1.2.1. Environmental Exposures

Using a matched case control study design conducted in a Dutch population over the period of 2000 to 2003, van Gageldonk-Lafeber et al. [50] reported that exposure to an individual(s) with respiratory complaints, inside or outside of the immediate household was an independent risk factor for attending their GP with an acute respiratory tract infection (adjusted OR = 1.9 and adjusted OR = 3.7, respectively). In contrast, patients with children in secondary education, who had dampness or mould at home, or had exposure to passive smoking were less likely to visit their GP compared to those without children, mould or dampness or passive smoking exposure respectively. Increased levels of dampness, but not mould, in the home has been associated with sinusitis [51].

Seasonal trends in occurrences of ARS have been reported. In a study of respiratory tract infections, Neumark et al. [33] reported seasonal variable in the incidence rate of sinusitis from 1999 through to 2005, with increased incidence in the first quarter of each year. For acute respiratory illnesses in 2000 to 2003, van Gageldonk-Lafeber et al. [35] reported similar seasonal trends to those of Neumark. Compared to July to September, van Gageldonk-Lafeber et al reported that the relative risk of acquiring an acute respiratory illness was 2.9 (95% CI: 2.8-3.0) in January to March, 1.8 (95% CI: 1.7-1.9) in October to December and 1.4 (95% CI: 1.3-1.5) in April to June. In an audit of complications of ARS, Babar-Craig et al. [52] reported that 69% of patients were admitted during the winter months of November to April. Similar patterns have been reported in acute exacerbations of CRS [53] and upper respiratory tract infections [54].

Climate variations have been reported to induce facial pain similar to ARS. Chinook, or föhn, is a weather event in which a rapidly moving warm, high-pressurised wind enters into a specific location. The pressure changes that occur during the Chinook induce facial pain similar to that experienced in sinusitis pain. Rudmik et al. [55] report that compared to controls, the presence of concha bullosa and spheno ethmoidal cell (Onodi cell; p=0.004), and larger maxillary sinus size (right, p=0.015; left, p=0.002) are all associated with complaints of Chinook headache.

However, as the Lund-Mackay score was higher in the control group, the authors conclude that CRS is unlikely to be associated with the Chinook induced facial pain.

Exposure to air pollution [47, 48, 56], irritants used in the preparation of pharmaceutical products [57], during photocopying [58] and forest fire smoke [59] have all been associated with an increase in the prevalence of symptoms of ARS.

3.1.2.2. Anatomical factors

Anatomical factors including Haller cells, concha bullosa, septal deviation, choanal atresia, nasal polyps and hypoplasia of sinuses have all been associated with ARS. In a sinus computed tomography study of recurrent ARS versus non rhinosinusitis controls, Alkire and Bhattacharyya [60] reported significantly higher Lund score (2.25 versus 1.27; p<0.001), higher frequency of Haller cells on radiograph (39.9% versus 11.9%; p=0.006) and smaller mean infundibular widths (0.591 mm versus 0.823 mm; p<0.001) compared to controls. They also reported a higher frequency of concha bullosa (41.7% versus 28.6%) and impinging septal spurs (27.8% versus 19.0%) than controls, although neither reached statistically significance.

Suonpaa and Antila [47] reported an increase in the occurrence of nasal polyps in their study of ARS between 1977-1981 and 1982-1986.

Table 3.1.2. ARS incidence and prevalence in secondary care studies.

Author, year, ref.	Evidence	Type of study
Iseh 2010 [44]	In north western Nigeria, 16.4% of 1661 patients seen in ENT facility had ARS	Retrospective case note review
Treebupachatsakul 2006 [46]	In Thailand, 1.4% of 292 patients attending Siriraj Hospital between April and October 2004 had ARS	Prospective cohort study
Ogunleye 1999 [45]	In Ibadan, Nigeria, 7% of 90 patients attending a secondary care clinic had ARS	Retrospective case note review.
Suonpaa 1990 [47]	Proportion of patients presenting with acute frontal sinusitis at a secondary care facility in Turku, South-western Finland increased by 3.14 fold between years of 1977-1981 and 1982-1986.	Retrospective case note review.

In patients with recurrent ARS, anatomical variations including Haller cells and septal deviation, nasal polyps, septal deviation, and choanal obstruction by benign adenoid tissue, or odontogenic sources of infections should be considered.

Odontogenic infections, or infections arising from dental sources, causing acute maxillary sinusitis have been reported in the literature. Bomeli et al. [61] reported that oroantral fistula and periodontal disease plus either a projecting tooth root or periapical abscess were significantly identified as sources of acute maxillary sinusitis. Furthermore they demonstrated that the greater the extent of fluid opacification and mucosal thickening, the greater the likelihood of an identifiable dental infective source. In a computed tomography (CT) radiological study of the maxillary sinus in elderly dentate and edentulous patients, Mathew et al. [62] reported an increased prevalence of mucosal thickenings (74.3 versus 25.6; $p<0.05$) and mucous cysts (2.1% versus 0) in dentate patients compared to edentate controls.

In a study of 76 children presenting with ARS, Eyigör and Basak [63] reported that 16 (21.1%) had septal deviation, and 25 (32.9%) had choanal obstruction by benign adenoid tissue.

3.1.2.3. Allergy

The role of allergy in ARS is the subject of much debate with literature both supporting and disputing a role for allergy in predisposing for ARS, as summarised in Table 3.1.3. In 1989, Savolainen [64] reported that 25% of 224 patients with acute maxillary sinusitis had allergy, as verified by allergy questionnaire, skin testing and nasal smears, with a further 6.5% of patients having probable allergy. However, upon comparison of those with and without allergy, no differences were found in the number of previous episodes of ARS, or bacteriological and radiological findings suggesting that the presence of allergy maybe incidental. In 1993, Ciprandi et al. [65] demonstrated that expression of the inflammatory adhesion molecule, ICAM-1, is elevated in patients with AR exposed to allergen challenge. As ICAM-1 has been shown to be a receptor molecule for rhinovirus, the authors hypothesise that increased expression of ICAM-1 maybe responsible for increased susceptibility to respiratory infections in patients with allergy [66]. More recently Melvin et al. [67] demonstrated that patients with AR and recurrent episodes of ARS had elevated expression of the toll-like receptor 9 (TLR9) in the sinonasal epithelium compared to patients with only AR, suggesting that TLR9 may be up-regulated in response to repeated microbial insults. The authors theorise that impairment of innate immune gene expression may predispose some patients with AR to subsequent development of recurrent ARS. In a mouse model of AR, An et al. [68] reported that mice with significant mucosal oedema and dilate venules due to ovalbumin induced AR (and sensitisation) had significantly higher polymorphonuclear neutrophils (PMN) and eosinophils following exposure to *S. pneumoniae* than mice with induced AR exposed to saline. Furthermore, mice without induced AR, but sensitised to ovalbumin and exposed to *S. pneumoniae*, had significantly lower PMN but comparable eosinophils and IL-5 levels to those sensitised and with AR, suggesting that an on-going allergic response, but not sensitisation, increases the likelihood of S pneumoniae sinus infection. Naclerio et al. [69] and Blair et al. [70] reported comparable results.

Clinically, ARS has been associated with atopy and AR. In a cross-sectional cohort study of 100 children presenting with recurrent upper respiratory tract infections compared to 164 healthy controls, Mbarek et al. [71] reported a significant association between allergy and rhinosinusitis ($p=0.001$), as well as recurrent upper respiratory tract infections ($p=0.01$), rhinopharyngitis ($p=0.02$) and acute otitis media ($p=0.01$). In a comparative case – control study of Israeli air force pilots, Ulanovski [72] reported that 33% of pilots with a history of AR and 21% of the control group had one or more episodes of ARS ($p=0.09$). Restricting to those pilots aged <26 years of age, the resultant findings were 57% and 29% ($p<0.001$), respectively. Stratification of pilots with a history of AR by pilot type showed that 54% of transport pilots, 34% of fighter pilot and 13% of helicopter pilots has also had one or more episodes of ARS, compared to the 28%, 15% and 15% of pilots in the control group. The authors theorise that the lower prevalence of ARS in the fighter pilot group as compared to the transport pilots with a history of AR may be attributable to vasoconstriction due to psychological and physiological stress exhibited during flight missions. In a retrospective analysis of patients presenting with frontal ARS between 1981 and 1990 at a secondary care facility in Kuopio, Ruoppi et al. [73] reported that 22 of the 91 (24%) patients identified had concomitant AR. Schatz et al. [74] reported that the odds of developing an episode of ARS was 4.4 times higher in patients with rhinitis than in healthy controls. Symptomatically, Eccles considered the association of sneezing in AR and also in ARS to indicate a potential link between the two conditions via stimulation of the nasal trigeminal nerves [75]. Indeed, symptom scores for 'sneeze' were higher in children with atopy and ARS than those with rhinosinusitis alone [76], while ARS has been shown to produce bilaterial large myelinated fibre hypersensitivity of the trigeminal nerves compared to healthy controls [77].

Evidence also suggests that AR is associated with impaired mucociliary clearance [78]. In a prospective study of 125 patients with AR, using the saccharine test, Vlastos et al. [78] reported that 23 patients with AR who were sinusitis prone had a significantly greater mucociliary clearance time as compared to 102 control patients with AR but not sinusitis prone (12 and 15 minutes,

respectively; p=0.02). Further research is required to explore this predisposition for rhinosinusitis in AR.

In 2009, Pant et al.[79] undertook a review of allergy in rhinosinusitis. In contrast to the above literature, Pant et al concluded that insufficient evidence exists to confirm seasonal or perennial AR as a significant predisposing factor for ARS. However, they do confirm that an association between IgE, mast cell, and eosinophil infiltration exists in some subtypes of CRS,

Table 3.1.3. Evidences in favour and against of allergy being a predisposing factor for Acute Rhinosinusitis (ARS).

Author, year, ref.	Evidence in favour	Type of study
Lin 2011 [76]	Atopic children with ARS have significantly higher levels of dizziness, sneeze, snore, itchy or burning eyes, eye congestion, tearing, anxiety, dyspnoea and chest tightness; and lower nasal peak inspiratory flow than non-atopic children with ARS	Cohort study
Eccles 2011 [75]	Sneezing in AR and in ARS is mediated via stimulation of the nasal trigeminal nerves	Review article
Melvin 2010 [67]	Elevated levels of toll-like receptor 9 (TLR9) found in patients with AR and recurrent episodes of ARS compared to AR only patients	Cohort study
Vlastos 2009 [78]	Patients with AR who are sinusitis prone shown to have increased muco-ciliary clearance time compared to AR patients not sinusitis prone	Cohort study
Ulanovski 2008 [72]	Pilots with a history of AR had more episodes of ARS than those who did not have a history of AR	Audit,
Mbarek 2008 [71]	Significant association between allergy and rhinosinusitis in a study of children with recurrent upper respiratory infection compared to health controls	Cross-sectional cohort study
Schatz 2008 [74]	Patients with AR are 4.4 times more likely to have an episode of ARS than healthy controls	Retrospective cohort study
Ciprandi 2006 [66]	Children with allergies have more frequent and severe respiratory infections than children without allergies	Cohort study
An 2007 [68] Naclerio 2006 [69] Blair 2001 [70]	In mouse models, an on-going local allergic response in the sinuses augments bacterial sinus infection	In vivo animal studies
Alho 2004 [80]	Abnormal nasal airflow and mucociliary clearance rates were more common in patients with AR than in patients with a history of recurrent ARS or health controls	Cohort study
Kirtsreesakul 2004 [81]	In mouse models, bacterial sinus infection in mice with an on-going local allergic response could be partially inhibited by the H_1-antagonist desloratadine	In vivo animal study
Ciprandi 1999 [82]	The antihistamine, terfenadine, down-regulates ICAM-1 expression and reduces rhinoconjunctivitis symptoms in children	Randomised, controlled trial
Braun 1997 [83]	Adjunct loratadine therapy to standard therapy improved control of some symptoms of ARS in patients with concomitant ARS compared to patients with AR and ARS given placebo	Randomised, placebo-controlled, clinical trial
Ciprandi 1993 [65]	Allergic children express the inflammatory adhesion molecule ICAM-1 which is a receptor for rhinovirus	Cohort study
Ruoppi 1993 [73]	24% of patients attending a secondary care facility for acute frontal sinusitis had concomitant AR	Retrospective cohort study
Savolainen 1989 [64]	25% of 224 patients with ARS had positive allergy skin test and allergy symptoms with a further 6.5% having probable allergy	Clinical study
Study, Author, year	**Evidence against**	**Type of study**
Iseh 2010 [44]	Only patients with CRS, not ARS, were found to have an allergic component to their disease.	Retrospective, cohort study
Pant 2009 [79]	Insufficient evidence to confirm involvement of seasonal or perennial rhinitis in ARS. IgE, mast cell and eosinophil infiltration exists in some subtypes of CRS but not ARS	Review article
Savolainen 1989 [64]	No difference in rates of sinus infections or bacterial or radiological findings between allergic and non-allergic patients.	Clinical study

but not ARS. In contrast to this review, Lin and cols. recently reported that children with atopy were more likely to develop ARS [76]. They reported that atopic children with ARS reported significantly higher symptoms (including dizziness, sneeze, snore, itchy or burning eyes, eye congestion and tearing) as well as significantly higher levels of anxiety, dyspnoea, chest tightness, and lower nasal peak inspiratory flow than non-atopic children with ARS. Alho [80] reported that during viral ARS (or cold), a greater proportion of patients with concomitant AR had abnormal nasal airflow, mucociliary clearance and higher ipsilaterial paranasal sinus CT scores than patients with a history of recurrent ARS or healthy controls.

3.1.2.4. Ciliary impairment

Ciliary impairment has been demonstrated to be a feature of both viral and bacterial rhinosinusitis [8]. This includes both the loss of cilia and ciliated cells as well as a disruption of normal mucociliary flow. Smoking and allergy have been implicated in the disruption of cilia function. Indeed impaired mucociliary clearance in AR patients predisposes patients to ARS [78].

Ciliary function is diminished during viral and bacterial rhinosinusitis. Exposure to cigarette smoke and allergic inflammation has also been shown to impair ciliary function, although research is required to understand these processes further.

Ciliary impairment has also been associated with cigarette smoking. In vitro studies have demonstrated that cigarette smoke condensate and cigarette smoke extract impairs ciliogenesis in a dose-dependent manner [84]. Clinical studies have also reported that exposure to passive smoking increases the levels of matrix metalloproteinase 9 (MMP-9), a gelatinase associated with tissue modelling is significantly increased in nasal secretions of children [85] exposed to passive smoking. As increased production of MMP-9 has been found in the acute allergic response in the nose and lungs, the implications for the involvement of MMP-9, ciliary function, allergic response, and smoking in ARS needs further exploration.

3.1.2.5. Primary Cilia Dyskinesia

Primary cilia dyskinesia (PCD) is a rare autosomal recessive disorder in which cilia are either immotile, or beat in such a pattern that there is failure to transport the airway mucous. PCD is associated with chronic upper airway symptoms including nasal discharge (episodic facial pain and anosmia) and bronchiectasis [86], with neonates presenting with continuous rhinorrhoea from the first day of life [87-89]. Limited information is available on the prevalence of PCD. In a Norwegian study conducted in 1947 and 1949, prevalence of PCD was estimated at 1:40,000 [90]. However, this radiological study was likely to be an underestimate due to limitations of standard chest radiographs in detecting bronchiectasis and that bronchiectasis may not have developed in the younger study patients. Using data from 1976 – 1990, the prevalence of PCD in Sweden has been estimated to range from 1:22,000 to 1:10,000 [91], the difference in prevalence due to the likely under-diagnosis of the condition. The highest prevalence, 1:4,100, was reported in a study of the impact of the Hiroshima and Nagasaki delayed atomic bombs [92]. The frequency of episodes of ARS in these patients groups is not reported.

In a study of 38 bronchiectasis patients, PCD was reported to be responsible for 13% of cases, and was more common in North African patients than European [93]. Barbato et al. [94], for the European Respiratory Society Task Force on PCD, report that recurrent ARS in PCD patients is rare, although episodes should be treated with 'adequate and prolonged antibiotic(s)' [95-97]. In agreement with the ERS Task Force, Bush et al. report that upper (and lower) airway infections should be treated aggressively, and that lung disease is usually stabilised once treatment is initiated. Although evidence exists to suggest that treating ARS will prevent recurrence or chronicity [49], whether this can applied to the PCD population is unknown. In the absence of lower airway infection, the impact of acute or recurrent ARS on the progression of PCD related bronchiectatic lung disease is unknown.

3.1.2.6. Smoking

Limited research exists on the impact of smoking on ARS. Using data from the 1970 National Health Interview Survey, and after excluding families with children with chronic respiratory illness, Bonham and Wilson [98] reported that children from households with one or more adult cigarette smokers had significantly more restricted activity and bed-disability days than did children from families with non-smoking adults. This difference was found to be due to children from families with active smokers having more episodes of acute respiratory illness (including ARS). Comparable significant results were found when families in which 45 cigarettes or more were consumed per day were compared to families with non-smoking adults. The authors concluded that higher cigarette consumption was associated with increased predisposition for acute respiratory illness. In a paediatric characterisation study of 76 patients with acute rhinosinusitis aged 4-18 years, Eyigör and Başak [63] reported that 51.3% (39 patients) were exposed to second hand smoke and 2.6% (2 patients) were active smokers. Based on their population, the authors concluded that exposure to primary or second hand smoke were predisposing factors for ARS.
In a study characterising the respiratory symptoms of adult postal workers in Zagreb, Croatia, the prevalence of sinusitis in

active smokers was 53.1% compared to 26.4% in non-smokers, although no information was available on whether the sinusitis was recurrent acute or chronic in nature [99].

Active smokers with on-going allergic inflammation have an increased susceptibility to ARS compared to non-smokers with on-going allergic inflammation, suggesting that exposure to cigarette smoke and allergic inflammation is mediated via different and possibly synergistic mechanisms. Research to elucidate these mechanisms is needed.

The impact of second-hand tobacco smoke on symptoms of rhinosinusitis has also been evaluated in patients with AR [100]. This study reported that patients with AR exposed to second hand smoke had more symptoms consistent with rhinosinusitis including facial pain and facial congestion or fullness, and a greater proportion had received medication for rhinosinusitis including antibiotics for respiratory problems in the previous 12 weeks compared to disease specific controls. Although the authors did not evaluate the occurrences of ARS, the greater proportion of patients requiring antibiotics for respiratory problems would suggest that patients exposed to second-hand tobacco smoke may have had more episodes of ARS or recurrent ARS, although the authors do not delineate between antibiotics for upper or lower airway respiratory problems.
Active and passive smoking has been shown to alter the normal bacterial flora present in the nasopharyngeal spaces, resulting in the colonisation of more potential pathogens than found in non-smokers [101]. Following smoking cessation, the microbial population has been shown to revert back to that found in non-smokers [102]. The impact of smoking cessation programmes on the incidence and prevalence of ARS is unknown.

In vitro and in vivo studies have recently shown to increased MMP-9 production in children exposed to passive smokers [85] and increased complement activation in human respiratory epithelial cells and mice exposed to cigarette smoke extract [103]. Whether increased MMP-9 production or complement activation due to exposure to cigarette smoke predisposes to ARS is unknown and requires further investigation.

3.1.2.7. Laryngopharyngeal reflux

Little is known about the association of ARS and laryngopharyngeal reflux. As reviewed by Pacheco-Galván et al. [104], epidemiological studies conducted between 1997 and 2006 have shown significant associations between GERD and sinusitis. However, in a recent systematic review, Flook and Kumar showed only a poor association between acid reflux, nasal symptoms, and ARS [105].

3.1.2.8. Anxiety and depression

Poor mental health or anxiety and depression have been significantly associated with ARS [106]. In a study of 47,202 college students aged 18 to 24 years, Adams et al. [106] reported that the prevalence of acute infectious illness, which included bronchitis, ear infection, sinusitis, and strep throat, ranged from 8% to 29%, while the prevalence of anxiety and depression ranged were 12% to 20%, respectively.

Poor mental health, anxiety, or depression is associated with susceptibility to ARS, although the underlying mechanisms are unclear.

3.1.2.9. Drug resistance

The most common bacterial pathogens causing acute bacterial rhinosinusitis include *S. pneumoniae, H. influenzae, S. pyrogenes M. Catarrhalis*, and *S aureus* [8]. Amoxicillin/clavulanate is the principal antibiotic for the treatment of mild ARS. Despite resistance to amoxicillin, it is estimated that approximately 80% of cases of mild ARS respond to amoxicillin, at a dose of 70-90 mg/kg/day. Indeed, Principi and Esposito report that most cases of *H. influenzae* and *M. catharralis* and approximately 15% of *S. pneumoniae* resolve spontaneously [107].

Amoxicillin is the most commonly used antibiotic for mild ARS. However, increasing resistance to amoxicillin, particularly in S. pneumoniae and H. influenzae infections need to be reviewed with caution. Furthermore, changes in bacterial pathogenicity in acute bacterial rhinosinusitis require consideration for antibiotic therapy.

The introduction of the Pneumococcal conjugate vaccine has led to changes in the pathogen profile of ARS. Brook and Gober [108] reported a reduction in the incidence of *S. pneumoniae* from 44% to 27%, and an increase in the incidence of *H. influenzae* from 37% to 44%, *S. pyrogenes* from 7% to 12% and *S. aureus* from 4% to 8% with no change in *M. catarrhalis* (from 13% to 14%).
Since the introduction of the Pneumococcal conjugate vaccine (PCV7), reductions in the frequency of *S. pneumoniae*, overall resistance and high level bacterial resistance have been coupled with indications for increasing levels of β-lactamase-producing *H. influenza* [109]. However, evidence of increasing antibiotic resistance in non-PCV7 serotypes of *S. pneumoniae* is emerging [110]. Rybak [111] reported for the US element of the PROTEKT longitudinal global surveillance study on antibiotic resistance, that for 2000-2001, *S. pneumoniae* resistance to beta-lactams, macrolides and fluoroquinolone, but not to telithromycin.

In 2004, Huang et al. reported that 72.4% *S. pneumonia*, 60.5% *H. influenzae*, and 58.3% *M. catarrhalis* resistance to first-line antibiotics. Sahm et al. [112] report that 40% of 847 sinus isolates were resistant to two or more of the antibiotics tested, and a doubling of the resistance to amoxicillin/clavulanate. In 2011, Lin et al. [76] report that 70% of isolates of *S. pneumoniae* and 71.4% of *H. influenzae* isolates from 69 children were resistant to amoxicillin/clavulanate.
Changes in bacterial pathogenicity in acute bacterial rhinosinusitis require consideration for antibiotic therapy.

Children with chronic disease who develop influenza-like symptoms should be monitored for bacterial ARS. The impact of chronic disease on the likelihood to develop ARS in adults is unknown.

3.1.2.10. Concomitant Chronic Disease

Concomitant chronic disease (bronchitis, asthma, cardiovascular disease, diabetes mellitus, or malignant cancer) in children has been associated with an increased risk of developing ARS secondary to influenza.
Loughlin et al. [113] reported that the overall incidence rate of developing ARS following influenza ranged from 0.9 to 1.3 in children aged 0 to 14 years. While the incidence of ARS subsequent to influenza in healthy children aged 5-14 years was 1.2 (95% CI: 0.9 – 1.5), this increased to 3.1 (95% CI: 1.5 – 5.8) in children with chronic disease (rate ratio: 2.7 (95% CI: 1.5 – 5.4). Increased monitoring of children with chronic disease who develop influenza maybe necessary.

3.2. Pathophysiology of ARS

Summary

Acute rhinosinusitis is a common disorder and it could be divided into acute viral rhinosinusitis and acute bacterial rhinosinusitis and is often preceded by a viral rhinitis or common cold. This study reviews the inflammatory mechanisms underlying viral rhinitis, acute viral rhinosinusitis and acute bacterial rhinosinusitis. First of all, the host needs to recognize the presence of microorganisms through 'pattern recognition', initiating the host defense mechanisms through activation of multiple signal pathways. Host defense mechanisms consist of both cellular immune responses and release of soluble chemical factors, which operate in the body through a complex interaction with cytokines and other mediators.

3.2.1. Viral ARS (common cold), post-viral ARS, and bacterial ARS: a continuum?

ARS could be divided theoretically into viral (common cold), post-viral and bacterial ARS (ABRS) and they usually appear in this consecutive order. However, viral, post-viral, and bacterial ARS show a considerable overlap both in their inflammatory mechanism as in their clinical presentation. Viral infection of the nose and sinuses induces multiple changes, including post-viral inflammation, which increase the risk of bacterial superinfection. These changes include epithelial damage and mechanical, humoral, and cellular defences.

ARS can be induced by viral and by bacterial infections.

3.2.2. Microbiology of viral (common cold), post-viral, and bacterial ARS

- Viruses.

The most common viruses isolated in adult viral rhinitis and rhinosinusitis, are rhinoviruses and coronaviruses. Rhinoviruses are thought to account for approximately 50% of all colds. Other viruses isolated in the common cold are influenza viruses, parainfluenza viruses, adenovirus, respiratory syncytial virus (RSV), and enterovirus [114].

Acute bacterial rhinosinusitis (ABRS) is generally preceded by a viral and or post-viral ARS.

- Bacteria.

The most common bacteria in ABRS are those belonging to the 'infernal trio' (*S. pneumoniae,* Haemophilus influenza, and *M. catarrhalis*) and *S. aureus*. Also other streptococcal species and anaerobic bacteria are seen in ABRS [115-117]. Payne and Benninger performed a meta-analysis of 25 studies concerning the microbiology of ABRS, analysing the prevalence of the most common bacteria in the middle nasal meatus and the maxillary sinus. The maxillary sinuses contained 26% *S. pneumoniae*, 28% *H. influenza*, 6% *M. catarrhalis*, and 8% *S. aureus*. These findings correlated with those in the middle meatus, being respectively 34%, 29%, 11% and 14% [115]. In a study comparing nasopharyngeal cultures from children pre and post the introduction of the Pneumococcal conjugate vaccine, Brook and Gober [108] reported a reduction in the incidence of *S. pneumoniae* from 44% to 27%, and an increase in the incidence of *H. influenzae* from 37% to 44%, *S. pyrogenes* from 7% to 12%, and *S. aureus* from 4% to 8% with no change in *M. catarrhalis* (from 13% to 14%).

3.2.3. Inflammatory mechanisms in viral (common cold), post-viral, and bacterial ARS

3.2.3.1. Invasion of microorganisms into the host

A variety of physical and biochemical barriers prevent entry from infectious agents into the body. First of all, the human body contains a variety of physical barriers against entry of microorganisms. Most important are the skin and airway mucosa. Epithelial cells are the first barrier in contact with viruses or bacteria. These release and express mediators and receptors to initiate elimination mechanisms. Mucus secretion by goblet cells prevents adherence of micro-organisms to the epithelial cells, thus preventing their entrance into the body. Microorganisms become trapped in the mucus and are mechanically removed from the airway by ciliary movements of ciliated cells [118].

Second, the human ecosystem performs a selection of potential microorganisms. The ecosystem is determined by multiple parameters such as temperature, pH, or O_2 tension. Only microorganisms that require an ecosystem that is similar to that of the internal environment of the human body are able to survive and infect human [118].

- Viruses

Viruses are necessary intracellular microorganisms, which require host cells for their replication. They attach to host cells, using a relatively specific intermolecular interaction between their nucleocapsid (in naked viruses) or viral membrane (in enveloped viruses) and molecules of the host cell membrane, which act as a receptor. This specific intermolecular interaction declares the observed specificity between certain types of viruses and specific organ systems [119].

Viral infection of the nose and sinuses induces multiple changes, which increase the risk of bacterial superinfection.

Rhinoviruses, for example, infect airway epithelial cells through binding on ICAM-1 receptors on de cell surface [120, 121]. This is followed by penetration of the virus into the cell and replication of the viral RNA [122, 123]. The expression of ICAM-1 is upregulated by the rhinoviruses itself, via IL-1beta and nuclear factor (NF)-KB-dependent mechanisms, thereby enhancing its own infectivity and promoting inflammatory cell infiltration [120, 122, 124]. Bianco et al. showed that ICAM-1 expression is enhanced by the Th2 cytokine IL-13 in the atopic airway [125]. Whereas in rhinovirus infection down regulates ICAM-1 levels on the infected cells, decreasing the available cellular binding sites for viral attachment and limiting host infectivity [121].

- Bacteria.

Bacterial superinfection depends on both host factors and bacterial factors [119].

A normal anatomical, histological and functional state of the host tissues usually prevents bacterial infection [119]. Factors that are shown to be associated with ABRS include pathogens, ciliary impairment, allergy (see further), Helicobacter pylori and laryngopharyngeal reflux and naso-tracheal intubation or presence of a naso-gastric tube [8]. Due to viral infection, allergy or other factors, multiple changes may occur in the nasal and paranasal tissue. Viral infection induces epithelial disruption, increases the number of goblet cells and decreases the number of ciliated cells [126]. Eventually, these changes contribute to the obstruction of the sinus ostia in the nasal cavity [127]. A transient increase in pressure develops in the sinus cavity due to mucus accumulation. Quickly followed by development of negative pressure in the sinus cavity, due to impaired sinus aeration with rapid absorption of the oxygen that is left into the sinus cavity [128]. Subsequently, this worsens local congestion, promotes further mucus retention, impairs normal gas exchange within the integrated airspace, decreases both the oxygen and pH content, impedes clearance of infectious material and inflammatory debris, and increases the risk for second bacterial infection [126, 127, 129, 130]. All these local changes in the nasal and paranasal space form an ideal environment for bacterial colonization and growth [131].

ABRS is mainly caused by: Streptococcus pneumoniae, Haemophilus influenza, Moraxella catarrhalis, and Staphylococcus aureus.

Viral infection of the nasal tissue may also directly increase bacterial adhesion to the nasal epithelial cells. Wang et al. noticed a significant increased adhesion of *S. aureus*, *S. pneumoniae*, and *H. influenza* on rhinovirus-infected cells [132]. They postulated that the increased expression of host cell adhesion molecules in the nasal epithelial cells, after rhinovirus infection, may be the mechanism for the increased susceptibility to ABRS associated with rhinovirus-induced upper respiratory infections [132].

Other studies confirmed preferential association and cooperation between viruses and bacteria, for example Influenza A virus and Streptococcal infection, and Human Rhinovirus 14 and *S. pneumoniae* [133]. The mechanism of this superinfection may be in relation to viral replication, which increases bacterial adhesion.

A variety of physical and biochemical barriers prevent entry from infectious agents into the noses and sinuses.

Next to host factors, also bacterial factors are involved in bacterial superinfection. *S. pneumoniae* and *H. influenza* are pathogenic because of the structure of their capsule, which gives them an invasive activity. Other bacteria, for example Streptococci, Staphylococci and Gram-negative bacteria, produce toxins directed against the defence system, leukocytes or epithelial cells, which allows easier invasion and development [119].

3.2.3.2. Defence systems of the host, after penetration of microorganisms into the body

3.2.3.2.1. General principles

If microorganisms succeed to enter the body, two main defensive strategies against the infection come into play. First a non-specific phase where the mucus and its contents (for example lysozyme, lactoferrin, and defensin) play a major role (innate immunity). The second including the immune response and inflammatory reaction (addaptive immunity).

- Viruses.

After penetration of the virus into the host cells, defence systems of the host are activated. Cells who carry viral pathogens inside need to be eliminated, in order to eliminate the virus from the body. It is thought that the innate immune system is sufficient to clear viral infection from the body [118].

- Bacteria.

Also in case of bacterial infection, the host immunity is required to eliminate the bacteria from the body. However, activation of the adaptive immune system is thought to be required to eliminate the bacteria and to clear the associated inflammation [134].

3.2.3.2.2. Pattern recognition and Toll-like receptors.

In order to work properly, the immune system must be able to recognize microbial patterns and differentiate these from molecular structures present on host cells. Specific pathogen classes express class specific molecules, the pathogen associated molecular patterns (PAMP). Activation of PAMP receptors, for example Toll-like receptors (TLR), induces multiple signal cascades, involving complement activation, haemostasis, phagocytosis, inflammation, and apoptosis, in response to pathogens. For example, activation of TLR-dependent signalling pathways contributes to activation of the adaptive immune response, through the expression of effector molecules such as inflammatory cytokines, chemokines, and other co-stimulatory molecules [135-137].

In human, ten distinct TLRs have been described. These are expressed in various combinations in cells of the immune system, as well as in other cell types [138]. mRNA of all ten TLRs has been described in human nasal airway tissue. Protein verification however, is still lacking for most TLRs in the nose [139]. Corresponding proteins have been documented for TLR-2, TLR-3, TLR-4 and TLR-5 [140].

- Viruses.

Kunzelmann et al. postulated that TLR-4 is involved in inhibition of ion-transport in response to viral respiratory infections. They studied the effect of RSV on ion-transport in tracheal epithelia in mice and showed that RSV inhibits Na+ transport in the epithelia in a few minutes after binding on the apical membrane. They also confirmed that this inhibition is mediated by protein kinase C (PKC) and toll-like receptor 4 (TLR-4) and attributes to the fluid accumulation seen after RSV infection [141]. Previous, inhibition of epithelial Na+ transport was also seen after infection with influenza virus of Para influenza virus [142, 143].

- Bacteria.

Bacteria can be recognized by the innate immune system through expression of unmethylated CpG motifs in their DNA, inducing activation of TLR-9 [144, 145]. The TLR-9 pathway is known for its ability to induce a Th1 immune response, thereby suppressing Th2-driven allergic responses [146, 147].
Mansson et al. showed that CpG administration in the human nose, increases nasal airway resistance, nasal nitric oxide production and secretion of IL-1beta, IL-6 and IL-8. The later, reflects the ability of CpG to induce a pro-inflammatory Th1-like immune response [148].
Another well-known PAMP in bacteria is lipopolysaccharide (LPS), which is part of the outer membrane of Gram-negative bacteria. LPS induced activation of TLR-4 pathways, causing increased transcription of nuclear factor-NF-KB genes, which regulated genes like those encoding cytokines and chemokines. [149-151]. This enhances the microbicidal activity of phagocytic cells and stimulates maturation and migration of dendritic cells. These mature dendritic cells show an increased antigen-presenting capacity and are involved in the activation of the adaptive immune response by stimulation of T lymphocytes. Thus, the TLR-4 signalling pathway forms a critical link between innate and adaptive immune responses [152, 153].

In *S. pneumoniae* infection, also lipoteichoic acid and pneumolysin have been shown to initiate inflammatory responses. This occurs through activation of the TLR-2 pathway. The TLR-2 pathway is shown to contribute to the adaptive, rather than the innate immune responses, by expression of co-stimulatory molecules and molecules such as MHC-II which are necessary to present bacterial antigens to Th cells. Cytokines

that result from the TLR-2 pathway, stimulate a Th1 response, which is very important to clear pneumococcal colonization [154-157]. It has been suggested that pneumolysin can also interact with TLR-4, inducing innate immune responses to pneumococci. However, Van Rossum et al found no confirmation of a role of TLR-4 in the clearance of pneumococcal colonization in their murine model [156, 158].

3.2.3.2.3. Soluble chemical factors

3.2.3.2.3.1. Defensin, lysozyme, C-reactive protein and the complement system

As mentioned above, the first defensive strategy of the host against infection consists of a non-specific phase, where the mucus and its contents (for example defensin and lysozyme) play a major role. Other important soluble chemical factors are acute phase proteins such as C-reactive protein, interferon, lactoferrin, sIgA, and the complement system [159].

- Viruses.

Defensin plays an important role in defence against both enveloped and non-enveloped viruses. This protein is present in immune cells, to assists in the killing of phagocytized pathogens. Defensins can bind to the microbial cell membrane, forming pore-like membrane defects that allow efflux of essential ions and nutrients [159].

Igarashi et al. analysed nasal lavage fluids for proteins and mast cell mediators after inoculation with rhinovirus. They found an increased secretion of total protein and both plasma proteins (albumin and IgG) and glandular proteins (lactoferrin, lysozyme and secretory IgA). They also showed that the nasal secretions during the initial response to the rhinovirus infection were predominantly due to increased vascular permeability [160].

- Bacteria.

In bacterial infection both lysozyme and defensin play an important role. Lysozyme is present in a number of secretions (saliva, tears and mucus) and exerts its defensive function by splitting the proteoglycan cell wall of bacteria. C-reactive protein (CRP), the best-known acute phase protein, has the capacity to react specifically against a part of the pneumococcal capsule. However, it also acts against a variety of other bacteria. Also the complement system is involved in host defence against bacteria, involving both the innate and adaptive immune system [118].

3.2.3.2.3.2. Kinins

- Viruses.

Bradykinin and lysylbradykinin are significantly elevated in nasal lavages of infected and symptomatic volunteers exposed to rhinovirus [161, 162]. Generation of kinins however, is also confirmed in other viral infections. Kinin generation is associated with increased neutrophil infiltration and correlates with increased production of the proinflammatory cytokine IL-1 [161-163]. They can stimulate glandular secretion of mucus, increase ciliary beat frequency, stimulate sensory nerves endings and elevate vascular permeability [164, 165]. Bradykinin-induced vascular permeability, however, has been reported to be mediated, at least in part, by nitric oxide [166].

- Bacteria.

Bradykinin release has also been demonstrated in response to bacterial infection. Bacterial proteases can activate the 'Hageman factor-kallikrein-kinin' cascade, leading to production of bradykinin. As mentioned above, bradykinin is an important factor in the enhancement of vascular permeability and can stimulate sensory nerves. Thereby explaining most of the inflammatory reaction, including oedema and pain [167]. Bradykinin generation has also been shown to result in activation of NOS, confirming the potential role of NO in this pathophysiological process [167]

3.2.3.2.3.3. Nitric oxide (NO)

NO is a gaseous molecule, synthesized by NO synthase (NOS), an enzyme that catalyses the oxidation of L-arginine to NO and L-citrulline. At least two types of NOS can be reported, constitutive NOS (cNOS) and inducible NOS (iNOS) [168]. cNOS is produced by many cells in the upper and lower respiratory system, such as parasympathetic vasodilator nerves, endothelial cells and ciliated mucosa cells [169]. iNOS is described in epithelium, macrophages, fibroblasts, neutrophils, endothelium and vascular smooth muscle, and is activated by proinflammatory cytokines and endotoxins [168, 170, 171]. NO is involved in many physiological and pathological processes in human, by exerting a role as cellular signalling molecule. Its actions in the body include vasoregulation, haemostasis, neurotransmission, immune defence, and respiration [168]. In the respiratory airway, it causes smooth muscle relaxation, affects ciliary beat frequency, mucus secretion and plasma exudation, and it is involved in neurotransmission, inflammation and cell-mediated immunity [172].

- Viruses.

NO concentrations are shown to be increased in asthma, allergic rhinitis (AR) and viral respiratory infections [168]. NO is generated in large amounts during infections, because of its antiviral and antimicrobial activity and through its upregulation of the ciliary motility [173-175].

In patients with rhinosinusitis, on the contrary, the levels of nasal NO (nNO) are significantly decreased. These reduced levels of nNO are likely because of reduced NO flow into the nasal lumen due to mucosal swelling and draining ostia obstruction, and removal of NO by reactive oxygen species [168, 176, 177]. It is

thought that the lack of NO may contribute to the pathogenesis of sinusitis.

- Bacteria.

During pneumococcal infection, NO is produced by iNOS in human and rodent macrophages. This might contribute to the intracellular killing of pneumococci, following their phagocytosis [178].

3.2.3.2.4. Nerve stimulation and neuromediators

Sympathetic nerve stimulation induces vasoconstriction and consequent decreases nasal airway resistance. Parasympathetic nerve stimulation on the other hand, promotes secretion from nasal airway glands and nasal congestion. The nasal mucosa also contains nerves of the non-adrenergic, non-cholinergic (NANC)-system. Neuropeptides from the latter nerves (substance P, neurokinin A and K, and calcitonin gene-related peptide) are suspected to play a role in vasodilatation, mucus secretion, plasma extravasation, neurogenic inflammation, and mast cell nerve interactions. However, the magnitude of their role is uncertain [179]. Further investigations concerning the role of the nervous system in ARS are required.

3.2.3.2.5. Cell-mediated immune response

In addition to the non-specific defence consisting of barriers and soluble chemical factors, a cell-mediated immune response is activated.

3.2.3.2.5.1. Phagocytosis - neutrophils, monocytes and macrophages

The innate immune system operates through phagocytosis of the microorganisms. Cells with phagocytic capacity are neutrophils, monocytes, and macrophages.

- Viruses.

Because of its intracellular nature, cell-mediated immune responses are essential to eradicate viral infection. This inflammatory cell reaction, consists mainly of neutrophils, monocytes, and macrophages. Increased neutrophil counts are seen in the nasal mucosa, nasal secretions, and peripheral blood, within 24 hours after inoculation. A couple of days later, recruitment of monocytes occurs. These monocytes become tissue macrophages, after they have crossed the endothelium [180].

- Bacteria.

Macrophages and neutrophils are also stimulated in bacterial infection. Gabr et al. investigated the immune response to acute infection with *S. pneumoniae*. The naïve host responded by activating the innate immune system. Polymorphonuclear cells and macrophages were recruited to the site of infection [181]

Neutrophils recruitment occurs due to release of chemotactic factors. Pneumolysin, the polysaccharide capsule, and lipoteichoic acid, may act as initiating factors for neutrophil recruitment during acute infection. Further, also complement factor C5a, high-molecular-weight neutrophil chemotactic factor, platelet-activating factor, IL-1 and IL-8, and leukotrienes, such as leukotriene B_4, may act as chemoattractants to neutrophils, independent of T helper cells [181].

3.2.3.2.5.2. Antigen presentation - Dendritic cells

The adaptive immune system becomes activated in specific stimulus. Specific antigens are presented to T lymphocytes (cytotoxic T cells, as well as T helper cells) by antigen-presenting cells, such as monocytes, macrophages, B-lymphocytes, and dendritic cells.

In the peripheral blood, two major subtypes of dendritic cells are identified, myeloid dendritic cells (MDC), and plasmacytoid dendritic cells (PDC) [182]. Hartmann et al. demonstrated the presence of PDC and MDC in the healthy nasal epithelium and in nasal epithelia from patients with different pathological conditions [183].

Antigen-presenting cells need to process the complex protein antigens into 'minimal antigenic peptides', which are presented to T cells on appropriate MHC molecules. Binding of this complex (antigenic peptide and MHC molecule) on the antigen-specific T cell receptor, initiates activation of the adaptive immunity [184].

- Viruses.

PDC play a key role in the detection and defence against viruses in the nasal epithelium. After recognizing viruses they start producing large amounts of IFN-alpha. Hartmann et al. showed that the healthy nasal epithelium contains relatively high numbers of PDC and MDC. Whereas PDC levels are decreased in asymptomatic patients with chronic nasal allergy and increased during infectious inflammation. These results indicate the importance of PDC against viral invaders, because of the presence of high numbers of PDC in the healthy nasal mucosa. This also explains why patients with allergy are more susceptible to a more severe course of viral infection [183].

- Bacteria.

PDC are also able to recognize CpG motifs within microbial DNA, resulting in activation of TLR-9 and production of large amounts of IFN-alpha and IFN-gamma. Thereby stimulating a Th1 response and counteracting a Th2 response [183].

Gabr et al. confirmed the role of macrophages in antigen presentation, and in the processing, recognition and presentation of the foreign antigens to other immune cells, particularly T helper cells [181].

The adaptive immune system generates an adequate immune response to a specific stimulus (antigen-presenting cells, T lymphocytes, B lymphocytes, and plasma cells).

3.2.3.2.5.3. Specific immunity – T lymphocytes and B lymphocytes

The adaptive immunity reacts on antigen presentation through formation of immune products (effector T lymphocytes and antibodies), which can generate a specific interaction with the stimulus.

- Viruses.

Interferon is a protein produced and released by infected cells. Both IFN-alpha and IFN-gamma have been recovered in nasal secretions and lavage fluids at the time of acute viral upper respiratory illnesses [185-188]. The type I interferon, IFN-alpha, induces a antiviral state in surrounding cells, and modulates the activity of other immune cells, such as T cells, NK cells, and myeloid dendritic cells [183].
Whilst the Th1 related IFN-gamma, a type II interferon, stimulates macrophage accumulation and activation, cytokine production, NK cells, and antigen specific B cell proliferation [189].
The immediate antiviral response of the host epithelial cells induces cytotoxic T lymphocyte recruitment, which is thought to be predominantly a Th1 cell mediated response [190]. Infected cells can be recognized and killed by these CTL lymphocytes, through the expression of proteins on their cell surface. Next, cell death can also be induced by Natural Killer (NK) cells, another type of cytotoxic lymphocytes [118].

- Bacteria.

In the defence against bacterial infection also T lymphocytes (especially Th1 cells) and antibodies play a major role. T lymphocytes recognizing the bacteria can release cytokines, which enhance the killing capacity of the phagocytes. They are also able to activate the specific immunity, thereby stimulating B-lymphocytes to produce specific antibodies.
Epithelial cells are thought to interact directly with T cells and to regulate their function. In addition to direct physical contact between the T cells and epithelial cells, there are several ligand/receptor molecules expressed on airway epithelial cells, which can bind to respective receptor/ligand complements on T cells [190]. The mechanisms underlying the capacity of epithelial cells to present antigens to and to stimulate T cells are unclear. Airway epithelial cells express homologues of B7 cosimulatory ligands [191, 192].
Heinecke et al. demonstrated that the proinflammatory cytokines TNF-alfa and IFN-gamma or IFN-gamma alone, selectively increased B7-H1 and B7-DC, but not B7-H2 and B7-H3. The inhibition of B7-H1 and B7-DC resulted in enhancement of IFN-gamma expression from T cells. Thus, B7-H1 and B7-DC on airway epithelial cells functioned to regulate T cell activation by inhibiting T-cell production of IFN-gamma [190].
Van Rossum et al. showed that mice, deficient in Th cells, did not clear pneumococcal colonization during a prolonged follow-up period [156]. Possibly due to lack of induction of a Th1 response, which has previously been shown to play a protective role in the host response to pneumococcal disease [193]. Further it is shown that the Th cell mediated acquired immune response is independent of the presence of antibodies. Thus indicating that the role of antibodies is limited in the clearance of pneumococcal colonization [194, 195].
Antibodies are produces against proteins and polysaccharides in the cellular membrane and its possible annexes, such as fimbriae and flagellae. Together with complement factor C3, the antibodies promote opsonisation and facilitate intracellular destruction of bacteria. The host can also generate antibodies against proteins in the cell wall or proteins, which inhibit the phagocytosis of bacteria. Finally, antibodies may also be formed against toxins produced by the bacteria [119].

3.2.3.2.6. Cytokines and other mediators

Multiple mediators and cytokines orchestrate the migration and activation of immune effector cells in response to infection. These proteins regulate chemotaxis, cellular differentiation and activation, by induction of adhesion molecule expression and by release of cytokines [180].

- Viruses.

Next to IFN-alpha and IFN-gamma, high levels of proinflammatory and anti-inflammatory cytokines including IL-1beta, IL-6, IL-8, IL-10, and TNF-alpha have been recovered in nasal secretions and nasal lavage fluids at the time of acute viral upper respiratory illnesses caused by RSV, parainfluenza virus, rhinovirus, influenza virus, and infections of unspecified aetiology [185-188, 196-199].
IL-1beta has a dual effect. It increases rhinovirus spread via ICAM-1 upregulation and initiates the host response to infection by enhancing the recruitment of immune effector cells into the inflammation site. It also induces the release of proinflammatory cytokines such as platelet activating factor and IL-8 [179, 200-202].

IL-6 is a proinflammatory cytokine, which has activating and proliferating effects on lymphocytes. IL-8, on the other hand, is a strong chemo-attractant for neutrophils [124, 180].
IL-10 is a regulatory cytokine with anti-inflammatory and Th2 stimulating properties. It can regulate immune responses by either preventing an inflammatory response or by limiting excessive ongoing inflammation, though inhibition of

production of a wide range of other cytokines. For example, Th1-related cytokines (TNF-alpha, IFN-gamma, IL-2, and IL-12), proinflammatory cytokine IL-18, and Th2-related cytokine IL-5 [203].

TNF-alpha is also a Th1-related cytokines. It induces activation of the antiviral host immune response through the stimulation of functional activities of cytotoxic T lymphocytes, NK cells and macrophages, and through the recruitment of inflammatory cells to the site of infection. Moreover, together with IL-12, it can promote the development of Th1 lymphocytes [203].
In allergic individuals, experimental rhinovirus infection also induces increase of granulocyte colony-stimulating factor (G-CSF) in nasal secretions and serum. G-CSF and IL-8 were rapidly induced in the nose after viral inoculation, and appeared to be related to neutrophil trafficking in the airway. Concerning G-CSF, it is suggested that either G-CSF contributes to neutrophil recruitment to the airway, or that airway neutrophils are a source of G-CSF during viral infection. Increases in nasal G-CSF also correlated with increases in blood neutrophils, suggesting that G-CSF produced in the nose enters the systemic circulation and acts on the bone marrow to increase neutrophilia in the blood [204, 205]. However, Linden et al. confirmed that G-CSF is only elevated in virus-infected patients with concomitant allergic rhinitis and not in non-allergic individuals [206].

- Bacteria.

Riechelmann et al. evaluated the nasal biomarker profile in acute and chronic rhinosinusitis. They determined cellular secretory products (inflammatory cell granule-derived proteins), IgE and cytokines in nasal secretions. They found high concentrations of IL-2, IL-4, IL-10, IL-12, IL-13, TNFα, and IFNγ in patients with ARS, compared to subjects with CRS with or without nasal polyps [207].
Van Rossum et al. studies the role of cytokines in the clearance of nasal pneumococcal colonization. First of all, they investigated the role of IL-12, a potent inducer of Th1 type response. IL-12, however, was not found to contribute to the clearance of the pneumococcal colonization in this study. Neither IL-4, a cytokine important in stimulation of a Th2 type response, was found to have a role in the clearance of colonization. However, these results do not exclude that clearance of colonization is Th1 dependent, since IL-12 is not the only inducer of a Th1 response [156, 208, 209].
IFN-gamma is also capable of directing the Th cells towards a Th1 response and has previously been shown to play an important role in the host defence against pulmonary infection with *S. pneumoniae* [156, 208, 209].
Next to IFN-gamma, also IL-17A has a role in the clearance of colonization. IL-17A is released by Th17 cells and induces mobilization of neutrophils, through induction of granulopoiesis and chemokines. In this pathway also IL-23, produced by dendritic cells, is involved [194, 210].

3.2.4. Allergy and ARS

As mentioned above, there exists a pathophysiological link between AR and rhinosinusitis [130].

- Viruses.

Avila et al. studied the effects of allergic inflammation of the nasal mucosa on the severity of rhinovirus colds. They found that the severity of cold symptoms was highly similar. However, the onset of cold symptoms was significantly delayed and the duration of cold symptoms was significantly shorter in the allergen group. There was no significant difference between the two groups in the increase of total cells and percentage of neutrophils in nasal lavage fluid. However, these changes paralleled the changes in symptoms, that is, they were delayed in the allergen group but of similar magnitude in both groups. Also the percentage of eosinophils did not increase in either group during cold. Cytokine measurement in nasal lavage fluid showed increases in IL-8 and IL-6 concentrations during common cold in both groups. Again, those changes were delayed in the allergen group but were of similar magnitude to those seen in the placebo group [211].

Skoner et al. compared the systemic cellular immune responses to experimental rhinovirus challenge in AR and non-AR subjects [212]. They found that rhinovirus infection induced significant acute increases in serum IgE, leucocyte histamine release and platelet aggregation, but caused no changes in serum IgE, serum IgA, serum IgM, and plasma histamine. This change was confined to the AR subjects, but there was no evidence that the acute rise in total serum IgE was due to an elevation of a pre-existing, pollen-specific serum IgE antibody [213].
Alho et al. studied the cellular and structural changes in the nasal mucosa during natural colds in subjects with AR and susceptibility to recurrent sinusitis, compared to healthy controls. They demonstrated that allergic subjects had elevated levels of eosinophils in the acute phase compared to the control group. The allergic and sinusitis-prone subjects also had elevated levels of epithelial T cells and low levels of mast cells in convalescence compared to the control group. In convalescence, the allergic subjects also had the highest numbers of intraepithelial cytotoxic lymphocytes, while such cells were absent in the sinusitis-prone subjects. The delayed accumulation of intraepithelial T cells could indicate a prolonged inflammatory reaction in the allergic and sinusitis-prone subjects, compared to the control subjects. They hypothesized that this late response of T cells consists of virus-specific T cells. The higher level of cytotoxic lymphocytes in allergic subjects during convalescence may be related to the

more severe mucosal changes in the paranasal sinuses that have previously been shown in subjects with AR during viral colds [214].

- Bacteria.

Alho et al. showed that subjects with allergic IgE-mediated rhinitis had more severe paranasal sinus changes on CT during viral colds, than non-allergic subjects [215]. The same investigators also found a higher proportion of abnormal nasal airflow and mucociliary clearance values in allergic subjects during viral colds, compared to healthy controls [216]. The latter, leading to impaired sinus functioning, could explain how allergy increases the risk of bacterial ARS.

Table 3.2.1. Inflammatory cells and mediators in Acute Rhinosinusitis (ARS).

Author, year, ref.	Tissue/patients	Cells	Mediators	Technique	Conclusions
Melvin 2010 [67]	Nasal epithelial cells of allergic ARS patients	Epithelial cells	TLR-9	Flow cytometry	TLR-9 is increased in allergic ARS patients versus allergic patients without ARS
Wang 2009[132]	Nasal epithelial cells, Rhinovirus infection	Epithelial cells	Adhesion molecules	qPCR, confocal microscopy	Adhesion molecules are increased after rhinovirus infection and facilitate bacterial infection
Heinecke 2008 [190]	Epithelial cells, rhinovirus infection	Epithelial cells	B7-H1 and B7-DC	qPCR Flow cytometry,	Induction of B7-H1 and B7-DC expression on airway epithelial cells after rhinovirus infection
Carraro 2007 [176]	Children with ARS and CRS		Nitric Oxide	Exhaled and nasal NO	Nasal NO is decreased in ARS and CRS and increases after antibiotic treatment
Klemens 2007 [217]	Nasal secretion, allergic and viral rhinitis		IL-1β, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-17, ECP, GCSF, GM-CSF	ELISA	Increased IL-1β, IL-6, IL-7, IL-17, IFN-γ, TNF-α, IL-8, G-CSF and GM-CSF and elastase in viral rhinitis.
Khoury 2006 [218]	Sinonasal mucosa mice, S. pneumoniae	T cells, eosinophils		Nasal lavage Bacterial counts	Increased bacterial counts when sensitisation is present
Hartmann 2006 [183]	Nasal tissue in controls, viral rhinitis, rhinosinusitis	mDC and pDC	CD1a, CD11c, CD14, CD16, CD19, CD20, CD56, CD80, CD86, CD123, and HLA-DR	qPCR, flow cytometry	pDC are higher after upper respiratory tract infections. pDC and mDC are almost absent after treatment with glucocorticoids
Passariello 2006 [133]	Cell culture epithelial		IL-6, IL-8, ICAM-1	ELISA	HRV promotes internalisation of S. aureus due to the action of cytokines and ICAM-1
Riechelman 2005 [207]	Nasal secretion / human ARS		IL-12, IL-4, IL-10, IL-13	IHC	Differential profile between ARS and CRS
Perloff 2005 [219]	Maxillary mucosa rabbits	Infection with pseudomonas	No	Electron microscopy	Presence of biofilm on maxillary sinus mucosa
Van Benten 2005 [203]	RSV infection in atopic vs. non atopic children		IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, IL-18, IFN-γ TNF-α	cytometric bead array	Reduced nasal IL-10 and enhanced TNF-α after rhinovirus and RSV infection
Yu 2004 [220]	Mice: S. Pneumonia induced ARS and allergic sensitisation	Eosinophils, polymorph-nuclear cells		Histology	Interference of TH2 cells with immune response in experimental ARS
Ramadan 2002 [221]	Virus-induced ARS (reovirus)	B cells T Cells	No	Histology	B and T cells interactions are still present after D14 and D21 confirming delayed immune response
Rudack 1998 [222]	Sinus mucosa ARS surgical cases	No	IL-8, IL-1β, IL-6, IL-5	ELISA	Increase IL-8, IL-1β, IL-6 during ARS

RSV, respiratory syncytial virus.

3.3. Diagnosis and Differential Diagnosis of ARS

Summary

ARS is a common condition that is often self-managed by patients without medical care being sought, and will usually improve spontaneously or with treatment. When patients do consult, this is usually to generalist primary care clinicians. The diagnosis is clinical and relies on the presence and duration of typical symptoms, particularly nasal blockage, discharge, facial pain or pressure and reduction in smell. ARS usually occurs as a complication of a viral acute upper respiratory tract infection, with persistence of symptoms beyond 10 days or worsening of symptoms after 5 days. Persistence of symptoms beyond 12 weeks signifies chronic rather than acute rhinosinusitis. Differentiation from other conditions such as viral URTI, allergic rhinitis, oro-dental disease and facial pain syndromes should be possible in most cases on clinical grounds, although investigations may be needed when diagnostic doubt remains. Septic complications are rare but serious, and all primary care clinicians should be aware of 'red flag' symptoms such as periorbital oedema and visual symptoms, which require urgent specialist assessment. Although antibiotics are commonly prescribed in community practice, ARS the symptoms of ARS often relate more to inflammation and disruption of sinus drainage mechanisms, and in most cases antibiotics is not required. Imaging, haematological and microbiological investigations and endoscopy are not routinely required in the diagnosis of ARS, but may be needed in particular settings, such as research studies or in high-risk patients.

3.3.1. Introduction

Post-viral ARS is a common condition in the community, usually following viral URTI.

ARS is a common condition, and is usually self-limiting. Many patients will self-manage or use over the counter remedies, so will not seek medical care or have a formal diagnosis made. When medical care is sought, most patients will consult with a primary care physician, although in some health systems may directly access specialist services. Although educational efforts have been made to familiarize General Practitioners (GPs) with the concepts of rhinosinusitis and the diagnostic criteria for the diagnosis of ARS [223], 'sinusitis' is commonly used as a diagnostic label, and as this is frequently considered by GPs an acute bacterial rather than inflammatory condition [224], antibiotics are extensively prescribed [225, 226]. The dissemination of the EP^{3}OS [8] and other recent guidelines [2, 227] emphasizing the inflammatory nature of ARS and providing standardization of diagnostic criteria and use of investigations has lead to more rational diagnosis and management in some [226, 228] but not all [229, 230] settings. In addition to misunderstandings concerning the inflammatory nature of ARS [229], concern over the risk of septic complications from untreated bacterial disease may be a factor in the ongoing high use of antibiotics in ARS. Observational evidence indicates, however, that complications are rare [231, 232] usually manifest early in the course of the illness with severe symptoms [233, 234], and that antibiotic treatment of ARS in general practice does not prevent complications [52, 232]. Guidelines agree that in uncomplicated cases, ARS is diagnosed on clinical criteria and supplementary investigations are not required [2]. In particular patient groups and in those with severe or atypical symptoms, additional diagnostic procedures may be needed, as discussed below. ARS is frequently an isolated clinical event and a self-limiting condition, although may be recurrent in some cases. There may be an association with dental disease in some [61].

3.3.2. Clinical Diagnosis in Primary Care

ARS is diagnosed by the acute onset of typical symptoms that include nasal blockage, discharge, facial pain or pressure and reduction in smell.

In primary care setting (and for epidemiological research), ARS is defined by symptomatology without detailed ENT examination or imaging. ARS is defined in section 2 of this guideline by the presence of major and minor symptoms for up to 12 weeks. ARS is sub-divided into 'acute viral rhinosinusitis' (synonymous with the 'common cold'), in which the duration of symptoms is less than 10 days, usually a self-limiting condition that frequently does not present to clinicians, and 'acute post-viral rhinosinusitis', defined by an increase in symptoms after 5 days or persistence beyond 10 days [8].

3.3.2.1. Assessment of ARS symptoms

Most acute viral URTI infections are self-limiting, and post-viral ARS should not diagnosed before 10 days duration of symptoms unless there is a clear worsening of symptoms after 5 days.

3.3.2.1.1. Symptoms of ARS

The subjective assessment of ARS is based on the presence and severity of symptoms.

- Nasal blockage, congestion or stuffiness
- Nasal discharge or postnasal drip, often mucopurulent
- Facial pain or pressure, headache, and
- Reduction/loss of smell

Besides these local symptoms, distant and systemic symptoms may occur.

Distant symptoms are pharyngeal, laryngeal, and tracheal irritation causing sore throat, dysphonia, and cough, and general symptoms including drowsiness, malaise, and fever. There is little reliable evidence of the relative frequency of different symptoms in ARS in community practice. Individual variations of these general symptom patterns are many [235-239]. Only a small proportion of patients with purulent rhinosinusitis, without coexisting chest disease, complain of cough [236]. In patients with a suspicion of infection, facial or dental pain (especially if unilateral) have been found to be predictors of acute maxillary sinusitis, when validated by maxillary antral aspiration [236] or paranasal sinus radiographs [237].The symptoms of ARS occur abruptly without a history of recent nasal or sinus symptoms. A history of sudden worsening of pre-existing symptoms suggests an acute exacerbation of chronic rhinosinusitis, which should be diagnosed by similar criteria and treated in a similar way to ARS.

3.3.2.1.2. Subjective assessment of symptoms: severity

Subjective assessment should address the severity and the duration of symptoms. The recommended method of assessing severity of symptoms is with the use of a visual analogue scale (VAS) recorded by the patient on a 10cm line giving a score on a measurable continuum of 1 to 10 (see chapter 2.2.3.). Disease-specific questionnaires measuring quality of life impairment are available [240, 241] but not commonly used in clinical practice; a good clinician will, however, informally assess the impact of ARS on their patient as part of a full clinical assessment. The VAS can be used to assess overall symptom severity and the severity of individual symptoms (see below). Asking patients to rate their symptoms as absent, mild, moderate or severe, may also assess symptom severity.

3.3.2.1.3. Subjective assessment of symptoms: duration

The sudden onset of symptoms of nasal blockage, obstruction, congestion and discharge is usually due to a self limiting viral infection, and ARS should not be considered in patients who have experience symptoms for less than 5 days unless they are unusually severe. Post-viral ARS should not be diagnosed in patients with symptoms for less than 10 days unless a marked worsening of symptoms occurs after 5 days, and features of severe pain and a pyrexia of >38°C are present. Symptoms occurring for longer than 12 weeks indicate the presence of chronic rhinosinusitis.

3.3.2.1.4. Assessment of specific individual symptoms

3.3.2.1.4.1. Individual symptoms

Nasal obstruction. Although nasal obstruction can be assessed objectively with techniques such as rhinomanometry, nasal peak inspiratory flow and acoustic rhinometry, these are rarely used in the diagnosis and assessment of ARS, which relies on patient report of obstruction and subjective assessment of severity, either by VAS score or by assessing obstruction as absent, mild, moderate or severe.

3.3.2.1.4.2. Individual symptoms: Nasal discharge

The presence and severity of nasal discharge (anterior or posterior nasal drip) is assessed by subjective report, and graded by VAS score or by patient subjective assessment as absent, mild, moderate or severe. Patient reported purulence of nasal discharge has been recommended as a diagnostic criterion for acute bacterial rhinosinusitis [227], and is prioritized by GPs as a feature indicating the need for antibiotics [226], with limited evidence to support this. Purulent nasal secretions have been reported to increase the likelihood ratio of radiological sinus opacity [237], and of obtaining a positive bacterial culture [242], although purulent rhinorrhoea with a unilateral predominance has a positive predictive value (PPV) of only 50%, and pus in the nasal cavity a PPV of only 17%, in the prediction of a positive bacterial culture of an aspirate of the maxillary sinus [236], so cannot be relied upon to accurately identify bacterial infection.

3.3.2.1.4.3. Individual symptoms: Smell abnormalities

Reduction of smell can be rated by patient subjective report as a VAS score or assessed as absent, mild, moderate, or severe. Subjective report of olfaction correlates well with objective tests [243-245] and loss of olfaction is commonly associated with ARS.

3.3.2.1.4.4. Individual symptoms: Facial pain and pressure

Facial pain and pressure commonly occur in ARS, although may also occur transiently in self-limiting viral upper respiratory tract infection (URTI). Facial or dental pain, especially when unilateral, has been found to be a predictor of acute maxillary sinusitis with fluid retention in patients with suspected bacterial infection when confirmed by maxillary antral aspiration [236] or paranasal sinus radiographs [237]. Pain on bending forwards and maxillary toothache, particularly when unilateral, are often interpreted by GPs as indicative of more severe disease and the need for antibiotics [226], with limited supportive evidence. Maxillary toothache is reported to increase the likelihood ratio of radiological sinus opacity to 2.5 [237], although the PPV of local unilateral pain for bacterial infection was only 41% in another study [236]. A further study reported that maxillary toothache was significantly associated with the presence of a positive bacteriological culture, predominantly of *S. pneumoniae* or *H. influenzae*, obtained by sinus aspiration or lavage [246].The severity of pain can be rated subjectively by patients as a VAS score or as absent, mild, moderate, or severe.

Bacterial infection may occur in ARS, but in most cases antibiotics have little effect on the course of the illness.

3.3.2.1.5. Clinical rules for the prediction of bacterial disease

A number of studies have attempted to provide clinicians with combinations of symptoms and signs predicting more severe disease, particularly in the prediction of a bacterial infection and the likelihood of a response to antibiotics. In a study of primary care patients aged 15 years or older with a clinical diagnosis of ARS which assessed the likelihood of specific symptoms and tests in predicting a fluid level or total opacity of any sinus on CT (as a gold standard of sinusitis), Lindbaek [247] reported four factors having a high likelihood ratio and independently associated with ARS. These were purulent rhinorrhoea, purulent secretion in cavum nasi, a raised ESR (>10), and 'double sickening' (i.e. a deterioration after an initial milder phase of illness). A combination of at least three of these four symptoms and signs gave a specificity of 0.81 and a sensitivity of 0.66 for ARS.

Berg [236] reported that 2 or more positive findings (from purulent rhinorrhoea with unilateral predominance, local pain with unilateral predominance, pus in the nasal cavity and bilateral purulent rhinorrhoea) provided 95% sensitivity and 77% specificity for ABRS. Williams [237] reported that fewer than 2 symptoms (from maxillary toothache, poor response to antihistamines or decongestants, purulent nasal secretions, abnormal transillumination and coloured nasal discharge) ruled out ABRS with a positive predictive value (PPV) of <40%, and 4 or more symptoms ruled in ABRS (PPV, 81%).

3.3.2.2. Clinical examination

3.3.2.2.1. Anterior rhinoscopy

Although anterior rhinoscopy alone is a very limited investigation, it should be performed in primary care setting as part of the clinical assessment of suspected ARS. It may reveal supportive findings such as nasal inflammation, mucosal oedema and purulent nasal discharge, and can sometimes reveal previously unsuspected findings such as polyps or anatomical abnormalities.

3.3.2.2.2. Temperature

The presence of a fever of >38°C indicates the presence of a more severe illness and the possible need for more active treatment, particularly in conjunction with more severe symptoms. A fever of >38°C is significantly associated with the presence of a positive bacteriologic culture, predominantly *S. pneumoniae* and *H. influenzae*, obtained by sinus aspiration or lavage [246].

3.3.2.2.3. Inspection and palpation of sinuses

Inspection and palpation of the maxillofacial area can reveal swelling and tenderness, which are commonly interpreted as indicating more severe disease [226] and the need for antibiotics, although the sensitivity and specificity of this symptom in the identification of ABRS is not established.

3.3.2.2.4. Nasal endoscopy

Nasal endoscopy is not generally available in routine primary care settings, and is not required in the clinical diagnosis of ARS, although may be required in research settings, and is discussed below.

3.3.2.3. Additional Investigations

3.3.2.3.1. Bacteriology

Microbiological investigations are not required for the diagnosis of ARS in routine practice, although may be required in research settings, or in atypical or recurrent disease. There is a reasonable correlation between specimens taken from the middle meatus under endoscopic control and sinus taps [248], and microbiological sampling may be indicated in more severe, recurrent or complicated presentations.

3.3.2.3.2. Imaging

Imaging studies and not required in the diagnosis of ARS in routine practice, although may be required to confirm the diagnosis in research settings, and are discussed further below.

3.3.2.3.3. C-Reactive Protein (CRP)

CRP is a haematological biomarker (available as rapid assay near-patient testing kits) and is raised in bacterial infection. Its use has been advocated in respiratory tract infection [247] as an aid to targeting bacterial infection and so in limiting unnecessary antibiotic use. Recent studies [249, 250] have suggested that in ARS, a low or normal CRP may identify patients with a low likelihood of positive bacterial infection who are unlikely to need or benefit from antibiotics, and CRP guided treatment has been associated with a reduction in antibiotic use without any impairment of outcomes. This can be regarded as an interesting but preliminary observation, and more research is needed before this test can be recommended as routine in the diagnosis of ARS and in the targeting of therapy. However, CRP levels are significantly correlated with changes in CT scans [251] and a raised CRP is predictive of a positive bacterial culture on sinus puncture or lavage [246, 252].

3.3.2.3.4. Procalcitonin

Procalcitonin has also been advocated as a potential haematological biomarker indicating more severe bacterial infection, and investigated as a tool for guiding antibiotic prescribing in respiratory tract infections in the community [253].

It is available as a near-patient manual assay that can provide results in 30 minutes, but with limited performance results [254], or as a laboratory test. At present, however, there is no evidence of its effectiveness as a biomarker in ARS.

3.3.2.3.5. Erythrocyte Sedimentation Rate (ESR) and plasma viscosity

Markers of inflammation such as ESR and plasma viscosity are raised in ARS, may reflect disease severity and can indicate the need for more aggressive treatment in a similar way to CRP. ERS levels are correlated with CT changes in ARS [251] and an ESR of >10 is predictive of sinus fluid levels or sinus opacity on CT scans [252]. A raised ESR is predictive of a positive bacterial culture on sinus puncture or lavage [246, 252].

3.3.2.3.6. Nasal Nitric Oxide (NO)

This gaseous metabolite is found in the upper and lower respiratory tract and is a sensitive indicator of the presence of inflammation and ciliary dysfunction. Measurement of nasal NO is relatively simple, requires simple patient co-operation by exhaling into the analyser, and is quick and easy to perform using chemiluminescence assay equipment. Measurement is feasible in routine clinical settings, and as the technology improves and cost of measurement apparatus reduces, may be practicable as a clinical tool. Preliminary evidence exists of feasibility of using exhaled NO measurement in primary care in asthma diagnosis and monitoring [255], but the feasibility of use of nasal NO in routine care has not been assessed. Very low levels of nasal NO may indicate primary ciliary dyskinesia, but may also occur insignificant sinus obstruction [256]. Elevated levels may suggest the presence of inflammation provided ostiomeatal patency is maintained. A recent pilot study [257] has suggested that monitoring of nasal NO levels may be useful in the diagnosis and management of ARS, but further research is needed.

3.3.2.3.7. Other investigations

Detailed tests of nasal airway function such as tests of mucociliary function, nasal patency, and olfaction are rarely performed in the diagnosis of ARS other than in specific research settings.

3.3.2.4. Differential Diagnosis of ARS in clinical practice

The symptoms of ARS are non-specific and may overlap with a number of other conditions, which should be differentiated.

3.3.2.4.1. Viral Upper Respiratory Tract Infection (URTI)

The symptoms of the common cold and of self-limiting viral URTIs overlap with those of post-viral ARS. Indeed, most episodes of ARS will start as a viral URTI, but with a prolonged illness beyond 10 days or with worsening symptoms after 5 days. Most common colds are associated with rhinovirus infection with symptoms peaking by 3 days [258], and the majority of patients do not seek medical care. The diagnosis is clinical and supportive advice, symptomatic treatment and reassurance are generally the only interventions required.

3.3.2.4.2. Allergic rhinitis

Allergic rhinitis (AR) is a common global condition affecting 10-20% of the adult population [259]. Allergic rhinitis is the most common form of non-infectious rhinitis and is associated with an IgE-mediated immune response against allergens, and is often associated with ocular symptoms. Since the nasal mucosa is continuous with that of the paranasal sinuses, congestion of the ostia may result in sinusitis, which does not exist without rhinitis, so AR may be part of an allergic rhinosinusitis with similar symptoms to those of ARS (and CRS). Symptoms of AR include rhinorrhoea (non-purulent), nasal obstruction, nasal itching, and sneezing, which are reversible spontaneously or with treatment. AR is subdivided into "intermittent" or "persistent" disease. Intermittent rhinitis may occur suddenly in response to exposure to a specific allergen, and so cause diagnostic confusion between AR and ARS. Seasonal AR is related to a wide variety of outdoor allergens such as pollens or molds, and sudden exposure to such aeroallergens or to others (e.g. cat and dog dander in sensitized individuals) can cause acute onset of symptoms. In AR, there will usually be a history of similar symptoms in response to similar exposures, often with a seasonal pattern. Non-specific irritants such as air pollution and viral infection may aggravate symptoms in symptomatic AR patients and induce symptoms in asymptomatic patients with subclinical nasal inflammation.

The diagnosis of AR and differentiation from ARS is made mainly on the basis of a prior history of allergy and atopy, and exposure to an allergen (usually an aeroallergen) to which the patient is sensitized. Ocular symptoms are common in AR, in particular in patients allergic to outdoor allergens, but not in ARS. Mucopurulent rhinorrhoea, pain, nasal obstruction without other symptoms and anosmia are uncommon in AR. Diagnostic tests for AR are based on the demonstration of allergen-specific IgE in the skin (skin tests) or the blood (specific IgE), and may be considered to clarify the diagnosis, particularly in those with severe or persistent symptoms.

3.3.2.4.3. Orodontal disease

Patients with orodontal disease may present to primary care physicians with ill-defined facial pain, with or without fever and toothache. The absence of other ARS-associated symptoms such as rhinorrhoea, nasal discharge and smell disturbance will make ARS a less likely diagnosis, although in some cases doubt may persist. A dental assessment and dental radiography may be required to clarify the diagnosis. ARS may occur more frequently

and have overlapping symptoms in patients with orodental disease [61].

3.3.2.4.4. Rare diseases

A number of less common conditions may occasionally present acutely with similar symptoms to ARS.

3.3.2.4.4.1. Intracranial sepsis

Intracranial sepsis is uncommon but it is crucial that primary care practitioners are aware of the warning signs of complicated and severe illness and refer promptly when the diagnosis is possible. Symptoms such as periorbital oedema, displaced globe, diplopia, ophtalmoplegia, reduced visual acuity, severe unilateral or bilateral frontal headache, frontal headache, focal neurological signs or meningism point to complications such as intracranial sepsis, or an alternative diagnosis and requite urgent diagnosis and appropriate management. (See Table 3.3.1).

3.3.2.4.4.2. Facial pain syndromes

A number of conditions can present acutely with facial pain and nasal symptoms, including migraine and cluster headaches. The differential diagnosis of facial pain is discussed in section 4. Bilateral pressure sensations without other nasal symptoms may be caused by tension headaches and mid facial segmental pain.

3.3.2.4.4.3. Vasculitis

Autoimmune vasculitides such as Wegener's granulomatosis and Churg-Strauss syndrome or sarcoidosis may involve the nose and sinuses and on rare occasions may present acutely. The presence of other suggestive symptoms and an atypical clinical course can alert the clinician to alternative diagnoses.

3.3.2.4.4.4. Acute invasive fungal rhinosinusitis

In immunosuppressed patients and in (uncontrolled) diabetics, acute invasive fungal rhinosinusitis may present in a similar way to ARS, but with severe and rapidly progressive symptoms [260, 261]. When this diagnosis is suspected, a more aggressive diagnostic approach is required as a delay in diagnosis worsens the prognosis.

3.3.2.4.4.5. CSF leak

Unilateral watery rhinorrhoea is uncommon and should raise suspicion of cerebrospinal fluid leakage [262].

3.3.3. Warning signs of complications of ARS

Septic complications of ARS represent a medical emergency and require prompt recognition by generalists and immediate referral to secondary care for assessment (Table 3.3.1).

Observational surveys suggest that these complications occur rarely but early in the course of the disease, and that outcomes are not influenced by the use or non-use of antibiotics in primary care [232, 234].

Table 3.3.1. Warning symptoms of complications in ARS requiring immediate referral / hospitalization.

Periorbital oedema/erythema
Displaced globe
Double vision
Ophtalmoplegia
Reduced visual acuity
Severe unilateral or bilateral frontal headache
Frontal swelling
Signs of meningitis
neurological signs
Reduced consciousness

Septic complications of ARS are uncommon, but vital to identify early. They occur early in the course of the illness and primary care clinicians need to be vigilant for danger signs and symptoms, such as high fever, systemic illness, periorbital oedema and reduced vision

3.3.4. Enhanced Diagnosis in specialist care

Although uncomplicated ARS is more likely to present to primary care physicians, in some health systems patients may present acutely to specialists or may be referred early for a specialist assessment, usually to a rhinologist or ENT specialist. Generally the diagnosis may be made clinically using the same clinical criteria outlined above, but sometimes more detailed diagnostic investigations may be applied. Immediate referral and/or hospitalization are indicated for any of the symptoms listed in table 3.1.1.

3.3.4.1. Nasal endoscopy

Nasal endoscopy may be used to visualize nasal and sinus anatomy and to provide biopsy and microbiological samples. Several microbiology studies [263-267] (Evidence Level IIb) have shown a reasonable correlation between specimens taken from the middle meatus under endoscopic control and proof puncture leading to the possibility of microbiological confirmation of both the pathogen and its response to therapy (Table 3.3.2). A meta-analysis showed an accuracy of 87% with a lower end confidence level of 81.3% for the endoscopically directed middle meatal culture when compared with maxillary sinus taps in acute maxillary sinus infection [248]. Some authorities recommend that a clinical diagnosis of acute bacterial rhinosinusitis should always be confirmed by endoscopy and culture [268], as many patients with clinical or

Table 3.3.2. Bacteriology of rhinosinusitis. Correlation of middle meatus versus maxillary sinus.

Author, year, ref.	Number of Samples	Type of Rhinosinusitis	Technique	Concordance
Joniau 2005 [267]	26	ARS	Endoscopic swab (MM) vs. maxillary sinus tap	88.5%
Casiano 2001 [266]	29	ARS (intensive care)	Endoscopic tissue culture (MM) vs. maxillary sinus tap	60.0%
Talbot 2001 [271]	46	ARS	Endoscopic swab (MM) vs. maxillary sinus tap	90.6%
Vogan 2000 [265]	16	ARS	Endoscopic swab (MM) vs. maxillary sinus tap	93.0%
Gold & Tami 1997 [264]	21	CRS	Endoscopic tap (MM) vs. maxillary aspiration during ESS	85.7%
Klossek 1996 [263]	65	CRS	Endoscopic swab (MM) vs. maxillary aspiration during ESS	73.8%

ARS: acute rhinosinusitis; CRS: chronic rhinosinusitis
MM: middle meatus; ESS: endoscopic sinus surgery

radiological evidence of ARS do not have positive bacterial microbiology; since this guideline favours the term 'acute post-viral rhinosinusitis', and favours anti-inflammatory rather than anti-infective therapy as first-line management, it is debatable how valid this advice is, particularly in settings where access to endoscopy is limited. Nasal endoscopy is possible in patients of all ages, including children, although does not provide additional information in most [269, 270].

3.3.4.2. Imaging

A number of different imaging modalities are possible in the diagnosis of ARS.

3.3.4.2.1. CT scanning

CT scanning is the imaging modality of choice to confirm the extent of pathology and the anatomy. However, it should not be regarded as the primary step in the diagnosis of the condition, except where there are unilateral signs and symptoms or other sinister signs, but rather corroborates history and endoscopic examination after failure of medical therapy. CT may be considered in very severe disease, in immuno-compromised patients, when there is suspicion of complications. A recent study suggests that routine CT scanning in ARS adds little useful information [251]. The demonstration of the complex sinonasal anatomy has however, been regarded as at least as important as confirmation of inflammatory change [272-274]. Considerable ethnic as well as individual differences may be encountered [275]. Many protocols have been described and interest has recently centered on improving definition whilst reducing radiation dose [276]. Incidental abnormalities have been reported on scanning in up to a fifth of the 'normal' population [277], although more recent data have suggested that healthy normal people should not have unexpected abnormal sinus scans [278]. In children, in whom plain radiographs are technically difficult, sinus scans are technically possible and are the imaging investigation of choice but similarly are only indicated if complications are suspected or if a lack of response to treatment occurs [279].

3.3.4.2.2. Plain sinus X Rays and transillumination

Plain sinus x-rays are insensitive and of limited usefulness for the diagnosis of rhinosinusitis due to the number of false positive and negative results [280-282]. Nevertheless it can be useful to prove ARS in research studies. Transillumination was advocated in the 1970's as an inexpensive and efficacious screening modality for sinus pathology [283]. The insensitivity and unspecificity makes it unreliable for the diagnosis of rhinosinusitis [284].

3.3.4.2.3. Ultrasound

Sinus ultrasound is insensitive and of limited usefulness for the diagnosis of ARS due to the number of false positive and negative results. However, the results in well-trained hands are comparable to X-ray in the diagnostics of ARS, and so it may be a useful investigation in some settings [285-287].

3.3.5. ARS diagnosis specific settings

3.3.5.1. Diagnosis for research

In research settings, a more formal diagnosis may be required. In such settings, a variable combination of symptoms, imaging findings, examination findings, and bacteriology samples (obtained from middle meatus or from sinus puncture) may be required for confirmation of the diagnosis as specified in the study protocol. The diagnostic criteria used must be specified in research studies to allow comparison of results between studies.

3.3.5.2. Diagnosis in the intensive care unit

ARS is common in ICU (with risk factors including naso-gastric tubes, mechanical ventilation, failure of defence mechanisms and pronged supine posture), and is associated with poor outcomes. Sepsis may involve multiple sinuses [288]. As a consequence, more aggressive diagnostic processes may be appropriate to confirm the diagnosis and to guide treatment. CT

scanning may confirm the diagnosis [289], and sinus puncture is safe in skilled hands and can provide important microbiological information to confirm the diagnosis and guide therapy [288].

3.3.5.3. Diagnosis in immunosuppressed patients

Immunosuppressed patients are much more vulnerable to complications of ARS, and a more aggressive diagnostic approach is required. Acute invasive fungal rhinosinusitis [290] is a serious disease with high mortality and morbidity and requires prompt diagnosis and treatment with open or endoscopic sinus surgery.

The diagnosis is histopathological, so early endoscopic evaluations indicated, with open biopsy if doubt remains [260, 261].

3.3.6. Recurrent ARS

The differentiation between CRS and recurrent ARS can be difficult, but relies on complete resolution of symptoms and signs between episodes. Some patients do have recurrent episodes of ARS, and may represent a distinct phenotype [291]. Such patients should be assessed for underlying risk factor, such as allergy and anatomical abnormalities [60], with consideration of imaging or endoscopic evaluation. Occult immunodeficiency may rarely occur in such patients, but routine screening has a low yield [292].

3.4. Management of ARS

Summary

The introduction of evidence-based management of ARS has a major impact on the physician's management of ARS patients. It has been proven clearly in many clinical studies that ARS resolves without antibiotic treatment in most cases. Symptomatic treatment and reassurance is the preferred initial management strategy for patients with mild symptoms. Intranasal corticosteroids in monotherapy or in adjuvant therapy to oral antibiotics are proven to be effective; however, in patients with severe ARS, oral corticosteroids can be used for short-term relief of headache, facial pain and other acute symptoms. Antibiotic therapy should be reserved for patients with high fever or severe (unilateral) facial pain. For initial treatment, the most narrow-spectrum agent active against the likely pathogens should be used. Herbal compounds have been commonly used in treatment of ARS, but only a few DBPC randomized studies have shown their efficacy. Hence, the benefit of herbal compounds in treatment of ARS need to be confirmed by more well designed and randomized clinical trials in future.

3.4.1. Introduction

ARS is a common disease that is managed in both primary care and specialized clinics, and by general practitioners (GPs),

Table 3.4.1. Evidence from systemic review or meta-analysis for antibiotics in treatment of Acute Rhinosinusitis (ARS).

Authors, year, ref.	Inclusion criteria	Number of		Conclusion
		Studies	Patients/ placebo	
Falagas, et al. 2009 [298]	RCTs	12	4,430	Short-course antibiotic treatment had comparable effectiveness to a longer course of therapy
Falagas, et al. 2008 [345]	RCTs	17	2,648	Antibiotics should be reserved for carefully selected patients with a higher probability for bacterial disease
Burton, et al. 2008 [346]	Extracts from the Cochrane library	NA	NA	A small treatment efficacy in patients with uncomplicated ARS
Ahovuo-Saloranta, et al. 2008 [297]	RCTs	5	631	Antibiotics have a small treatment efficacy in patients with uncomplicated ARS. 80%patients improve within two weeks without antibiotics
Young, et al. 2008 [295]	RCTs	9	2,547	Antibiotics are not justified even if a patient reports symptoms for longer than 7-10 days
Williams JW Jr, et al. 2008 [299]	RCTs	49	13,660	For acute maxillary sinusitis confirmed radio-graphically or by aspiration, current evidence is limited but supports the use of penicillin for 7 to 14 days
Rosenfeld, et al. 2007 [347]	DBPC randomized trials	13	NA	Over 70% of patients with ARS are improved after 7 days, with or without antimicrobial therapy
Arroll B. 2005 [348]	Review of the Cochrane reviews	4	NA	The use of antibiotics for acute purulent rhinitis and acute maxillary sinusitis seems to be discretionary rather than prohibited or mandatory, at least for non-severe cases
Stalman, et al. 1997 [349]	DBPC randomized trials	3	NA	The effectiveness of antibiotic treatment in acute maxillary sinusitis in a general practice population is not based sufficiently on evidence

RCTs: randomized controlled trials; DBPC: double-blind, placebo-controlled; NA: not applicable

otolaryngologists and paediatricians. Therefore, consensus in the management of ARS amongst GPs and different specialists who commonly treat ARS is very important. However, it needs to be noticed that when analysing studies for scientific evidences in the treatment of ARS (no matter of the investigated drug) several of them present a mixture of patients with common cold and either post-viral or bacterial ARS (i.e. corticosteroids and antibiotics in ARS, Williamson IG 2007 [312]).

ARS resolves without antibiotic treatment in most cases. Symptomatic treatment and reassurance is the preferred initial management strategy for patients with mild symptoms.

It has been stated clearly in position papers and various meta-analyses that ARS resolves without antibiotic treatment in most cases [8, 293-295]. Symptomatic treatment and reassurance is the preferred initial management strategy for patients with mild symptoms. Antibiotic therapy should be reserved for patients with high fever or severe (unilateral) facial pain. For initial treatment, the most narrow-spectrum agent active against the likely pathogens (Streptococcus pneumoniae and Haemophilus influenzae) should be used, rather than a general broad-spectrum agent [293].

3.4.2. Treatment of ARS with antibiotics

According to data from a National Ambulatory Medical Care Survey (NAMCS) in the USA, rhinosinusitis is the fifth most common diagnosis for which an antibiotic is prescribed. In 2002, rhinosinusitis accounted for 9% and 21% of all paediatric and adult antibiotic prescriptions respectively [296], although the usage of antibiotics in the treatment of mild, moderate or uncomplicated ARS has been shown to be not useful by most randomized controlled studies (Table 3.4.1) and is not recommended by almost all clinical guidelines [8, 293-296]. A recent multi-nations study in Asia showed that overuse of antibiotics is still an alarming problem among GPs, otolaryngologists, and paediatricians [9].

A recent Cochrane study was performed to compare antibiotics against placebo, or between antibiotics from different classes in the treatment of acute maxillary sinusitis in adults [297]. A total of 59 studies were included in this review; six placebo-controlled studies and 53 studies comparing different classes of antibiotics or comparing different dosing regimens of the same antibiotic. Among them, 5 studies involving 631 patients provided data for comparison of antibiotics to placebo, where clinical failure was defined as a lack of cure or improvement at 7 to 15 days follow up. These studies found a slight statistical difference in favour of antibiotics, compared to placebo, with a pooled risk factor (RR) of 0.66 (95% confidence interval (CI) 0.44 to 0.98). However, the clinical significance of the result is equivocal, also considering that cure or improvement rate was high in both the placebo group (80%) and the antibiotic group (90%).

Based on six studies, where clinical failure was defined as a lack of total cure, there was significant difference in favour of antibiotics compared to placebo with a pooled RR of 0.74 (95% CI 0.65 to 0.84) at 7 to 15 days follow up. None of the antibiotic preparations was superior to another. This study concluded that antibiotics have a small treatment effect in patients with uncomplicated ARS in a primary care setting with symptoms for more than seven days. Eighty percent of patients treated without antibiotics improve within two weeks. Clinicians need to weigh the small benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population level [297].

Although antibiotics for ARS should be reserved for selected patients with substantial probability of bacterial disease, accurate clinical diagnosis is often difficult to attain. Short-course antibiotic treatment had comparable effectiveness to a longer course of therapy for ARS. Shortened treatment, particularly for patients without severe disease and complicating factors, might lead to fewer adverse events, better patient compliance, lower rates of resistance development and fewer costs [298].

In an earlier Cochrane study [299], the authors aimed to examine whether antibiotics are indicated for ARS, and if so, which antibiotic classes are most effective. Primary outcomes were: a) clinical cure, and b) clinical cure or improvement. Secondary outcomes were radiographic improvement, relapse rates, and dropouts due to adverse effects.

A total of 49 trials, involving 13,660 participants, were evaluated with antibiotic treatment for acute maxillary sinusitis. Compared to controls (5 studies), penicillin improved clinical cures (relative risk (RR) 1.72; 95% CI 1.00 to 2.96). Treatment with amoxicillin did not significantly improve cure rates (RR 2.06; 95% CI 0.65 to 6.53) but there was significant variability between studies. Radiographic outcomes were improved by antibiotic treatment. Comparisons between classes of antibiotics (10 studies) showed no significant differences between newer non-penicillins (cephalosporins, macrolides, minocycline) versus penicillins (amoxicillin, penicillin V) with RR for cure 1.07 (95% CI 0.99 to 1.17); and newer non-penicillins versus amoxicillin-clavulanate (RR for cure 1.03; 95% CI 0.96 to 1.11). Compared to amoxicillin-clavulanate (17 studies), dropouts due to adverse effects were significantly lower for cephalosporin antibiotics (RR 0.47; 95% CI 0.30 to 0.73). Relapse rates within one month of successful therapy were 7.7%. The authors conclude that, for acute

maxillary sinusitis confirmed radiographically or by aspiration, current evidence is limited but supports the use of penicillin or amoxicillin for 7 to 14 days. Clinicians should weigh the moderate benefits of antibiotic treatment against the potential for adverse effects [299].

Antibiotic therapy should be reserved for patients with severe ARS, especially with the presence of high fever or severe (unilateral) facial pain. Clinicians should weigh the moderate benefits of antibiotic treatment against the potential for adverse effects.

Comparison between various antibiotics in term of their dose and duration, efficacy and side-effect of treatments are summarized in three tables, where a total of 42 prospective, randomized, double-blind, placebo controlled (n=9, Table 3.4.2), or comparisons between antibiotics (n=25, Table 3.4.3), or comparisons of different dosages (n=5) or durations (n=3) of treatment (Table 3.4.4) are listed. In general, a short-course treatment, particularly for patients without severe disease and complicating factors, might lead to fewer adverse events, better patient compliance, lower rate of resistance development and fewer costs [298].

Table 3.4.2. Studies on "short-term" antibiotics, compared to placebo, used in the treatment of Acute Rhinosinusitis (ARS). Only studies with a design of prospective, randomized, double-blind, and placebo-controlled (Ib) were selected.

Author, year, ref.	Drug	Dose / Duration	Number of patients	Effects Outcomes	 %	Side effects %	Level of evidence
Hadley 2010 [350]	Moxifloxacin	5 days	73	Clinical success rates	78.1	38.2	Ib
	Placebo		45		66.7	40.7	
Wald 2009 [351]	Amoxicillin/ potassium clavulanate	90mg/kg + 6.4mg/ kg for 14 days	28	Cure	50		Ib
	Placebo		28		14		
Kristo 2005 [352]	Cefuroxime axetil	125mg BD/10 days		Complete cure, absence of prolonged symptoms/complications	Difference of 6%		Ib
Bucher 2003 [353]	Amoxicillin/clavulanic acid	875/125mg BD /6 days	252	Time to cure, number of days of activity restriction, frequency of adverse effects	Adjusted hazard ratio = 0.99		Ib
	Placebo	6 days					
Varonen 2003 [354]	Antibiotics (amoxicillin, doxycycline or penicillin V)	750 mg, 100mg, 1500 mg BD/7 days	146	Clinical cure rates at test-of-cure visit	80		Ib
	Placebo	BD/7 days			66		
Hansen 2000 [355]	Penicillin V		133	Pain score, illness score, CRP/ESR	71		Ib
	Placebo				37		
Stalman 1997 [349]	Doxycycline			Resolution of facial pain and resumption of daily activities	Adjusted hazard ratio of 1.17, 1.31	17%	Ib
	Placebo						
Lindbaek 1996 [356]	Penicillin V and amoxicillin		83	Subjective status, difference in clinical severity score	86		Ib
	Placebo		44		57		
Wald 1986 [357]	Amoxicillin		30	Clinical assessment at 3 and 10 days	67		Ib
	Amoxicillin-clavulanate potassium		28		64		
	Placebo		35		43		

BD: twice daily; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate

Table 3.4.3. Studies on "short-term" antibiotics, compared to other antibiotics, used in the treatment of ARS. Only studies with a design of prospective, randomized, double-blind (Ib) were selected.

Author, year, ref.	Drug	Dose/Duration	Number of Patients	Effects		Side-Effects %	Level of Evidence
				Outcomes	%		
Marple, et al. 2007 [358]	Azithromycin ER	Single 2g dose	270	Resolution of > or = 3 rhinosinusitis symptoms	32.6	23.3	Ib
	Levofloxacin	500 mg QD/10 days	261		23.4	15.3	
Upchurch, et al. 2006 [359]	Faropenem medoxomil	300mg BD/10 days	861	Clinical response	81.8	similar	Ib
	Cefuroxime axetil	250mg BD/10 days			74.5		
Tellier, et al. 2005 [360]	Telithromycin	800mg OD/5 days		Clinical cure and bacteriologic eradication rates	80.9%	Similar, mostly GIT	Ib
	Amoxicillin - clavulanate	500/125mg TDS/10 days			77.4%		
	Cefuroxime axetil	250mg BD/10 days					
Murray, et al. 2005 [361]	Azithromycin microsphere	Single 2g dose	256	Clinical efficacy at the test-of-cure visit	94.5		Ib
	Levofloxacin	500mg OD/10 days	251		92.8		
Henry, et al. 2004 [362]	Cefdinir	600mg OD/10 days	123	Clinical and radiologic response at Test-of-cure visit	83	8	Ib
	Levofloxacin	500mg OD/10 days	118		86	1	
Gehanno, et al. 2004 [363])	Pristinamycin	1g bid/4 days	220	Clinical cure rates	91.4		Ib
	Cefuroxime axetil	250mg bid/5 days	214		91.1		
Ferguson, et al. 2004 [364]	Telithromycin	800mg OD/5 days	349	Clinical cure rates at test-of-cure visit	87.4		Ib
	Moxifloxacin	400mg OD/10 days			86.9		
Buchanan, et al. 2003 (365)	Telithromycin	800mg OD/5 days	593	Clinical cure rates at test-of-cure visit	85.2		Ib
	Cefuroxime axetil	250mg BD/10 days			82		
Luterman, et al. 2003 [366]	Telithromycin	800mg OD/5 days	434	Clinical cure rates at test-of-cure visit	~75	Similar frequency, GIT	Ib
	Telithromycin	800mg OD/10 days			~75		
	Amoxicillin/clavulanic acid	500/125mg TDS/10 days			~75		
Henry, et al. 2003 [367]	Azithromycin	500mg OD/3 days	312	NA	88.8	Azithromycin was better tolerated than amoxicillin/ clavulanic acid	Ib
	Azithromycin	500mg OD/6 days	311	NA	89.3		
	Amoxicillin/clavulanic acid	500/125mg TDS/10 days	313	NA	84.9		
Siegert, et al. 2003 [368]	Faropenem daloxate	300mg BD/7 days	452	Clinical cure rates at test-of-cure visit	89	2.2 (diarrhoea)	Ib
	Cefuroxime axetil	250mg BD/7 days			88.4	2.9	
Klossek, et al. 2003 [369]	Moxifloxacin	400mg OD/7 days	452	Clinical cure rates at test-of-cure visit	96.9	16.9	Ib
	trovafloxacin	200mg OD/10 days			92.1	22.3	
Siegert, et al. 2000 [370]	Moxifloxacin	400mg OD/10 days	242	Clinical cure rates at test-of-cure visit	96.7	5.7	Ib
	Cefuroxime axetil	250mg BD/10 days	251		90,7	4.4	
Burke, et al. 1999 [371]	Moxifloxacin	400mg OD/10 days	223	Clinical cure rates at test-of-cure visit	90	37	Ib
	Cefuroxime axetil	250mg BD/10 days	234		89	26	

Author, year, ref.	Drug	Dose/Duration	Number of Patients	Effects		Side-Effects %	Level of Evidence
				Outcomes	%		
Henry, et al. 1999 [373]	Cefuroxime axetil	250mg BD/10 days	132	Clinical cure rates at test-of-cure visit	equal	29	Ib
	Amoxicillin/clavulanate	500/125mg TDS/10 days	131			17	
Clifford, et al. 1999 [374]	Ciprofloxacin	500mg BD/10 days, placebo 4 days	236	Clinical success observed 6-10 days after therapy	84		Ib
	Clarithromycin	500mg BD, 14 days	221		91		
Henry, et al. 1999 [375]	Sparfloxacin	400mg dose on day 1, 200mg OD/9 days	252	Clinical success observed 6-10 days after therapy	83.1	59.7	Ib
	Clarithromycin	500mg BD/14 days	252		83.4	48.4	
Lasko, et al. 1998 [372]	Levofloxacin	500mg OD/10-14 days	117	Clinical cure rates at test-of-cure visit	93.9	22.5	Ib
	Clarithromycin	500mg BD/10-14 days	221		93.5	39.3	
Hayle, et al. 1996 [376]	Azithromycin	500mg OD/3 days	221	Clinical success at the end of therapy (D25)	79	33	Ib
	Phenoxymethylpenicillin	1.3g TDS/10 days	217		76	40.1	
Gehanno, et al. 1996 [377]	Sparfloxacin	200mg OD/5 days after 400mg on day 1	193	Clinical symptoms + bacteriological or radiological data	82.6	2.6	Ib
	Cefuroxime axetil	250mg BD/8 days	189		83.2	3.8	
Von Sydow, et al. 1995 [378]	Cefpodoxime proxetil		117		96	20	Ib
	Amoxicillin		113		91	16	
Kohler, et al. 1995 [379]	Cefcanel daloxate	300mg BD/10 days	229	Clinical cure or improvement	83.3	15.7	Ib
	Cefaclor	250mg TDS/10 days	119		89.3	13.4	
Unknown author, 1993 [380]	Loracarbef	400mg BD/10 days	168	Clinical cure or improvement	98.2	11.7	Ib
	Doxycycline	200mg first dose, 100mg OD/10 days	164		92.2	10.6	
Husfeldt, et al. 1993 [381]	Ofloxacin	400mg OD/7-14 days	136	Clinical cure	94.9	11.6	Ib
	Erythromycin	500mg BD/7-14 days	144		94.4	19.5	
Scheld, et al. 1986 [382]	Cyclacillin	500mg TDS/10 days	26	Clinical cure	91	Infrequent and similar	Ib
	Amoxicillin	500mg TDS/10 days	27		91		
	Bacampicillin	1200mg BD	22		86.3		

OD: once daily; BD: twice daily; TDS; three times daily.

Antibiotics overuse has been reported in some European countries [300, 301] to have directly resulted in an increased prevalence of antimicrobial resistance in Europe [302, 303].

Although such data is still unavailable in Asia, a recent survey study showed that, even for mild ARS (common cold), medical treatments were still recommended by 87% of GPs, 83.9% of otolaryngologists, and 70% of paediatricians [9]. The top three first-line treatments prescribed were antihistamines (39.2%), nasal decongestants (33.6%), and antibiotics (29.5%). Antibiotics usage was much more often used as the first line treatment of moderate (45.9%) and severe (60.3%) ARS. Even more alarmingly, 13.6% of the participants used a combination of more than two antibiotics classes for treatment of even mild ARS.

The global threat posed by resistant microorganisms has

Table 3.4.4. Studies on "short-term" antibiotics, comparing different duration and dosages, used in the treatment of Acute Rhinosinusitis (ARS). Only studies with a design of prospective, randomized, double-blind (Ib) were selected.

Author, year, ref.	Drug	Dose / Duration	Number of patients	Effects		Side effects %	Level of evidence
				Outcomes	%		
Poole, et al. 2006 [383]	Levofloxacin	750mg/5 days	152	Clinical success	91.4	Similar	Ib
	Levofloxacin	500mg/10 days	149		88.6		
Gehanno, et al. 2004 [384]	Cefotiam hexetil	200mg BD/5 days	1018	Clinical cure rates	85.5	Similar, 3.36	Ib
	Cefotiam hexetil	200mg BD/10 days			85.3		
Ferguson, et al. 2002 [385]	Gemifloxacin	320mg OD/5 days	218	Clinical cure rates at test-of-cure visit	Difference = 0.44%	Well tolerated	Ib
	Gemifloxacin	320mg OD/7 days	203				
Roos, et al. 2002 [386]	Telithromycin	800mg OD/5 days	123	Clinical cure rates at test-of-cure visit	91.1	Well tolerated	Ib
	Telithromycin	800mg OD/10 days	133		91.0		
Murray, et al. 2000 [387]	Clarithromycin ER		122	Clinical cure rates at test-of-cure visit	85	1	Ib
	Clarithromycin IR		123		79	7	
Seggev, et al. 1998 [388]	Amoxicillin/ clavulanate potassium	875/125mg 12 hourly/14 days	134	Clinical success at the end of therapy	93	Similar	Ib
	Amoxicillin/ clavulanate potassium	500/125mg 8 hourly/14 days			88		
Zeckel, et al. 1995 [389]	Loracarbef	200mg BD/10 days	106	Favourable clinical responses	81.1	Similar	Ib
	Loracarbef	400mg BD/10 days	103		81.6		
Sorri, et al. 1981 [390]	Bacampicillin	400mg TDS	25	Clinical assessment	92		Ib
	Bacampicillin	1200mg BD	22		86.3		

OD: once daily; BD: twice daily; TDS; three times daily.

become an international health issue, a product of careless antibiotics abuse. Therefore, for initial treatment, the most narrow-spectrum agent active against the likely pathogens (Streptococcus pneumoniae and Haemophilus influenzae) should be used [293].

3.4.3. Treatment with intranasal corticosteroids

3.4.3.1. Treatment with intranasal corticosteroids

In the EP^{3}OS 2007 document, intranasal corticosteroids were recommended for the treatment of ARS, both in moderate (monotherapy) and severe (with oral antibiotics) disease.

Intranasal corticosteroids are recommended for the treatment of ARS, both in moderate (monotherapy) and severe (with oral antibiotics) disease.

Most studies on corticosteroids in ARS have determined the effect of topical corticosteroids when used as adjunct therapy to antibiotics (Table 3.4.5) [304-309]. Recently a double-blind, double-dummy, placebo-controlled study was published in which topical corticosteroid treatment was used as monotherapy and compared to antibiotics [310]. In this study mometasone furoate (MF) was used and compared to both amoxicillin and placebo in ARS. MF 200 µg twice daily was significantly superior to placebo and amoxicillin in improving the symptom score. Used once daily MF was also superior to placebo but not to amoxicillin. This is the first study to show that topical corticosteroids when used twice daily are effective in treating ARS as monotherapy and is more effective than amoxicillin when used twice daily. Data of this study are also supported by two other studies with a similar design (Table 3.4.5) [311,1367]. However, in another study, neither antibiotics nor topical corticosteroids alone or in combination were effective in altering the symptom severity or the duration of bacterial ARS [312]. However, this study has included patients with 4 days of symptoms, which only satisfy the inclusion criteria of common cold but not ARS.

In a recent Cochrane analysis, the results of four DBPC studies with a total of 1945 patients support the use of intranasal

Table 3.4.5. Treatment with nasal corticosteroids in Acute Rhinosinusitis (ARS), either in monotherapy or as adjunct therapy to oral antibiotics.

Author, year, ref.	Drug	Antibiotic	Number of patients	Effect	X-ray	Level of evidence
1. Cochrane database systemic review						
Zalmanovici 2009 [313]	Intranasal corticosteroids	No	1,943 (four studies)	Higher doses of intranasal corticosteroids (mometasone furoate 400 mcg versus 200 mcg) had a stronger effect on improvement or complete relief of symptoms	ARS confirmed by radiological evidence or by nasal endoscopy	Ia
2. Monotherapy						
Keith 2012 [1367]	Fluticasone furoate	No	737	Significant effect on total symptoms score, nasal congestion/stuffiness, and postnasal drip	Not done	1b
Williamson 2007 [312]	Budesonide	No	240	Neither an antibiotic (amoxicillin) nor a topical steroid alone or in combination was effective as a treatment for acute sinusitis in the primary care setting	Not done	Ib
Bachert 2007 [311]	Mometasone furoate	No	340	Significant improvement in mean total symptom score and in all SNOT-20 items compared with placebo	Not done	Ib
Meltzer 2005 [310]	Mometasone furoate	No	981	Significant effect on total symptoms sinus headache. significantly superior to placebo and amoxicillin	Not done	Ib
3. Adjunct therapy with antibiotics						
Nayak 2002 [304]	Mometasone furoate	Amox/clav.	967	Total symptom score (TSS) was improved (nasal congestion, facial pain, rhinorrhoea and postnasal drip)	No statistical difference in CT outcome	Ib
Dolor 2001 [305]	Fluticasone propionate	Cefuroxime axetil	95	Significant effect. effect measured as clinical success depending on patients self-judgment of symptomatic improvement	Not done	Ib
Meltzer 2000 [306]	Mometasone furoate	Amox/clav	407	Significant effect in congestion, facial Pain, headache and rhinorrhoea. No significant effect in postnasal drip	No statistical difference in CT outcome	Ib
Barlan 1997 [307]	Budesonide	Amox/clav	89 (children)	Improvement in cough and nasal secretion seen at the end of the second week of treatment in the BUD group	Not done	Ib
Meltzer 1993 [308]	Flunisolide	Amox/clav	180	Significant effect: overall score for global assessment of efficacy was greater in the group with flunisolide	No effect on x-ray	Ib
Qvarnberg 1992 [309]	Budesonide	Erythromycin	20	Significant effect on nasal symptoms, facial pain and sensitivity; final clinical outcome did not differ	Mucosal thickening =no effect	`Ib

CT: Computed Tomography.

corticosteroids as a monotherapy or as an adjuvant therapy to antibiotics (evidence level Ia) [313]. Higher doses of intranasal corticosteroids had a stronger effect on improvement or complete relief of symptoms; for mometasone furoate 400 µg versus 200 µg, (RR 1.10; 95% CI 1.02 to 1.18 versus RR 1.04; 95% CI 0.98 to 1.11). No significant adverse events were reported and there was no significant difference in the drop-out and recurrence rate for the two treatment groups and for groups receiving higher doses of intranasal corticosteroids. In the future, further randomized clinical studies are needed to study the efficacy and appropriate use of antibiotics and intranasal corticosteroids as mono- or combined therapy in the treatment of ARS with different severities.

3.4.3.2. Oral corticosteroids adjunct therapy

The result of a recent Cochrane analysis suggests that oral

corticosteroids as an adjunctive therapy to oral antibiotics are effective for short-term relief of symptoms (e.g., headache, facial pain, nasal decongestion and etc.) in ARS (evidence level Ia) [314].

Gehanno et al. [315] tried 8 mg methylprednisolone three times daily for 5 days as adjunctive therapy to 10 days treatment with amoxicillin clavulanate potassium in patients with ARS (criteria: symptoms < 10 days, craniofacial pain, purulent nasal discharge with purulent drainage from the middle meatus, opacities of the sinuses in x-ray or CT scan) in a placebo controlled study. No difference was seen in therapeutic outcome at day 14 between the groups (n=417) but at day 4 there was a significant reduction of headache and facial pain in the steroid group (Table 3.4.6). In a multicentre study Klossek et al. [316] assessed in a double blind, randomised study in parallel groups the efficacy and tolerance to prednisone administered for 3 days in addition to cefpodoxime in adult patients presenting with an ABRS (proven by culture) with severe pain. The assessments made during the first 3 days of treatment showed a statistically significant difference in favour of the prednisone group regarding pain, nasal obstruction and consumption of paracetamol (Table 3.4.6). There was no difference between the two groups after the end of the antibiotic treatment. The tolerance measured throughout the study was comparable between the two groups. Pain is significantly relieved during treatment with prednisone but after 10 days on antibiotics there was no difference between the two groups.

The long-term use of systemic steroids bears the well-recognized risk of these drugs. Since evidence on the use of corticosteroids in patients with ARS is scarce, high-quality trials assessing the efficacy of systemic corticosteroids both as an adjuvant and a monotherapy in the primary care setting should be initiated to provide a more definite answer on their use. These trials should report both short-term (< two weeks) and long-term (> two weeks) effects as well as information on relapse rates and adverse events [314].

3.4.3.3. Prophylactic treatment of recurrent episodes

In a study by Puhakka et al. [317], fluticasone propionate (FP, 200 µg four times daily) or placebo were used for 6 days in 199 subjects with an acute common cold, 24-48 hours after onset of symptoms, to study the preventive effects of FP on risk for development of ARS. Frequency of sinusitis at day 7 in subjects with a positive culture of rhinovirus in nasopharyngeal aspirates, based on x-ray, was 18.4% and 34.9% in FP and placebo group respectively (p=0.07) thus indicating a non-significant effect of FP. Indeed, there is very low evidence for a prophylactic effect of nasal corticosteroids in prevention of recurrence of ARS episodes.

3.4.4. Other treatments

A large number of trials and Cochrane reviews are performed in viral rhinosinusitis. In general the studies are of low quality making clear recommendations difficult.

3.4.4.1. Oral antihistamines

There is no indication for the use of antihistamines (both intranasal and oral) in the treatment of post viral ARS, except in co-existing allergic rhinitis.

Oral antihistamines are frequently prescribed drugs especially for mild ARS [9]. Antihistamines are standard treatment for IgE-mediated allergic diseases such as allergic rhinitis, where histamine (released by mast cells and basophils) is one of the major effectors of allergic reaction [318, 319]. The pathophysiology of ARS is felt to be secondary bacterial infection due to the impairment of mechanical, humoral and cellular defences and epithelial damage caused by viral infection (common cold) [8]. Antihistamines may be marginally more effective at reducing symptoms of runny nose and sneezing at 2 days in viral rhinosinusitis [1365]. There is no indication for the use of antihistamines (both intranasal and oral) in the treatment of postviral ARS, except in co-existing allergic rhinitis.

3.4.4.2. Nasal decongestants

Nasal decongestants are commonly applied in the treatment of ARS in order to decrease congestion and in the hope of improving better sinus ventilation and drainage, as well as to provide symptomatic relief of nasal congestion. Experimental trials on the effect of topical decongestants by CT [320] and MRI scans [321] on ostial and ostiomeatal complex patency have confirmed marked effect on reducing congestion of inferior and middle turbinates and infundibular mucosa, but no effect on ethmoidal and maxillary sinus mucosa. Experimental studies suggest beneficial anti-inflammatory effect of xylometazoline and oxymetazoline by decreasing nitric oxide synthetase [322] and their anti-oxidant action [323].

In contrast to previous in vitro trials on the effect of decongestants on mucociliary transport, a controlled clinical trial (evidence level II) by Inanli et al. suggested improvement in mucociliary clearance in vivo, after 2 weeks of oxymetazoline application in acute bacterial rhinosinusitis, compared to fluticasone, hypertonic saline and saline, but it did not show significant improvement compared to the group where no topical nasal treatment was given. Also, the clinical course of the disease between the groups was not significantly different [324]. This is in concordance with previous randomized controlled trial in adult acute maxillary sinusitis (evidence level Ib), which did not prove any significant impact of decongestants when added

to a penicillin treatment regime in terms of daily symptoms scores of headache and obstruction and sinus x-ray scores [325]. Therefore, the results of this study suggest that decongestion of the sinus ostia is not of primary importance during the course of healing of ARS.
A single dose of a decongestant (oral norephedrine, topical oxymetazoline, oral pseudoephedrine, nasal xylometazoline may be marginally more effective than placebo at reducing congestion at 3 to 10 hours in patients with viral rhinosinusitis[1365]. Decongestant treatment did not prove superior to saline, when added to antibiotic and antihistamine treatment in a randomized double-blind placebo-controlled trial for acute paediatric rhinosinusitis (evidence level Ib) [326]. However, a double blind, randomized, placebo controlled trial demonstrated a significant protective effect of a 14-day course of nasal decongestant (combined with topical budesonide after 7 days) in the prevention of the development of nosocomial maxillary sinusitis in mechanically ventilated patients in the intensive care unit. [327]. Radiologically confirmed maxillary sinusitis was observed in 54% of patients in the active treatment group and in the 82% of the controls, respectively, while infective maxillary sinusitis was observed in 8% and 20% of the groups, respectively [327]. Clinical experience, however, supports the use of the topical application of decongestants to the middle meatus in ARS but not by nasal spray or nasal drops (Evidence level IV).

Recently, a systematically review (Cochrane analysis) of the efficacy of decongestants, antihistamines and nasal irrigation in children with clinically diagnosed ARS was reported [328]. Of the 402 studies found through the electronic searches and handsearching, none met all the inclusion criteria (any one of these drugs versus placebo or no medication). It concludes that no evidence to determine whether the use of antihistamines, decongestants or nasal irrigation is efficacious in children with ARS.

In another Cochrane review the effectiveness of antihistamine-decongestant-analgesic combinations in reducing the duration and alleviating the symptoms of the common cold in adults and children was assessed. The authors included 27 trials (5117 participants) of randomised controlled trials investigating the effectiveness of common cold treatments. Fourteen trials studied antihistamine-decongestant combinations. The authors conclude that current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children (recommendation A). They recommend to weighed the benefits against the risk of adverse effects. They found is no evidence of effectiveness in young children [1363].

3.4.4.3. Nasal or antral irrigation

Nasal irrigation with saline solution has a limited effect in adults with ARS.

Nasal irrigation is a procedure that rinses the nasal cavity with water, isotonic or hypertonic saline solutions. Other synonyms have also been used in the literature such as nasal douche, wash, or lavage. A number of randomized controlled trials have tested nasal and antral irrigation with isotonic or hypertonic saline in the treatment of ARS and CRS. Although saline is considered as a control treatment itself, patients in these randomized trials were assigned to different modalities of application of saline or hypertonic saline, or hypertonic compared to isotonic saline. The results between the groups were compared. Most of them offer evidence that nasal washouts or irrigations with isotonic or hypertonic saline are beneficial in terms of alleviation of symptoms. Hypertonic saline is preferred to isotonic saline in the treatment of rhinosinusitis by some authors in the USA, mostly based on a paper indicating that it significantly improves nasal mucociliary clearance measured by saccharine testing in healthy volunteers [329].

A randomized trial (Ib) by Adam et al. [330] with two controls compared hypertonic nasal saline to isotonic saline and no treatment in 119 patients with common cold and ARS (which were the majority). Outcome measures were subjective nasal symptoms scores (congestion, secretion, headache) at day-3, day-8/-10 and the day of symptom resolution. Rhinosinusitis patients (98%) were also treated with antibiotics. There was no difference between the groups and only 44% of the patients would use the hypertonic saline spray again. Thirty-two percent noted burning, compared with 13% of the normal saline group.

Antral irrigation did not offer significant benefit when added to standard 10-day antibiotic treatment in (4 antibiotics+ decongestants vs. antral washouts; 50 patients per group) ARS, demonstrating approximately 5% better cure rate in each group for washouts than for decongestants, which was not significant [331].

More recently, a review of the Cochrane data from randomised controlled trials (3 RCTs with 618 participants) comparing topical nasal saline treatment to other interventions in adults and children with clinically diagnosed acute URTIs (common cold and rhinosinusitis) has been reported. Most results showed no difference between nasal saline treatment and control. However, there was limited evidence of benefit with nasal saline irrigation in adults. One study showed a mean difference of 0.3 day (out of eight days) for symptom resolution, but this was not

significant. Nasal saline irrigation was associated with less time off work in one study. Minor discomfort was not uncommon and 40% of babies did not tolerate nasal saline drops [332].

Another systematic review of literature was performed to determine whether nasal douching is effective in the treatment of ARS and in preventing recurrent upper respiratory tract infections. The results showed that nasal douching with saline solution has a limited effect in adults with ARS (level of evidence Ia). It is effective in children with ARS in addition to the standard medication (level of evidence Ib) and can prevent recurrent infections (level of evidence IIb) [333].

3.4.4.4. Heated, humidified air

Heated, humidified air has long been used by sufferers of the common cold. The theoretical basis is that steam may help congested mucus drain better and heat may destroy the cold virus as it does in vitro. Six trials (394 trial participants) were included. Three trials in which patient data could be pooled found benefits of steam for symptom relief for the common cold (odds ratio (OR) 0.31; 95% confidence interval (CI) 0.16 to 0.60). However, results on symptom indices were equivocal. In conclusion steam inhalation has not shown any consistent benefits in the treatment of the common cold, hence is not recommended in the routine treatment of common cold symptoms until more double-blind, randomized trials with a standardised treatment modality are conducted (recommendation A(-)) [1364].

3.4.4.5. Physical interventions to interrupt or reduce the spread of respiratory viruses in viral rhinosinusitis

A cochrane review was performed to systematically review the effectiveness of physical interventions to interrupt or reduce the spread of respiratory viruses. The randomized studies suggest respiratory virus spread can be prevented by hygienic measures, such as handwashing, especially around younger children. The incremental effect of adding virucidals or antiseptics to normal handwashing to decrease respiratory disease remains uncertain. Case-control studies suggested that implementing barriers to transmission, isolation, and hygienic measures are effective at containing respiratory virus epidemics. There was limited evidence that social distancing was effective especially if related to the risk of exposure (recommendation A)[1358].

3.4.4.6. Ipratropium bromide

A Cochrane review was performed to determine the effect of ipratropium bromide versus placebo or no treatment on severity of rhinorrhoea and nasal congestion in children and adults with the common cold. Seven trials (2144 participants). Four studies (1959 participants) addressed subjective change in severity of rhinorrhoea. All studies were consistent in reporting statistically significant changes in favour of IB. Nasal congestion was reported in four studies and was found to have no significant change between the two groups. The authors conclude that for people with common cold, the existing evidence, which has some limitations, suggests that Ipratropium bromide is likely to be effective in ameliorating rhinorrhoea. Ipratropium bromide had no effect on nasal congestion and its use was associated with more side effects compared to placebo or no treatment although these appeared to be well-tolerated and self-limiting (recommendation A)[1361].

3.4.4.7. Probiotics

A Cochrane review was performed to assess the effectiveness and safety of probiotics for preventing acute URTIs. The authors included 14 RCTs, but only available data to meta-analyse could be extracted from 10 trials (3451 participants). Probiotics were better than placebo in reducing the number of participants experiencing episodes of acute URTIs, the rate ratio of episodes of acute URTI and reducing antibiotic use (recommendation A) [1362].

3.4.4.8. Vaccination

Vaccination has no direct effect in treatment of ARS. However, routine childhood vaccination has affected frequency and bacteriology of acute otitis media (AOM) and acute bacterial rhinosinusitis [341]. It was found that immunization leads to increase of host's resistance capabilities, decrease of acute respiratory disease incidence and changes in structure of complications due to infection [342]. In another study, a significant shift occurred in the causative pathogens of acute maxillary sinusitis in children in the 5 years after the introduction of vaccination of children with the 7-valent pneumococcal vaccine (PCV7) as compared to the previous 5 years. While the proportion of S. pneumoniae declined by 18%, the proportion of *H. influenzae* increased by 8% [108].

3.4.4.9. NSAID's, Aspirin or acetominophen

In a multicentre, randomized, double-blind, double-dummy, placebo-controlled study, 392 patients with URTI received a single dose of aspirin 500 or 1,000 mg, acetaminophen 500 or 1,000 mg, or matching placebo [343]. Significant reductions were seen in the mean intensity of headache, achiness, and feverish discomfort with all active treatments ($P < 0.001$), but not in sinus sensitivity to percussion or sore throat (evidence level Ib).
A Cochrane review was performed to determine the effects and adverse effects of NSAID's versus placebo and other treatments on the signs and symptoms of the common cold. The review included nine RCTs, describing 37 comparisons: six were NSAID's versus placebo, and three were NSAID's versus NSAID's (1064 patients with common cold). NSAID's did not significantly reduce the total symptom score, or duration of

colds. However, for outcomes related to the analgesic effects of NSAID's (headache, ear pain, and muscle and joint pain) NSAID's produced significant benefits. There was no evidence of increased frequency of adverse effects in the NSAID's treatment groups. The authors recommend NSAID's for relieving discomfort or pain caused by the common cold [1357].

3.4.4.10. Zinc

The Cochrane review Zinc and the common cold included 15 randomized controlled double-blind trials. It was concluded, that zinc would shorten the duration of the episode of common cold and also could be used as a prevention so that the risk of developing an episode of common cold would be decreased. It is too early to give general recommendations for the use of zinc as we do not have sufficient knowledge about the optimal dose, formulation and duration of treatment. Further research should focus on the effect of zinc in patients who are at increased risk of developing complications after common cold (recommendation C) [1352,1356].

3.4.4.11. Vitamin C

The role of vitamin C (ascorbic acid) in the prevention and treatment of the common cold has been a subject of controversy for many years, but is widely sold and used as both a preventive and therapeutic agent. A Cochrane study was performed encompassing thirty trials involving 11,350 study participants in the meta-analysis on the relative risk (RR) of developing a cold whilst taking prophylactic vitamin C. The failure of vitamin C supplementation to reduce the incidence of colds in the normal population indicates that routine mega-dose prophylaxis is not rationally justified for community use. But evidence suggests that it could be justified in people exposed to brief periods of severe physical exercise or cold environments [1366] (Level of evidence Ia, recommendation C).

3.4.4.12. Mucolytics

Mucolytics are used as adjuncts to antibiotic and/or decongestant treatment in ARS in order to reduce the viscosity of sinus secretion. From a recent survey study in France, 45% patients with acute maxillary sinusitis were prescribed with mucolytics [228]. Although some drugs have been shown to have mucolytic effect and were recommended as adjunct treatment for ARS, the benefit of such treatment is not clear due to the lack of standardization in pharmacodynamic and pharmacokinetic properties of these drugs, and also double-blinded, placebo-controlled (DBPC) randomized studies to prove their efficacy.

There is an early RCT study (report in Italian) suggests that bromhexine is superior to placebo [334]. In a recent randomized and DBPC study, the use of erdosteine as a mucolytic agent in children with ARS does not directly affect the success of treatment [335]. In future, more standardization of mucolytics and larger scale DBPC randomized studies still need to be done in order to fully assess the efficacy of mucolytics in the treatment of ARS.

3.4.4.13. Herbal compounds

There are only a few DBPC randomized studies performed in order to assess the efficacy of herbal compounds in treatment of ARS, which is not representative of the full spectrum of herbal remedies used in the treatment of ARS. More such studies and meta-analysis are needed in order to understanding the pharmacodynamic and pharmacokinetic properties of the active compound from the herbs and their mechanisms in treatment of ARS.

Complementary/alternative medicines are extensively used in the treatment of both ARS and CRS, but evidence-based recommendations are difficult to propose due to the lack of randomized controlled trials and methodological problems in many clinical studies or trials. To date, there are only a few DBPC randomized studies performed in order to assess the efficacy of herbal compounds in treatment of ARS (Table 3.4.7), which is not representative of the full spectrum of herbal remedies used in the treatment of ARS. Also, the active compounds of the herbal compounds have not been discovered, purified and standardized yet. More such studies and meta-analysis are needed in order to understanding the pharmacodynamic and pharmacokinetic properties of the active compound from the herbs and their mechanisms in treatment of ARS. All this information is necessary to allow us to make an evidence-based recommendation, and thus we are unable to accept or reject herbal medicines in the treatment of ARS at present (recommendation C).

In a Cochrane study, the effect of pelargonium sidoides (P. sidoides) extract in treatment of acute respiratory tract infections has been reviewed [336]. There was only one study in patients with ARS and another one with the common cold included in analysis based on the RCT criteria [337, 338]. In conclusion, P. sidoides may be effective in alleviating symptoms of ARS and the common cold in adults, but doubt exists [336].

In another DBPC, randomized, multi-centre study (evidence level Ib), the efficacy of Myrtol standardized (4 capsule of 300 mg/day for 6±2 days) in the treatment of ARS (n=331) was assessed. The results showed a statistically significant difference

Table 3.4.7. Treatment with herbal compounds or homeopathic in ARS (DBPC studies).

Authour, year, ref.	Drug	Dose / Duration	Number of patients	Effects		Side effects %	Level of evidence
				Outcomes	Data		
Pfaar, 2012 [392]	Cyclamen europaeum	Spray once daily for 15 days (adjunct to Amoxicillin 500mg/8h, 8 days)	48	Change in mean total ARS symptom scores on Day 7	3.2±2.3 (better improve pain and endoscopic findings on Days 7 and 15 as compared to placebo)	Nasal burning and mild epistaxis	Ib
		Placebo (adjunct to Amoxicillin 500mg/8h, 8 days)	51		2.7 ±2.2		
Bachert 2009 [337]	EPs 7630, from Pelargonium sidoides	60 drops, 3 daily, for 22 days	51	Mean changes in sinusitis severity score after 7 days	5.5	Well tolerated	Ib
	Placebo	matching placebo	52		2.5		
Tesche 2008 [393]	Cineole	2 capsules (200 mg), 3 daily, for 7 days	75	Reduction of symptom-sum-score before and after 4 and 7 days of treatment	Day 4: 6.7±3.4 Day 7: 11±3.0	Well tolerated	Ib
	Placebo (Alternative herbal preparation with five different components)	Alternative herbal preparation	75		Day 4: 3.6±2.8 Day 7: 8.0±3.0		
Zabolotny 2007 [394]	Sinfrontal	22 days	57	(a) Reduction of sinusitis severity score at Day 7 (b) Complete remission at Day 21	(a): 5.8±2.3 (b): 68.4%	Well tolerated in both groups	Ib
	Placebo (saline inhalation, paracetamol and over-the-counter medications, but not antibiotics, were allowed)	22 days	56		(a): 2.6±1.8 (b): 8.9%		
Friese 2007 [395]	Homeopathic	7 days	72	Reduction of sinusitis sum score at Day 7	6.2	Well tolerated in both groups	Ib
	Placebo	7 days	72		0.7		
Kehrl 2004 [396]	Cineole	2 capsules (200 mg), 3 daily, for 7 days	76	Reduction of sinusitis sum score at Day 7	12.6	Mild, heartburn and exanthema	Ib
	Placebo	matching placebo	76		6.4		
Gabrielian 2002 [397]	Andrographis paniculata fixed combination Kan Jang	Andrographis paniculata extract 85 mg and Kan Jang (10 mg/tab) 4 tab, 3 daily, for 5 days	95	Reduction in individual mean symptom score	0.55	Well tolerated	Ib
	Placebo	matching placebo	90		0.20		
Federspil 1997 [339]	Myrtol standardized	4 capsule of 300 mg daily, for 6±2 days	109	Difference in symptoms score (the corresponding value) before and after treatment	10.5	Similar distribution of undesired events in all 3 study groups	Ib
	Essential oil (unregistered)	4 capsule of 300 mg daily, for 6±2 days	110		10.9		
	Placebo	matching placebo	111		9.2		

in the improvement of total sinusitis symptoms score, which had changed by 10.5 and 9.2 points for the treatment with Myrtol standardized and placebo, respectively [339]. A need for antibiotic treatment after Myrtol was 23%, compared to 40% for placebo. This drug has been recommended for treatment of ARS and CRS in the German Society of Oto-Rhino-Laryngology clinical guidelines [340].

In another Cochrane study the effectiveness and safety of Chinese herbal medicines for the common cold was evaluated.

Fourteen studies involving 2440 patients were included. The methods of all studies were rated of poor quality. Included studies used "effective drugs" as controls; however, the efficacy of these control drugs was not reported. In six studies, five herbal preparations were found to be more effective at enhancing recovery than the control; and in the other eight studies, five herbal preparations were shown to be equal to the control. There was a strong probability of different biases in all of the included studies. Chinese herbal medicines may shorten the symptomatic phase in patients with the common cold. However, because of the lack of high quality clinical trials the authors were unable to recommend any kind of Chinese herbal preparation for the common cold [1353].

Also a Cochrane study was performed to determine whether garlic (allium sativum) was effective for either the prevention or treatment of the common cold, when compared to placebo, no treatment or other treatments. There was only one relevant trial that suggested that garlic may prevent occurrences of the common cold, but the authors recommended more studies to validate this finding. Claims of effectiveness appear to rely largely on poor quality evidence (recommendation C)[1356].

3.4.4.14. Cromoglycate

In a randomized double-blind study, comparison was made between sodium cromoglycate and placebo (saline) given as nasal sprays, to control symptoms of post-catarrhal hyperreactive rhinosinusitis [344]. There was an improvement in symptoms in about 50% of the patients in each treatment group, but no significant differences between these two treatments in rhinopharyngeal symptoms, ultrasonic scanning of mucosal thickness in the maxillary sinus, or in the patients' evaluation of rhinitis symptoms (evidence level Ib -).

3.4.4.15. Echinacea

There are 10 RCTs performed on the efficacy on Echinacea of wich 5 found that echinacea significantly reduced overall symptom score compared with placebo and 5 RCTs found no significant difference between groups. The weakness of trial methods and differences in interventions make it difficult to draw conclusions about effectiveness (recommendation C)[1365].

3.4.4.8.4. Other Studies without evidence

The is no evidence from RCTs or DBPC studies for other treatments such as anti-mycotics, bacterial lysates, capsaicin, furosemide, proton pump inhibitors, increased fluid intake [1360] and anti-leukotrienes in ARS.

3.5. Complications of ARS

Summary

Orbital, intracranial, and osseous complications of ARS represent rare but potentially serious clinical events. Periorbital complications include preseptal cellulitis, orbital cellulitis, subperiosteal, and intraorbital abscess and their prompt recognition and management (including i.v. antibiotics and drainage, as required) is vital in order to avoid long-term sequelae. Intracranial complications include epidural or subdural abscesses, brain abscess, meningitis, encephalitis, and superior sagittal and cavernous sinus thrombosis. They may present with non specific signs and symptoms and their diagnosis requires a high index of suspicion. Osseous complications result from osteomyelitis of the facial skeleton associated with the progress of inflammation and may present as Potts Puffy tumour or a frontocutaneous fistula.

3.5.1. Introduction

In the pre-antibiotic era, complications of rhinosinusitis represented common and dangerous clinical events. Today, thanks to more reliable diagnostic methods (CT, MRI), improved surgical techniques and the wide range of available antibiotics, their incidence and related mortality have dramatically decreased. In some cases however, if sinus infection is untreated or inadequately treated, complications can still develop [232]. Complications of rhinosinusitis are classically defined as orbital, osseous, and endocranial 2 though rarely some unusual complications can develop (Table 3.5.1) [398-402].

3.5.2. Epidemiology of complications

The incidence of ARS complications is approximately 3 per million of population per year and is not reduced by antibiotic prescription

Epidemiological data concerning the complications of rhinosinusitis vary widely and there is no consensus on the exact prevalence of the different types of complications. Moreover, the relationship between ARS or CRS and the various complications is not clearly defined in the literature. In patients hospitalised with sinusitis, the reported rate of complications varies from 3.7%8 to 20% 9, although, by selecting for severe sinus disease, these series clearly overestimate the incidence of complications. Complications are typically classified as orbital (60-75%), intracranial (15-20%) and osseous (5-10%) [403]. Overall, sinus disease is the presumed underlying cause of about 10% of intracranial suppuration [404, 405], while sinus disease is related to 10% (preseptal cellulitis) to 90% (orbital cellulitis/ supberiosteal abscess/intraorbital abscess) periorbital infections [406]. What is perhaps more clinically relevant is the incidence of

Table 3.5.1. Epidemiological data of complications in ARS.

Author, year, ref.	Country	Age	Disease	Patients	Incidence of complications (per million population per year)	Orbital	Intracranial	Bone	Soft tissue
Piatt 2011 [231]	USA –National inpatient database (1997, 2000, 2001, 2003, 2006)	Children	ARS	695	2.7 – 4.3				
Hansen 2011 [232]	Netherlands (National database - 2004)	Adults / children	ARS	48	(48/16.3 million=) 3 (1:12,000 ARS episodes - children, 1:32,000 – adults)	67% (32)	33% (16)		
Babar-Craig 2010 [52]	UK – national questionnaire	Adults and Children	ARS	78	N/A	76%	9%	5%	
Stoll 2006 [414]	France (2001-2003)	Adults and adolescents	ARS	43 (30 in 12 months)	(30/12 million=) 2.5	35% (15)	37% (16)		18% (8)
Oxford 2005 [407]	USA	Children	ARS/ CRS	104	N/A	91% (95)	16% (17	3% (3)	
Younis 2002 [408]	USA	Adults and Children	ARS/ CRS	82	N/A	53% (43)	46% (38)	3% (2)	
Ogunleye 2001 [409]	Nigeria	adults	ARS/ CRS	33	N/A	41% (13)	5% (2)	32% (11)	18% (6)
Eufinger 2001 [410]	Germany	adults/ children	ARS	25	N/A	88% (22)	20% (5) 2 pt. had both)		
Mortimor 1997 [411]	South Africa	Adults / Children	ARS/ CRS	63	N/A	81% (51)	13% (8)	10% (6)	24% (15)

N/A, not applicable.

complications in patients with acute rhinosinusitis and in the population as whole (Table 3.5.1).

Four studies (attempted to) collect nationwide or large-scale data: Hansen et al [232], reported 48 ARS complications in 2004 in the Netherlands, corresponding to an incidence of 3 per million of population per year (or approximately 1 per 12,000 ARS episodes in children and 1 per 36,000 episodes of ARS in adults). Very similar results were reached by a US study [231] which recorded an annual incidence of intracranial complications in children between 2.7 and 4.3 per million per year. A French study with a 12 million catchment area recorded a yearly incidence of 2.5 ARS complications per million of population, excluding paediatric patients [414]. In almost all studies males are significantly more frequently affected than females [231, 232, 412] and ARS was more often the precipitating factor in children, while CRS with or without NP was more important in adults [411, 443]. In all studies, the commonest complications were orbital appearing at least twice as often as intracranial with osseous being the least common [232, 410, 411]. There was a clear seasonal pattern of complications, mirroring the incidence of URTIs and appearing more often during winter months [231]. While orbital complications tend to occur primarily in small children, intracranial complications can occur in any age, with predilection for the second and third decade of life [232, 413]. It is important to note that both the Dutch study [232] and the study by Babar-Craig [52], which was based on returned questionnaires by members of the British Rhinology Society and probably underestimated the incidence of complications, showed that prescribing of antibiotics for ARS does not prevent the occurrence of complications. These facts, together with the risk of antibiotic resistance and of masking intracranial complications argue strongly against the routine use of antibiotics in ARS.

The commonest complications of ARS are orbital, appearing approximately twice as often than intracranial and followed by osseous involvement.

Table 3.5.2. Orbital complications of ARS.

Study author, year	N	Age	Type of complications	Management
Huang 2011 [415]	64	Children	Subperiosteal/intraorbital abscess 56% (36) Preseptal/orbital cellulitis 44% (28)	IV abx only: 53% (34) Medical and surgical: 47% (30)
Georgakopoulos 2010 [427]	83	Children	Preseptal cellulitis 83% (69) Orbital cellulitis 12% (10) Subperiosteal abscess 5% (4)	Medical only: 95% (79) Surgical and medical: 5% (4)
Siedek 2008 [443]	127	Adults and children	Preseptal cellulitis 36% (46) Orbital cellulitis 44% (56) Subperiosteal abscess 6% (8) Intraorbital abscess 14% (17) (NB: Classification used makes comparisons problematic)	Medical only:51% (65) Surgical: 49% (62)
Eviatar 2008 [436])	52	Children	Preseptal cellulitis 92% (48) Subperiosteal abscess 8% (4)	Medical : 98% (51) Surgical: 2% (1)
Mekhitarian 2007 [417]	25	Children	Preseptal cellulitis 96% (24) Subperiosteal abscess 4% (1)	Medical: 92% (23) Surgical: 8% (2)
Oxford 2006 [441]	43	Children	Subperiosteal abscess 100% (43)	Medical: 42% (18) Surgical: 58% (25)
Mortimor 1997 [411]	51	Adults and children	Preseptal cellulitis 55% (28) Orbital cellulitis 10% (5) Subperiosteal abscess 33% (17) Intraorbital abscess 2% (1)	Not stated

3.5.3. Orbital complications of ARS (Table 3.5.2)

3.5.3.1. Classification

The most common complications of rhinosinusitis are orbital, and they are associated in order of decreasing frequency with the ethmoid, maxillary, frontal and rarely the sphenoid sinus [232, 410, 414-417]. The spread of infection directly via the thin and often dehiscent lamina papyracea [416] or by veins [418] occurs with relative ease. It is important to note that orbital complications in children may occur without pain [419].

According to Chandler's classification orbital complications may progress in the following steps [403]:

- (preseptal cellulitis),
- orbital cellulitis,
- subperiosteal abscess,
- orbital abscess, and
- (cavernous sinus thrombosis)

Although this classification is the most commonly used, it does present some problems: The orbital septum is the anterior limit of the orbit, hence "preseptal cellulitis" should be classified as an eyelid, rather than an orbital infection, as suggested by Velasco e Cruz [420] and Voegels [421]. Indeed, preseptal cellulitis is infrequently associated with sinusitis and its clinical picture, its management and its prognosis differentiate it from all other orbital infections [422]. Orbital involvement ("postseptal cellulitis") presents with swelling, exophthalmos and impaired, painful extra-ocular eye movements with diplopia– all (beyond swelling) features that do not exist in preseptal cellulitis and differentiate it from true orbital involvement [423].

Additionally, cavernous sinus thrombosis as suggested by Mortimer already in 1997 [411] is an intracranial complication and not necessarily the end stage of orbital infection, while it is more often associated with sphenoid [424] rather than ethmoid or frontal sinus infection, which are the most common sources of infection in orbital cellulitis.

Periorbital or orbital cellulitis may result from direct or vascular spread of the sinus infection. As the spread of sinus infection through the orbit follows a well-described pattern, the initial manifestations are oedema and erythema of the medial aspects of the eyelid. Spread of infection from the maxillary or frontal sinus produces swelling of the lower or upper eyelid, respectively [425].

The advice of an ophthalmologist should always be sought and objective assessment of proptosis (exophthalmometer), orbital pressure (tonometer), visual acuity, colour vision and eye movements should always be clearly documented [411].

3.5.3.2. Preseptal cellulitis

Preseptal cellulitis (inflammation of the eyelid and conjunctiva) [426] involves the tissue anterior to the orbital septum and is readily seen on CT scan as soft tissue swelling. It occurs often as a complication of upper respiratory tract infection, dacryocystitis or skin infection and less often sinusitis [427-430] and it presents with orbital pain, eyelid oedema, erythema and (sometimes) fever. Typically there is no associated proptosis and no limitation of eye movement, although this may be difficult to

assess especially in small children [432]. Preseptal cellulitis usually responds to an oral antibiotic but if not aggressively treated, may spread beyond the orbital septum [431]. In most cases, preseptal cellulitis is a clinical diagnosis and does not mandate a CT scan [422].

3.5.3.3. Orbital cellulitis

Unlike preseptal cellulitis, orbital cellulitis, orbital abscess and subperiosteal abscess all occur more often as complications of acute rhinosinusitis [427, 429, 432]. As the inflammatory changes involve the orbit, proptosis develops together with some limitation of ocular motion, indicating orbital cellulitis. Typical signs are conjunctival oedema (chemosis), a protruding eyeball (proptosis), ocular pain and tenderness, as well as restricted and painful movement of the extraocular muscles [411, 433, 434].

This complication requires aggressive treatment with intravenous antibiotics, as well as the exclusion of subperiosteal or intraorbital abscess.

Any child with proptosis, reduced or painful eye movement (ophthalmoplegia), or decreased visual acuity (initially manifesting itself with reduced green/red colour discrimination) should have a CT scan with i.v. contrast of the sinuses with orbital detail to distinguish between orbital cellulitis and intraorbital or subperiosteal abscess. If a concomitant intracranial complication is suspected or in cases of uncertainty, MRI can provide valuable additional information [435-437]. All three conditions (orbital cellulitis, subperiosteal and intraorbital abscess) cause proptosis and limited ocular movement. Evidence of an abscess on the CT scan, progressive orbital findings or vision (especially colour vision) impairment after initial i.v. antibiotic therapy are indications for orbital exploration and drainage. Repeated ophthalmologic examinations of visual acuity should take place and i.v. antibiotic therapy may be converted into oral when the patient has been afebrile for 48 hours and the ophthalmological symptoms and signs are resolving [438].

3.5.3.4. Subperiosteal and orbital abscess

A Subperiosteal abscess forms between the periorbita and the sinuses and is extraconal – i.e. is located outside the ocular muscles. The clinical features of a subperiosteal abscess are oedema, erythema, chemosis and proptosis of the eyelid with limitation of ocular motility and as a consequence of extra-ocular muscle paralysis, the globe becomes fixed (ophthalmoplegia) and visual acuity diminishes. In most series, high fever and raised leucocyte count as well as left turn were strongly associated with (subperiosteal or intraorbital) abscess formation [439].

An orbital abscess is intraconal (contained within the space defined by the ocular muscles) and generally results from diagnostic delay or immunosuppression of the patient [440] with a frequency of between 13% [416] and 8.3% [437] in paediatric studies of orbital complications.

In case of orbital complications, clinical or radiological evidence of an abscess or lack of clinical improvement after 24-48 hours of i.v. antibiotics are indications for prompt surgical exploration and drainage, preferably endoscopic.

Investigations. A CT scan of the sinuses with orbital sequences may help to distinguish between cellulitis and orbital or subperiosteal abscess. In the case of a subperiosteal abscess the CT usually reveals oedema of the medial rectus muscle, lateralization of the periorbita, and displacement of the globe downward and laterally. When the CT scan shows obliteration of the detail of the extraocular muscle and the optic nerve by a confluent mass, the orbital cellulitis has progressed to an intraorbital abscess, in which there is sometimes air due to anaerobic bacteria. The predictive accuracy of a clinical diagnosis has been found to be 82% and the accuracy of CT 91%. MRI may be useful in cases of diagnostic uncertainty or when intracranial complications are suspected [408, 441, 442].

Table 3.5.3. Indications for surgical intervention in orbital complications of ARS

1.	Evidence of subperiosteal or intraorbital abscess in CT or MRI (with potential exceptions stated above).
2.	Reduced visual acuity/reduced colour vision/affected afferent pupillary reflex or inability to assess vision.
3.	Progressing or not improving orbital signs (diplopia, ophthalmoplegia, proptosis, swelling, chemosis) after 48 hours intravenous antibiotics .
4.	Progressing or not improving general condition (fever, infection parameters) after 48 hours of intravenous antibiotics.

Management. Evidence of an abscess on the CT scan or absence of clinical improvement after 24-48 hours of i.v. antibiotics are indications for orbital exploration and drainage [437]. An ophthalmologist should check visual acuity from the early stages of the illness. Intravenous antibiotic therapy should cover aerobic and anaerobic pathogens. It can be converted to an oral preparation when the patient has been afebrile for 48 hours [435]. Current consensus states that preseptal and orbital cellulitis should be treated with antibiotics while subperiosteal and intraorbital abscesses require surgical exploration (which

should include not just the drainage of the abscess but also of the paranasal sinuses [439]. In such cases, the consensus is to attempt to drain the abscess endoscopically by opening the lamina papyracea and draining the abscess after completing an endoscopic ethmoidectomy. External approaches to lateral and medial orbital abscesses are also used if necessary (Table 3.5.3).

However, there have been a number of recent studies showing good outcomes with i.v. antibiotics in small children with subperiosteal abscesses [432, 440, 443]. In such cases, and provided there is :

- clear clinical improvement within 24-48 hours,
- no decrease in visual acuity,
- small (<0.5-1 ml in volume) medially located subperiosteal abscess,
- no significant systemic involvement,
- patient's age is less than 2-4 years,

there can be an argument for withholding surgical drainage [435].

Prognosis – Follow up. Blindness may result from central retinal artery occlusion, optic neuritis, corneal ulceration, or pan-ophthalmitis. Sepsis not infrequently can spread intracranially as well as anteriorly into the orbit [234].

3.5.4. Endocranial complications

Intracranial complications may present with non-specific symptoms and signs (high fever, headache, lethargy, reduced consciousness) or with focal neurologic or increased intracranial pressure signs

These include epidural or subdural abscesses, brain abscess, meningitis, cerebritis, and superior sagittal and cavernous sinus thrombosis [231, 404, 412, 417, 435, 444].

The clinical presentation of these complications can be non-specific, being characterized simply by high fever with severe, intractable headache, or even be silent [411, 442]. The majority however, usually presents with more specific signs and symptoms that suggest intracranial involvement, such as nausea and vomiting, neck stiffness and altered mental state [234, 411, 412, 440, 445]. Intracranial abscesses are often heralded by signs of increased intracranial pressure, meningeal irritation, and focal neurologic deficits, including third, sixth or seventh cranial nerve palsies [411, 423, 440]. Although an intracranial abscess can be relatively asymptomatic, subtle affective and behavioural changes often occur showing altered neurologic function, altered consciousness, gait instability, and severe, progressive headache [431, 446].

Endocranial complications are most often associated with frontoethmoidal or sphenoid rhinosinusitis [412]. Infections can proceed from the paranasal cavities to the endocranial structures by two different routes: pathogens, starting can pass through the diploic veins to reach the brain; alternatively, they can reach the intracranial structures by eroding the sinus bones or haematologically [445].

All cerebral complications start as encephalitis, but as necrosis and liquefaction of brain tissue progresses, a capsule develops resulting in brain abscess. Studies show a high incidence of anaerobic organisms or mixed aerobic-anaerobic in patients with CNS complications (Table 3.5.4).

A CT scan with contrast is essential for diagnosis as it allows an accurate definition of bone involvement. MRI is increasing being utilised, being more sensitive than CT [448], as well as have an additional value in cavernous sinus thrombosis [412, 445] where an MRI may be necessary [450] or in cases with soft tissue involvement. Moreover, if meningitis is suspected, a lumbar puncture could be useful [445] but only after the exclusion of an abscess using imaging.

High dose long-term i.v. antibiotic therapy followed by burr hole drainage, craniotomy or image guided aspiration as needed, are usually required for successful treatment [451, 452]. Combined drainage of the paranasal sinuses (often the frontal sinus) can be performed endoscopically [448], albeit is in no way as a substitute for the drainage of the intracranial abscess [447]. Pathogens most commonly involved in the pathogenesis of endocranial complications are Streptococcus and Staphylococcus species and anaerobes [404, 451].

3.5.5. Cavernous sinus thrombosis

When the veins surrounding the paranasal sinuses are affected, further spread can lead to cavernous sinus thrombophlebitis causing sepsis and multiple cranial nerve involvement [431]. Such a complication has been estimated at 9% of intracranial complications [444, 445] and is a fortunately rare and dramatic complication of ethmoidal or sphenoidal sinusitis [453].

The main symptoms are bilateral lid drop, exophthalmos, ophthalmic nerve neuralgia, retro-ocular headache with deep pain behind the orbit, complete ophthalmoplegia, papilloedema and signs of meningeal irritation associated with spiking fevers and prostration [425]. Full blood count may show increased white blood cell count with neutrophilia and polymorphotcytosis, while lumbar puncture may show non specific meningeal inflammation and blood cultures will help to culture the offending organism [445].

The cornerstone of diagnosis is MR venogram, demonstrating

Table 3.5.4. Endocranial complications in ARS (studies including more than 10 patients).

Author, year, ref.	N	Complications	Mortality / further defects
Hansen 2011 [232]	16	9 subdural empyema 3 meningitis 2 epidural abscess 2 intracerebral abscess 1 encephalitis 1 superior sagittal sinus thrombosis	Mortality 19% Morbidity 19%
DelGaudio 2010 [447]	23	8 epidural 10 subdural 2 intracerebral abscesses 3 meningitis	Mortality 4% Morbidity 12%
Bayonne 2009 [412]	25	Epidural abscesses Subdural abscesses Meningitis	Sequelae 16% Mortality 0%
Germiller 2006 [448]	25 (mean age 13 y)	13 epidural abscesses 9 subdural abscesses 6 meningitis 2 encephalitis 2 intracerebral abscess 2 cavernous sinus thrombophlebitis	Morbidity 8% Mortality 4%
Quraishi 2006 [449]	12 (mean age 14 y)	2 frontal lobe abscess 8 subdural abscess 1 subdural abscess 1 2 cavernous sinus thrombophlebitis 2	Mortality 8% Morbidity 16 %
Oxford 2005 [407]	18 (mean age 12 y)	7 epidural abscess 6 subdural abscess 2 intracerebral abscess 2 meningitis 1 cavernous sinus thrombosis	No mortality Morbidity 11%
Younis 2002 [408]	39	7 epidural abscess 4 subdural abscess 21 meningitis 4 intracerebral abscess 1 superior sagittal sinus thrombosis	Sequelae 10% No mortality
Jones 2002 [440]	47	Subdural abscess 38% Meningitis 2% Epidural abscess 23% Intracranial abscess 30%	Mortality 2% Morbidity 19%
Albu 2001 [444]	16	6 meningitis 6 frontal lobe abscess 5 epidural abscess 4 subdural abscess 2 cavernous sinus thrombosis	Mortality 6% Morbidity 25%
Gallagher 1998 [445]	15	Meningitis 18% Cerebral abscess 14% Epidural abscess 23%	Mortality 7% Morbidity 13%
Clayman 1991 [413]	24	Meningitis 29% Cerebral abscess 46% Epidural abscess Subdural abscess 8% Cavernous sinus thrombosis 8% Sagittal vein thrombosis 4%	Mortality 4% Morbidity 33%

absence of venous flow in the affected cavernous sinus. High-resolution CT scan with contrast can also show filling defects. A mortality rate of 30% and a morbidity rate of 60% remain in the adult population. No data are available for the paediatric population in which the mortality rate for intracranial complications is 10% to 20% [454]. The use of anticoagulants in these patients remains controversial [425] but is probably indicated provided imaging shows no evidence of any intracerebral haemorrhagic changes [455]. Steroids may help to reduce inflammation and are likely to be helpful, administered with concomitant antibiotics. Drainage of the offending sinus (almost always the sphenoid) is indicated.

3.5.6. Bone complications

Sinus infection can also extend to the bone producing osteomyelitis and eventually involving the brain and nervous system. Even if the most frequent intracranial spread is due to frontal sinusitis, any sinus infection can lead to such a complication [425]. The most common osseous complications are osteomyelitis of the maxillary (typically in infancy) or frontal bones [398].

As vascular necrosis results from frontal sinus osteitis, an osteomyelitis of the anterior or posterior table of the frontal sinus is evident. On the anterior wall it presents clinically with "doughy" oedema of the skin over the frontal bone producing a mass (Pott's puffy tumour) whereas from the posterior wall spread occurs directly or via thrombophlebitis of the valveless diploic veins leading to meningitis, peridural abscess or brain abscess [425]. The infection can proceed anteriorly by breaching.

In this context, Gallagher [445] reviewed the files of 125 patients with complicated rhinosinusitis and found that osteomyelitis developed in about 9% of cases. The sinus walls were affected in 32% of patients in Ogunleye's data [409]. Lang in 2001 recorded 10 cases of subdural empyema in adults and children secondary to frontal sinus infection: among them four had Pott's puffy tumour and one had periorbital abscess [456].

Signs and symptoms of intracranial involvement are soft tissue oedema (especially of the superior lid), high fever, severe headache, meningeal irritation, nausea and vomiting, diplopia, photophobia, papillary oedema, coma and focal neurological signs. Ocular signs can appear contra laterally. Contrast-enhanced CT scan confirms the diagnosis. A lumbar puncture, though contraindicated if intracranial pressure is elevated, can also be useful.

Therapy includes a combination of i.v. broad-spectrum antibiotics administration and surgical debridement of sequestered bone and drainage [425].

Table 3.5.5. Unusual complications of ARS.

Study Author, Year	Complication
Mirza 2001 [398] Patel 2003 [399]	Lacrimal gland abscess
Park 2010 [457]	Orbital hematoma
Gradoni 2010 [458] Sethi [459]	Nasal septal abscess
Sibbery 1997 [460]	Nasal septal perforation
Wu 2008 [461]	Frontocutaneous fistula
Laurens 2008 [462]	Clival osteomyelitis with VI nerve palsy
Righini 2009 [463]	Acute ischemic stroke
Rimal 2006 [464]	Septicaemia

Management of ARS complications is always multidisciplinary – the advice of an ophthalmologist in cases of orbital involvement and of neurologist/neurosurgeon in intracranial involvement is mandatory

3.5.7. Unusual complications of rhinosinusitis

3.5.8. Follow-up of complications

It is important to note that some complications may occasionally appear simultaneously (for example Potts Puffy tumour and intracranial extension, orbital and intracranial complications). A follow up of such patients for a minimum of 6 months is advised, in order to monitor for complete resolution of disease as well as exclude disease recurrence or any complication of treatment.

3.6. Paediatric ARS

Summary

ARS in children is a common entity that usually occurs in the context of an upper respiratory viral illness. In the children where this illness is not self-limited and extends beyond 7-10 days, many agree that a bacterial infection is likely. The diagnosis is mostly based on history of symptoms and their duration as well as physical findings. In most cases this is a self-limited process but, treatment with antibiotics seems to accelerate resolution. Whether this benefit outweighs the risks associated with frequent antibiotic prescriptions remains to be clarified. Intranasal steroids might be useful adjuncts to antibiotics in the treatment of ARS and very limited evidence in older children suggests that they may be useful as a single agent in the treatment. Ancillary therapy in the form of nasal irrigations, antihistamines, decongestants, or mucolytics have not been shown to be helpful.

3.6.1. Definition of ARS in children

ARS is most often viral in aetiology and self-limited.

Acute rhinosinusitis in children is defined as the sudden onset of two or more of the symptoms (discoloured nasal discharge, nasal blockage/obstruction/ congestion, cough at daytime and night-time) for less than 12 weeks, with validation by telephone or interview. Symptom free intervals may exist if the problem is recurrent.

As in adults, common cold / viral ARS is defined as duration of symptoms for less than 10 days; post-viral ARS as increase of symptoms after 5 days or persistent symptoms after 10 days; and suggestive of ABRS when are present at least 3 symptoms/signs among discoloured discharge (with unilateral predominance) and purulent secretion in cavum nasi, severe local pain (with unilateral predominance), fever (>38ºC), elevated ESR/CRP, and double sickening (i.e. a deterioration after an initial milder phase of illness) (see also chapter 2).

3.6.2. Paranasal Sinus Development

Not all sinuses are well developed at birth. The frontal sinuses are indistinguishable from the anterior ethmoid cells and they grow slowly after birth so that they are barely seen anatomically at 1 year of age. After the fourth year, the frontal sinuses begin to enlarge and can usually be demonstrated radiographically in around 20-30% of children at age 6 years [465]. Their size continues to increase into the late teens and more than 85% of children will show pneumatized frontal sinuses on CT scanning at the age of 12 years (465). When volume estimates are generated from examining 3D reconstructions of CT scans, the volume is around 2 ml around age 10 years and reaches adult size around age 19 with mean volume after full growth being 3.46 ml [466].

At birth, the ethmoid and maxillary sinuses are the only sinuses that are large enough to be clinically significant as a cause of rhinosinusitis. In one study, more than 90% of subjects showed radiographically visible ethmoid sinuses at birth [465]. The ethmoid sinuses rapidly increase in size until 7 years of age and complete their growth by age 15-16 years with a mean volume after full growth averaging 4.51 ml [466]. The maxillary sinuses are usually pneumatized at birth and the volume in patients at 2 years of age is around 2 ml [466]. The sinus grows rapidly reaching around 10 ml in volume around age 9 years and full growth volume by 15 years averaging 14.8 ml. Much of the growth that occurs after the twelfth year is in the inferior direction with pneumatisation of the alveolar process after eruption of the secondary dentition. By adulthood, the floor of the maxillary sinus is usually 4-5 mm inferior to the floor of the nasal cavity.

At birth, the size of the sphenoid sinus is small and is little more than an evagination of the sphenoethmoidal recess. By the age of 7 years, the sphenoid sinuses have extended posteriorly to the level of the sella turcica and over 85% of patients have pneumatized sphenoid sinuses visualized on CT scanning by age 8 years [465]. The sphenoid sinuses exhibit a growth spurt between 6-10 years of age and growth is completed by the age of 15 years with the mean volume after full growth averaging 3.47 ml [466]. By the late teens, most of the sphenoid sinuses have aerated to the dorsum sellae and some further enlargement may occur in adults.

3.6.3. Classification and diagnosis

The clinical diagnosis of ARS in children is challenging related to the overlap of symptoms with other common childhood nasal diseases such as viral upper respiratory tract infections and allergic rhinitis as well as the challenges related to physical examination. The symptoms are often subtle and the history is limited to the observations and subjective evaluation by the child's parent. Because some younger children might not tolerate nasal endoscopy, clinicians are sometimes hindered in their physical examination and have to rely on history and or imaging studies for appropriate diagnosis.

Symptom profiles of ARS in children include fever (50-60%), rhinorrhoea (71-80%), cough (50-80%), and pain (29-33%) [8]. In a recent study of 69 children between the ages of 3 and 12 years, ARS was diagnosed by purulent nasal drainage for more than 7 days and abnormal findings in the maxillary sinuses on Water's projection. In these children, the most troublesome symptoms were postnasal drip, nasal obstruction, and cough [76]. In a mail survey of American general pediatricians, symptoms thought to be very important in the diagnosis of ARS included prolonged symptom duration, purulent rhinorrhoea, and nasal congestion [230].

In children, ARS most often presents as either a severe upper respiratory tract illness with fever >39°C, purulent rhinorrhoea and facial pain or, more commonly, as a prolonged URTI with chronic cough and nasal discharge. In a study of the relationship between symptoms of acute respiratory infection and objective changes within the sinuses utilizing MRI scans, 60 children (mean age=5.7 yrs.) were investigated who had symptoms for an average of 6 days before scanning [467]. Approximately 60% of the children had abnormalities in their maxillary and ethmoid sinuses, 35% in the sphenoid sinuses, and 18% in the frontal sinuses. In 26 children with major abnormalities, a follow up MRI scan taken 2 weeks later showed a significant reduction in the extent of abnormalities irrespective of resolution of clinical symptoms. This study reinforces the notion that, like in adults, every upper respiratory tract infection is essentially an episode of rhinosinusitis with common involvement of the paranasal sinuses by the viral process.

Few viral ARS episodes progress to bacterial ARS.

Despite the lack of good studies, most clinicians and investigators agree that the diagnosis of bacterial ARS can be made after a viral URTI when children have persistent URI symptoms for >10 days without improvement (nasal discharge, daytime cough worsening at night) or an abrupt increase in severity of symptoms after initial improvement of symptoms of

a URTI, or a URTI that seems more severe than usual (high fever, copious purulent nasal discharge, periorbital oedema and pain) [8, 96, 468].

In a longitudinal study of 112 children aged 6-35 months, 623 URTIs were observed over a 3-year period and episodes of sinusitis as defined above were documented by the investigators [31]. Eight percent of the URIs were complicated by sinusitis, with 29% of the episodes diagnosed because of an increase in the severity of symptoms before 10 days of illness and the remaining diagnosed on the basis of persistent symptoms beyond 10 days. The occurrence of sinusitis in the context of URIs was 7% in the 6-11 month age group and in children over 24 months, and 10% in children who were 12-23 months old. In an older, but similar, study, 159 full term infants were followed prospectively for a 3 year period and the frequency of URIs and complicating sinusitis were evaluated [469]. The authors calculated the percentage of children experiencing symptoms beyond 2 standard deviations from the mean duration of respiratory symptoms (in days) and took that as an indicator of ARS. This value varied with age and ranged between 16 and 22 days. The incidence based on these assumptions ranged between 4 and 7.3% and was highest for children in their first year of life and in day care. On average, a child younger than 5 years of age has 2 to 7 episodes of URTI per year [470, 471], and a child attending day care may have up to 14 episodes per year [472]. With the incidence rates reported above, the number of acute sinusitis episodes in children every year is sizeable.

Distinguishing between ARS and CRS is based on duration of illness in both children and adults. ARS is defined by symptoms lasting <12 weeks with complete resolution of symptoms. Symptoms lasting ≥12 weeks without complete resolution of symptoms are consistent with CRS. A very common clinical scenario in children presenting to the otorhinolaryngologist's office is that of CRS with upper respiratory tract infection-induced acute exacerbations.

3.6.4. Differential diagnosis

When a child presents with symptoms of ARS as listed above, the differential diagnosis must include intranasal foreign body and unilateral choanal stenosis. In these entities, the symptoms are usually unilateral and can be relatively easily differentiated clinically from ARS by history and physical examination, including nasal endoscopy. AR will usually not manifest with purulent drainage as part of the clinical presentation. Adenoiditis can have a very similar clinical presentation including anterior and posterior purulent drainage and cough and is very relevant in the differential diagnosis in the paediatric age group. In a study of adenoid size evaluated by MRI in a patient cohort with no symptoms related to the adenoids or adenoid disease, adenoid size was larger in the paediatric age group and declined with advancing age [473]. Peak size was between 7 and 10 years of age and largest dimensions were in the 4-15 years age group. In an attempt to differentiate between adenoiditis and ARS based on endoscopic findings, Marseglia and colleagues performed a cross sectional study of 287 consecutive children in whom ARS was suspected based on symptoms lasting for more than 10 days [270]. Nasal endoscopy was performed and the diagnosis of ARS was made if purulent discharge was identified in the ostiomeatal or sphenoethmoidal areas, and the diagnosis of adenoiditis was made if there was purulent drainage over the adenoids. Based on those criteria, rhinosinusitis was confirmed in 89.2% of the patients and was isolated in 80.8% and coupled with adenoiditis in 19.2%. Adenoiditis alone was confirmed in 7% of the cohort. Combined involvement of the sinuses and adenoids was more frequent in younger patients (2-5 years age group) whereas isolated rhinosinusitis was more frequent in older children. Although this study can be criticized by the manner in which the diagnosis was made as one would expect drainage from the sinuses to involve the adenoids as it moves posteriorly in the nose, and the lack of a more objective measure to diagnose rhinosinusitis such as a CT scan, the data supports the high coexistence of infection of the adenoids and the paranasal sinuses in the above clinical context. It is also evident that based on clinical presentation alone, the differentiation between adenoiditis and ARS in children is very difficult.

3.6.5. Bacteriology

Wald et al. studied the bacteriology of ARS in 1981 [474]. They obtained cultures from children with maxillary sinus opacification documented by Water's X-ray by means of sinus taps and found that *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* were the organisms most frequently isolated from maxillary sinus aspirates in these children. Several studies since then have confirmed that the most common organisms responsible for bacterial ARS in children are *S. pneumoniae*, *H. influenza, M. catarrhalis, S. pyogenes*, and anaerobes [8]. Unlike the visit rate for acute otitis media in children younger than 18 years, which has decreased between 1998 and 2007 following the introduction of the heptavalent pneumococcal conjugate vaccine in the United States, the visit rate for ARS has remained stable at 11-14 visits per 1000 children [475]. In a later study, Hwang et al performed a retrospective review of all paediatric patients requiring intervention for ARS over a seven-year period [476]. They reported that instead of the common bacteria noted above, *S. viridans* was the major culprit in sinus cultures. Brook et al. found anaerobic bacteria in acute infections as well, however, these organisms are most frequently seen in maxillary CRS due to odontogenic causes. The predominant anaerobic

bacteria were gram-negative bacilli such as Peptostreptococcus and Fusobacterium [477, 478].

3.6.6. Diagnostic Workup

A complete physical exam should follow a carefully obtained medical and family history. The nasal exam in children should begin with anterior rhinoscopy examining the middle meatus, inferior turbinates, mucosal character, and presence of purulent drainage. This is often accomplished easily using the largest speculum of an otoscope, or alternatively, a head light and nasal speculum. Topical decongestion may be used to improve visualization. Nasal endoscopy that will allow superior visualization of the middle meatus, adenoid bed, and nasopharynx is strongly recommended in children who are able to tolerate the examination. An oral cavity exam may reveal purulent postnasal drainage, cobblestoning of the posterior pharyngeal wall, or tonsillar hypertrophy.

Obtaining a culture is usually not necessary in the context of uncomplicated ARS. Obtaining a culture might be useful in patients who have not responded to conventional medical treatment within 48-72 hours, in immune-compromised patients, in the presence of complications, and if the child presents with severe illness and appears toxic [8, 479]. Although the golden standard would be a maxillary sinus tap, this is a relatively invasive procedure, and is difficult to perform in a child in the office. Middle meatal cultures under endoscopic visualization have shown promise in correlating with antral cultures. In children, data regarding the usefulness of this approach are limited and are mostly based on studies in CRS and will be discussed in the relevant chapter.

While the diagnosis of ARS in the paediatric population is generally made on clinical grounds, computed tomography (CT) is the imaging modality of choice [279].

The recommendations of the American Academy of Paediatrics, published in 2001, state that CT should be reserved for those patients with symptoms persisting after 10 days of appropriate therapy and in patients with suspected complications (especially in the brain and in the orbit) [96]. In children with the clinical diagnosis of rhinosinusitis, the most commonly involved sinus is the maxillary sinus (99%) followed by the ethmoid sinus (91%) [480]. MRI of the sinuses, orbits, and brain should be performed whenever complications of rhinosinusitis are suspected.

3.6.7. Medical Treatment of Acute Rhinosinusitis

Most episodes of ARS are self-limited and will resolve spontaneously.

3.6.7.1. Antibiotics

Antibiotics are the most frequently used therapeutic agents in ARS (Table 3.6.1). Published trials in children and adults were reviewed in a recent meta-analysis of randomized controlled trials evaluating antibiotic treatment for ARS in which 3 of the 17 evaluated studies were performed in the paediatric age group [345]. In total, 3291 outpatients (2915 adults and 376 children) were treated in the trials included in the meta-analysis. The diagnosis of ARS in the trials was based on clinical criteria in most studies and radiologic and other laboratory criteria in the rest. In most studies, inclusion of patients with viral upper respiratory tract infections was avoided by enrolling patients whose symptoms were of more than 7-10 days duration. The results suggest that, compared with placebo, antibiotics were associated with a higher rate of cure or improvement within 7-15 days with the rate of resolution of symptoms being faster with antibiotics in most randomized controlled trials. The overall positive effect in favour of antibiotics was significant but modest. No difference in cure was found when a subgroup

Table 3.6.1. Antibiotics for Acute Rhinosinusitis (ARS) in children.

Author, study, ref.	Intervention / disease	Outcome	Time to effect	Level of evidence
Wald 2009 [351]	Amox/clav vs. Placebo in ABRS	Significantly higher cure rate on antibiotic (50%) vs. placebo (14%) (p=0.01).	Faster resolution (NS) with antibiotics (2.26 days) vs. placebo (2.6 days)	Ib
Falagas 2008 [345]	Antibiotics vs. Placebo Metanalysis in ABRS	Significant, but modestly, higher cure rate (improvement) with antibiotics within 7-15 days	Faster resolution with antibiotics compared to placebo	Ia
Poachanukoon 2008 [481]	Cefditoren vs. Amox/clav in ARS	Comparable rates of improvement for Cefditoren (78.8%) and Amox/clav (84.7%)	Time to improvement was 3 days in both groups	Ib

NS, non-significant

ABRS, acute bacterial rhinosinusitis

analysis was performed for age. A more recent randomized, placebo-controlled trial not included in the meta-analysis evaluated the efficacy of amoxicillin (90 mg/kg) with potassium clavulanate (6.4 mg/kg) or placebo in children 1-10 years of age with a clinical presentation compatible with bacterial ARS (persistent symptoms, acutely worsening symptoms or severe symptoms) [351]. Symptom scores were obtained at multiple time points and the children were evaluated at day 14 from onset of treatment and their condition rated as cured, improved, or failed. Twenty eight patients in each group completed the study and their average age was around 5 years. Children receiving the antibiotic were more likely to be cured (50% vs. 14%, p=0.01) and less likely to experience treatment failure (14% vs. 68%, p<0.001) than children receiving placebo. Similar to other studies, there were more side effects in the antibiotic treated group compared to the placebo treatment (44% vs. 14% of children, p=0.014). In another randomized, controlled study in patients 1-15 years of age with clinical and radiographic signs and symptoms of ARS, patients received either a cephalosporin (cefditoren 8-12 mg/kg daily) or amoxicillin/clavulanate (80-90 mg/kg amoxicillin daily) for 14 days [481]. The results show comparable, not statistically different, rates of improvement at 14 days: 78.8% for cefditoren and 84.7% for amoxicillin/clavulanate. The median time to improvement was 3 days in both groups and the rate of diarrhoea was significantly higher in the patients treated with amoxicillin/clavulanate (18%) compared to those treated with cefditoren (4.5%).

Most of these studies could be criticized for potentially including patients with ongoing viral URIs and selecting patients on the basis of clinical symptoms and exam only, without radiologic documentation. The results, however, suggest that most cases of uncomplicated acute sinusitis will improve irrespective of treatment used but will do so faster, and will have a higher chance of improvement, if given antibiotics. Based on this evidence, it would seem reasonable to recommend only symptomatic treatment for uncomplicated episodes of ARS in children. Antibiotic therapy would be reserved to children with complications, or concomitant disease that could be exacerbated by ARS (asthma, chronic bronchitis). In some situations, children with purulent rhinorrhoea are prevented from staying in day-care and thus have created problems for working parents. Whether an acceleration of improvement of the symptoms with antibiotics in these children is worth the increased risk of antimicrobial resistance remains to be determined. (Strength of recommendation: A).

Antibiotic therapy seems to accelerate resolution of ARS in children but whether an acceleration of improvement of the symptoms with antibiotics in these children is worth the increased risk of antimicrobial resistance remains to be determined.

When considering antibiotic choices, uncomplicated ARS in a child who has not received multiple previous courses of antibiotics can still be treated with amoxicillin (40 mg/kg/day or 80 mg/kg/day). Other reasonable and safe choices are amoxicillin/clavulanate and cephalosporins that provide good coverage of typical organisms, especially those producing β-lactamase [8]. If hypersensitivity to any of the above antimicrobials is suspected, alternative choices include trimethoprim/sulfamethoxasole, azithromycin, or clarithromycin. Clindamycin is useful if anaerobic organisms are suspected but provides no coverage against gram-negative organisms.

3.6.7.2. Intranasal Steroids

Intranasal steroids might have a beneficial ancillary role in the treatment of ARS.

In a paediatric trial, 89 children with ARS received amoxicillin-clavulanate and were randomized to receive either budesonide or placebo nasal sprays for 3 weeks [307]. There were significant improvements in the scores of cough and nasal discharge at the end of the second week in the steroid group compared to placebo suggesting a benefit of adding intranasal steroids to antibiotics in the treatment of ARS. Several trials in mixed adult and paediatric populations (usually 12-14 years and older) have demonstrated similar benefits of using an intranasal steroid along with an antibiotic for the treatment of ARS [306, 482]. Therefore there is reasonable evidence to support the addition of an intranasal steroid to antibiotics in the treatment of ARS (Strength of recommendation: A). Finally, in a randomized, placebo controlled, trial in patients older than 12 years with ARS, mometasone 200 mcg twice daily (twice the allergic rhinitis dose) was more effective in controlling symptoms than placebo and amoxicillin [310]. Thus, there is also some evidence that a high dose of intranasal steroids in older children might be effective as monotherapy for ARS. However, generalizing to younger children is not justified in the absence of more studies.

Table 3.6.2. Ancillary therapy for Acute Rhinosinusitis (ARS) in children.

author	Intervention / disease	Outcome	Age Group	Level of evidence
Shaikh 2010 [328]	Decongestants, antihistamines, and nasal irrigation Systematic review in ARS	No well conducted studies to address these treatments	Children (<18 yrs.)	Ia (-)
Unuvar 2010 [335]	Erdosteine vs. placebo	No significant difference between the groups	Children (8.5±3.2 yrs.)	Ib (-)
Barlan 1997 [307]	Amox/clav with Budesonide or Placebo	Significant improvements in cough and nasal discharge at the end of the second week in the steroid group ($p<0.05$)	Children (Budesonide: 7.3±3.4 yrs.; Amox/clav: 6.6±2.9 yrs.)	Ib

(-), evidence of negative studies

3.6.7.3. Ancillary therapy

Ancillary therapies have not been shown to be helpful in ARS.

A systematic review of the literature was undertaken to evaluate the efficacy of decongestants (oral or intranasal), antihistamines, and nasal irrigation in children with clinically diagnosed acute sinusitis [328]. Randomized controlled trials (RCTs) or quasi-RCTs that evaluated children 0-18 years of age with ARS defined as 10-30 days of rhinorrhoea, congestion or daytime cough were included. Of 402 articles reviewed 44 references were retrieved and were all excluded because they did not satisfy the set criteria. The authors conclude that there is no evidence to determine whether the use of the above mentioned agents is efficacious in children with ARS. In a more recent publication, erdosteine, a mucolytic agent, was investigated in a randomized, placebo controlled trial [335]. Eighty one patients completed the study and their average age was 8.5 years and they all had symptoms consistent with ARS. They were randomized to receive either erdosteine or placebo for 14 days and their symptoms recorded. Both treatment groups had an improvement in symptoms on day 14 but there were not statistically significant differences between the active and placebo groups. Therefore, there is really no good evidence to support the use of ancillary therapies in the treatment of ARS in children (Table 3.6.2) (Strength of recommendation: A-, negative).

4. Chronic Rhinosinusitis with or without nasal polyps (CRSwNP or CRSsNP)

4.1. Epidemiology and predisposing factors

4.1.1. Summary

The overview of the currently available literature illustrates the paucity of accurate information on the epidemiology of CRSsNP and CRSwNP, especially in European countries, and highlights the need for large-scale epidemiologic research exploring their prevalence and incidence. Only by the use of well standardized definitions for CRSs and wNP, and well-defined inclusion criteria for epidemiologic research, will it be possible to obtain accurate epidemiologic data on the natural evolution of these diseases, the influence of ethnic background and genetic factors and the factors associated with the disease manifestation.

4.1.2. Introduction

Chronic rhinosinusitis with (CRSwNP) and without nasal polyps (CRSsNP) in its many forms, constitutes one of the commonest conditions encountered in medicine and may present to a wide range of clinicians from primary care to accident and emergency, pulmonologists, allergists, otorhinolaryngologists and even intensivists and neurosurgeons when severe complications occur [483].

4.1.3. Epidemiology of CRSwNP and CRSsNP.

There is a deficit of epidemiologic studies exploring the prevalence and incidence of CRSsNP and CRSwNP especially in European countries.

4.1.3.1. CRSsNP.

The paucity of accurate epidemiologic data on CRS contrasts with the more abundant information on microbiology, diagnosis and treatment options for these conditions. When reviewing the current literature on CRS, it becomes clear that giving an accurate estimate of the prevalence of CRS remains speculative, because of the heterogeneity of the disorder and the diagnostic imprecision often used in publications. In a survey on the prevalence of chronic conditions, it was estimated that CRS, defined as having 'sinus trouble' for more than 3 months in the year before the interview, affects 15.5% of the total population in the United States [484] ranking this condition second in prevalence among all chronic conditions. Subsequently the high prevalence of CRS was confirmed by another survey suggesting that 16% of the adult US population has CRS [485]. However, the prevalence of doctor-diagnosed CRS is much lower; a prevalence of 2% was found using ICD-9 codes as an identifier [486]. Corroboration of the definitive diagnosis of CRS should be done with nasal endoscopy [487] or CT [488] As the diagnosis of CRS has primarily been based on symptoms, often excluding dysosmia, this means that the diagnosis of CRS is often overestimated [11, 488]. The majority of primary care physicians do not have the training or equipment to perform nasal endoscopy, which also leads to overdiagnosis [489]. Interestingly, the prevalence rate of CRS was substantially higher in females with a female/male ratio of 6/4 [484].
In Canada, the prevalence of CRS, defined as an affirmative answer to the question 'Has the patient had sinusitis diagnosed by a health professional lasting for more than 6 months?' ranged from 3.4% in male to 5.7% in female subjects [490]. The prevalence increased with age, with a mean of 2.7% and 6.6% in the age groups of 20-29 and 50 59 years, respectively. After the age of 60 years, prevalence levels of CRS levelled off to 4.7% [490]. In a nationwide survey in Korea, the overall prevalence of CRS, defined as the presence of at least 3 nasal symptoms lasting more than 3 months together with the endoscopic finding of nasal polyps and/or mucopurulent discharge within the middle meatus, was 1.01% [491], with no differences between age groups or gender. By screening a non-ENT population, which may be considered representative of the general population in Belgium, Gordts et al. [492] reported that 6% of subjects suffered from chronic nasal discharge. A comparative study in the north of Scotland and the Caribbean found that in ORL clinics in both populations there was a similar prevalence of CRS (9.6% and 9.3% respectively) [493].

Recently, a postal questionnaire on the EPOS criteria was sent to a random sample of adults aged 15-75 years in 19 centres in Europe. The Global Allergy and Asthma Network of Excellence (GA2LEN) study concluded that the overall prevalence of CRS by EP^{3}OS criteria was 10.9% (range 6.9-27.1) [12]. A very recent study in Sao Paulo using personal interviews and defining CRS based on the EPOS criteria found a prevalence of 5.5% [1368].

Recent data have demonstrated that CRS affects approximately 5–15% of the general population both in Europe and the USA. The prevalence of doctor-diagnosed CRS was 2-4%.

4.1.3.2. CRSwNP

Epidemiologic studies rely on nasal endoscopy and/or questionnaires to report on the prevalence of nasal polyps. Large NP can be visualized by anterior rhinoscopy, whereas nasal endoscopy is warranted for the diagnosis of smaller NP. Nasal endoscopy is, therefore, a prerequisite for an accurate estimate of the prevalence of NP, as not all patients that claim to have NP actually have polyps on nasal endoscopy [494]. Thus, surveys based on questionnaires asking for the presence of NP, may provide us with an overestimation of the self-reported prevalence of NP. Recently, a French expert panel of ENT specialists elaborated a diagnostic questionnaire/algorithm with 90% sensitivity and specificity [495]. In the light of epidemiologic research, a distinction needs to be made between clinically silent NP or preclinical cases, and symptomatic NP. Asymptomatic polyps may transiently be present or persist, and hence remain undiagnosed until they are discovered by clinical examination. On the other hand, polyps that become symptomatic may remain undiagnosed, either because they are missed during anterior rhinoscopy and/or because patients do not see their doctor for this problem. Indeed, one third of patients with CRSwNP do not seek medical advice for their sinonasal symptoms [496]. Compared to patients with CRSwNP not seeking medical attention, those actively seeking medical care for CRSwNP had more extensive NP with more reduction of peak nasal inspiratory flow and greater impairment of the sense of smell [497].

In a population-based study in Skovde, Sweden, Johansson et al. [494] reported a prevalence of nasal polyps of 2.7% of the total population. In this study, NP were diagnosed by nasal endoscopy and were more frequent in men (2.2 to 1), the elderly (5% at 60 years of age and older) and asthmatics. In a nationwide survey in Korea, the overall prevalence of polyps diagnosed by nasal endoscopy was 0.5% of the total population [498]. Based on a postal questionnaire survey in Finland, Hedman et al. [499] found that 4.3% of the adult population answered positively to the question as to whether polyps had been found in their nose. Using a disease-specific questionnaire, Klossek et al. [496] reported a prevalence of NP of 2.1% in France. From autopsy studies, a prevalence of 2% has been found using anterior rhinoscopy [500]. In Denmark after removing whole naso-ethmoidal blocks, nasal polyps were found in 5 of 19 cadavers [501]. and in 42% of 31 autopsy samples combining endoscopy with endoscopic sinus surgery [502]. The median age of the cases in the 3 autopsy studies by Larsen and Tos ranged from 70 to 79 years. From these cadaver studies, one may conclude that a significant number of patients with NP do not feel the need to seek medical attention or that the diagnosis of NP is often missed by doctors. It has been stated that between 0.2% and 1% of people develop NP at some stage [503]. In a prospective study on the incidence of symptomatic NP, Larsen and Tos [504] found an estimated incidence of 0.86 and 0.39 patients per thousand per year for males and females, respectively. The incidence increased with age, reaching peaks of 1.68 and 0.82 patients per thousand per year for males and females respectively in the age group of 50-59 years. When reviewing data from patient records of nearly 5,000 patients from hospitals and allergy clinics in the US in 1977, the prevalence of NP was found to be 4.2% [505], with a higher prevalence (6.7%) in the asthmatic patients. In general, NPs occur in all races and becomes more common with age [496, 506-509]. The average age of onset is approximately 42 years, which is 7 years older than the average age of the onset of asthma [510-512]. NPs are uncommon under the age of 20 [513] and are more frequently found in men than in women [499, 504, 514], except in the studies by Settipane [505] and Klossek [496].

Szczeklik et al. [515] studied the natural history of asthma and CRS in 16 clinical centres in 10 European countries. Rhinitis was the first symptom of the disease. It appeared on average at an age of 30 yrs. It was perennial, difficult to treat and led to loss of smell in 55% of patients. In an average patient, 2 yrs alter commencement of rhinitis, the first symptoms of asthma appeared. Intolerance to aspirin and/or other NSAIDs became evident 4 yrs later. Nasal polyps were diagnosed at about the same time in 60% of subjects. There was a close linear association between mean age at onset of rhinitis, asthma, NSAID intolerance and nasal polyps [515].

4.1.4. Factors associated with CRSwNP and CRSsNP

4.1.4.1. Ciliary impairment

As may be concluded from the section on anatomy and pathophysiology, ciliary function plays an important role in the clearance of the sinuses and the prevention of chronic inflammation. Secondary ciliary dyskinesia is found in patients with CRS, and is probably reversible, although restoration takes some time [516]. As expected in patients with Kartagener's syndrome and primary ciliary dyskinesia, CRS is a common problem and these patients usually have a long history of respiratory infections.

In patients with cystic fibrosis (CF), the inability of the cilia to transport the viscous mucus causes ciliary malfunction and consequently CRS. NPs are present in about 40% of patients with CF [517]. These polyps are generally more neutrophilic than eosinophilic in nature.

4.1.4.2. Allergy

Review articles on CRS have suggested that atopy predisposes to its development [518, 519]. It is tempting to speculate that allergic inflammation in the nose predisposes the atopic individual to the development of CRS. Both conditions share the same trend of increasing prevalence [520, 521] and are frequently associated. It has been postulated [522] that swelling of the nasal mucosa in allergic rhinitis at the site of the sinus ostia may compromise ventilation and even obstruct sinus ostia, leading to mucus retention and infection. Furthermore, there has been an increase in the body of opinion that regard the mucosa of the nasal airway as being in a continuum with the paranasal sinuses and hence the term 'rhinosinusitis' was introduced [523]. However, critical analysis of the papers linking atopy as a risk factor to CRS reveal that whilst many of the studies suggest a higher prevalence of allergy in patients presenting with symptoms consistent with rhinosinusitis than would be expected in the general population, there may well have been a significant selection process, because the doctors involved often had an interest in allergy [524-528].

A number of studies report that markers of atopy are more prevalent in populations with CRS. Benninger reported that 54% of outpatients with CRS had positive skin prick tests [529]. Among CRS patients undergoing sinus surgery, the prevalence of positive skin prick tests ranges from 50% to 84%, of which the majority (60%) have multiple sensitivities [64, 530, 531]. However, the role of allergy in CRS is questioned by other epidemiologic studies showing no increase in the incidence of infectious CRS during the pollen season in pollen-sensitized patients [532]. Taken together, epidemiologic data show an increased prevalence of allergic rhinitis in patients with CRS, but the role of allergy in CRS remains unclear. Notwithstanding the lack of hard epidemiologic evidence for a clear causal relationship between allergy and CRS, it is clear that failure to address allergy as a contributing factor to CRS diminishes the probability of success of a surgical intervention [533]. Among allergy patients undergoing immunotherapy, those who felt most helped by immunotherapy were the subjects with a history of recurrent rhinosinusitis, and about half of the patients, who had had sinus surgery before, believed that the surgery alone was not sufficient to completely resolve the recurrent episodes of infection [533].

Between 0.5 to 4.5% of subjects with allergic rhinitis have NP [505, 534, 535], which compares with the normal population [536]. Kern found NP in 25.6% of patients with allergy compared to 3.9% in a control population [536]. On the other hand, the prevalence of allergy in patients with NP has been reported as varying from 10% [537], to 54% [538] and 64% [539]. Contrary to reports that have implicated atopy as being more prevalent in patients with NP, others have failed to show this [513, 535, 539-541]. Recently, Bachert at al. [542] found an association between levels of both total and specific IgE and eosinophilic infiltration in NP. These findings were unrelated to skin prick test results.

Although intradermal test to food allergens are known to be unreliable, positive intradermal tests to food allergens have been reported in 70 % [543] and 81% [544] of NP patients compared to respectively 34% and 11% of controls. Based on questionnaires, food allergy was reported by 22% [496] and 31% [508] of patients with NP, which was significantly higher than in non-NP controls [496]. Pang et al. found a higher prevalence of positive intradermal food tests (81%) in patients with NP compared to 11% in a small control group [545]. Further research is needed to investigate a possible role for food allergy in the initiation and perpetuation of NP.

Considerable overlap between asthma and nasal comorbidities confirm a close relationship between nasal disease and asthma.

4.1.4.3. Asthma

CRSwNP and asthma are also frequently associated in the same patients, but their inter-relationship is poorly understood [318]. Studies on radiographic abnormalities of the sinuses in asthmatic patients have shown a high prevalence of abnormal sinus mucosa [545, 546]. All patients with steroid-dependant asthma had abnormal mucosal changes on CT compared to 88% with mild to moderate asthma [547]. GA2LEN studied over 52,000 adults aged 18-75 years and living in 19 centres in 12 countries and concluded that there was a strong association of asthma with CRS. The association with asthma was stronger in those reporting both CRS and allergic rhinitis [13].

Wheezing and respiratory discomfort are present in 31% and 42% of patients with CRSwNP, and asthma is reported by 26% of patients with CRSwNP, compared to 6% of controls [496, 548]. Alternatively, 7% of asthmatic patients have NP [505], with a prevalence of 13% in non-atopic asthma and 5% in atopic asthma [513]. NP take between 9 and 13 years to develop, but only two years in aspirin-induced asthma [515]. Ten percent develop both polyps and asthma simultaneously and the remainder develop polyps first and asthma later [506]. Women that have nasal polyps are 1.6 times more likely to be asthmatic and 2.7 times to have allergic rhinitis [509]. Asthmatic patients with CRSwNP have more nasal symptoms. Alobid et al. [549] showed that patients with CRSwNP have an impaired sense of smell, that asthma -particularly persistent asthma- has a further impact on sense of smell, and that loss of smell may be used as a clinical tool to identify the severity of both NP and asthma.

4.1.4.4. Aspirin sensitivity

In patients with aspirin sensitivity, 36-96% have CRSwNP.

In patients with aspirin sensitivity 36-96% have CRSwNP [513, 534, 551-555] and up to 96% have radiographic changes affecting their paranasal sinuses [556]. Patients with aspirin sensitivity, asthma and NP are usually non-atopic and the prevalence increases over the age of 40 years. The children of patients with asthma, NP, and aspirin sensitivity had NP and rhinosinusitis more often than the children of controls [557]. Concerning hereditary factors, HLA A1/B8 has been reported as having a higher incidence in patients with asthma and aspirin sensitivity [558] although Klossek et al. [496] found no difference between gender in 10,033 patients. Zhang et al. [559] found that IgE antibodies to enterotoxins can be found in the majority of NP patients who are aspirin sensitive.

4.1.4.5. Immunocompromised state

Among conditions associated with dysfunction of the immune system, congenital immunodeficiencies manifest themselves with symptoms early in life. However, dysfunction of the immune system may occur later in life and present with CRS. In a retrospective review of refractory sinusitis patients, Chee et al. [560] found an unexpectedly high incidence of immune dysfunction. Of the 60 patients with in vitro T-lymphocyte function testing, 55% showed abnormal proliferation in response to recall antigens. Low immunoglobulin (Ig), IgA and IgM titres were found in 18%, 17%, and 5%, respectively, of patients with refractory sinusitis. Common variable immunodeficiency was diagnosed in 10% and selective IgA deficiency in 6% of patients. Therefore, immunological testing should be an integral part of the diagnostic pathway of patients with CRS. In a cross-sectional study to assess the overall prevalence of otolaryngologic diseases in patients with HIV infection, Porter et al. [561] reported that rhinosinusitis was present in more than half of the HIV-positive population, ranking this condition one of the most prevalent diseases in HIV-positive individuals. However, the relevance of these data is questioned as there was no difference in sinonasal symptom severity between HIV-positive and AIDS patients nor was there a correlation between CD4+ cell counts and symptom severity. In a more detailed study, Garcia-Rodrigues et al. [562] reported a lower incidence of CRS (34%), but with a good correlation between low CD4+ cell count and the probability of CRS. It should also be mentioned here that atypical organisms like Aspergillus spp, Pseudomonas aeruginosa and microsporidia are often isolated from affected sinuses and that neoplasms such as non-Hodgkin lymphoma and Kaposi's sarcoma, may account for sinonasal problems in patients with AIDS [563].

4.1.4.6. Genetic factors. (See also section 4.5)

Although CRSsNP has been observed in family members, no genetic abnormality has been identified linked to CRS. However, the role of genetic factors in CRS has been implicated in patients with cystic fibrosis and primary ciliary dyskinesia [564] and there is some evidence in CRSwNP.

4.1.4.7. Pregnancy and endocrine state

During pregnancy, nasal congestion occurs in approximately one-fifth of women [565]. The pathogenesis of this disorder remains unexplained, but there have been a number of proposed theories. Besides direct hormonal effects of oestrogen, progesterone and placental growth hormone on the nasal mucosa, indirect hormonal effects such as vascular changes may be involved. Whether pregnancy rhinitis predisposes to the development of rhinosinusitis, is not clear. In a small prospective study, Sobol et al. [566] report that 61% of pregnant women had nasal congestion during the first trimester, whereas only 3% had sinusitis. In this study, a similar percentage of non-pregnant women in the control group developed sinusitis during the period of the study. Also in an earlier report, the incidence of sinusitis in pregnancy was shown to be quite low, i.e. 1.5% [567]. In addition, thyroid dysfunction has been implicated in CRS, but there is only limited data on the prevalence of CRS in patients with hypothyroidism.

4.1.4.8. Local host factors

There is no evidence for a causal correlation between nasal anatomic variations in general and the incidence of CRS.

Certain anatomic variations such as concha bullosa, nasal septal deviation and a displaced uncinate process, have been suggested as potential risk factors for developing CRS [568]. However, some of the studies that have made this assertion have equated mucosal thickening on CT with CRS [569] when it has been shown that incidental mucosal thickening occurs in approximately a third of an asymptomatic population [570]. Bolger et al. [571] and Nouraei et al. [572] found no correlation between CRS and bony anatomic variations in the nose. Holbrook et al [573] also found no correlation between sinus opacification, anatomical variations and symptom scores. Nonetheless, one should mention here that no study has so far investigated whether a particular anatomic variation can impair drainage of the ostiomeatal complex per se. Whilst some authors have postulated that anatomical variations of the paranasal sinuses can contribute to ostial obstruction [574] there are several studies that show the prevalence of anatomical variations is no more common in patients with CRSs or wNP than in a control

population [570, 575, 576].
One area where conjecture remains is the effect of a deviated septum. There are a number of studies that show no correlation between septal deviation and the prevalence of CRS [498, 577]. Whilst there is no recognised method of objectively defining the extent of a deviated septum, some studies have found a deviation of more than 3mm from the midline to be more prevalent in rhinosinusitis [578, 579] whilst others have not [575, 577, 580]. In spite of the observation that sinonasal complaints often resolve after surgery, this does not necessarily imply that anatomic variation is aetiologically involved. CRS of dental origin should not be overlooked when considering the aetiology of CRS. Obtaining accurate epidemiologic data on the incidence of CRS of dental origin is not possible as the literature is limited to anecdotal reports though there is some evidence that odontogenic sinusitis may be increasing [581].
Taken together, there is no evidence for a causal correlation between nasal anatomic variations in general and the incidence of CRS.

4.1.4.9. Biofilms (See also section 4.2)

Many pathogenic bacteria colonize the surface of the NPs forming biofilms. They are not a primary etiologic agent in NP, but a contributor significantly adding more inflammation. Clinically, cases of NP with presence of biofilms are correlated with severe forms of the disease and worse postoperative outcome [550, 582].
Methicillin-resistant Staphylococcus aureus (MRSA) does not appear to pose a significant risk of morbidity in our patient population. However, ongoing concern regarding the increasing prevalence of *S. aureus* and antimicrobial resistance in chronic sinonasal disease highlights the importance of using culture-directed antimicrobial therapy with the goal of minimizing future resistance patterns [583] Bhattacharyya and Kepnes [584] analyzed 701 bacterial isolates among 392 culture samples from patients with CRS. They concluded that antibiotic resistance seems to be emerging for erythromycin at a rate higher than for other antibiotics like methicillin, clindamycin, gentamicin, tetracycline, sulphamethoxazole, and levofloxacin. Although not increasing in prevalence, MRSA maintains a significant presence in CRS with associated increased levels of antibiotic resistance. Bachert et al. [585] investigated 70 patients and demonstrated that mucosal inflammation in nasal polyps orchestrated by Th2 cytokines and amplified by *S. aureus* enterotoxins is characterized by an increased eosinophilic inflammation and formation of IgE antibodies.

4.1.4.10. Environmental factors (See also section 4.2.)

Cigarette smoking was associated with a higher prevalence of CRS in Canada [11] and exposure to secondhand smoke is common and significantly independently associated with CRS [561], whereas this observation was not confirmed in a nationwide survey in Korea [489]. GA(2)LEN study demonstrated that smoking was associated with having CRS in all parts of Europe (GALEN study) [492]. Recently, other lifestyle-related factors are undoubtedly involved in the chronic inflammatory processes of CRSsNP. For instance, low income was associated with a higher prevalence of CRSsNP [11]. In spite of in vitro data on the toxicity of pollutants on respiratory epithelium, there exists no convincing evidence for the aetiologic role of pollutants and toxins such as ozone in CRSsNP. Koh et al. [562] investigated the relationship between CRS and occupation and concluded that there were significantly increased prevalence ratios of CRS in plant and machinery operators and assemblers, elementary occupations, crafts and related trade workers, and the unemployed.
The role of environmental factors in the development of CRSwNP is unclear. No difference in the prevalence of CRSwNP has been found related to the patient's habitat or pollution at work [508]. One study found that a significantly smaller proportion of the population with polyps were smokers compared to an unselected population (15% vs. 35%) [508], whereas this was not confirmed by others [496]. One study reports on the association between the use of a woodstove as a primary source of heating and the development of NP [586].

4.1.4.11. Iatrogenic factors

Among risk factors of CRS, iatrogenic factors should not be forgotten as they may be responsible for the failure of sinus surgery. The increasing number of sinus mucocoeles seems to correlate with the increase in endoscopic sinus surgery procedures. Among a group of 42 patients with mucocoeles, 11 had prior surgery within 2 years prior to presentation [587]. Another reason for failure after surgery can be the recirculation of mucus out of the natural maxillary ostium and back through a separate surgically created antrostomy resulting in an increased risk of persistent sinus infection [588].

4.1.4.12. Helicobacter pylori and laryngopharyngeal reflux

H. pylori DNA has been detected in between 11% [589] 33% of sinus samples from patients with CRSsNP but not from controls [590]. Flook and Kumar [105] reviewed nineteen papers describing varying studies on CRS and acid reflux. There is not enough evidence to consider anti-reflux therapy for adult refractory CRS and there is no evidence that acid reflux is a significant causal factor in CRSsNP.

4.1.4.13. "Osteitis"

This is considered fully in Section 5b but the study by Telmesani and al-Shawarby [591] is noteworthy. They studied 50 patients undergoing FESS for the first time and 32 patients undergoing

revision surgery. Histopathological examination was performed for specimens taken from the bony septa of the ethmoid with the overlying mucosa. Bony changes were seen in only 30% of primary NP compared to 87.5% in recurrent cases.

4.2. Inflammatory mechanisms in chronic rhinosinusitis with or without polyps (CRSwNP or CRSsNP)

4.2.1. Summary: Aetiology and Pathogenesis of CRS

Historically, idiopathic CRS was attributed to either the end stage of an incompletely treated case of acute RS (CRSsNP) or severe atopy (CRSwNP). The limitations of these assessments were clear to many but relatively few hypotheses have been proposed as alternatives. The first attempt to address aetiology and pathogenesis in broad terms was the 'fungal hypothesis', which attributed all CRS to an excessive host response to Alternaria fungi [592, 593]. Although most investigators have rejected the basic tenets as originally proposed, fungi are still believed by many to play a role as a disease modifier in at least some forms of CRS. Defects in the eicosanoid pathway, most closely associated with aspirin intolerance, have also been proposed as a potential cause of CRSwNP in general [594, 595]. Specifically, increased synthesis of pro-inflammatory leukotrienes and decreased synthesis of anti-inflammatory prostaglandins (PGE2) have been proposed as a mechanism not just for aspirin-sensitive nasal polyps but also aspirin-tolerant CRSwNP. While some theoretical evidence supports this line of thought in CRSwNP, enthusiasm is muted by the limited clinical efficacy of leukotriene pathway inhibitors. The 'staphylococcal superantigen hypothesis' proposed that exotoxins foster nasal polyposis via effects on multiple cell types [542, 596]. The net effect is Th2 skewing, Treg inhibition, accentuated eosinophil and mast cell activity and heightened tissue damage and remodeling. It remains unclear why superantigen effects can be demonstrated in only approximately half of CRSwNP patients; hence, staphylococcal superantigens are generally seen by many as disease modifiers, rather than discrete aetiologic agents [594]. The 'immune barrier hypothesis' proposed that defects in the co-ordinated mechanical barrier and/or the innate immune response of the sinonasal epithelium manifests as CRS [25]. These defects theoretically lead to increased microbial colonization with a panoply of microbial agents, accentuated barrier damage and a compensatory adaptive immune response [597]. One potential molecular mechanism for this hypothesis would include local defects in the STAT 3 pathway, which has been identified in some forms of CRS [598]. Systemic defects in STAT 3 have been identified in Job's disease, a disorder with some striking similarities to CRSwNP [599]. The 'immune barrier hypothesis' does not specifically address the Th subset skewing observed in many CRS subtypes, including the Th2 pattern and B cell infiltrate observed in Western CRSwNP patients. This implies additional, as yet undetermined, mechanisms or defects that foster an inappropriate local, adaptive response in the sinonasal mucosa. Genes that may be involved in Th2 skewing include TSLP, IL-33, IL-25 and genes in the strong B cell response include BAFF, CXCL12 and CXCL13 [600-602]. An excessive and/or inappropriate Th2 adaptive response in this setting may further compromise barrier function and diminish innate immunity, thereby creating a self-perpetuating cycle of disease. In the most severe forms of CRSwNP, new evidence supports the generation of local autoantibodies further accentuating tissue damage [23]. Lastly, biofilms have been suggested as a potential entity that can cause CRS [603]. It can be speculated that a defect in the immune barrier might facilitate formation of biofilms. The mechanism of biofilm formation and worsening of CRS remain unclear but biofilms on the sinus mucosa have been likened to those mediating periodontal disease [604].

Epithelial damage and/or host barrier dysfunction results in colonization with *S. aureus*. Subsequent secretion of superantigenic toxins has effects on multiple cell types including epithelial cells, lymphocytes, eosinophils, fibroblasts and mast cells. Locally, the net effect is to help the organism evade the host immune response. The primary host effects are a skewing of the inflammatory response in the Th2 direction, generation of local polyclonal IgE, promotion of eosinophil survival and mast cell degranulation and alteration of eicosanoid metabolism. The sum of these local tissue effects is believed to foster polyp formation. The capability of *S. aureus* to reside within airway epithelial cells likely only augments this process.

CRS can be typically described as a dysfunctional host-environment interaction at the site of interface, which occurs in the nose and paranasal sinuses

The current hypotheses that discuss CRS aetiology and pathogenesis are less in conflict than might appear. Superantigens for example, have been shown to modulate eicosanoid metabolism [605, 606] suggesting a link between two of the proposed theories. Furthermore, the presence of intracellular *S. aureus* in epithelial cells from CRSwNP but not CRSsNP or controls, suggests defective local immune and/or barrier function [607, 608]. One mechanism may be the induction of M2 macrophages, which have diminished phagocytic properties, by enhanced local Th2 immunity induced by superantigens [594, 609, 610]. It has been suggested that *S. aureus*

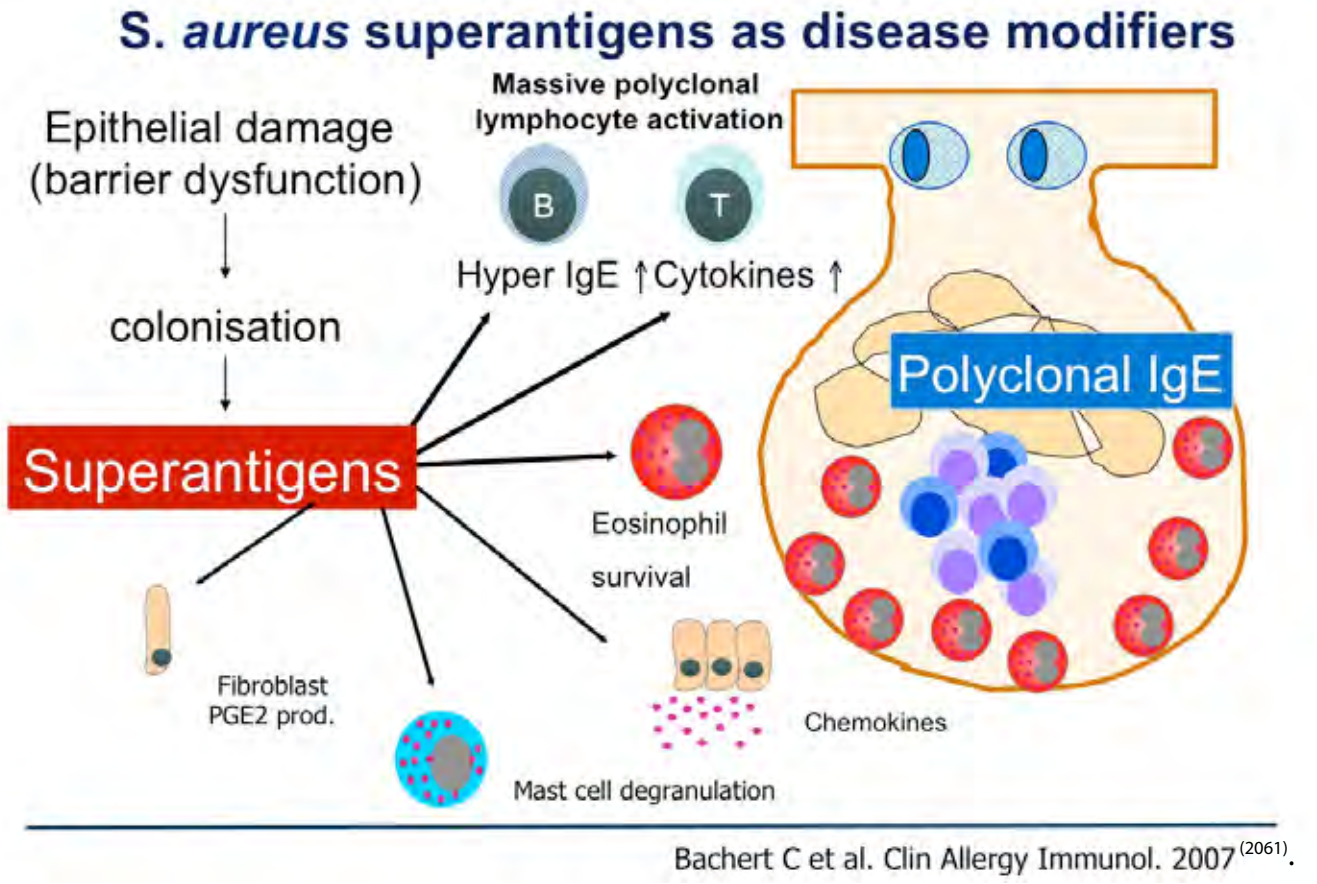
biofilms have the ability to skew the cytokine milieu in the Th2 direction independently of superantigens [603]. Lastly, fungi have substantial intrinsic protease activities, which may degrade tight junctions accentuating host barrier compromise [25, 597]. The interplay between exogenous agents and host defects conceptually links the theories although the relative importance and validity of various components remains in flux.

Host factors that determine susceptibility to CRS depend, in part, on genetic variation across key pathways governing the immunobiology of the nasal mucosa [25]. Cystic fibrosis (CF) is the prototypic case of 'genetic' CRS wherein dysfunction of the CFTR gene triggers defective innate immune and barrier functions [611]. In the case of CF, simple Mendelian genetics apply but a wide variation of sinus disease expression is nevertheless observed, despite identical mutations in the CFTR gene [612]. Consequently even in CF, the most straightforward case of genetic CRS, multiple genes are involved in an individual patient determining clinical phenotype [613]. Early attempts to identify additional genetic loci important in CRS have been undertaken and this is a work in progress [614]. Comprehensive genome wide association studies (GWAS) studies have yet to been performed in CRS, but multiple studies have been done in related chronic inflammatory disorders including asthma [615].

In terms of aetiology and pathogenesis, these studies as well as others, suggest the involvement of not only multiple genetic loci but also the importance of environmentally-determined epigenetic changes [616-619]. Hence, host susceptibility to complex diseases such as CRS likely reflects the combined effects of variation in not only the DNA base sequence but also the DNA methylation and histone modification patterns caused by past environmental exposures. Ongoing environmental stresses confront the susceptible host, which may lead to development of the chronically inflamed state known as CRS.

The model of CRS, in which interplay between multiple host factors and environmental stressors takes centre-stage, makes the observed variability in inflammatory tissue infiltrates and clinical phenotype readily explicable. At the time of the last EPOS review, CRS was divided into CRSsNP, a Th1 disorder, and CRSwNP, a Th2 disorder [620]. More recent studies have demonstrated that this paradigm does not apply worldwide, in particular for CRSwNP, as some Asian polyps exhibit Th1, Th17 and KCN cytokine profiles [621]. A new hypothesis has been proposed suggesting that CRSsNP is characterized by fibrosis, high levels of TGF-β and increased Treg activity while CRSwNP exhibits oedema, low TGF-β levels and low Treg activity [594, 622]. Further studies will be necessary to test the validity of this

Figure 4.2.1.: Overview of the 'superantigen hypothesis' of CRS..

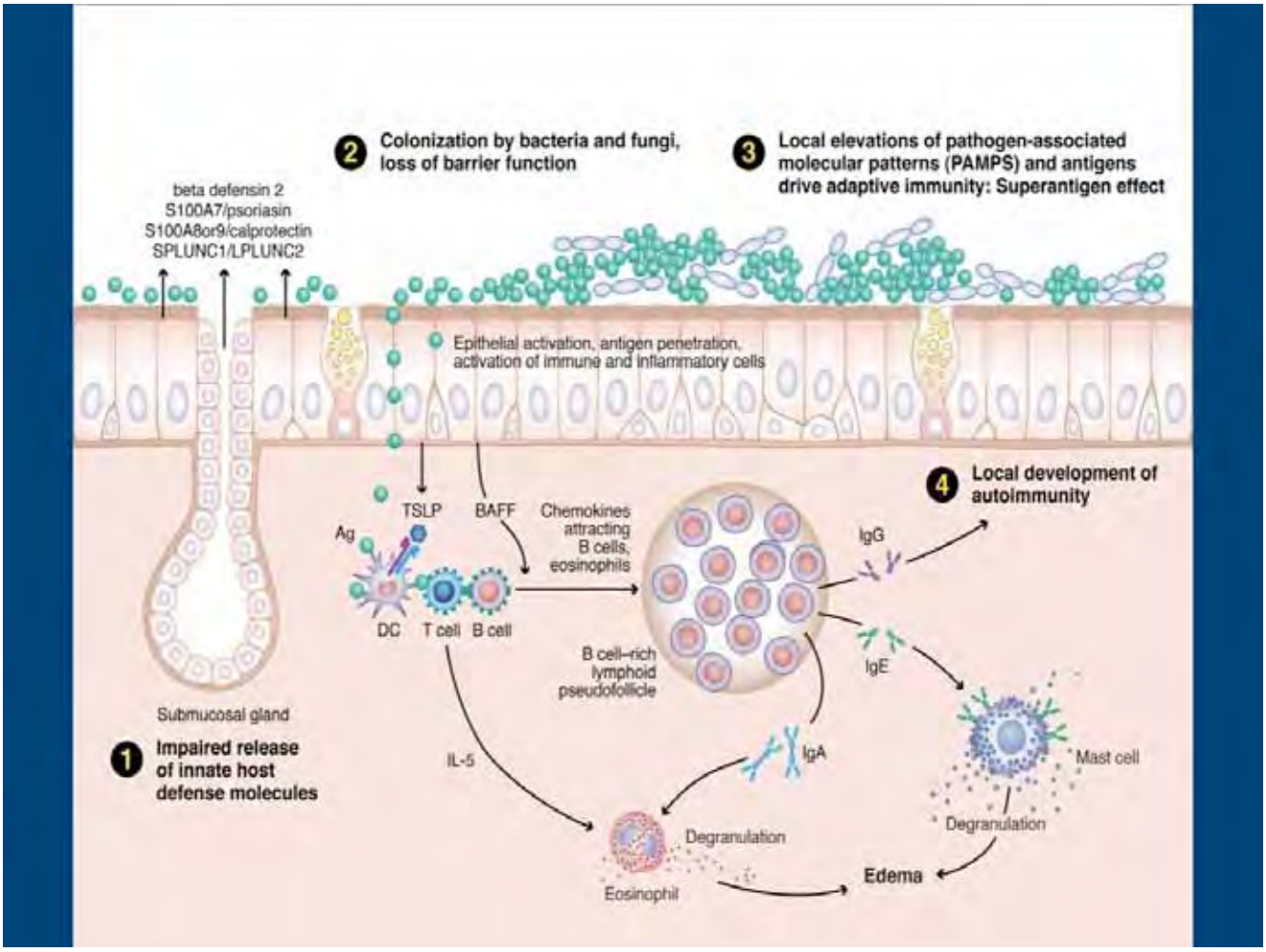


revised proposal. Nevertheless, racial and cultural differences across the globe almost assuredly modulate susceptibility and response patterns of the host. Variations in the nasal bacterial colonization patterns observed worldwide [623] indirectly supports this concept and further suggests that ongoing environmental stressors likely also vary with culture and geography.

Since the last EPOS document there has been significant progress toward understanding the aetiology and pathogenesis of CRS. CRS is still described as 'multifactorial' and there is no clearly delineated single molecular pathway that explains the journey from injury to tissue change [20].

There is however, an emerging consensus that the persistent inflammation that defines CRS results from a dysfunctional host-environment interaction involving various exogenous agents and changes in the sinonasal mucosa. In concert with the definition of CRS as an inflammatory disorder, there has been movement away from pathogen-driven hypotheses. This overall concept is in agreement with the current understanding of the aetiology and pathogenesis of chronic mucosal inflammatory disorders in general, which describe a balance of interactions between the host, commensal flora, potential pathogens and exogenous stresses [624].

Figure 4.2.2: Overview of the 'immune barrier hypothesis' of CRS.



1: Intrinsic host deficits in nasal epithelium results in reduced production of innate immune anti-microbial molecules.

2: Local immune deficits permit the colonization and overgrowth of microbial agents.

3: Intrinsic patterns within microbial agents are capable of activating epithelial cells through pre-programmed pathways. The integrity of the epithelial barrier is disrupted secondary to epithelial activation allowing increased direct stimulation of T and B-cells through antigen or epithelial mediated pathways.

4: These pro-inflammatory factors lead to dysregulation of the local inflammatory microenvironment leading to local pseudofollicle formation and site-specific immunoglobulin production. Local antibody mediated effects degranulate eosinophils and basophils releasing cytotoxic and vasoactive mediators into the nasal mucosa..

4.2.2. Introduction

Chronic rhinosinusitis (CRS) is a clinical syndrome characterized by persistent symptomatic, inflammation of the mucosa of the nose and paranasal sinuses. The inflammation that defines this disorder occurs at the interface with the external environment, suggesting the still unproven hypothesis that CRS results from an inappropriate or excessive immune response to foreign agents resulting in persistent mucosal inflammation, cellular influx, radiographic changes and clinical disease [25]. The widespread adoption of the term 'rhinosinusitis' in preference to 'sinusitis' indirectly supports the perspective that foreign material brought in through the airway, or perhaps from the nasopharynx, acts on the nasal mucosa first, with secondary effects-direct and indirect-on the sinus mucosa [14, 594]. In a very small percentage of cases such as dental or iatrogenic sinusitis, this pathway is reversed with processes in the sinus cavity leading to secondary nasal inflammation. CRS may also, in rare cases, develop secondary to inflammatory processes intrinsic to the mucosa in the presumed absence of exogenous stimuli (e.g. Wegener's granulomatosis, sarcoidosis). Lastly, CRS may occur in association with distinct host genetic factors (cystic fibrosis) or systemic immunodeficiency. In the overwhelming majority of CRS cases however, the etiology and pathogenesis remains unclear. This section will focus on idiopathic CRS, with references to other better-defined inflammatory disorders only as they reveal general principles of the immune response of the sinonasal mucosa.

Idiopathic CRS has been typically divided into CRSsNP and CRSwNP based on endoscopic findings. In terms of aetiology and pathogenesis, CRSsNP is more tightly linked to mechanical obstruction of the ostio-meatal complex (OMC) while CRSwNP is generally attributed to a more diffuse mucosal response [625]. A minority of investigators still hold that the distinction between the two groups is primarily one of disease-intensity and duration [20, 626, 627]. The weight of current research however, would suggest separate, but likely overlapping inflammatory mechanisms and for research purposes this separation facilitates data analysis and determination of molecular pathways of disease [628]. Most investigators, and most lines of research however, assume that the inflammation seen in idiopathic CRS results primarily from a dysfunctional host-environment interaction [25]. Identification of the exogenous agents, which drive the secondary inflammatory mechanisms, has been a major research focus for many years.
This section will provide an overview of currently proposed environmental inflammatory triggers followed by a review of the literature concerning the host mucosal response in CRS, separating out specific agents and mechanisms based on disease phenotype to the extent currently possible.

4.2.3. Inflammatory triggers

4.2.3.1. Bacteria

Bacteria have an established role in the aetiology of acute rhinosinusitis (ARS) and it has long been speculated that incompletely treated bacterial ARS leads to the development of CRS. While bacteria may well trigger acute infectious exacerbations, the role of bacteria in the initial establishment of CRS remains unclear. This section will provide an overview of evidence for and against bacteria as aetiologic agents in CRS with emphasis on recent data.

The nasal microbiota is complex and multiple methods, with varying degrees of sensitivity and specificity, have been utilized to determine the bacterial density and composition in health and disease [629]. Analysis of samples obtained from the vestibule, measured using molecular techniques, demonstrate multiple bacterial species but a preponderance of the staphylococci and corynebacterium [630, 631]. An inverse correlation between the two families was observed, suggesting an antagonistic relationship [632]. In addition, the presence of *S. epidermidis* appears to compete with *S. aureus* [633]. The normal microbiota of the middle meatus may, of course, be quite different than the anterior nostril but these principles likely apply. Healthy sinus cavities, studied using conventional techniques only, appear to have substantially less bacterial colonization than the nasal airway [634]. Although not yet tested, more sensitive techniques would likely reveal the presence of a significant bacterial load in the sinuses, given the documented colonization of the lower airway even in healthy individuals [630]. Colonizing commensal bacteria in the nose and possibly the sinuses may be important not only in interfering with the growth of pathogens, but also modulating the host immune response [635]. This latter effect has been studied in the mouse airway. Animals reared in germ-free environments and lacking commensals, generated accentuated Th2 responses to ovalbumin challenge [636]. This effect was reversed when the commensals were replaced. In the human gut, commensals induce Treg responses [624, 637] but whether similar effects occur in the human airway remains unclear. Nevertheless, these findings suggest that commensal bacteria, interacting through the innate immune system, may play a major role in physiologic immune regulation in the upper airway [638].

The nasal and sinus microbiota in CRS has thus far been studied primarily only using conventional techniques. Higher rates of Staphylococcus epidermidis were seen in controls when compared to CRS [639]. When ARS and CRS are compared, the majority of reports demonstrate increased rates of *S. aureus*, gram negative rods and anaerobes in CRS [3, 640-647]. Other investigators however, have demonstrated no differences between the nasal bacteriology of CRS and normal controls [648,

649). In cases of unilateral CRS, similar microbiological floras were demonstrated in both diseased and non-diseased sides (650) and culture results did not change after clinically successful sinus surgery (651). Overall, these studies have challenged the role of bacteria in CRS aetiology and pathogenesis, although some of the disparities are likely due to variations in methodology (3), concomitant allergic rhinitis (652), prior antibiotic treatment and source of material for analysis (nasal or sinus). Some investigators have discounted any pathologic role for *S. epidermidis*, while others do not. The presence of organisms within epithelial cells (653, 654) or in biofilm quora, likely also produces variation in the rate of bacterial identification using conventional techniques. Application of molecular techniques may begin the process of fully defining the nasal microbiota in CRS. Recently, a prospective study of samples obtained from the middle meatus, using the 16S ribosomal DNA technique, revealed a polymicrobial flora in CRS that was distinct from controls (655). Results indicated a preponderance of anaerobes in CRS. Larger studies using metagenomic techniques (656) are likely needed to fully address this issue as the density and composition of the microbial community may play a significant role in regulating host response (624, 657, 658). Specifically, the lower airway microbiota is disordered in asthma and this has been proposed to play a role in disease pathogenesis (630). Whether effects are seen in CRS remains uncertain. Lastly, it should be kept in mind that the vast majority of data has been collected on Caucasian patients in western countries and the bacterial colonization rates in other races and geographic regions may be vastly different in both health and disease (659).

S. aureus is the most common traditional bacterial pathogen identified in CRS patients in western countries (660). The incidence of staphylococcus is much lower in Asian CRSwNP (623) but the presence or absence of bacteria, or any microbial agent, does not mandate or eliminate a role in disease causation. Host evidence of bacteria specific effects does exist for Staphylococcus aureus however, suggesting a role in pathogenesis if not aetiology in at least a subset of CRSwNP patients. Substantial evidence implicating this organism in CRSwNP has accumulated over the last decade, giving rise to the "Staphylococcal Superantigen Hypothesis", which proposes that colonizing *S. aureus* secretes superantigenic toxins (SAgs) that amplify local eosinophilic inflammation and foster polyp formation (542, 596). In support of this hypothesis, culture studies have indicated a high correlation between the presence of staphylococcus and nasal polyposis (661). These results were supported by the recent demonstration of intracellular *S. aureus* in CRSwNP, but not in CRSsNP or control patients (607, 608). In addition, approximately 50% of CRSwNP patients demonstrate B and T cells responses in the tissue consistent with prior local staphylococcal superantigen exposure (542, 662-666). These include specific IgE against SAgs as well as clonal proliferation of polyp T cells indicative of local SAg exposure. In addition, SAg toxins have been detected in a portion of CRSwNP patients but not controls (667). These in vivo findings are immunologic 'footprints' of a staphylococcal superantigen effect, which can be demonstrated in approximately 50% of Caucasian nasal polyps as well as a lower percentage of Asian polyps. From a mechanistic standpoint, in vitro studies indicate that SAg-induced cytokine release tends to be pro-inflammatory and Th2 skewed, promoting IL-4 and IL-5 but down regulating TGF-β and IL-10 (668-670). SAgs also manipulate eicosanoid metabolism in a pro-inflammatory fashion (605, 606), augment granulocyte migration and survival (671) and furthermore, another staphylococcal toxin (SpA) fosters mast cell degranulation (668). Staphylococcus increased cytokine and MMP expression in polyp and inferior turbinate organ cultures, presumably through a superantigen effect (672). It has also recently been suggested that staphylococcal superantigens may induce glucocorticoid insufficiency through induction of the β isoform of the glucocorticoid receptor (673). Overall, these studies indicate that SAgs have the capacity to foster the Th2 cytokine and remodeling profile observed in Western nasal polyps. Moreover, the demonstration of a local SAg effect correlates with the severity of the eosinophilic inflammation (585). Thus far, there is no evidence of a role for superantigens in CRSsNP, suggesting a distinct aetiology and pathogenesis.

Biofilms and/or intracellular residence of bacteria may increase resistance to standard therapy

In summary, while staphylococcal superantigens appear to amplify and modulate inflammation in nasal polyposis, evidence for a direct aetiologic role is lacking (594). The relatively common intranasal presence of toxigenic staphylococci suggests that unknown host factors likely determine disease expression (674). In addition, approximately 50% of Western polyp patients studied have no evidence of SAg responses yet have a similar phenotypic picture, suggesting that superantigens are not necessary for the typical inflammatory response seen in CRSwNP. Lastly, cystic fibrosis patients exhibit a high rate of staphylococcal colonization and polyp formation yet no evidence of a SAg effect and a strikingly distinct histology and cytokine profile (25). These considerations lead most investigators to view *S. aureus* as a disease modifier rather than a discrete aetiologic agent but these findings are, nevertheless, molecular evidence indicating staph specific effects (675, 676).

Bacterial biofilms have also been implicated in CRS aetiology and pathogenesis. Biofilms are highly organized structures composed of communities of bacteria encased within a

protective extracellular matrix. The formation of bacterial biofilms on surfaces such as the sinonasal mucosa reflects a universal strategy for survival in conditions less than optimal for growth [677, 678]. Biofilms serve to protect bacteria from both host defenses and antibiotics [679] and are believed to be a source of recurrent exacerbations in CRS through the periodic release of free-floating bacteria [680]. Biofilms are largely absent from controls but have been recovered from both CRSsNP and CRSwNP patients. Reported rates of biofilms in CRS populations vary from 30-100%, likely due to differences in detection methodology [681-690]. Multiple bacterial species have been associated with CRS biofilms including *H. influenza*, *S. aureus*, *S. pneumonia*, P. aeruginosa and *M. catarrhalis* [677, 678, 684, 687, 689]. The presence of *S. aureus* and P. aeruginosa biofilms has been associated with an unfavorable outcome post surgery [686, 691], while the presence of *H. influenza* biofilms was associated with a favorable outcome and milder disease [692]. In particular, S. aureus has been associated with a particularly poor prognosis [693]. It has been suggested that *S. aureus* biofilms foster a Th2 adaptive immune response independent of any staph superantigen effect [603]. In contrast, an earlier report demonstrated a shift toward Th1 inflammation in CRS biofilm patients [694]. This study was not limited to Staphylococcal biofilms, however. In addition, the differing results may reflect different patient populations in each study, specifically the presence or absence of nasal polyps, rather than intrinsic capabilities of the biofilm to skew the host response. Very recent studies suggest that disruption of the host epithelium may permit biofilm mediated inflammatory effects on the sinonasal tissues [695]. Overall, it is widely accepted that biofilms are a bacterial adaptation facilitating resistance to host defenses and antibiotics, helping to foster recalcitrant disease. Moreover, it is also possible that biofilm directed therapies will prove useful in the management of CRS. However, it remains much less clear whether biofilms have any role in the initial establishment of CRS [696].

4.2.3.2. Fungi

The role of fungi in CRS has generated much controversy in the last decade [697, 698]. The use of sensitive detection techniques has indicated that fungi are a ubiquitous intranasal presence, identified in close to 100% of both CRS patients and controls [592, 699]. As opposed to controls however, patients with CRS also exhibited eosinophils in the nasal tissues and lumen, with no increase in IgE mediated mould allergy [592]. These observations formed the basis of the "Fungal Hypothesis of CRS", which proposed that an excessive, non-IgE mediated host response to common airborne fungi is the primary pathogenic trigger in most forms of CRS, both polypoid and non-polypoid, varying only in intensity [593, 700, 701]. The primary evidence cited to support this theory was the relative hyper reactivity of peripheral blood mononuclear cells (PBMC) from CRS patients in response to stimulation with supra-physiologic doses of Alternaria antigen in vitro [702]. PBMCs from CRS patients expressed significantly higher levels of Th1 and Th2 cytokines upon exposure to Alternaria extract and this heightened response was presumed to reflect an immunologic sensitization of T cells to Alternaria, suggesting it was particularly important in inciting the CRS inflammatory response. As further evidence, nasal mucus or tissue from CRS patients triggered eosinophil migration [703] and a 60-kDa component of the Alternaria fungus was later shown to trigger eosinophil de-granulation via PAR receptor activation in vitro [704]. These data were interpreted to suggest that Alternaria served a dual role: first, Alternaria proteins are presented to sensitized T cells inducing a cytokine response that serves to attract and activate eosinophils. Second, Alternaria serves as the target of the eosinophils, triggering de-granulation through a surface PAR receptor, with subsequent mucosal damage. This effector role for eosinophils against fungi was proposed despite the fact that eosinophils do not normally participate to a significant degree in the host defense response targeting fungal organisms [705]. Further challenges to the "Fungal Hypothesis" included the observation that the majority of patients in these studies [702, 703] had concomitant asthma, and the heightened cytokine responses from PBMCs as well as the eosinophil migration may reflect priming from this asthma rather than CRS [25, 697, 698]. Furthermore, attempts to replicate the fungal-induced cytokine responses from PBMCs by other investigators failed, clearly indicating the absence of a universal hyper-responsiveness to fungal antigens in CRS patients [706, 707]. Nevertheless, interest in fungi spawned a series of drug trials using topical intranasal anti-fungal agents that initially provided mixed support for the overall hypothesis [708-711]. An extensive, multi-centre, blinded, randomized trial using intra nasal amphotericin failed to show any evidence of efficacy, however [712]. More significantly, a follow up study indicated that amphotericin had no significant effect on any pro-inflammatory chemokine, cytokine or growth factor in the CRS lavage samples [713]. Overall, the current literature does not support the routine use of topical anti-fungals for CRS [714] and support for the fungal hypothesis as originally proposed is scant.

Evidence for a fungal-specific role in the aetiology of most CRS cases is lacking

The view of fungi as the universal or even primary antigenic stimulus in CRS, has largely faded [715, 716], but this does not eliminate fungi as a factor in CRS aetiology or pathogenesis for at least three reasons.

a. Fungi, particularly Alternaria, contain intrinsic proteases that can non-specifically activate protease-activated receptors (PAR) present on the apical surface of nasal epithelial cells with secondary effects on eosinophils and neutrophils [717, 718].

Non-specific effects of a protease may be significant, given that epithelial-based protease activated receptors (PAR) are known to be up-regulated in CRS and this signaling may result in significant inflammation in the presence of high levels of fungal organisms [25, 719, 720].

b. Fungi may play a role in the aetiology and pathogenesis of allergic fungal rhinosinusitis (AFRS), classically defined as: [25] nasal polyposis [14] characteristic thick eosinophilic mucin and [594] characteristic CT scan findings [625], type 1 hypersensitivity to fungal antigens by serology or skin tests and [626] fungal elements in the mucin detected by culture or histology [721, 722]. AFRS has been proposed to be an immunologically distinct subset of CRS [723]. In support of this, peripheral blood mononuclear cells (PBMCs) from AFRS patients were demonstrated to secrete Th2 cytokines in response to fungal antigens [724]. In addition to this systemic sensitization, AFRS patients also demonstrate fungal-specific IgE in the eosinophilic mucin [725] and the mucosa [726]. The implications of these observations remain far from clear however, as CRSwNP patients with similar, thick eosinophilic mucin but without fungal allergy or gross fungi on histology clearly exist [290]. Significantly, the presence or absence of fungal allergy or gross fungi in the eosinophilic mucin had no effect on histology, inflammatory cell infiltrate, tissue eosinophilia or fungal-specific PMBC proliferation [727-729]. A small microarray study also showed very few differences in gene expression profiles in the absence of fungi in the mucin [730]. The similarities among the groups irrespective of the presence of fungi or fungal allergy have been interpreted by some investigators to indicate that allergy to fungus cannot be the primary pathophysiologic force driving the inflammation in AFRS [79, 731]. Further studies will be necessary to resolve the issue [722].

c. The cell walls of fungi contain the polysaccharide polymer chitin, which is recognized by pattern recognition receptor(s) in airway epithelial cells triggering innate immune responses [732]. Chitin induces a local Th2 immune response in vivo mouse studies, with mucosal infiltration by eosinophils, basophils and Th2 lymphocytes [733]. Chitin also induces the enzyme acid mammalian chitinase (AMCase), which acts to degrade the chitin apparently as a defense mechanism, in turn, down regulating the Th2 inflammation [732]. AMCase can also be elevated in asthmatic inflammation independent of chitin and in this setting it actually drives Th2 inflammation [732, 734]. In the upper airway, epithelial cells also express AMCase and levels are significantly higher in nasal polyps [735-738]. Similarly, chitin stimulates AMCase expression by sinonasal epithelial cells in culture [739]. While these results are interesting, the clinical significance of chitin or AMCase in lower airway disease remains uncertain, and any role for AMCase or chitin in the etiology or pathogenesis of CRS is even more speculative.

In summary, while high levels of fungi may theoretically have direct immuno-stimulatory effects, with the possible exception of AFRS, we lack any consistent in vitro or in vivo evidence demonstrating that fungal antigens are the primary targets of the mucosal T cell or B cell responses observed in CRS. Therefore, despite initial enthusiasm for the fungal hypothesis as the basis for all chronic sinus disease, the current state of basic science evidence coupled with the failure of clinical trials with amphotericin [713], indicates that a central role for fungi in CRS is unlikely.

4.2.3.3. Allergens

The potential role of inhaled allergens in the aetiology and pathogenesis of CRS is controversial, much of which stems from the lack of uniform definitions of both CRS and atopy, variability in allergy testing methodologies and potential referral bias in patients receiving allergy testing [79, 740]. From a pathophysiological standpoint, allergic rhinitis (AR) occurs through host sensitization to antigenic foreign protein across a mucosal barrier via dendritic cells and naive CD4+ lymphocytes, with the generation of antigen specific Th2 lymphocytes and IgE secreting plasma cells. Subsequent antigenic challenge across the mucosa results in cross linking of IgE bound to the surface of mast cells and subsequent de-granulation as well as the release of additional Th2 cytokines leading to recruitment of inflammatory cells including eosinophils. The pathogenesis of CRS is much less clear but at least some of these mechanisms are operative. Clinically, the symptoms of AR also overlap with CRS to a substantial degree [26] but are generally less severe than those present in most forms of CRS. Studies in CRS indicate that inflammation in the sinus mucosa and nasal mucosa are similar in profile if not disease intensity establishing the term 'rhinosinusitis' [14]. Recent studies have indicated that nasal challenge with allergen leads to secondary maxillary sinus inflammation [741]. This is in accordance with reports demonstrating CT changes induced in ragweed allergic rhinitis [742]. Technically speaking then, AR could actually be termed allergic rhinosinusitis exhibiting not only nasal, but also chronic sinus mucosal inflammation, at least in more severe circumstances such as perennial AR, which has a markedly more intense inflammatory profile than intermittent AR [743]. Hence, perennial AR could be included under the CRS definition: inflammation of the nasal and sinus mucosa of over 12 weeks duration. From this perspective, much of the confusion in regard the role of AR in CRS becomes clear. AR can be viewed as just one mechanism of sinonasal mucosal inflammation, that is comparatively well understood from a molecular perspective, sharing the same effector cells, cytokines and inflammatory mediators active in many forms of CRS. The contribution of AR to the total inflammatory picture in CRS is typically relatively mild however, since the presence of allergic rhinitis (as defined by positive RAST or skin testing) did not influence symptom severity, extent of disease on CT scan or likelihood of surgical

failure when compared to non-allergic CRS [744-746]. Furthermore, avoidance and immunotherapy relieved some associated rhinitis symptoms but did not reverse sinonasal disease [79].

In summary then, while more severe, perennial forms of allergic rhinitis might technically fulfill the definition of CRS, evidence is weak in support of a role for AR in the aetiology of the typical case of CRS. The most reasonable conclusion appears to be that AR should generally be considered a superimposed problem, which contributes in a variable but relatively mild way to the sinonasal inflammation seen in most CRS patients. Notable potential exceptions may be the patients with severe CRSwNP associated with [25] multiple positive skin tests, suggesting a generalized barrier failure [14, 23] allergic fungal rhinosinusitis [722] as discussed above and [594] patients with local polyclonal IgE in the absence of systemic atopy [542, 596]. It has been suggested that this subgroup of patients manifests a superantigen driven local polyclonal IgE response to a diffuse array of environmental agents with resultant massive chronic mast cell stimulation [747].

4.2.3.4. Viruses

The defense against respiratory viruses involves both innate and adaptive immunity [748]. These protective responses trigger sinus inflammation demonstrable on CT scans but the effects are presumed to be transient [749] and despite the frequency of viral upper respiratory infections (URIs), relatively little attention has been paid to any association with CRS. In assessing a role for viruses in the aetiology and pathogenesis of CRS, the topic will be divided into 3 hypotheses:
1. viruses are a chronic source of mucosal inflammation,
2. viruses trigger the initial insult that pre-disposes to CRS and
3. viruses trigger acute exacerbations of CRS [750].
Evidence that viruses can be a chronic source of sinonasal inflammation triggering CRS is relatively scant. Viruses have the capacity to incorporate into host DNA and theoretically establish latent infections in the upper respiratory mucosa. A recent study demonstrated rhinovirus in 21% of epithelial cell samples from the inferior turbinates of CRS patients and 0% in controls [751]. A follow up study testing for a wide array of upper respiratory viruses failed to confirm this however, demonstrating 0% in both patients and controls [750]. Taken together, these studies do not suggest a significant role for viruses in the stimulation of chronic inflammation in CRS. A role for viruses in triggering the initial event that predisposes to the development of CRS is also lacking. Although this hypothesis has not been tested in CRS, early childhood viral infections have been linked to the subsequent development of asthma years later [752]. The mechanism remains unclear but may relate to virally-induced durable epigenetic changes in host tissues that manifest as disease when challenged later in life [753].
With regard to exacerbations of airway disease, viral infections have been clearly implicated in exacerbations of asthma and COPD [754-757]. Viral URIs are also presumed to precede most episodes of acute bacterial rhinosinusitis. With regard to CRS exacerbations, in vivo data is lacking but it has been proposed that viral infection in combination with cigarette smoke fosters epithelial activation contributing to acute exacerbations of CRS [758]. These in vitro studies using double stranded RNA plus cigarette smoke triggered increased RANTES expression in nasal epithelial cells, which should foster an eosinophilic response in vivo. In summary, the potential relationship between viral infection and CRS is relatively unstudied. Nevertheless, given the documented ability of viral upper respiratory infections to disrupt the upper airway epithelial barrier [759], it is clearly possible they play a role in the aetiology and pathogenesis of CRS.

4.2.3.5. Environmental Toxins

Exposure to toxins such as tobacco smoke, ozone, sulphur dioxide, nitrogen dioxide and particulate air pollutants (e.g. diesel exhaust fumes) have the potential to trigger damage to the epithelium and, in principle, accentuate airway inflammation. These agents induce oxidative and nitrosative stress with production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that have the capacity to cause tissue damage [759]. The significance of most toxin exposures in CRS is unclear, although a number of studies have focussed on the effects of tobacco smoke. The prevalence of CRS has been reported to be higher in smokers [760, 761] and smokers have a less favorable response to surgery [762, 763]. The deleterious effects of cigarette smoke relevant to CRS include alterations in secretion and ciliary beat frequency [764] as well the induction of bacterial biofilms [765]. Based on in vitro data, it has been proposed that cigarette smoke in combination with viral infection contributes to acute exacerbations and eosinophilic inflammation in CRS patients [758]. ROS and RNS from tobacco smoke induces pro-inflammatory cytokine secretion [765], epithelial apoptosis [766, 767] and diminished airway epithelial barrier function [768]. Overall, data suggest that cigarette smoke likely can contribute to the inflammation in CRS in exposed individuals, but evidence for a role in the initial establishment of the disorder is lacking. In particular, a recent study has suggested that in contrast to the lower airways, the pro-inflammatory effects of tobacco smoke in the upper airway appear to be down-regulated over time [769]. Outcome studies have also failed to show a strong negative effect from smoking [770]. These findings would argue against a significant role for tobacco smoke in CRS aetiology.

4.2.4. Host Inflammatory Pathways in CRS

Sinonasal mucosa serves as the site of interface with inhaled irritants, aero-allergens, commensal organisms and pathogens. Mucociliary clearance, physical exclusion, and the innate and

adaptive immune responses all serve as a barrier, protecting host from environment. The major environmental agents thus far implicated in CRS were discussed in the preceeding segment but their pathophysiologic importance remains unclear. In the normal patient, these common entities are cleared without tissue damage or the establishment of a chronic process. It has been proposed that alterations in the host mucosal innate immune response may predispose to the development of CRS [25, 597]. This hypothesis shifts emphasis away from identifying singular environmental or microbial agents and implicates host susceptibility as the major factor in CRS pathogenesis. A recent expert panel has gone further, proposing the question whether all CRS patients may be immunodeficient in some fashion [628]. If correct, it should be kept in mind that the majority of idiopathic CRS patients do not suffer from chronic inflammatory pathology outside of the airway. The association of asthma and CRS is well established, but the prevalence of other chronic inflammatory disorders in the CRS population was not found to be significantly above background [771]. These observations suggest the corollary hypothesis: immune abnormalities, if present in CRS, will be mediated by processes centred in the airway mucosa. Regardless of the ultimate validity of these concepts, the mucosal inflammation in CRS is highly variable in character, an observation predictable given the broad definition of this entity. Currently, the most widely accepted sub types of idiopathic CRS are the forms with and without nasal polyps, as the gross finding of ballooned mucosa suggests a distinct pathway or pathways in this subset of patients. These two groups are themselves heterogeneous, however, and incompletely characterized from a standpoint of pathogenesis. Distinguishing the molecular pathways that characterise or underlie CRS inflammation should be of value in determining pathophysiology, further defining sub types of CRS and ultimately, guiding new therapeutic approaches (628). The following segment will review the current literature on the various components of the sinonasal mucosal defense system, with emphasis on areas relevant to CRS.

4.2.4.1. Mechanical Barrier

The mechanical barrier of the sinonasal mucosa consists of the mucus, motile cilia and respiratory epithelial cells linked by adhesion complexes that include apical tight junctions. Mucociliary transport is the first line of defense, trapping foreign material in the mucus blanket and moving it out of the sinuses and nasal cavity towards the nasopharynx. The source of nasal secretions includes submucosal glands, goblet cells, epithelial cell proteins, lacrimal secretion and vascular transudate. Respiratory mucus includes a low viscosity inner sol layer and a high viscosity outer gel layer, which rides along the tips of the extended cilia. The major protein components of respiratory secretions are the mucin glycoproteins with peptide backbones and oligosaccharide side chains; these glycoproteins likely play a significant role in organizing the mucus, secondarily influencing host-microbial interactions [772]. In addition, mucins bind surface adhesins on microorganisms limiting their ability to access the epithelium and facilitating mucociliary transport out of the nasal cavity [773]. The relevance of this process to CRS is underscored by the high prevalence of sinonasal inflammation observed in patients with gene defects affecting mucociliary flow such as cystic fibrosis (chloride transport) and Kartagener's syndrome (ciliary dyskinesia) [773]. Individuals that are heterozygous for CFTR mutations are also more likely to suffer from CRS [774]. Furthermore, in idiopathic CRS there is evidence for ciliary dysfunction in explanted epithelial cells [775]. Clinically, increased mucus viscosity correlates with disease severity in CRS [776] and drugs that reduce viscosity have been proposed as therapeutic agents [777-779].

Host defects in the mechanical barrier, mucociliary flow and the innate immunity (e.g. lactoferrin and S100 proteins) have been associated with CRS

Breakdown of the mechanical components of an epithelial barrier can play an important role in permitting foreign proteins to stimulate an immune response and this has been proposed as a major factor in the aetiology of asthma [768]. Airway epithelial cells are linked by an apical intercellular adhesion complex composed of tight junctions, intermediate junctions, desmosomes and hemidesmisomes. In CRSwNP, significantly decreased levels of the desmosomal proteins DSG2 and DSG3 [780] and tight junction proteins claudin and occludin [781] have been reported. Expression of the epithelial protein LEKT1 is also significantly decreased in CRSwNP [782]. This protein, encoded by the gene SPINK5, acts as a protease inhibitor involved in regulating the processing of the tight junction proteins critical to epithelial barrier function in the skin. Interestingly, mutations in SPINK5 are shown to be responsible for Netherton syndrome- a rare autosomal recessive condition that results in flaky skin, fragile hair and severe atopy [783]. Lower levels of protease inhibitors like LEKT1 in CRS epithelium may result in increased susceptibility to endogenous and exogenous protease activity [597]. Fungi, bacteria and many allergens all possess significant intrinsic protease activity, which, in the presence of deficient endogenous protease inhibitors such as LEKT1, may render the mechanical barrier more vulnerable to protease attack and greater mucosal penetration of foreign proteins. Further functional evidence for barrier dysfunction in CRS is demonstrated by higher rates of ion permeability in cultured epithelial monolayers derived from CRS patients when compared with normal controls [784]. Increased ion transport has been proposed as a mechanism for tissue oedema seen in nasal polyps [785, 786].

Taken together, these studies suggest that defective mucociliary function may play a role in the pathogenesis of CRS broadly, while mechanical barrier disruption has been more closely linked to CRSwNP.

4.2.4.2. Epithelial Cells

4.2.4.2.1. Receptors

In addition to the physical barrier, sinonasal epithelial cells (ECs) play an active role in both the innate and acquired immune response [787, 788]. Membrane bound and cytoplasmic pattern recognition receptors (PRRs) that recognize pathogen associated molecular patterns (PAMPs) have been identified on airway epithelial cells [139, 159, 789-791]. PAMPs are conserved molecular patterns found in parasites, viruses, yeasts, bacteria and mycobacteria; recognition by host epithelial cells through PRRs results in the release of innate protective agents as well as chemokines and cytokines that attract innate cellular defenses (e.g. neutrophils). In addition to PAMPs, cells also sense cellular damage through damage-associated molecular patterns (DAMPs) [159, 792]. The combined signal of foreign material plus cellular damage triggers an innate response and sets in motion, and ultimately helps determine the nature of, the adaptive immune response [793].

Prominent amongst the PRRs are the Toll-like receptors (TLRs), currently a family of 10 integral membrane glycoproteins that recognize extracellular or intracellular PAMPs such as bacterial cell-surface lipopolysaccharides (LPS) or unmethylated CpG islands found in pathogen DNA. Engagement of the TLRs by a PAMP triggers intracellular signaling through adapter proteins like MyD88 or TRIF that in turn can effect pro-inflammatory gene expression through the activation of nuclear transcription factors such as NF-kB, AP-1 and IRF3 [794]. Given that TLR2, TLR3, TLR4 and TLR9 in particular are expressed on airway epithelium, it is likely they play an important role in mediating host inflammation, with potential derangements contributing to the development of CRS [795]. This hypothesis is supported by the quantitative increase in TLR2 mRNA seen in cystic fibrosis polyps and in some studies of CRSsNP, [796, 797], as well as reported decreases in mucosal TLR2 and TLR9 mRNA in samples from CRSwNP [791, 798]. These results have not been confirmed at the protein level nor is there data demonstrating a functional deficit of TLR signaling in CRS patients. Nevertheless, this remains a theoretical mechanism that can account for chronic mucosal inflammation and merits further exploration. Data regarding dysregulation of other PRRs in CRS is sparse, although NOD-like receptors (NLRs) are expressed in nasal and sinus epithelial cells [799]. A single study indicated that levels were increased in CRSwNP epithelium and this level was decreased after nasal steroid use [800].

In addition to PRRs, sinonasal epithelial cells also express protease-activated receptors (PAR) [720]. Although not classically considered host defense molecules, these receptors are activated by a variety of endogenous and exogenous proteases, including those associated with bacteria, fungi and allergens [801]. Triggering of PAR receptors invokes the NFκβ signaling pathway that results in cytokine and chemokine production, cellular recruitment and potentially, skewing of the both the innate and acquired immune response [794, 802]. In vitro studies on the nasal epithelium have indicated that PAR-2 activation triggers IL-8 release and this response can be elicited by Staphylococcus aureus-derived proteases [720, 803]. Other investigators have suggested that fungal proteases may act on PAR receptors to drive both a neutrophilic and eosinophilic response [718]. As mentioned earlier LEKT1 protein, a natural anti-protease, is reduced in CRSwNP epithelium [782]. In addition to protecting tight junctions discussed above, this protein should also serve to shield epithelial-based PAR receptors. In a model of skin disease, a recent study demonstrated that the absence of LEKT1 leads to the expression of the Th2 skewing molecule TSLP via activation of PAR-2 [804]. It has been suggested that LEKT deficiency may contribute to the pathogenesis of CRS via inappropriate PAR stimulation as well (597). This may be of particular significance given that CRSsNP and CRSwNP both express higher levels of PAR2 in comparison to normal ECs [720].

4.2.4.2.2. Epithelial Cell Response: Host defense molecules

Epithelial cells secrete a vast arsenal of antimicrobial molecules in several classes including enzymes (lysozyme, chitinases and peroxidases), opsonins (complement and pentraxin-3), permeabilizing proteins (A defensins, B defensins and cathelicidins such as LL-37), collectins (surfactant protein-A, surfactant protein-D and mannose-binding lectin) and binding proteins (lactoferrin and mucins) [611, 805, 806]. Studies of CRS patients have not demonstrated a universal trend in the expression of these antimicrobial molecules. Levels for complement components, LL-37, surfactant protein A (SP-A) and Acid Mammalian Chitinase demonstrated increases, presumably compensatory, in CRS patients [735, 807-811]. Lactoferrin and the S100 group of antimicrobials were decreased in CRS, however [686, 812, 813]. The S100 proteins are products of a multi-gene family widely expressed in epithelial cells. In addition to direct anti-microbial effects, these have diverse effects on cell differentiation and wound healing, linking the mechanical barrier and classic anti-microbial properties [814]. PLUNC (Palate Lung Nasal Epithelial Clone), another secreted antimicrobial protein, is decreased in CRSwNP [815]. PLUNC is secreted by glandular rather than surface epithelium and this protein may have particular relevance for CRS as it possesses anti-biofilm properties.

Sinonasal epithelial cells (ECs) play an active role in both the innate and acquired immune response

Presence of diminished host defense molecules in CRS suggests the hypothesis that a primary sinonasal innate immune defect may contribute to local microbial proliferation and the development of CRS in a subset of patients [597]. There is some evidence however that Th2 cytokines can cause nasal epithelial cells to down regulate the production of innate immune molecules such as human beta-defensin 2 and surfactant protein A [816]. This suggests the alternative hypothesis that an inappropriate Th2 effector response at the mucosal surface may account for the observed innate immune deficiencies. Mechanistic studies to uncover whether diminished EC innate immune responses in CRS are constitutive and pre-exist the onset of CRS or are inducible responses to Th2 inflammation are still incomplete. Nevertheless, innate immune responses in ECs can be induced by the T cell cytokine IL-22, which works through its receptor IL-22R [817, 818]. Binding of IL-22 to its receptor activates the transcription factor STAT 3, which mediates mucosal host defense and epithelial repair [819, 820]. In airway ECs, the STAT 3 pathway regulates production of host defense molecules including the S100 family [821]. Studies in the gut and lung indicate that this pathway is critical in the regulation of inflammatory responses at the epithelial surface in general [822]. In CRSwNP, diminished expression of IL-22R has been reported [823] and separate studies have indicated that the STAT 3 pathway is blunted in CRSwNP [598]. Interestingly, STAT 3 mutations have been indentified in Hyper IgE syndrome (HIES or Job's syndrome), which is associated with eosinophilia, high IgE, staph abscesses and recurrent sino-pulmonary infections [599]. The similarities between CRSwNP and some aspects of Job's syndrome suggest the hypothesis that nasal polyposis may result from local (sinonasal) impairment of the STAT 3 pathway [598].

4.2.4.2.3. Epithelial Cell Response: Cytokines and Chemokines

Airway epithelial cells produce a variety of inflammatory cytokines, typically in response to PRR and PAR receptor stimulation [794]. A partial list includes IL-1, TNF-α, IFNα/β, GM-CSF, eotaxins, RANTES, IP-10, IL-6, IL-8, GRO-α, MDC, SCF, TARC, MCP-4, BAFF, osteopontin, IL-25, IL-32, IL-33 and TSLP [24, 600, 805, 824-826]. In addition to driving pain, swelling, vascular dilation and leak and other hallmarks of inflammation, many of these cytokines have chemokine properties attracting various leukocytes including eosinophils, mast cells, neutrophils, dendritic cells and lymphocytes. EC cytokines are also believed to play a key role in dendritic cell polarization, shaping the nature of the T cell response to antigens [827].

Given the important role of ECs in mucosal immunity, altered nasal EC cytokine release may play a role in CRS pathogenesis. The contribution of EC gene expression to the overall mucosal cytokine milieu can be difficult to determine. Quantitative cytokine studies in CRS have been done on whole tissue biopsies for the most part, as the techniques needed to analyze isolated nasal EC secretion are more problematic. In vivo epithelial scrapings and in vitro EC cultures both have limitations: the former is generally limited to mRNA analysis as adequate protein samples are difficult to obtain while the latter is technically difficult and prone to potential cell culture effects. In vitro studies have most commonly demonstrated elevated EC cytokine secretion from CRS patients as opposed to normals, presumably reflecting their activated state [717, 828-830]. Interest has centered on potential effects on eosinophils; elevated GM-CSF, eotaxins and RANTES from ECs likely contributes to the recruitment and survival of these cells in CRSwNP. One study did demonstrate decreased IL-8 in cultures from CRSsNP patients suggesting that diminished neutrophil recruitment may play a role in pathogenesis [831]. Recent in vivo studies demonstrated elevated EC expression of IL-32 in CRSsNP [832]. In CRSwNP, elevated secretion of IL-6 [598] and BAFF [600] were observed, and this was at least in part from EC activity. BAFF (also called BLys or TNFSF13B) triggers B-cell proliferation and class switching, and these processes may have particular significance in CRS pathophysiology [600]. BAFF is secreted by multiple cell types and will be discussed more extensively in the section on B cells.

EC cytokines have established effects on multiple cell types, including not only effector cells but also dendritic cells. Relevant to CRS, in vitro studies indicate that ECs from nasal polyps have the capacity to skew dendritic cell polarization in the Th2 direction [833]. Mechanistically, it has been suggested that a subset of EC cytokines (IL-25, IL-33 and TSLP) are key determinants of dendritic cell polarization and subsequent T cell differentiation in response to mucosal antigens [601, 787, 788, 834]. Specifically, these cytokines have the capacity to skew T cell differentiation in the Th2 direction, the pattern observed in Western CRSwNP patients. TSLP, in particular, has the ability to act directly on dendritic cells, shaping the T cell profile as well as directly and indirectly (through mast cells) recruiting eosinophils [601, 827]. Whether TSLP is relevant to CRS pathogenesis is unclear, however a recent paper demonstrated elevated TSLP activity using a bioassay of supernatant from nasal polyp explants [835].

These results were independent of allergic status. Subsequent papers have also implicated TSLP in polyposis [836-838]. Levels of other epithelial cytokines with Th2 properties, such as IL-33, have been reported as higher in recalcitrant CRSwNP [839] and

Table 4.2.1. Inflammatory cells in Chronic Rhinosinusitis with nasal polyps (IHC; immunohistochemistry; RT-PCR; reverse-transcriptase protein chain reaction; ELISA: enzymo-linked immunosorbent assay).

Author, year, ref.	Tissue, Patients	Cell type	Technique	Conclusion
Fokkens, 1990 (2062)	nasal polyps healthy nasal mucosa allergic rhinitis nasal mucosa	T lymphocytes B Lymphocytes eosinophils neutrophils dendritic cells Ig+ cells	IHC	
Jankowski, 1996 (1477)	nasal polyps sinonasal mucosa (CRS	eosinophils	IHC	CRS with NP: more than 10% eosinophils compared to CRS without NP
Drake-Lee, 1997 (2045)	nasal polyps inferior turbinate	mast cells	IHC	Greater mast cell degranulation in CRS with NP compared to healthy inferior turbinate
Haas, 1997 (856)	nasal polyps healthy nasal mucosa	dendritic cell	IHC	Dendritic cells are present in NP
Jahnsen, 1997 (2046)	nasal polyps	endothelial cells	flow cytometry RT-PCR	Endothelial cells express VCAM-1, induced by IL-4 and IL-13, with a role in eosinophils and T lymphocyte recruitment
Loesel, 2001 (2047)	nasal polyps healthy nasal mucosa	mast cells	fluorescence microscopy	Number of mast cells is not different between controls and CRS with NP
Seong, 2002 (2048)	nasal polyps	epithelial cells	ELISA RT-PCR	In CRS with NP: inflammatory mediators may over-express MUC8 mRNA in NP and downregulate MUC5AC
Sobol, 2002 (862)	nasal polyp from cystic fibrosis (CF) NP from non-CF	neutrophils	IHC	There is a neutrophil massive activation in CF-NP compared to non CF-NP
Wittekindt, 2002 (1007)	nasal polyps healthy nasal mucosa	endothelial cells	IHC	VPF/VEGF expression was higher in NP than in healthy nasal mucosa
Shin, 2003 (717)	eosinophils from healthy volunteers incubated with CRS with NP polyp epithelial cell	epithelial cells	ELISA	Eosinophils in nasal secretions are activated by GM-CSF, which is produced by nasal epithelial cells
Chen, 2004 (2049)	nasal polyps healthy nasal mucosa	epithelial cells	IHC RT-PCR	CRS with NP epithelial cells express increased amounts of LL-37, an antimicrobial peptide
Claeys, 2004 (863)	nasal polyps sinonasal mucosa (CRS) healthy nasal mucosa	macrophages	real-time RT-PCR	CRS with NP: MMR has a higher expression than in CRS without NP and controls
Watanabe, 2004 (828)	nasal polyps	epithelial cells	IHC	Clinical efficacy of glucocorticoids on NP epithelial GM-CSF production, which prolongs eosinophil survival.
Gosepath, 2005 (2050)	nasal polyps healthy nasal mucosa	endothelial cells	IHC	VPF/VEGF are increased in NP compared to healthy nasal mucosa, suggesting a role in both the formation of NP and induction of tissue edema
Kowalski, 2005 (824)	nasal polyps	epithelial cells, stem cell factor (SCF)	ELISA RT-PCR	Epithelial cells release stem cell factor (SCF)
Conley, 2006 (663)	nasal polyps antrochoanal polyp	S. aureus superantigens of the T-cell receptor	flow cytometry	S .aureus SAg-T-cell interactions in 35% of CRS with NP lymphocytes
Hao, 2006 (992)	nasal polyps healthy nasal mucosa	T lymphocytes	IHC	Inverse median ratio of CD4+/CD8+ T cells as compared to the middle turbinate
Schaefer, 2006 (829)	nasal polyps sinonasal mucosa (CRS) healthy nasal mucosa	epithelial cells	IHC ELISA	NP endothelial and epithelial cells are the main source of CC chemokine eotaxin-2

Author, year, ref.	Tissue, Patients	Cell type	Technique	Conclusion
Van Zele, 2006 [620]	nasal polyps sinonasal mucosa (CRS) healthy nasal mucosa	T lymphocytes plasma cells eosinophils neutrophils	IHC	CRS with NP: increase in T lymphocytes numbers and activated T-lymphocytes, CD4+/CD8+ T cells, and eosinophils than CRS without NP and controls. CRS with NP: increased number of neutrophils and more MPO compared to healthy controls but not to CRS without NP
Ramanathan, 2007 [798]	nasal polyps healthy nasal mucosa	epithelial cells	flow cytometry RT-PCR	TLR9 is down-regulated in NP epithelial cells and involved in innate immunity functions
Sachse 2010 [608]	CRSwNP, CRSsNP and control tissue	Epithelial cells	PNA-FISH; EM; ELISA	Staph invasion of sinonasal epithelial cells occurs in CRSwNP
Ayers 2011 [860]	AFS, CRSsNP and control sinus tissue	Dendritic cells	IHC	Dendritic cells are increased in CRSwNP and AFS vs. controls and CRSsNP
Kirsche 2010 [859]	CRSwNP, CRSsNP and control tissue	Dendritic cells	Flow cytometry	Low myeloid dendritic cells may be present in CRSwNP
Krysko 2011 [609]	CRSwNP and control	macrophages	IHC	M2 macrophages increased in CRSwNP; phagocytosis impaired
Mjoesberg 2011 [973]	Nasal polyps	Innate type II lymphocytes	flow cytometry	Innate type II lymphocytes are present in high levels in nasal polyps
Payne 2011 [627]	Nasal polyps	Inflammatory cell types	IHC; PCR; ELISA	Polyps can be divided in eosinophilic and non-eosinophilic (NE). NE polyps demonstrate glandular hypertrophy and dense collagen deposition.

genetic studies also suggest that variation near the IL-33 gene is associated with CRSwNP [840]. In regard to IL-25, there is no current evidence for elevated expression or activity of this cytokine in CRS. Overall, crosstalk between ECs and dendritic cells remains an active area of CRS research.

ECs likely play a significant role in mediating not only the innate response, but also shaping the subsequent adaptive immune response. Whether primary variations in ECs responses underlie CRS aetiology and pathogenesis is unclear but interfering with EC cytokine expression for therapeutic purposes is an area of active research [841, 842]. Furthermore, in contrast to the up-regulation of antimicrobials in EC, corticosteroids down regulate EC cytokine secretion [828, 843, 844]. This bimodal effect of corticosteroids on ECs may be a key mechanism accounting for their efficacy in CRS.

4.2.4.2.4. Epithelial Cell Response: Co-stimulatory molecules

In addition to cytokine mediated regulation of T-cells mentioned above, airway epithelial cells also express homologues of the B7 co-stimulatory family [192]. Expression of these cell surface ligands, which have the ability to down regulate T-cell responses, are increased in CRS patients and induced by TNF-α and IFN-γ [191]. Induction of B7 molecules also occurs via viral infection [190]. The clinical significance of this down regulation of T-cells and its possible relevance to viral exacerbations of CRS remains unclear.

4.2.4.2.5. Epithelial Cell Response: Inflammatory Enzymes, ROS and RNS

Enzymes involved in the generation of reactive oxygen species (ROS) are important in multiple epithelial processes including mucin production, epithelial repair, innate immunity and response to environmental toxins [805]. Oxidative enzymes are important in the generation of hypothiocyanite, an important antimicrobial that selectively kills microorganisms and spares host cells; this pathway is defective in cystic fibrosis [805]. Environmental toxins induce ROS production, which is counteracted by various scavenger enzymes and anti-oxidants in airway epithelial cells. If these protective mechanisms are overwhelmed, pro-inflammatory cytokines are induced; additional oxidative stress can lead to cell death [845].

Reactive nitrogen species (RNS) also play a significant role in several biologic processes and RNS can also interact with ROS in disease causing tissue damage [759]. In particular, there has been a great deal of interest in a potential role for nitric oxide in CRS. Nitric oxide (NO) is produced by nitric oxide synthase (NOS) and there are 3 relevant enzymes in the airway: inducible NOS (iNOS), and endothelial and neural NOS (eNOS and nNOS), which are constitutive. A variety of cells types possess iNOS, including epithelial cells and macrophages. Stimuli for induction of iNOS include various chemokines, cytokines, allergens, viruses, pollutants, hypoxia, bacterial toxins and viruses [805]. In general, constitutive NO acts as an intracellular messenger and neurotransmitter, induced NO mediates inflammatory

and antimicrobial effects and can also regulate apoptosis. The sinuses produce very high amounts of NO and it has been proposed that this limits bacterial colonization of these structures given the proximity of the nasal and oral cavity [846]. NO also regulates ciliary beat frequency [847] and studies have indicated low levels of nasal NO in CRSsNP [848]. The lowest levels of NO have been reported in CRSwNP, and levels increase with treatment [849, 850]. These reports have generated a large number of studies on the topic of nitric oxide and CRS, but the role of nasal NO in health and disease has not been clarified, in part due to variations in methodology. No study to date has correlated nNO levels with any clinical, molecular or pathological measure of sinus mucosal inflammation [851]. In terms of aetiology and pathogenesis of CRS, it has been suggested that metabolic pathways are abnormal in nasal polyposis [852] and that high NO levels are important in keeping microbial colonization levels low within the paranasal sinuses [853]. In particular, high levels of NO have inhibitory effects of S. aureus biofilm growth [854] but these levels may actually promote growth of other bacteria. The clinical relevance also remains unclear since ESS, which has a high success rate in most studies, reduces the NO concentration in operated sinuses [855]. Moreover, a fundamental criticism of existing work on the topic is that all studies measure NO in the sinus lumen, rather than at the mucosal surface and in the respiratory mucus where innate defenses operate [851].

4.2.4.3. Dendritic Cells and Macrophages

Dendritic cells (DCs) activate both innate and adaptive immunity via antigen capture, presentation of antigen to immature T cells and secretion of soluble inflammatory mediators. Crosstalk between epithelial cells and DCs (see discussion above) is believed crucial to the determination of any subsequent T cell response to mucosal antigen and these cells serve as a bridge between the innate and adaptive response [601]. DCs have been described in the nasal mucosa [856] and a recent study indicates that multiple subsets are present [857]. Studies in CRS have been limited but functional DCs are present in polyp mucosa [858]. It has been suggested that myeloid dendritic cells are decreased in the polyps when compared to CRSsNP or control nasal tissues and this accounts for the observed Th2 skewing [859]. Other investigators demonstrated increased DCs in CRSwNP vs. either CRSsNP or control mucosa [860]. In this study, elevated DC chemoattractants CCL2 and CCL20 were present in polyp mucosa suggesting recruitment of immature DCs to the sinonasal mucosa. DCs were increased in CRSsNP vs. control mucosa but the difference was not significant. Levels of Vitamin D3, an immunoregulatory molecule with known effects on DCs, were low in CRSwNP suggesting a potential role for replacement therapy [833]. More broadly, the key role of DCs in the mucosal immune response makes them attractive targets for the management of chronic airway inflammation; in particular, modulating epithelial/DC crosstalk may have therapeutic value [601].

Macrophages are innate immune cells with diverse roles: removal of particulates, primary response to pathogens; tissue homeostasis; coordination of the adaptive immune response; inflammation; tissue repair [861]. The classical macrophage activation pathway (M1) is driven by Th1 cytokines that trigger a pro-inflammatory response necessary to kill intracellular pathogens. The alternative pathway is driven by Th2 cytokines in the local milieu leading to M2 macrophages; this process is important in the defense against helminthes, humoral immunity and tissue repair [861]. Macrophages (presumably mostly M1) are elevated in the sinonasal mucosa of cystic fibrosis (CF) patients in comparison to controls and CRS [862]. M2 macrophages, which express elevated levels of the macrophage mannose receptor (MMR), are present in high levels of CRSwNP patients as opposed to CRSsNP, CF and controls [609, 797, 863]. Eosinophils, via CCL23, may be key to the recruitment of macrophages in CRSwNP, which then convert to the M2 type in the Th2 milieu [610]. These polyp-derived macrophages appear to have an impaired ability to phagocytose S. aureus, which may contribute to the pathophysiology of CRSwNP [609]. In addition, M2 macrophages derived from nasal polyps secrete high levels of CCL18, a cytokine known to be chemotactic for DCs, naïve t cells and Th2 cells all of which may contribute to the pathogenesis of CRSwNP [832].

4.2.4.4. Eosinophils

Eosinophils are circulating granulocytes whose function at mucosal surfaces is immune defense, primarily against multi-cellular parasites. In addition, it has been suggested that eosinophils play a significant role in tissue remodeling and repair in both health and disease [864]. Their presence in high numbers in the respiratory mucosa however, has long been associated with disease, most prominently asthma and allergic rhinitis. Eosinophils are also an important cell type in chronic rhinosinusitis, and CRS was at one time considered by many to be a purely eosinophilic disease. Eosinophilic damage to the sinonasal mucosa was believed to be the central pathophysiologic mechanism of CRS and the hallmark of the disorder [38, 865]. Significantly, the degree of eosinophilia in CRS was independent of the concomitant presence of allergic rhinitis, suggesting distinct but possibly overlapping pathophysiologic processes [744, 866]. In addition, the degree of tissue eosinophilia in CRS correlates with objective disease severity and co-morbid asthma [542, 867-870]. The introduction of the 'fungal hypothesis' (see section on fungi) further enhanced the role of the eosinophil; toxic mediators released by eosinophils targeting fungi were proposed as the common upstream pathway for all forms of CRS [592, 699]. Variation in the degree of tissue eosinophilia in surgical specimens was believed to reflect

the presence or absence of allergic rhinitis, prior corticosteroid use or simply disease-intensity. It was always clear however, that non-eosinophilic forms of nasal polyposis existed, most obviously in cases of cystic fibrosis [871] but this was considered an exception. The concept of tissue eosinophilia is relative however, and some cases of CRS demonstrated relatively minimal eosinophilia and the predominant influx of other cell types. Notably, separation of CRS tissue specimens into CRSsNP and CRSwNP demonstrated that tissue eosinophilia was much higher in the polypoid form [620, 866, 872-874]. This close association, independent of atopy, suggested that eosinophils may be critical to polyp formation but the relationship between CRSwNP and mucosal eosinophilia is not maintained in Asian polyps [875] as well as a demonstrable minority of Western/ Caucasian polyps [626]. While approximately 80% of Caucasian polyps are eosinophilic, less than 50% of Asian polyps demonstrate tissue eosinophilia above that seen in control tissues [875-877]. In addition, the majority of CRSsNP worldwide appears to be relatively non-eosinophilic, at least in comparison to Caucasian polyps. Taken together, these studies indicate that eosinophils are not absolutely necessary for nasal polyposis or CRS to be present. Although this might appear to diminish the importance of these cells in CRS, a recent longitudinal study demonstrated that high tissue eosinophilia correlated directly with the need for revision surgery [878]. A second well done prospective study divided patients by polyp status and tissue eosinophilia. Results indicated that CRSsNP patients with high tissue eosinophilia, while less common, nevertheless demonstrated the least improvement of the four groups with surgical therapy [879]. Consequently, while eosinophils are not essential for CRS to exist, they appear to be a biomarker for severe, recalcitrant disease, at least in Caucasians, and may still be the cell that mediates this relatively poor prognosis [880].

Eosinophil levels and Th2 cytokine skewing are most closely associated with Western CRSwNP.

The mechanism of recruitment and activation of eosinophils in CRS involves 3 main processes:
1 the local expression of eosinophil-attracting chemokines by the epithelium and other cell types
2 priming and survival promoting effects of cytokines such as GM-CSF and IL-5 and
3 the expression of adhesion molecules by endothelium especially VCAM-1.
The relevant chemokines are RANTES, Eotaxin 1-3, MCP 1-4, all primarily secreted by nasal epithelial cells and all of which work through CCR3 [841, 881-891]. In allergic inflammation, other cellular sources, such as dendritic cells and macrophages, may be the most important sources of eotaxin and other CCR3 ligands.

The regulation of epithelial chemokine expression is complex, but the Th2 cytokines IL-4 and IL-13 play a key role working through STAT6 and NF-κβ [892, 893]. Other stimuli such as chitin (see above) may play a role as well [739]. In addition, eosinophils secrete eotaxin 1-3 as well as RANTES, suggesting a possible amplifying effect enhancing local eosinophil recruitment (891, 894). The relevant cytokines GM-CSF and IL-5 induce increased migration, adhesion and survival of eosinophils in nasal polyp tissue. GM-CSF was identified first, and is produced in particular, by epithelial cells [524, 895-899]. IL-5 is also an important priming and survival factor for eosinophils in nasal polyps [900-903]. Initially, IL-5 levels in nasal polyp tissue were believed to correlate with atopic status [524] but multiple follow up studies indicated that IL-5 status-and hence any effect on eosinophils-was independent of systemic allergy [542, 900, 904, 905]. The most relevant adhesion molecule appears to be VCAM-1, which mediates rolling, adhesion and transendothelial migration of eosinophils in vitro. Several groups have demonstrated increased expression in nasal polyps and levels correlate with the presence of eosinophils [883, 906-910]. A recent study indicated high VCAM-1 levels correlated with risk of post surgical recurrence [910]. P-selectin is an additional adhesion molecule that may also play a role in eosinophil accumulation within nasal polyps [911] while L-selectin appears to regulate eosinophil accumulation in CRSsNP [18, 912].

Asian polyps are less eosinophilic than Western CRSwNP, exhibiting a Th1/17 cytokine skewing

The overall process of eosinophil recruitment, activation and survival in CRS, when present, is likely driven primarily by Th2 cytokines via the mechanisms discussed above. The critical upstream cellular sources of these Th2 cytokines in eosinophilic CRS remain unclear, but presumably include Th2 helper T-cells. In CRSwNP, substantial evidence exists that staphylococcal superantigens promote mucosal eosinophilia primarily by accentuating local Th2 cytokine release via actions on these T-cells, although other mechanisms may also be relevant [542, 621]. Very recent evidence has further suggested that staphylococcal biofilms may play an additional role driving eosinophilia in CRS, independent of polyp status or superantigens [603]. The mechanism for this potential effect is uncertain and further studies will be necessary to validate this hypothesis. As mentioned earlier, based primarily on in vitro data, the 'fungal hypothesis' proposed that Alternaria fostered tissue eosinophilia via accentuation of Th2 cytokine release from sensitized T-cells [593, 702]. Two follow up studies failed to confirm these in vitro observations however [706, 707] and the weight of evidence does not support a major role for fungi in most forms of CRS at this time [25, 697, 713, 913]. Other factors including IL-33, TSLP, IL-25, PAR

receptors, complement proteins, eicosanoids and Stem Cell Factor may play an upstream role in CRS tissue eosinophilia but evidence is currently very limited [601, 718, 809, 824, 835, 840, 914, 915].
Once present and activated, eosinophils are believed to damage the mucosa through degranulation and release of toxic mediators with resulting epithelial sloughing and tissue oedema [865, 916, 917]. In addition to direct toxic effects, eosinophils in nasal polyps express CCL23, which acts to recruit macrophages and monocytes, whose products may also contribute to the inflammation in CRSwNP [610].The mechanism for eosinophil de-granulation in CRS is unclear but data from other tissues suggests that crosslinking of receptors for IgA is an important trigger [918, 919]. Effects on eosinophils by IgA can occur even in the absence of antigen binding [920]. High levels of IgA have been identified in nasal polyps suggesting that this immunoglobulin may play a key role in vivo [621, 921]. Lastly, it has been proposed that the epithelial barrier in CRS is already weakened [25, 782], thus eosinophilic degranulation should only accentuate the process.
In addition to the above noted pathologic effects, eosinophils in lower airway disease foster fibrotic changes of the sub epithelial

Table 4.2.2. Inflammatory mediatos (cytokines, chemokines, adhesion molecules, eicosanoids, and matrix metalloproteinases) in Chronic Rhinosinusitis without nasal polyps (IHC: immunohistochemistry; RT-PCR: reverse-transcriptase protein chain reaction; ELISA: enzymo-linked immunosorbent assay; CRS; chronic rhinosinusitis without nasal polyps; NP: chronic rhinosinusitis with nasal polyps; FESS: functional endoscopic sinus surgery).

Author, year, ref.	Tissue, Patients	Marker	Technique	Conclusion
Hamilos, 1993 [526]	nasal polyps sinonasal mucosa (biopsies	GM-CSF, IL-3	IHC	Cellular sources of GM-CSF and IL-3 in NP remain to be determined
Xaubet, 1994 [899]	nasal polyps sinonasal mucosa	GM-CSF	IHC	Eosinophil infiltration into the respiratory mucosa (allergic reaction, CRS with nasal polyps) is modulated by epithelial cell GM-CSF
Mullol, 1995 [1643]	nasal polyps sinonasal mucosa	IL-8, GM-CSF, IL-1 , IL-6, IL-8, TNF-α	ELISA RT-PC	Nasal Polyps may represent a more active inflammatory tissue (more cytokines) than healthy nasal mucosa
Bartels, 1997 [886]	nasal polyps sinonasal mucosat	CC-chemokines eotaxin, RANTES and MCP-3	ELISA	Expression of eotaxin and RANTES but no MCP-3 is elevated in atopic and non-atopic NP compared to normal mucosa
Bachert, 1997 [900]	nasal polyps sinonasal mucosa	IL-1 , IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, TNF-α, GM-CSF, IL-1RA, RANTES, GRO-α	ELISA	IL-5 plays a key role in eosinophil pathophysiology of nasal polyps and may be produced by eosinophils.
Ming, 1997 [2063]	nasal polyps healthy sinonasal mucosa allergic rhinitis mucosa	IL-4, IL-5, IFN-γ mRNA	RT-PCR Southern blot	CRSwNP and allergic rhinitis may differ in the mechanism by which IL-4 and IL-5 are increased
Simon, 1997 [901]	nasal polyps	IL-5	ELISA RT-PCR	IL-5 is an important cytokine that may delay the death process in NP eosinophils
Bachert, 1998 [904]	nasal polyps	Th1, Th2 cytokines	Elispot	Th1 and Th2 type cytokines are upregulated in NP, irrespective of allergen skin test results.
Bachert, 2001[542]	nasal polyps sinonasal mucosa	IL-5, IL-4, eotaxin, LTC4/D4/E4, sCD23, histamine, ECP, tryptase, total and specific IgE for allergens and S. aureus enterotoxins	ELISA Immuno-CAP	association between increased levels of total IgE, specific IgE, and eosinophilic inflammation in NP
Gevaert, 2003 [929]	nasal polyps sinonasal mucosa	Soluble IL-5R	RT-PCR	antagonistic soluble isoform is upregulated, the signal transducing transmembrane isoform is down-regulated in nasal polyps, mainly in asthma.
Wallwork, 2004 [1708]	CRS nasal mucosa (in vivo & in vitro)	TGFβ-1, NF-kB	IHC	clarythromycin inhibites TGFβ-1 and NF-kB only in vitro
Watelet, 2004 [2051]	sinonasal mucosa (FESS)	MMP-9, TGFβ-1	IHC ELISA	correlation with the tissue healing quality
Watelet, 2004 [1004]	sinonasal mucosa (FESS)	TGFβ-1	IHC ELISA	CRS without NP: increased expression of TGFβ-1 compared to NP

Author, year, ref.	Tissue, Patients	Marker	Technique	Conclusion
Elhini,2005 (2052)	ethmoidal sinus mucosa	CCR4+, CCR5+	IHC real time PCR	CRS patients: increase of CCR4+ in atopics and decrease of CCR5+ in non-atopics
Pérez-Novo, 2005 (1046)	sinonasal mucosa	COX-2 PGE2	real time PCR ELISA	CRS: COX-2 and PGE2 are more expressed than in NP
Toppila-Salmi, 2005 (912)	maxillary sinus mucosa (surgery)	L-selectin ligands	IHC	Increased expression in CRS endothelial cells
Lane, 2006 (790)	ethmoidal mucosa (surgery)	TLR2, RANTES, GM-CSF	real time PCR	CRS: increase compared to healthy controls
Lee, 2006 (808)	sinonasal mucosa	CCL-20	IHC real time PCRS	Increased expression of CCL 20 in CR
Olze, 2006 (890)	nasal polyps turbinate mucosa	eotaxin, eotaxin-2, and -3	ELISA	Eotaxin is expressed in CRS
Pérez-Novo, 2006 (915)	nasal mucosa	CysLT receptors EP Receptors	real time PCR	CRS: CysLT and EP receptors are more expressed than in NP
Rudack, 2006 (2053)	sinonasal mucosa	GRO-α , GCP-2, IL-8, ENA-78	HPLC + bioassay	Expression of GRO- and GCP-2 in CRS
Watelet, 2006 (2054)	sinonasal mucosa (FESS)	MMP-9	IHC	Correlation between MMP-9 expression and tissue healing quality
Van Zele 2006 (620)	CRSsNP; CRSwNP and control sinus tissue	Inflammatory cytokines	PCR; ELISA	CRSwNP is Th2 skewed; CRSsNP is Th1 skewed
Douglas 2007 (706)	PBMC from CRS and controls	cytokines	PCR	Staph SA but not Alt extracts stimulated cytokine response; no difference between patients and controls
Ahmed 2008 (1018)	Polyp and control tissue	Capillary density	Confocal microscopy	No active angiogenesis in polyps
Kato 2008 (600)	CRSwNP, CRS and controls	BAFF, IgA, B cells	PCR, ELISA, IHC	BAFF expression is higher in polyps and correlates with IgA and B cells
Lu 2008 (826)	CRSwNP, CRSsNP and controls	Osteopontin (OPN)	ELISA; IHC	OPN is unregulated in CRS vs. controls, with highest levels in CRSwNP
Patou 2008 (668)	Nasal poly tissue and controls	cytokines	ELISA; tissue explants	SEB staph toxin triggers Th2 skewed inflammation; staph protein A triggers mast cell degranuation
Ramanathan 2008 (816)	SNEC from CRS and controls	TLR-9; beta defensins; spA	SNEC culture; PCR	Th2 cytokines down regulate some SNEC antimicrobial factors
Van Bruaene 2008 (984)	Sinus tissue from CRSwNP, CRSsNP and c ontrol	FOX3P; GATA-3; T-bet; RORc; cytokines	PCR; ELISA; IHC	Low FOX3P and TGFβ, High T-beta and GATA-3 in CRSwNP vs. CRSsNP and controls
Zhang 2008 (22)	Belgian and Asian CRSwNP and control tissues	T cell cytokines	PCR and ELISA	Th2 cytokines elevated in Belgian polyps; Th1/Th17 cytokines elevated in Asian polyps. Both have decreased FOX3P and TGF β vs. control tissue
Allakhverdi 2009 (835)	Nasal polyps	TSLP	Functional assay	Elevated TSLP activity in nasal polyps
Ahn 2009 (726)	AFS, CRSsNP and control sinus tissue and IT	IgE in tissue	IHC, ELISA	More fungal and non fungal IgE is expressed in AFS vs. CRSsNP and control
Cao 2009 (877)	Asian CRSwNP, CRSsNP and control tissue	Th cytokines; TGF;	PCR;ELISA; IHC	Asian polyps have Th1, Th17 and Th2 response patterns; CRSsNP is Th1
Gevaert 2009 (930)	CRSwNP and control sinus tissue; peripheral blood eosiinophils	Soluble and TM IL-5R alpha	PCR, Flow, ELISA	TM IL-5 alpha is down regulated in polyps while SOL-IL-5 alpha is u -regulated
Lalaker 2009 (739)	SNEC from CRSwNP and controls	AMCase; eotaxin 3	PCR	Chitin stimulates AMCase and eotaxin 3
Lee 2009 (1009)	Nasal lavage and polyps	VEGF	PCR; ELISA; IHC Flow	VEGF is elevated in CRSwNP tissue and lavages

Author, year, ref.	Tissue, Patients	Marker	Technique	Conclusion
Orlandi 2009 [707]	PBMC from CRS and controls	Cytokines and fungal specific IgE	ELISA	IL-5 responses to alternaria extract were not predictive of CRS
Park 2009 [736]	Nasal polyp and IT	AMCase; ChT	PCR; westerns and IHC	Polyps have elevated levels of Chitinases
Patou 2009 [949]	Nasal polyps and IT	Histamine; leuokotrienes; PGD2	Tissue explants	Enhanced mediator release from Mast cells in polyps vs. inferior turbinates
Van Bruaene 2009 [1000]	Sinus tissue from CRS and controls	TGF-β; TGF-β receptor; collagen	PCR; IHC; ELISA	High collagen, TGF, TGF receptor in CRSsNP; less collagen, low TGF, TGF receptor in CRSwNP
Van Zele 2009 [809]	Nasal secretions and tissue from CRSwNP and controls	C3a; C5a; ECP; MPO; macroglobulin	ELISA; IHC	Complement system is activated in CRSwNP
Bachert 2010 [585]	Belgian and Asian CRSwNP patients	T cell cytokines; IgE	PCR; ELSIA	Th2 inflammation, IgE to staph and asthma more common in Belgian CRSwNP; Th17 more common in Asian polyps
Ebbens 2010 [18]	CF, antrochoanal and CRSwNP polyps	L-selectin	IHC	L- selectins ligand are elevated in CF and CRSwNP polyps
Lee 2010 [811]	Maxillary sinus lavage	Anti-microbial lipids	Westerns; chromatography	CRS patients had increased anti-microbial lipids
Li 2010 [990]	CRSwNP, CRSsNP and controls from Asian patients	TGF, MMPs, TIMPs; collagen; FOX3P	IHC; ELISA; PCR	TGF, TIMPs , FOX3P and collagen lower in Asian polyps vs. CRSsNP ;
Patadia 2010 [602]	CRSwNP, CRS and controls	B-cell chemokines and their receptors	ELISA and PCR	BCA-1 and SDF-1alpha elevated in polyps
Perez-Novo 2010 [1052]	CRSwNP	CRTH2; PGD2	Tissue explants	PGD2 from mast cells recruits Th2 cells in polyps
Peters 2010 [598]	CRS and control tissue	IL-6; IL-6r; STAT3	Western; ELISA;IHC	IL-6 levels are high in polyps but STAT3 pathway may be defective
Reh 2010 [839]	SNEC culture CRSwNP	IL-33	PCR	Increased IL-33 may be associated with severe CRSwNP
Schlosser 2010 [810]	AFS, CRSwNP and control tissue	Complement proteins: C3, C5, C7, factor B	PCR; IHC	Complement proteins are increased in CRSwNP and AFS vs. controls
Tieu 2010 [813]	Tissue and lavages in CRS and controls	S100 proteins A7, A8 and A9	ELISA; IHC	S100 proteins are decreased in nasal lavages and epithelium of CRS patients.
Van Crombruggen 2010 [14]	Ethmoid sinus and IT from CRS and controls	Various cytokines	ELISA	Similar mediator profiles seen in ethmoid and IT tissue in CRS
Ba 2011 [623]	Nasal polyp and turbinate	Inflammatory cytokines	ELISA	Cytokine pattern may correlate with type of colonized bacteria
Erbek 2010 [2055]	CRSwNP and control tissue	ADAM-33	IHC	ADAM-33 is elevated in polyps
Foreman 2011 [603]	CRS and control sinus tissue	SA igE and Th2 cytokines	Elisa	Presence of staph biofilm skewed Th2 inflammation independent of SA
Kimura 2011 [838]	CRSwNP , AR and NAR mucosa	TSLP	PCR; IHC	TSLP levels higher in polyps vs. AR and NAR;
Li 2011 [988]	Nasal polyps	P63; p73	PCR; IHC	Nasal polyps express higher levels of p63, possibly important in remodeling
Mansson 2011 [800]	CRSwNP and control tissue	NOD	PCR and IHC	NODs mRNA expression is increased in polyps
Mulligan 2011 [833]	SNECs from CRSwNP, CRSsNP and controls	cytokines	Tissue culture, Flow,	Polyp SNECs trigger dendritic cell maturation and skew toward Th2 polarization independent of antigen exposure

Author, year, ref.	Tissue, patients	Marker	Technique	Conclusion
Okano 2011 [2056]	Dispersed polyps	cytokines	ELISA	Fungal extracts produced less cytokine response than Staph SA
Peterson 2011 [832]	CRS and control tissue	CCL18	ELISA; Westerns; IHC	CCL18 increased in CRSwNP; co-localized with M2 macrophages
Poposki 2011 [610]	Sinus tissue from controls, CRSsNP and CRSwNP	CCL23	ELISA; IHC;PCR	CCL23 is secreted by eosinophils; may recruit Macs and dendritic cells
Roca-Ferrer 2011 [595]	Fibroblasts from CRSwNP, Samter's and and controls	PGE2; COX-1; COX-2	ELISA; westerns	COX and PGE2 levels are reduced in nasal polyps with an without ASA intolerance
Rogers 2011[781]	CRSwNP and control mucosa	Tight junction proteins	Confocal microscopy	TJ proteins occludin and claudin-1were reduced in polyp epithelium
Sejima 2011 [1021]	Sinus tissue from CRSwNP, CRSsNP and c ontrol	Fibrinolytic components	ELISA	uPA was increased in both CRSwNP and CRSsNP vs. controls; Inhibitor (PAI-1) is over expressed in CRSsNP only
Shun 2011[1016]	Polyp fibroblasts	VEGF; IL-8	Westerns	Hypoxia induces Cyr61 which stimulates VEGF and IL-8
Tan 2011 [23]	CRS and control tissue	Anti-nuclear autoantibodies	ELISA; Westerns; IHC	Anti-nuclear IgA and IgG autoantibodies are present in NP
Van Bruaene 2011 [1001]	Sinus and nasal tissue from early stage CRSsNP and controls	TGF-β; inflammatory cytokines	ELISA	Elevations in TGF-β may pre-date changes in inflammatory cytokines; remodeling and inflammation may be distinct processes in CRS
Wood 2011 [695]	Sinus mucosa from CRS and controls	Respiratory viruses	PCR	No evidence for chronic viral infection in CRS mucosa
Zhang 2011 [747]	AR and nasal polyp tissue	Mast cell mediators	ELISA	polyclonal IgE in nasal polyps is functional
Keswani 2011 [24]	SNEC and tissue from CRS and controls	IL-32	PCR; ELISA;IHC	Elevated IL-32 may play distinct roles in CRSsNP vs. CRSwNP

tissues with the laying down of extracellular proteins [922, 923]. Eosinophil production of PDGF as well as TGFα and β-1 may alter the structure of affected nasal mucosa [924-926]. Ultrastructural studies on nasal polyps treated with anti-IL-5 will be required to more definitively address the role of eosinophils in the remodeling of CRS sinonasal tissue (see below).

The association of eosinophilia with refractory disease makes this cell a potentially important target in CRS. Eosinophils are steroid-responsive [927] and this likely explains at least some of the therapeutic effects of glucocorticoids in CRS [27]. A large body of literature indicates that glucocorticoids can inhibit eosinophil recruitment, survival and activation in CRS [880]. A recent double-blind trial using oral corticosteroids demonstrated clinical efficacy as well as reduced IL-5 and ECP in nasal secretions [928]. Targeted therapy using anti-IL-5 in CRSwNP has shown promise as well. IL-5 and its receptor are both elevated in Caucasian (eosinophilic) nasal polyps [929, 930]. Clinical trials using anti-IL-5 antibodies demonstrated evidence for reduced polyp eosinophilia as well as clinical efficacy [931, 932].

4.2.4.5. Neutrophils

Neutrophils are circulating immune effector cells with an established role in the early phagocytosis and killing of extracellular microbes. Recruitment to mucosal sites is typically driven by microbial stimulation of PRRs, with release of cytokines that trigger endothelial expression of selectins, integrin ligands and chemokines. The main chemokine fostering neutrophil recruitment in CRS appears to be IL-8, in part released by nasal epithelial cells in response to PAR-2 stimulation [720]. The role of the neutrophil in CRS remains unclear but the highest sinus tissue levels are seen in CF patients [862]. For other forms of CRS, differences appear to depend on ethnicity as well as the presence or absence of nasal polyps. In Caucasians, neutrophilic infiltration can be demonstrated in CRS, with slightly lower levels observed in CRSsNP than in CRSwNP [620, 873, 874]. In concert, studies have shown upregulation of IL-8 in both CRSwNP and CRSsNP [620, 933-935]. Neutrophils did not appear to replace eosinophils in CRS mucosa, rather they were superimposed on the process; hence the term 'neutrophilic' rhinosinusitis was not considered completely appropriate for CRSsNP [874]. Nevertheless, the degree of neutrophilic infiltrate was comparable between CRSsNP and CRSwNP as opposed to the eosinophilic infiltrate, which was significantly less in CRSsNP. As a corollary, it has been suggested that CRSsNP is more distinctly a neutrophilic process, while CRSwNP is more eosinophilic based on the relative degree of tissue infiltration

[936]. Furthermore, in the subpopulation of CRSwNP patients with relatively low eosinophilic infiltration, it has been suggested that neutrophils may be the major pathologic driver of disease, analogous to 'neutrophilic' asthma [19].
In studies of polyps from Chinese patients, neutrophilic and eosinophilic infiltration appeared to be less than that seen in Caucasian polyps but the degree of eosinophilia was much more reduced, hence these polyps were relatively neutrophilic [22, 875]. A later study on Chinese patients from a different region indicated that Asian CRSsNP patients were comparably much more neutrophilic than Asian CRSwNP patients [877]. In the subset of Asian polyps that were non-eosinophilic however, significant neutrophilia was observed suggesting distinct underlying pathogenic processes within the CRSwNP group [877]. Overall, it should be kept in mind that Asian polyps may be quite different in cellular and cytokine profile throughout the continent.
Traditionally, neutrophils have been considered an acute response cell with a relatively short tissue half-life, therefore reasons for their accumulation in CRS are not completely clear. Recent studies have however, expanded the role of neutrophils beyond phagocytocis of extracellular organisms based in part on their diverse repertoire of effector molecules, which they express upon appropriate stimulation. In particular, neutrophils, may play a significant role in the resolution of inflammation as well as the pathology of the chronic inflammatory state [937]. Chronic neutrophilic inflammation is observed in lung disorders such as COPD and CF, mediating extensive tissue injury and contributing to organ dysfunction. Neutrophil products include various proteolytic enzymes, which may alter the protease-antiprotease balance triggering damage and remodeling.
The excessive accumulation of neutrophils may be driven by the products derived from the breakdown of extracellular matrix, namely N-acetyl Pro-Gly-Pro (PGP) [938]. PGP is normally metabolized but the process is impeded by cigarette smoke, with resulting inappropriate neutrophil accumulation in COPD (939). In CF lungs, low extracellular chloride levels, driven by the CFTR defect, has been proposed to diminish physiologic PGP breakdown [939]. Whether these processes take place in CF polyps or neutrophilic CRS in general is unknown. Interestingly, this pathway links smoking with neutrophilic inflammation, a process suggested by a separate line of research in CRS [765]. Nevertheless, they suggest a significant potential role for neutrophils in the pathophysiology of CRS and further suggest a molecular hypothesis for the negative effect of tobacco smoke on treatment outcomes.

4.2.4.6. Mast Cells

Mast cells are resident cells of the sinonasal mucosa with physiologic roles in innate immunity and wound healing [940]. Activation of mast cells results in the release of pre-formed granules including histamine, serotonin, proteoglycans and serine proteases; in addition, de novo synthesis and secretion of various eicosanoids, chemokines and cytokines also takes place. Physiologic activation of mast cells in immune defense works in part through PPR stimulation [940]. In nasal disease states, mast cell de-granulation has been most commonly implicated in allergic rhinitis via antigen-driven IgE cross-linking. In CRS, most interest has centered on a role for mast cells in nasal polyposis, in part due to the potential to induce, augment and maintain eosinophilic inflammation through IgE-dependent and IgE-independent processes [941, 942]. In particular, polyp explant studies have demonstrated that mast cell de-granulation may be triggered directly by protein A (SpA), a staphylococcal surface protein [668]. Mast cell prostaglandins have been implicated in Th2 lymphocyte recruitment and activation in nasal polyps [669]. These results suggest that mast cells can activate Th2 lymphocytes independently of T-cell receptor activation, with attendant secretion of Th2 cytokines [943]. Stem cell factor, secreted by epithelial cells, may be important in the recruitment of mast cells in nasal polyps [824]. Release of pre-formed mediators from mast cells should foster tissue oedema while serine proteases will effect PAR receptors, degrade the extracellular matrix (ECM) and diminish barrier integrity.
Interestingly, data are mixed as to whether mast cell numbers are increased in CRSwNP in comparison to either CRSsNP or even control tissues [542, 727, 874, 944-949]. Nevertheless, functional studies suggest that mast cells in nasal polyps are much more active and may display a heightened sensitivity to external triggers in vivo [949]. Overall however, the relative importance of mast cells in the pathogenesis of CRSwNP remains unclear. Targeted medications designed to inhibit upstream mast cell functions are an area of active research that may help elucidate their importance [950].

4.2.4.2.7. Cells, Plasma Cells and Immunoglobulins

Mucosal immunoglobulin secretion by cells of the B lymphocyte lineage is an important part of the adaptive immune response. In the nasal mucosa, B cells undergo proliferation, differentiation and immunoglobulin class switching to become mature plasma cells capable of substantial local antibody secretion.
In overview, tonic secretion of sIgA works in concert with other innate protective factors and mucociliary flow to limit mucosal colonization without tissue-damaging inflammation [951]. In general, this IgA is relatively low affinity, generated via a T-independent process, and secreted by extrafollicular B cells. In the case of an active breach of the respiratory mucosa, IgA secretion increases but it also receives help from IgG and a robust inflammatory response ensues. In general, this is high affinity IgA, T-dependent and generated by follicular B cells and plasma cells. IgM and IgD also play a role. IgD is the least understood imunoglobulin but interestingly, it is present in significant amounts in the respiratory mucosa [952]. Although its

precise role is still unclear, IgD exerts protective effects not only through antigen binding, but also its capacity to arm basophils with IgD highly reactive against respiratory bacteria [953]. Basophils have recently been discovered to possess the capacity to function as antigen presenting cells by migrating back to lymphoid organs to initiate Th2 and B cell responses [954]. Hence, IgD-activated basophils may initiate or enhance innate and adaptive responses both systemically and at the mucosa [952].
IgE is mostly closely associated with the pathophysiology of allergic rhinitis but it plays several important physiologic roles as well including antigen presentation, increased mast cell survival, defense against viruses, bacteria, fungi and parasites and mucosal homeostasis [729, 940].
In CRS, polyp homogenates demonstrate high levels of immunoglobulins, notably IgA, IgE and IgG, in comparison to CRSsNP and control tissues, apparently in response to bacterial and fungal antigens [542, 600, 786, 807, 921, 955-957]. Levels in polyp homogenates do not correlate with levels in serum, suggesting that significant immunoglobulin synthesis occurs locally in the nasal mucosa [958-960]. In parallel with these findings, high levels of B cells and plasma cells have been reported in nasal polyps in comparison to CRSsNP and control tissue [600, 874, 921]. Evidence for a dysregulated adaptive B-cell immune response is further suggested by the presence of germinal center like follicles in nasal polyps [960] and the entire process is likely orchestrated by local proliferation and systemic recruitment of B cells [600, 602].

Elevations of tissue B cells, plasma cells and immunoglobulins are associated with CRSwNP.

In regard to elevated IgE in nasal polyps, levels have been shown to be independent of systemic atopy but they do correlate with the presence of IgE to staphylococcal superantigenic toxins [542]. Approximately 50% of Caucasian CRSwNP and 20% of Chinese CRSwNP patients demonstrate local IgE to these toxins as well as a concomitant polyclonal IgE response to a diverse array of environmental antigens in polyp homogenates [542, 621]. The presence of IgE to these toxins correlated with not only high levels of polyclonal IgE but also high tissue levels of ECP (eosinophil cationic protein) and co-morbid asthma [621].
In regard the mechanism, studies of polyp explants exposed to staphylococcal superantigens revealed polyclonal T cell activation with a Th2 cytokine polarization [668, 670]. In addition to pro-eosinophilic effects, this cytokine milieu should favour IgE production indirectly by triggering B cell class switching towards IgE production [596]. Furthermore, staphylococcal protein A (SpA) has direct proliferative effects on B cells in vitro, possibly further driving the IgE process in nasal polyps [596]. Very recent studies have demonstrated that the polyclonal IgE in nasal polyps is functional and can trigger mast cell de-granulation, suggesting a significant role for IgE in the pathophysiology of this subset of CRSwNP patients [961]. The therapeutic potential of anti-IgE for nasal polyposis has been suggested [962] but trials have thus far been equivocal [963].

In regard to elevated IgA in nasal polyps, recent studies have implicated BAFF (also called BLyS or TNFSF13B), a cytokine of the TNF family favoring B cell proliferation and immunoglobulin class switching [600]. High levels of BAFF are present in nasal polyp tissue in comparison of controls and CRSsNP tissue; moreover, the levels of BAFF correlate with the number of B cells in the nasal polyp [600]. Transgenic BAFF mice develop autoimmune disorders [964]; further studies in polyp homogenates demonstrated IgA and IgG anti-nuclear autoantibodies at locally elevated levels in nasal polyp tissue in the absence of systemic autoimmunity in some patients with CRSwNP [740]. The presence of these autoantibodies was detected at higher frequency in the most recalcitrant patients who had undergone multiple revision surgical procedures, suggesting an autoimmune component in the most severe subset of CRSwNP.

The presence of both abundant class-switched immunoglobulins and available antigen is likely to play an important role in propagating the inflammatory response through antibody-mediated mechanisms [955]. As noted in other sections of this review, CRSwNP is associated with increased infiltration of inflammatory effector cells including eosinophils, mast cells, macrophages and neutrophils, which de-granulate or phagocytose in response to immune complexes [874, 965]. The potential impact of IgE and mast cell activation in CRSwNP was already noted. Similarly, IgA is an extremely potent trigger of eosinophilic degranulation and hence may be a key to local mediator release within polyp tissue as well [919]. A potential role for IgD is CRS is thus far speculative, however the capacity to arm basophils is intriguing and this immunoglobulin may play a significant upstream role in fostering a Th2 cytokine milieu in nasal polyposis.

4.2.4.8. T Cells and cytokine patterns

Comparatively few studies have examined the topic of T cell activity in the nasal mucosa relative to the gut, skin and lower airways. In addition, many studies have been performed in vitro, and the in vivo factors mediating T cell responses, in particular Th polarization across mucosal barriers remains a subject of active research. In regard to CRS, the absence of a widely accepted animal model compounds the problem; hence, much of our understanding of T cell activity in nasal mucosa is based on extrapolation. In the immune response of the nose, dendritic cells (DCs) act as the initial antigen presenting cells (APCs) sampling and then presenting antigens to naïve T lymphocytes in draining lymph nodes or local lymph aggregates. Circulating

basophils may also enter the tissue and serve along side or instead of resident DCs to function as APCs as well [966]. Following antigen presentation, naïve CD4+ lymphocytes will differentiate into one of several T cell lineages, determining the nature of the adaptive immune response. The subsets include Th1 and Th2 as well as the more recently described Th17 and inducible T regulatory cells; each has distinct molecular, cellular and functional properties [967, 968]. Other subsets have also been recently proposed, including Th9 and Th22, and more are likely to follow. In vitro studies indicate that for the Th1 subset, the key transcription factor is T-bet, the canonical cytokine is IFN-γ and the classical cellular infiltrate is macrophage-rich. Th1 responses are particularly effective against viruses and intracellular bacteria, including mycobacteria. For Th2, the transcription factor is GATA-3, the associated cytokines are IL-4, IL-5 and IL-13 and the cellular response eosinophilic. Th2 protective responses are geared against parasites, particularly those too large to undergo phagocytosis. For Th17, the transcription factor is RORc and the associated cytokine IL-17A and the cellular response classically neutrophilic. Extracellular bacteria, particularly Staphylococcus aureus [969], are prime targets. T regulatory cells are characterized by the transcription factor FOXP3 with the purpose of limiting excessive responses by the other lineage subsets. These differentiated effector T cells migrate into the mucosa where they re-encounter the same antigen, this time likely presented by both macrophages and DCs acting as APCs. The resultant binding of antigen to the T cell receptor (TCR) activates the cell, resulting in a cytokine release pattern characteristic for each Th subtype, mediating the appropriate effector response.

The in vivo factors that determine T cell differentiation are obviously critical, but currently somewhat speculative in the nasal mucosa. In general, the differentiation of naïve CD4+ cells into a particular lineage is the integration of multiple signals, including T-cell receptor strength, co-stimulatory and innate immune signals, and cytokine milieu [967, 968]. This process is greatly influenced by crosstalk between epithelial cells (ECs) and the local DCs [601]. ECs, as well as other resident innate cell types (mast cells, NK cells, macrophages, basophils, eosinophils), sense exogenous, primarily microbial agents via PAR, Toll receptor, NLR and other PRR leading to expression of various cytokines and chemokines as mentioned in the earlier sections. Cellular damage is also detected via DAMPs. Collectively, these resident cells are therefore able to sense both damage and danger and respond with the appropriate cytokine array, secondarily influencing the correct effector T cell response to address the particular challenge. In addition to these resident cells influencing DC polarization, it has recently been recognized that circulating innate lymphoid cells (ILCs) migrate to the site of stimulation and also play a role [970]. They have been recognized separately in a number of tissues and thus have diverse names including NK cells, LTi cells, nuocytes, innate T cells, natural helper cells and CD34+ hemopoietic progenitor cells [835, 970-973]. These ILCs are presumably responding to chemokine homing signals emanating from resident mucosal cells including ECs and are termed innate because they recognize foreign substances via PPRs rather than through TCRs or immunoglobulin. Capable of responding rapidly, ILCs function in a transitional effector cell role, bridging innate and adaptive immunity. Distinct subsets of ILCs have been proposed and the lineage relationship is not yet clear. Nevertheless upon stimulation, ILCs release cytokines that, among other functions, will influence DC polarization. While Th1 and Th17 ILCs have been described, in the case of CRSwNP, ILCs thus far identified are Th2 skewed, responding to epithelial cytokines such as IL-25, IL-33 and TSLP with the production of IL-4, IL-5 and IL-13 [601, 974]. Whether these cells play a role in CRSsNP is unclear, but earlier results suggest they may have a prominent role in CRSwNP since exceptionally high numbers of ILCs are found in nasal polyps [835, 973]. No studies have been done on ILCs in Asian polyps or CF polyps, which might very well be distinct.

The collective cytokine response from resident cells and migrating ILCs is believed to be pivotal in shaping T cell differentiation. The typical in vivo T cell effector responses are mixed however, and the Th subtypes display some heterogeneity as well [975, 976]. Nevertheless, the lineage subsets tend to be mutually inhibitory resulting in a degree of polarization to particular subsets at a site of action [968, 976]. Under physiologic conditions, the typical adaptive response to harmless antigens is immunologic tolerance, with generation of Tregs and a baseline controlled Th2 response. Although the nasal mucosa has not been studied in vivo, this pattern presumably results from appropriate levels of TGF-β, IL-2, IL-4 and TSLP secretion influencing DC polarization [834, 968]. TGF-β fosters Treg differentiation. IL-4 is required for Th2 differentiation in vitro but evidence suggests this restriction may be circumvented in vivo [977, 978]. Alternatively, IL-4 may be secreted by resident mast cells or basophils. It is not known whether circulating innate immune cells play any significant role in baseline homeostasis. The net effect is a non-inflammatory response, primarily consisting of IgA secretion, which limits adherence of microbes to the epithelium [951].

Homeostasis across mucosal barriers is geared towards eliminating microbes and other antigens without tissue-damaging inflammation [951]. When the mucosal barrier is breached, an appropriate protective immune response with some degree of inflammation must be generated, with ECs and other innate immune cells helping to guide the response. In the case of a protective Th1 response directed against intracellular microbes, ECs and other resident and infiltrating cells including

NK cells, trigger IL-12, IL-18 and IFN-γ release, the essential cytokines fostering Th1 differentiation. When subsequently challenged by antigen, effector Th1 cells secrete large amounts of IFN-γ, TNF-α and TNF-β with several key protective effects: [25] macrophage activation with enhancement of phagocytic properties [14] B cell help and class switching to production of IgG subclasses with opsonizing and complement fixing capabilities [594] enhanced antigen presentation of macrophages and [625] local tissue inflammation and neutrophil activation [979].

Protective Th2 responses are directed against parasites, and cytokines such as TSLP, IL-33 and possibly IL-25 may play roles, with the net effect being a milieu favoring a much stronger skewing of Th2 T cell differentiation than seen under homeostatic conditions [834]. Circulating ILCs likely contribute to the Th2 cytokine milieu as mentioned above [973]. Basophils, mast cells and NKT cells (natural killer T cells) are possible sources of IL-4, which may be essential for the process as mentioned above [977]. When subsequently challenged by antigen, Th2 effector cells secrete large amounts of Th2 cytokines IL-4, IL-5 and IL-13, which may drive more TSLP secretion by ECs, creating a positive feedback loop [977]. The net protective effects of these Th2 cytokines includes [25] recruitment, activation and survival enhancement of eosinophils, in particular by IL-5 (14) immunoglobulin class switching to IgE and IgG4 via IL-4 and IL-13 [594] increased mucus production via IL-13 and [625] alternative macrophage activation by IL-4 and IL-13. IgE and IgA are capable of binding parasites, sterically inhibiting their ability to invade, but these immunoglobulins do not trigger phagocytosis or complement fixation. Mast cell binding to this surface IgE triggers de-granulation with release of inflammatory mediators and substances toxic to the parasites. Similarly, eosinophils may bind IgA with release of granules toxic to the parasites as well. Alternatively, high tissue IL-5 levels may also foster eosinophil degranulation in the absence of IgA. Mast cell and eosinophil degranulation trigger inflammation and some degree of tissue damage, which are both inevitable and necessary, but have long-term negative consequences. Lastly, alternative macrophage activation will trigger expression of macrophage mannose receptor (MMR) and secretion of cytokines that stimulate collagen synthesis and fibrosis. While these granuloma-forming activities may be protective in certain settings, they can have significantly negative effects on end-organ function.

In the case of a protective response against extracellular bacteria and fungi, Th17 responses are preferentially invoked via resident cell cytokine responses including IL-1β and IL-6 [968, 980]. As mentioned above, TGF-β alone fosters Treg differentiation; however TGF-β together with IL-6 will foster Th17 differentiation and the presumed sources of IL-6 are macrophages, DCs and ECs [981]. Th17 cells produce large amounts of IL-17A, IL-17F and IL-22 with several protective effects both directly and indirectly including [25] neutrophil recruitment [14] neutrophil activation [594] neutrophil proliferation and [625] innate antimicrobial production by airway epithelial cells [980].

In addition to the CD4+ helper T cell subsets discussed above, CD8+ cytotoxic T cells, natural killer (NK) cells, NKT and memory T cells also play significant roles in mucosal immunity. Naive CD8+ T cells differentiate and proliferate following exposure to antigen presented by DCs. CD4+T cells provide signals that amplify the process and may be absolutely essential in the case of some antigens. The net result is the generation of cytotoxic lymphocytes (CTLs) whose primary function is to eliminate intracellular microbes mainly by killing infected cells. Infected cells display microbial antigens on the surface together with class I MHC molecules, and this complex is recognized by the TCR. The infected cells undergo apoptosis from toxic granule exposure or via a ligand-receptor mediated process. CTLs are frequently localized to the epithelium; the TCRs of these lymphocytes often show limited diversity suggesting they have a restricted response repertoire and may be focused on commonly encountered luminal antigens. NK cells have a similar function to CTLs but their receptors are distinct from TCRs and they also do not need to undergo differentiation or maturation. They recognize stressed/infected cells via differential expression of a heterogeneous group of endogenous surface ligands rather than foreign antigen; the result is lysis of the stressed cell. They also secrete IFN-γ, which activates macrophages and fosters Th1 differentiation. NKT cells are a numerically small population of lymphocytes that have characteristics of both T cells and NK cells. They have TCRs but with limited variability, typically against lipid antigens, distinguishing them from typical T cells which only recognize protein antigens. They are also a source of IFN-γ. Memory lymphocytes are generated alongside the differentiation and maturation of the effector CTL and Th lineages and are actually the predominant T lymphocyte subset in nasal polyps [982].These memory cells are present in the mucosa and respond to subsequent antigen challenge.

The role of T cells in chronic airway inflammation has been a subject of great interest since the discovery of Th1/Th2 paradigm 25 years ago; consequently most studies have focused on the CD4+ lineage subsets [983]. Given the chronic inflammation that defines CRS, the presence of elevated levels of T cells in both CRSsNP and CRSwNP relative to control tissues is not surprising [620, 874, 984]. It has been proposed however, that the various T cell effector lineages orchestrate distinct phenotypes of CRS [22, 620, 984]. Establishing the predominant T effector pattern may therefore help determine pathophysiology, guide treatment, or even predict outcome. Early work in this

area demonstrated elevations of both Th1 and Th2 cytokines in CRS, with higher levels of Th2 cytokines associated with atopy [524]. Follow up studies failed to confirm this latter finding, indicating that Th2 cytokine levels were independent of atopy [900]. Later studies began the actual process of separating disease phenotype and cytokine response. These results indicated that in Caucasians, CRSsNP is a skewed Th1 disorder, with relatively higher levels of IFN-γ while CRSwNP is a skewed Th2 disorder with relatively higher levels of IL-5 [620]. In addition, CRSwNP had evidence for a relative lack of T regulatory function based on decreased FOXP3 expression [984, 985]. Studies on Asian CRS tissues have yielded some differences and some similarities. Decreased Treg function with CRSwNP appears to be similar in both Asian and Caucasian polyps [22, 877]. CRSsNP in Asians was shown to be relatively Th1 biased, similar to Caucasians as well [877]. Asian CRSwNP patients demonstrated a Th1/Th17 cytokine bias, with less IL-5 than Caucasian polyps, consistent with the lower eosinophilic and higher neutrophilic tissue infiltration [22, 875, 877, 986, 987]. Other investigators however, showed no differences between Asian CRSwNP and Caucasian CRSwNP with regard to IL-5 or eosinophilia but this has been interpreted to reflect wide variations in environmental and/or genetic factors across the continent [988, 989].

Asian and Western CRSwNP both exhibit low TGF-β and diminished Treg activity relative to CRSsNP

Recently, comparative expression analyses of the key canonical cytokines IFN- γ, IL-5 and IL-17 were performed in both Chinese and Belgian polyps. This is the most comprehensive study of its kind to date and it confirmed the Th2 bias in Western/Caucasian polyps and the Th1/Th17 bias in Chinese polyps [621]. The study further revealed that a substantial proportion of Chinese polyps were negative for all 3 key cytokines, termed therefore KCN polyps (key cytokine negative). Most significantly, high IL-5, polyclonal IgE with IgE to staphylococcal exotoxins and co-morbid asthma clustered in both groups [621]. A later follow up study has associated the inflammatory cytokine pattern with bacterial colonization indicating that KCN polyps are associated with gram negative bacterial colonization while the smaller Th2 skewed subset of Chinese polyps is preferentially colonized by gram positive organisms [623]. While the rate of Staphylococcus aureus colonization is much lower even in the IL-5 positive Chinese polyps, these results are in relative agreement with published findings in Caucasian CRSwNP patients further connecting this organism with Th2 cytokine expression [661]. While these findings are interesting, it remains unclear whether the cytokine patterns can predict clinical phenotype or response to therapy. Despite differences in levels of inflammatory cytokines, low FOX3P expression appears to be characteristic of both Asian and Caucasian polyps patients indicating that diminished Treg activity may be a key factor in polyp formation [22, 984, 990].

NK, NKT and CD8+ T cells are relatively unstudied in CRS. NK cells are present and apparently elevated vs. control tissue in both CRSsNP and CRSwNP but any specific role in the disease process is unclear [731, 874, 982]. Normal nasal mucosa demonstrates a ratio of CD4+ to CD8+ cells of approximately 2:1 [535, 991]. In nasal polyps, relatively more CD8+ T-cells have been demonstrated but the implications for pathogenesis remain unclear [877, 982, 992]. Studies on Asian CRSsNP patients also showed a higher proportion of CD8+ cells [877]. Given the potential role of viruses and other intracellular pathogens in CRS in general and acute exacerbations in particular, further studies on NK, NKT and CD8+ cells may be quite important.

In summary, there is substantial evidence for [25] a down regulation of Treg activity in CRSwNP and [14] upregulation of Th 1, 2 and 17 in various forms of CRS. Current evidence indicates that CRSsNP tends to be a relatively Th1 biased disorder in both Caucasians and Asians. CRSwNP is Th2 biased in Caucasians while Th1/Th17 biased in Asians. CF nasal polyps are likely Th17 biased but this has not been directly assessed [981]. While these studies represent data aggregates, individual patient outliers are present in each group and it remains to be demonstrated whether these outliers are distinct in terms of aetiology and clinical behavior.

4.2.4.9. Remodeling

Tissue remodeling refers to modifications of the normal composition and structural organization of tissues, typically in response to stress such as chronic inflammation. Characteristic patterns of airway remodeling have been associated with several chronic inflammatory lower airway disorders including cystic fibrosis, pulmonary fibrosis, COPD and asthma [993]. Remodeling also takes place in the upper airway when subjected to chronic inflammation such as seen in allergic rhinitis and CRS with changes that include fibrosis, epithelial alterations, basement membrane thickening, goblet cell hyperplasia, sub-epithelial oedema and inflammatory cell infiltrates [985, 994]. In general, the histopathologic changes have been likened most closely to those observed in asthma [701, 994]. Recent reports indicate that the lower airway epithelium and underlying cells function as a unit, termed the epithelial-mesenchymal unit (EMTU); structural and functional defects in the airway epithelium in asthma are proposed to trigger persistent epithelial activation with secondary, and ultimately irreversible changes in the underlying tissues [768, 995]. Studies in the upper airway have begun to suggest that similar pathways may be operative. Areas of hyperplasia and sloughing are apparent in CRSwNP epithelium [988, 996]. Other studies suggest

that diminished epithelial healing, weaker mechanical barrier and diminished innate antimicrobial secretion may be characteristic of CRSwNP [25, 782]. Increased ion transport and higher rates of ion permeability have been observed in nasal polyp epithelia supporting this concept [784-786].Taken together, these studies suggest the hypothesis that a permissive, relatively vulnerable epithelial barrier in CRS results in secondary changes in the underlying mucosal tissues.

Remodeling of the extracellular matrix (ECM) of the lamina propria in CRS patients has been extensively studied and somewhat distinct remodeling patterns have been associated with subsets of disease. The ECM is a network of collagenous and non-collagenous structures that surround cells in the airway and affect many aspects of cellular behavior including migration, differentiation, survival and proliferation [993]. PDGF is one factor that has been implicated in lower airway ECM remodeling and it may play a role in the upper airway of CRS patients with asthma as well [997]. In CRS however, the ECM is grossly characterized by areas of oedema and fibrosis, with the latter dominating in CRSsNP and the former dominating in CRSwNP [998]. The precise molecular factors mediating this differential remodeling pattern are not completely clear, but current evidence suggests a key role for the pleotropic cytokine TGF-β. Although not all studies agree [859], low levels of TGF-β have been demonstrated in CRSwNP and high levels in CRSsNP [984]. TGF-β modulates ECM deposition in the airway [999] and it has been suggested that low levels in CRSwNP contribute to decreased tissue repair and collagen formation with secondary albumin deposition and tissue oedema, while high levels in CRSsNP mediate basement membrane thickening, excessive collagen deposition and fibrosis [990, 1000]. TGF-β also has an established role in Treg differentiation as mentioned earlier. It should be noted that low Treg activity and low TGF-β are two factors that appear consistent in both Asian and Caucasian polyps despite clear differences in inflammation, suggesting a key, possibly integrated role in polyp formation [594]. In regard CRSsNP, a very recent study focused on early stage disease, suggested that increased TGF-β is present prior to the onset of a significant inflammatory response [1001]. Overall, these findings give credence to the hypothesis that CRS is primarily a remodeling disease, rather than an inflammatory disorder, best characterized and possibly best treated based on remodeling patterns [594].

The ECM is dynamic, reflecting the net balance of synthesis and degradation that is regulated, in part, by the actions of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [1002]. It has been proposed that an imbalance between these factors, mediated by TGF-β, triggers the oedema seen in CRSwNP [594]. This hypothesis is supported by data suggesting differential expression levels of MMPs and TIMPs in CRSwNP when compared to CRSsNP and control tissue [622, 775, 990, 1003-1005]. In addition, extracellular matrix metalloproteinase inducer (EMMPRIN) is also elevated in CRSwNP as opposed to controls, suggesting high levels of ECM degradation in polyps [811]. Lastly, a recent ex vivo study suggested that S. aureus may promote polyposis by altering the MMP/TIMP milieu [672]. While these studies suggest a role for MMPs and TIMPS in CRS remodeling in general and polyp formation in particular, further studies are necessary to elucidate a clear molecular pathway of disease pathogenesis.

Asian and Western CRSwNP exhibit similar remodeling patterns of oedema and decreased tissue collagen deposition.

Angiogenic factors have also been associated with upper airway remodeling of the lamina propria in CRS, in particular CRSwNP, suggesting that angiogenesis may be a driving force in polyp formation. Angiogenin, a factor that induces blood vessel formation, has been associated with CRSwNP (1006). Vascular endothelial growth factor (VEGF), a key protein that modulates both angiogenesis and vascular permeability, is much more highly expressed in nasal polyp tissue than in CRSsNP or control tissues [1007-1009]. Expression is seen primarily in the epithelium where it is believed to trigger epithelial hyperplasia [1009]. Endothelial expression of VEGF has been hypothesized to mediate the profound oedema seen in CRSwNP tissues [1010]. The pathophysiological trigger for these angiogenic factors is unclear, but relative hypoxia has been demonstrated in the maxillary sinuses of CRS patients [1011]. Hypoxia is a potent inducer of VEGF from nasal fibroblasts in vitro [1012, 1013], likely acting through hypoxia-inducible factor (HIF-1α) [1014]. This suggested the hypothesis that hypoxia, in part through ostiomeatal complex (OMC) occlusion, drives HIF-α expression secondarily triggering VEGF, TGF-β, nitric oxide synthetase, MMPs and IL-8 [626, 627, 1015, 1016] support of this hypothesis, microarray analysis demonstrated substantial up-regulation of HIF-α in non-eosinophilic polyps in comparison to control tissue [1017]. It should be kept in mind however, that VEGF appears to upregulated in both eosinophilic and non-eosinophilic polyps but not CRSsNP. The latter is a disease more closely associated with OMC obstruction and presumably, hypoxia [625]. The high blood flow to the nose and paranasal sinuses would seem to limit actual tissue hypoxia in CRS. Moreover, one would anticipate an extremely low polyp recurrence rate following aggressive surgery, if hypoxia were the primary driver of angiogenesis and subsequent polyp formation. Lastly, and perhaps most importantly, carefully performed histologic studies have failed to demonstrate that angiogenesis, regardless of the inciting agent, is a significant driving force in polyp growth [1018]. This report suggests that the rate of angiogenesis required to meet the needs of the polyp are relatively low and can be driven by metabolic or mechanical factors, rather than

being an integral part of the pathology as it is in neoplastic disease [1019].

Components of the coagulation cascade have been implicated in CRS pathogenesis, primarily in regard to effects on tissue remodeling. Airway inflammation is associated with increased vascular permeability and leakage of plasma proteins into the extravascular space. Thrombin levels are significantly increased in the nasal secretions of patients with CRSwNP and asthma and it was proposed that this results in increased VEGF secretion from epithelial cells via a PAR-1 receptor pathway [1020]. In addition, fibrinolytic components have been associated with CRS. Plasminogen activators such as uPA are elevated in CRSwNP tissues compared to controls and CRSsNP [1021]. Levels of the uPA inhibitor plasminogen activator inhibitor-1 (PAI-1) were elevated in CRSsNP and this correlated closely with TGF-β levels suggesting a mechanistic link [1021]. Further studies will be necessary to establish the clinical relevance to ECM changes seen in CRS.

Remodeling of the underlying bone has also been observed in CRS [1022] and the presence of remodeled osteitic bone has been proposed as an explanation for persistent disease [1023, 1024]. The mechanism for this process remains unclear and no study has yet recovered microorganisms from the bone of CRS patients. Nevertheless, non-infectious inflammatory cytokines may drive bone and tissue remodeling in a wide array of disorders. In particular, the cytokines osteopontin (OPN) and periostin (POSTN) are members of a family of recently described tissue remodeling proteins [1025] that may be relevant to CRS. OPN has been implicated in both bone remodeling [1026] and Th2 airway inflammation [1027] in humans and studies have demonstrated particularly high levels in CRSwNP [826]. A study has also suggested that OPN may modulate ECM deposition in CRSwNP, perhaps in relationship to TGF-β [1028]. POSTN, also called osteoblastic-specific factor 2, has an established role in bone formation and is also up-regulated in CRSwNP [1028, 1029]. In summary, while these cytokines are possible candidates mediating the bone remodeling observed in CRS, it remains unclear whether this process plays a clinically significant role in CRS pathogenesis [1030].

Mucus secretion with goblet cell and glandular hyperplasia are other features of upper airway remodeling in CRS, with changes in both the quantity and viscosity of the mucus [1031, 1032]. These changes are likely mediated by cytokines including TNF-α, IL-8 and IL-13 [1033]. Glandular hyperplasia and hypertrophy have been primarily associated with CRSsNP [998, 1034]. MUC5AC and MUC5B are the main secreted mucins in the human airway, with MUC5A being produced primarily by goblet cells [1035]. Differential expression of mucin genes is observed in CF, CRSsNP, CRSwNP and antrochonal polyps [1032, 1035, 1036]. These mucins ultimately affect viscosity presumably accounting for the thin, watery mucus typical of CRSwNP and thick mucus observed in CF [1032]. It has been suggested that the positive effects of long-term macrolides for CRS seen in some studies [16] may in part, reflect reversal of pathologic increases in mucus viscosity [1037]. Practically speaking however, there are over 20 mucin genes and a wide range of factors likely influences production in the individual patient [1038-1040].

4.2.4.10. Eicosanoids and the Arachidonic acid pathway

Eicosanoids are signaling molecules with immunologic and inflammatory properties generated by oxidative metabolism of arachidonic acid (AA) [1041, 1042]. Disturbances in this pathway have been most closely associated with aspirin-sensitive nasal polyposis, but abnormalities have also been suggested to potentially underlie aspirin-tolerant CRSwNP as well. There are several families of classical eicosanoids with distinct properties: [25] leukotrienes [14], prostaglandins (PGD2, PGE2 and PGF2) [594]; prostacyclin (PGI2); and thromboxane (TXA2) [625]. Leukotrienes are generated by lipoxygenase (5-LO) activity, while the other 3 are generated by cyclooxygenase enzyme (Cox-1 and Cox-2) activity. Also relevant are the lipoxans, technically termed non-classical eicosanoids, which are generated by 12/15 lipoxygenase (12/15-LO) activity. In general, lipoxans and PGE2 have anti-inflammatory effects while the rest are all pro-inflammatory.

Leukotriene formation requires 5-LO activity that gives rise to the LTA4 precursor; subsequent enzyme activity results in the production of LTB4, LTC4, LTD4 and LTE4. The latter three are known as the cysteinyl leukotrienes, formerly termed slow reacting substance of anaphylaxis (SRSA), and require leukotriene C4 synthase activity (LTC4 synthase). Genetic polymorphisms in LTC4 synthase have been associated with CRSwNP in some studies [1043] and it has been suggested that this enzyme may be the engine of aspirin intolerance [1044, 1045]. The primary sources of leukotrienes in the airway mucosa are mast cells and eosinophils, with effects including increased vascular permeability, vasodilation, leukocyte chemotaxis, broncho-constriction and mucus secretion. Leukotrienes have a short tissue half-life, working locally by binding to a least 2 receptors: CYSLTR1 and CYSLTR2. CYSLTR1 antagonists (e.g. Montelukast and Zafirlukast) have been used for the management of AR, asthma and to a lesser extent nasal polyposis. Studies in CRS demonstrated levels of cysteinyl leukotrienes that were significantly higher in eosinophilic polyps compared to control tissue independent of atopy [1043]. A later study confirmed and extended these findings demonstrating the highest levels of cysteinyl leukotrienes in aspirin sensitive polyps, followed by CRSwNP, CRSsNP and then normal mucosa [915, 1046]. Corresponding increases were also seen in expression of the enzymes 5-LO and LTC4 synthase [1046].

The action of Cox-1 or Cox-2 enzymes results in the generation of prostanoids: prostaglandins, prostacyclin and thromboxane. Cox-1 is constitutively expressed while Cox-2 is inducible, the latter typically up-regulated in inflamed tissues, while the former can be influenced by topical glucocorticoid treatment [1047]. Subsequent activity of the corresponding synthase enzymes produces PGD2 and PGE2 and from the perspective of airway disease, these are the most notable prostanoids [1042]. PGD2 acts via binding to prostanoid receptors triggering pro-inflammatory effects including chemotaxis, de-granulation and enhanced survival of eosinophils [1048-1050] as well as migration of Th2 lymphocytes [1051]. Increased PGD2 synthase enzyme levels were demonstrated in CRSwNP [1052] and differential PGD2 receptor expression was associated with polyposis [1053]. PGE2 may be more significant from a clinical perspective, as it triggers bronchodilation acting via the EP2 prostanoid receptor [1054]. In addition, PGE2 exhibits an array of primarily anti-inflammatory, protective effects by direct inhibition of leukotriene production [1055]. Interestingly, PGE2 levels, cox-2 levels and PGE2 synthase levels are all decreased in nasal polyps [1010, 1046, 1052, 1056]. Expression of the E-prostanoid receptors may also be altered in CRS [915]. Studies have suggested that staphylococcal superantigenic toxins (SAg) may interact with the PGE2 pathway as well. SAg suppresses the PGE2 pathway while PGE2 blunts the pro-inflammatory effects of SAgs [605, 606]. Most significantly, a recent study demonstrated that in contrast to normal fibroblasts, polyp fibroblasts fail to up-regulate the cox pathway in response to inflammatory stimuli [595].

Abnormalities of the eicosanoid pathway have been associated with CRSwNP, with an up-regulation of the pro-inflammatory leukotriene pathway and a down-regulation of the primarily anti-inflammatory PGE2 pathway

In summary, alterations in the eicosanoid pathways have been identified most prominently in CRSwNP, with an up-regulation of the pro-inflammatory leukotriene pathway and the down-regulation of the primarily anti-inflammatory PGE2 pathway. It has been suggested that this pro-inflammatory environment, perhaps modified by colonized Staphylococcus aureus, may be central to the aetiology of nasal polyposis [594].

4.2.5. Microarray studies

Microarray studies have been used on CRS tissues, primarily nasal polyps, in an effort to (a) understand the pathophysiology; (b) explore the mechanism of corticosteroid efficacy; and (c) serve as a platform to guide future investigations. The first study compared tissue from patients with AR vs. those with AR plus nasal polyps. Increased expression of the mammaglobulin gene was seen in nasal polyps, in comparison to patients with rhinitis alone; other genes associated with neoplastic growth were also up-regulated [1057]. Another early study compared nasal polyps before and after oral glucocorticoid treatment. In this study, uteroglobulin- also known as CC10 -demonstrated the greatest increase while β-defensin showed the most marked down-regulation in response to corticosteroids (1058). Uteroglobulin has established diverse anti-inflammatory and immunomodulatory properties.

Microarray techniques have also been utilized to directly compare nasal polyps to normal control tissues. Relative to normal tissue, the most up-regulated genes in polyps included statherin, prolactin-induced protein (PIP), lactoferrin and deleted in malignant brain tumor 1 (DMBT1), while the most down-regulated gene was uteroglobulin/CC10 [1059]. The polyp patients were separated into 2 groups: oedematous polyps which were highly eosinophilic and glandular polyps which were less eosinophilic. Immunohistochemical studies indicated that lactoferrin, DMBTI and PIP were increased in the glands of only the 'glandular-type' polyps, not the oedematous polyps. CC10/uteroglobulin was present primarily in the epithelium of normal controls and greatly decreased in both forms of polyposis. Interestingly, this study did not see significant changes in expression of many of the genes commonly associated with CRSwNP including IL-4, IL-5 and GM-CSF [3]. Expanded microarrays and bio-informatic analyses were used in a larger study comparing 3 groups of patients (10 in each group): normal controls, aspirin-sensitive polyps (ASA) and aspirin-tolerant polyps (CRSwNP) [1029]. This study demonstrated substantial agreement between the 2 polyp phenotypes but increased expression of periostin and met protoncogene and decreased expression of PIP was seen relative to control tissues. Periostin is a protein that is highly expressed in the airway epithelium of asthma patients believed to play a role in TGF-β activation, collagen deposition, fibrosis and remodeling [1060]. The Met gene (or c-Met) encodes hepatocyte growth factor receptor (HGFR), an epithelial membrane receptor known to bind hepatocyte growth factor (HGF). HGF and HGFR expression are increased in CRSwNP [1061]. From a functional perspective, this ligand-receptor binding is believed to play a role in wound healing and inflammation in lower airway epithelium. In the human upper airway, preliminary evidence suggests that genetic variation in the c-Met pathway is associated with CRSwNP [1062], perhaps through the loss of HGF mediated down regulation of the effects of Th2 cytokines [1063]. Pip protein, whose expression is decreased in the polyp phenotypes, has immunologic and water transport functions but no clear pathophysiologic role in CRS.

Smaller studies, analyzing more narrow phenotypes have also utilized microarray technology. Anand et al., analyzed tissue from non-allergic, CRSsNP patients compared to controls and

Table 4.2.3. Microarray studies.

Author, year, ref.	Gene expression
Fritz 2003 [1057]	Mammaglobulin elevated in polyps
Benson 2004 [1058]	Uterogloblin up-regulated, β-defensin down-regulated in polyps treated with steroids
Liu 2004 [1059]	Statherin, PIP, lactoferrin, DMBT1 increased in polyps; uteroglobin decreased in polyps
Stankovic 2008 [1029]	Periostin, met protoncogene increased in ASA and CRSwNP; PIP decreased in ASA and CRSwNP
Rho 2006 [1061]	HGF and HGFR increased in CRSwNP
Anand 2006 [1064]	IL-6, IL-12A, IL-13, TNF-α increased in CRSsNP
Wang 2006 [1065]	IL-17and IL-17R increased in polyps
Figueiredo 2007 [1067]	IL-5 increased in polyps, TGF-β increased in inflamed mucosa
Payne 2008 [1017]	IL-4, IL-13, IFN-γ down-regulated in polyps; IL-6, IL-8, SCF, HIF-1X up-regulated in polyps
Wu 2009 [1069]	CCL20 increased in polyps
Rostkowska-Nadolska 2011 [1070]	IL-8, MMP-10, NOS2A, ALOX15 increased in polyps; ALOX12, LTF, DMBT1 decreased in polyps

ASA, aspirin-sensitive polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; DMBT1, deleted in malignant brain tumor protein 1; HIF-1α, hypoxia inducible factor 1α; IFN-γ, interferon-gamma; PIP, prolactin-induced protein; SCF, stem cell factor; TGF-β, transforming growth factor beta 1;

demonstrated increased expression of IL-6, IL-12A, IL-13 and TNF-α in disease [1064]. Wang et al., compared Asian polyps with normal tissue and noted increased expression of IL-17 and IL-17R in the CRSwNP patients [1065]. Lee et al., compared polyps and control mucosa, with results that generally concurred with the findings of Stankovic et al. [1066]. Orlandi et al., compared classic AFS patients and eosinophilic mucin rhinosinusitis patients (EMRS) [730]. The 2 groups differed only in the ability to identify fungi by routine histology or culture and gene expression profiles demonstrated marked similarities to each other as opposed to dramatic differences to controls. Figueiredo et al., compared polyp tissue and surrounding non-polypoid tissue from non-atopic patients, with control tissues. Results indicated increased IL-5 expression in the polyps and increased TGF-β expression in the adjacent inflamed mucosa [1067]. A study by Bolger et al., demonstrated that systemic glucocorticoids decreased expression of several chemokine and leukotriene receptor genes [1068]. A small study by Payne et al., focused on non-eosinphilic polyps, demonstrating significant down regulation of IL-4, IL-13 and IFN-γ with up-regulation of IL-6, IL-8, SCF (Stem Cell Factor) and hypoxia inducible factor 1α (HIF-1α) in polyps versus control tissues [1017]. These results were interpreted to suggest that NE polyps have a distinct pathogenesis. A later study by Wu et al. comparing atopic Asian polyps to both normal tissue and AR tissue revealed significantly increased expression of CCL20 in the polyp cohort [1069]. Lastly, a very recent study comparing nasal polyps and control tissue demonstrated significantly increased expression of IL-8, MMP10, NOS2A and ALOX15 in polyps; decreased expression of ALOX12, LTF and DMBT1 was also seen [1070].

The results of these studies reveal substantial differences, despite apparent similarities in clinical phenotypes in many cases. As a specific example comparing two of the largest studies, results from Liu et al.[1059], demonstrated that statherin, PIP, lactoferrin and DMBT1 were elevated while uteroglobulin was decreased. In contrast, Stankovic et al.[1029], reported that statherin, PIP, lactoferrin and DMBT1 were decreased and uteroglobulin was unchanged. Variations in patient selection, experimental technique, sample size and pre-operative treatment account, at least in part, for differences. Despite enormous promise, the application of microarray technology has thus far failed to result in any major breakthrough in our understanding of CRS.

4.3. Diagnosis

4.3.1. Summary

A range of diagnostic tests is available to validate the clinical symptoms and signs of rhinosinusitis. However, for the majority of patients, the diagnosis is made in primary care based on symptoms alone. Objective investigations exist to corroborate the diagnosis, notably endoscopy and CT scanning which can be semi-quantitatively scored to assist in the stratification of disease and its response to therapy. Additional tests may help in the differential diagnosis of aetiological and predisposing factors but some remain the preserve of tertiary research facilities.

4.3.2. Assessment of rhinosinusitis symptoms

4.3.2.1. Symptoms of rhinosinusitis

Subjective assessment of rhinosinusitis is based on symptoms:

- nasal blockage, congestion or stuffiness;
- nasal discharge or postnasal drip, often mucopurulent;
- facial pain or pressure, headache, and
- reduction/loss of smell.

Besides these local symptoms, there are distant and general symptoms. Distant symptoms are pharyngeal, laryngeal and tracheal irritation causing sore throat, dysphonia and cough, whereas general symptoms include drowsiness, malaise and fever. Individual variations of these general symptom patterns are many [235-239, 1071].

The symptoms are principally the same in acute (ARS) and chronic rhinosinusitis with and without nasal polyposis (CRSw/ sNP), but the symptom pattern and intensity may vary. Acute forms of infections have usually more distinct and often more severe symptoms.

4.3.3. Diagnosis of ARS

Acute rhinosinusitis in adults is defined as a sudden onset of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/ posterior nasal drip):
± facial pain/pressure,
± reduction or loss of smell
for <12 weeks;

This may be supported by endoscopic signs of purulent discharge from the middle meatus, oedema/ mucosal obstruction primarily in the middle meatus
Imaging is rarely performed except in severe/complicated cases

4.3.4. Diagnosis of CRS

Chronic rhinosinusitis, with or without nasal polyps in adults is defined as:

- inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
- ± facial pain/pressure
- ± reduction or loss of smell

for ≥12 weeks

This should be supported by demonstrable disease
Either endoscopic signs of:

- nasal polyps, and/or
- mucopurulent discharge primarily from middle meatus and/or
- oedema/mucosal obstruction primarily in middle meatus

and/or

- CT changes:
- mucosal changes within the ostiomeatal complex and/or sinuses

Using this symptomatic definition [8], the GA2LEN study has demonstrated significant variation in the prevalence of self-reported CRS across Europe, with a mean of 10.9% of participants, but a range of 6.9% (Brandenburg, Helsinki) to 27.1 (Coimbra) [12]. As a percentage of EP3OS-defined CRS patients, the prevalence of component symptoms of CRS was 83.7% blocked nose, 63.6% nasal discharge, 64.7% pain or pressure, and 48.5% reduced sense of smell.

It is appropriate that the definition is symptom based, as it is this that drives patients to seek medical care for their CRS. However, the presence of supporting findings is important to exclude differential diagnoses. A recent study of 125 patients with CRS based on symptoms found 40% had no radiological evidence of disease on CT scan [1072]. In a subset of the GA2LEN study [11], 61.7% of symptom-positive subjects had a positive endoscopy, while 38.0% of symptom negative subjects had a positive endoscopy. Symptom-based CRS was significantly associated with a positive endoscopy (OR 2.62: 95% CI 1.57 – 4.39, p<0.001).

Symptoms remain the mainstay of diagnosis in primary care

In a group of patients meeting the 1997 Rhinosinusitis Task Force (RSTF) definition [523] of chronic rhinosinusitis (≥3 symptoms from a defined list, with severity rating of>5/10) were subjected to same-day endoscopy and CT scanning, seventeen (22%) of 78 patients had positive endoscopic and CT results [1073]. There were 20 (26%) of 78 patients with negative endoscopic and positive CT results. Six (8%) patients had positive endoscopic and negative CT results, and 35 (45%) had negative endoscopic and negative CT results. Thus, only 55% of symptom-positive CRS had positive supporting findings. The lower rates of positive endoscopy in this series may reflect the less strict symptom criteria used in the study, including 'minor' symptoms such as headache, fatigue and cough within the definition. The sensitivity of endoscopy was rather low (46%), but the positive and negative predictive values indicating the proportion of patients with and without disease was better, at 74% and 64% respectively.
Since this study, new guidelines have been issued by the AAO-HNS, with diagnostic criteria broadly in line with the EP^{3}OS criteria above. Bhattacharya et al repeated the validation study in a group of 202 patients, of which 178 met the symptomatic criteria. Of the symptom positive group 50.6% had neither positive changes on CT nor positi7ve endoscopy, while of the symptom negative group, 45.8% had positive CT or endoscopy [1074]. Therefore, using the findings of disease on either CT or endoscopy as the 'gold standard', symptoms alone have a sensitivity of 89%, specificity of 12%, PPV of 49% and NPV of 54%. It is notable that 31% of patients failing to meet symptom or endoscopic criteria had positive CT scans (LM≥4).

4.3.5. Symptoms reported in CRS

An overlap of symptoms with ARS, those of chronic rhinosinusitis are typically of lesser intensity. In addition to the diagnostic symptoms listed above, there are several minor symptoms including ear pain or pressure, dizziness, halitosis, dental pain, distant and general symptoms including nasal, pharyngeal, laryngeal and tracheal irritation, dysphonia and

cough, drowsiness, malaise and sleep disturbance, presenting in numerous combinations [235, 239].

There is a surprising paucity of epidemiological studies reporting symptoms in CRS. Most studies utilise a questionnaire asking patients to rate the severity of specific symptoms, thus encouraging patients to report only on those listed, and to report symptoms that they might not have done so if asked to provide a list of symptoms without guidance. Consequently, different patterns are reported in the published literature, depending on the questionnaire utilised in the study. For example, in a study using the 'Cologne questionnaire', the most commonly reported symptoms of CRS were nasal obstruction (92%), postnasal drip (87%) and 'dry upper respiratory tract syndrome' (68%) [239]. Another study asking patients to rate the severity of symptoms included in the RSTF diagnostic criteria reports nasal obstruction (84%), postnasal drip (82%), and facial congestion (79%) as the most prevalent [1075].

Nasal obstruction is one of the most commonly reported symptoms of CRS. It consists of 3 main components; congestion due to dilation of the venous sinusoids as a result of inflammation and oedema, nasal fibrosis and nasal polyposis, and may only be partly reversible by topical decongestant.

Nasal discharge may be anterior or posterior, and may vary greatly in composition. Patients may report profuse watery discharge or thick purulent secretions. Facial pain is perhaps one of the most variable symptoms, with reported prevalence in patients with CRS ranging from 18 % [1076] – 77.9% [1075]. In a large longitudinal study, diagnosis of CRS is associated with a ninefold increased risk of reporting chronic headache compared with the general population, and symptoms were significantly improved after treatment with nasal surgery and nasal corticosteroids [1077]. Facial pain and it's differential diagnosis is discussed in more detail in section 4d. Olfactory disturbance is common, due to physical prevention of odorants reaching the olfactory cleft, and oedema in this area. A recent population-based epidemiological study found that a history of nasal polyps was a significant risk factor for olfactory impairment (OR = 2.33, 95% CI, 1.13–4.59) [1078]. In a study of 367 patients [1079] with a diagnosis of CRS, the presence of polyposis was associated with significantly increased risk of hyposmia (OR 2.4, 95% CI 1.3-4.2, P = 0.003) and anosmia (OR 13.2, 95% CI 5.7-30.7, P < 0.001) compared with non-polyp CRS. The pathophysiology behind these and other symptoms found in CRS is discussed elsewhere [75].

Sleep impairment is a significant problem for patients with inflammatory disorders of the upper respiratory tract, such as CRSsNP and CRSwNP. Nasal congestion is associated with sleep-disordered breathing and is thought to be a key cause of sleep impairment. Poor sleep can lead to fatigue, daytime somnolence, impaired daytime functioning as reflected in lower levels of productivity at work or school, and a reduced quality of life [483, 1080, 1081]. Treatment with intranasal corticosteroids has been shown to reduce nasal congestion in inflammatory disorders of the upper respiratory tract. There is a growing amount of evidence that a reduction in congestion with intranasal corticosteroids is associated with improved sleep, reduced daytime sleepiness, and enhanced patient quality of life [1082].

Serrano et al. [547] showed in a population-based, cross-sectional, case-control study that NP patients have a two-fold higher risk of suffering sleep disturbance. A quarter of NP patients (24.6 per cent) reported a feeling of general discomfort due to their nasal condition, during the day as well as the night in most of these cases (61.2 per cent).

4.3.6. Assessment of symptom severity

The severity of the overall symptoms of CRS can be estimated using many different grading tools.

- recorded as such: no symptom, mild, moderate or severe
- recorded as numbers: from 0 to 5 or as many degrees as needed;
- recorded as VAS score on a line giving a measurable continuum (0 – 10 cm).

Both the strength or degree and duration of symptoms should be assessed. The duration of the symptoms is evaluated as symptomatic or symptom-free moments in given time periods, i.e. as hours during the recording period or as day per week. "No symptom" can be regarded as a consistent finding in most studies.

A validation study has shown 'mild disease' to be defined as a VAS score of 0-3 inclusive, moderate as >3-7 inclusive, and severe as ≥7. In general, overall quality of life is more likely to be affected with scores of 5 or more [1083].

In addition the severity of individual symptoms can be measured, including different aspects of quality of life. This is done using validated questionnaires, described below.

Endoscopy and CT scanning corroborate the clinical symptoms and signs

4.3.7. Examination

4.3.7.1. Anterior rhinoscopy

Anterior rhinoscopy alone is of limited value, but nonetheless, remains the first step in examining a patient with these diseases.

4.3.7.2 Nasal Endoscopy

This may be performed without and with decongestion and semi-quantitative scores for polyps, oedema, discharge, crusting and scarring (post-operatively) can be obtained at baseline and at regular intervals following therapeutic interventions eg at 3, 6, 9 and 12 months [5] (table 4.3.1). Nasal endoscopy affords significantly better illumination and visualization compared to anterior rhinoscopy for examination of the middle and superior meati as well as the nasopharynx and mucociliary drainage pathways. Bhattacharyya et al. confirmed the added utility of nasal endoscopy in the diagnosis of chronic rhinosinusits [1074]. However, in post surgical CRS patients, nasal endoscopy does not necessarily correlate with symptoms [1084].

4.3.7.3. Nasal cytology, biopsy and bacteriology

Generally cytology has not proved a useful tool in diagnosis of rhinosinusitis although a formal biopsy may be indicated to exclude more sinister and severe conditions such as neoplasia and the vasculitides. Techniques include lavage with 0.9% saline, microsuction, nasal brushes, disposable scrapers with a cupped end or small mucosal samples taken with Gerritsma forceps. These are largely used for clinical research. However, a correlation has been shown between the cellular content obtained by middle meatal and broncho-alveolar lavage in patients with CRS and asthma [1086].

Swabs, aspirates, lavages and biopsies may also be used to obtain microbiological samples. Several microbiology studies [263-267] (Evidence Level IIb) have shown a reasonable correlation between specimens taken from the middle meatus under endoscopic control and proof puncture of the maxillary sinus or swabs from the ethmoid taken per-operatively leading to the possibility of microbiological confirmation of both the pathogen and its response to therapy (Table 4.3.2). A meta-analysis showed anccuracy of 87% with a lower end confidence level of 81.3% for the endoscopically directed middle meatal culture when compared with maxillary sinus taps in acute maxillary sinus infection [248].

More sophisticated techniques exist for the detection and identification of bacteria including immunohistochemistry and the detection and amplification of microbial RNA and DNA. Fluorescent in situ hybridization (FISH) and confocal microscopy are utilised to demonstrate bacteria in biofilms [582].

4.3.7.4. Sinus Transillumination

This technique was advocated in the 1970's as an inexpensive and efficacious screening modality for sinus pathology. However, the insensitivity and unspecificity makes it unreliable for the diagnosis of rhinosinusitis [1]. More recently with the introduction of balloon sinuplastly, transillumination has been used for confirmation of proper placement of guide wires.

4.3.7.5. Imaging

The plain sinus x-ray, despite low cost and availability has limited usefulness for the diagnosis of rhinosinusitis due to underestimation of bony and soft tissue pathology compared to computed tomography (CT) and magnetic resonance imaging (MRI).

CT scanning is the modality of choice for the paranasal sinuses due to optimal display of air bone and soft tissue. However, it should not be regarded as the primary step in the diagnosis of the condition, except where there are unilateral signs and symptoms or other sinister signs, but rather corroborates history and endoscopic examination after failure of medical therapy. Much attention has recently been given to the radiation exposure associated with CT scans, the use of which have increased 20 fold in the last 30 years [1088, 1089]. Thus several protocols have been developed to decrease radiation exposure with comparable or improved resolution [1090, 1091]. Cone beam technology is becoming increasingly available and is associated with lower radiation exposure than conventional imaging. A study comparing cone beam CT (CBCT) with multislice CT (MSCT) for the sinuses in an anthropomorphic phantom model showed the effective dose of CBCT was 30uSv as compared with 200uSv and 1400uSv for low dose and standard protocols using MSCT [1092].
MRI does not have the radiation risk and has improved soft tissue definition over CT scan with an ability to differentiate between soft tissue masses and retained/obstructed secretions. Thus, MRI compliments CT in the workup of suspected neoplastic processes. Comparison of staging accuracy of sinonasal disease between CT and MRI demonstrates close correlation between the two modalities [1093].

It should be noted that incidental abnormalities are found on scanning in up to a fifth of the 'normal' population [1]. Thus, in the absence of symptoms, diagnosis of CRS based on radiology alone is inappropriate.

A range of staging systems based on CT scanning have been described but the most commonly used is the Lund-Mackay system which is based on localization with points given for degree of opacification: 0 = normal, 1 = partial opacification, 2 = total opacification. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The osteomeatal complex is graded as 0 = not occluded, or 2 = occluded deriving a maximum score of 12 per side [1094]. This scoring system has been validated in several studies [1095, 1096].

Table 4.3.1. Endoscopic appearance scores [1071, 1085].

Characteristic	Baseline	3 mo	6 mo	1 y	2 y
Polyp left (0,1,2,3)	-	-	-	-	-
Polyp, right (0,1,2,3)	-	-	-	-	-
Oedema, left (0,1,2,)	-	-	-	-	-
Oedema, right (0,1,2,)	-	-	-	-	-
Discharge, right (0,1,2)	-	-	-	-	-
Postoperative scores to be used for outcome assessment only:					
Scarring, left (0.1,2)	-	-	-	-	-
Scarring, right (0.1,2)	-	-	-	-	-
Crusting, left (0,1,2)	-	-	-	-	-
Crusting, right (0,1,2)	-	-	-	-	-
Total points	-	-	-	-	-

Polyp:

0-Absence of polyps;

1-polyps in middle meatus only;

2-polyps beyond middle meatus but not blocking the nose completely;

3-polyps completely obstructing the nose.

Oedema: 0-absent; 1-mild; 2-severe.

Discharge: 0-no discharge; 1-clear, thin discharge; 2-thick, purulent discharge.

Scarring: 0-absent; 1-mild; 2-severe.

Crusting: 0-absent; 1-mild; 2-severe.

Table 4.3.2. Bacteriology of Rhinosinusitis; Correlation of middle meatus versus maxillary sinus.

Author, year, ref.	No of Samples	Type of Rhinosinusitis	Technique	Concordance
Gold & Tami, 1997 [264]	21	Chronic	Endoscopic tap (MM) v maxillary aspiration during ESS	85.7%
Klossek et al, 1998 [263]	65	Chronic	Endoscoic swab (MM) v maxillary aspiration during ESS	73.8%
Vogan et al, 2000 [265]	16	Acute	Endoscoic swab (MM) v maxillary sinus tap	93%
Casiano et al, 2001 [266]	29	Acute (Intensive Care)	Endoscopic tissue culture (MM) v maxillary sinus tap	60%
Talbot et al, 2001 [271]	46	Acute	Endoscopic swab (MM) v maxillary sinus tap	90.6%
Ozcan et al , 2002 [1087]	193	Chronic	Endoscopic swab (MM) v ethmoid swab during ESS	91.6%
Joniau et al 2005 [267]	26	Acute	Endoscopic swab (MM) v Maxillary sinus tap	88.5%

MM: middle meatus; ESS: endoscopic sinus surgery

4.3.8. Additional assessment tools

A wide range of other diagnostic tests are available to assist with the differential diagnosis and to define predisposing and aetiological factors but many are only available in research departments

4.3.8.1. Mucociliary function

4.3.8.1.1. Nasomucociliary clearance

The use of saccharin, dye or radioactive particles to measure mucociliary transit time has been available for nearly thirty years [1097-1099]. It allows one to recognize early alterations of sinosinusal homeostasis. Although a crude measure, it has the advantage of considering the entire mucociliary system and is useful if normal (< 35 minutes). However, if it is prolonged, it does not distinguish between primary or secondary causes of ciliary dysfunction.

Nasomucociliary clearance has also been measured using a mixture of vegetable charcoal powder and 3% saccharin to demonstrate a delay in patients with CRS as compared to normal, hypertrophied inferior turbinates and septal deviation [1100].

4.3.8.1.2. Ciliary beat frequency

Specific measurements of ciliary activity using a phase contrast microscope with photometric cell [1101, 1102] have been used in a number of studies to evaluate therapeutic success [1103, 1104] (Evidence Level IIb). The normal range from the inferior turbinate is over 8Hz but these techniques are available in only a few centres to which those suspected of primary ciliary dyskinesia are referred. The final gold standard of ciliary function involves culture techniques for 6 weeks [1105].

4.3.8.1.3. Electron microscopy

This may be used to confirm the presence of specific inherited disorders of the cilia as in primary ciliary dyskinesia [1106].

4.3.8.1.4. Nitric oxide

This metabolite found in the upper and lower respiratory tract is a sensitive indicator of the presence of inflammation and ciliary dysfunction, being high with inflammation and low in ciliary dyskinesia It requires little patient co-operation and is quick and easy to perform using chemiluminescence, but the availability of measuring equipment at present limits its use. The majority of nitric oxide is made in the sinuses (chest < 20 ppb, nose 400-900 ppb, sinuses 20 25 ppm) using an LR 2000 Logan Sinclair nitric oxide gas analyser (values may differ with different machines). Less than 100ppb from the upper and <10ppb from the lower respiratory tract would be highly suspicious of PCD. However, whilst very low levels in the nose can indicate primary ciliary dyskinesia, they may also be due to significant sinus obstruction eg severe nasal polyposis [849]. Conversely elevated levels suggest nasal inflammation but ostiomeatal patency [849] [Evidence Level IIb]. It can be used, as an outcome measure after therapy [16, 1107] (Evidence Level IIa) but variable baseline levels limit its value in the diagnosis and management of ARS and CRS other than to exclude inherited defects in mucociliary clearance.

4.3.8.2. Nasal airway assessment

4.3.8.2.1. Nasal inspiratory peak flow

This inexpensive, quick and easy test is a useful estimate of airflow which can be performed at home as well as in the hospital setting. However, it measures both sides together and has little direct role in the assessment of chronic rhinosinusitis. It could be used to assess gross reduction in nasal polyposis and compares well with rhinomanometry [1108, 1109] (Evidence Level IIb). However, peak nasal inspiratory flow (PNIF) does appear to correlate with nasal obstruction symptoms [1110]. Normative data is now available in an adult Caucasian population [1111] and for children and adolescents in Brazil and the Netherlands [1112, 1113]. Expiratory peak flow is less often used as mucus is expelled into the mask and the technique may be associated with eustachian dysfunction.

There is a relationship between NIPF and oral pulmonary expiratory flow (PEF) in that the greater the value of PEF, the greater the NIPF [1114]. A minimally clinically important difference of 20L/min has been shown for NIPF [1115] (Evidence Level IIa).

4.3.8.2.2. Rhinomanometry (active anterior and posterior)

The measurement of nasal airway resistance by assessing nasal flow at a constant pressure is again of limited usefulness in chronic rhinosinusitis and nasal polyposis but can be useful in confirming that improvement in nasal congestion is the result of reduction in inflammation in the middle meatus rather than mechanical obstruction [1103] (Evidence Level IIb). The long term mean coefficient of variation (CV) for test-retest over a five month period has been shown to be 27% compared to a short-term CV of 7-17% within one hour which limits its usefulness [1116] (Evidence Level IIa).

4.3.8.2.3. Acoustic rhinometry

The distortion of a sound wave by nasal topography allows quantification of area at fixed points in the nose from which volume may be derived. Standardisation of the technique has been recommended [1117] and it is a useful test of nasal patency especially in children as little active co-operation is required [1118-1120]. It can be used to demonstrate subtle changes, both as a result of medical and surgical intervention, comparable to or better than CT scanning [16, 1109, 1121-1123] (Evidence Level IIa).

4.3.8.2.4. Rhinostereometry.

This also measures subtle changes in mucosal swelling, largely in the inferior turbinates [1124, 1125] (Evidence Level IIb) and is therefore not directly applicable to assessment of chronic rhinosinusitis and nasal polyposis.

4.3.8.3. Olfaction

4.3.8.3.1. Threshold Testing

Fluctuations in the sense of smell are associated with chronic rhinosinusitis. This may due to a conductive loss secondary to obstruction [1110], or to degenerative alterations in the olfactory mucosa due to the disease or its treatment eg. repeated nasal surgery [1]. Recently, transgenic technology has also demonstrated that local inflammation within the olfactory epithelium can generate olfactory loss [1126].

The estimation of olfactory thresholds by the presentation of serial dilutions of pure odourants such as pm carbinol have been used in a number of studies [1104, 1121, 1127-1129] (Evidence Levels IIb, III).

4.3.8.3.2. Other quantitative olfactory testing

Scratch and sniff test using patches impregnated with micro-encapsulated odorants are available [256] and have been utilised in studies of both chronic rhinosinusitis and nasal polyposis [1109]. A cruder screening test, the Zurich Smell Diskette test may also be used and has the advantage of pictorial representation of the items [1130, 1131]. Also on a national footing, the Barcelona Smell Test has been developed, comprising 24 odorants and has been compared with the Zurich Smell Diskette Test [245]. More complex tests exist [1132] e.g. 'Sniff 'n' sticks' which combines threshold, discrimination and odour identification and which can be used to perform unilateral testing [1133]. A combined supra-threshold detection and identification test has been devised as a cross-cultural tool in the European population [1134], the results of which are presented in an appendix in EPOS2007 [1] (Evidence Level III).

Sources of some commercially available and validated olfactory tests are also mentioned in the appendix [1].

4.3.8.4. Aspirin and other challenges

Objective experiments to differentiate patient groups according to severity or aetiology of rhinosinusitis have been done by provocation with histamine or metacholine [1135, 1136] which test mucosal hyper-reactivity. The tests can differentiate sub-populations with statistical significance, but because of considerable overlap of results, the tests have not achieved the equivalent position as the corresponding tests in asthma diagnosis.

Diagnosis of aspirin hypersensitivity is important as it will provide the patient with a long list of common drugs that must not be taken to avoid the risk of a severe reaction. It diagnoses a particular type of asthma and sinonasal disease and allows the choice of a specific therapy ie aspirin desensitisation.

The oral aspirin challenge test was introduced to clinical practice in the early 1970s [1137] and since then has been validated [1138-1140]. An inhalation test was introduced in 1977, which is safer and faster to perform than the oral one though less sensitive [1141-1143]. Unlike the oral challenge, it does not produce systemic reactions. Nasal challenge was introduced in the 1980s [1144, 1145] and is recommended for patients with predominantly nasal symptoms or those in whom oral or inhaled tests are contraindicated because of the asthma severity. A negative nasal challenge should be followed by oral challenge. Lysine aspirin, the truly soluble form of aspirin must be used for both respiratory routes. Test procedures have been reviewed in detail [1146] and the sensitivity and specificity of the tests are shown in Table 4.3.3. The sensitivity of nasal challenge has been shown to be increased by prolonging the detection time from 2 to 3 hours [1147]. The challenges must be performed under medical supervision and results measured with symptoms, acoustic rhinometry or anterior rhinomanometry and pulmonary function.

4.3.9. Laboratory assesments – C-reactive protein (CRP)

Known since 1930, C-reactive protein is part of the acute phase response proteins. Its principal properties are short half-life (6-8 h), rapid response (within 6 hours) and high levels (x500 normal) after injury. It activates the classical complement pathway, leading to bacterial opsonization. Studies have shown that the CRP value is useful in the diagnosis of bacterial infections [1148]. However, among patients suspected of an infectious disease, CRP levels up to 100 mg/l are compatible with all types of infections (bacterial, viral, fungal, and protozoal) [1149].

Sequential CRP measurements will have greater diagnostic value than a single measurement and changes of the CRP values often reflect the clinical course. When used in general practice the diagnostic value of CRP is found to be high in adults with pneumonia, sinusitis and tonsillitis. Measurement of CRP is an important diagnostic test but the analysis should not stand-alone but be evaluated together with the patient's history and clinical examination [1150].

CRP is most reliably used for exclusion of bacterial infection: two values less than 10 mg/l and 8 12 hours apart can be taken to

Table 4.3.3. Diagnosis of aspirin sensitivity.

History ±	Challenge sensitivity (%)	Specificity (%)
Oral	77	93
Bronchial	77	93
Nasal	73	94

exclude bacterial infection [1149] and is now available in general practice at the point-of-care [249].

A range of other blood tests may be undertaken in specific cases as part of the differential diagnosis. This may include full blood count including eosinophils, ESR, evaluation of renal, liver and thyroid function, humoral immunity markers (immunoglobulins, IgG subclasses, IgE and IgG to Aspergillis, specific antibody levels to tetanus, haemophilus, pneumococcus) and response to immunization if low, cellular immunity markers (T and B cell and ratios), HIV, ACE and ANCA [1151].

4.3.10. Validation of subjective symptoms assessment

4.3.10.1. Nasal obstruction

Validation of subjective assessment of nasal obstruction or stuffiness has been done by studying the relationship between subjective and objective evaluation methods for functional nasal obstruction. However, the patient's interpretation of nasal blockage has been shown to vary from true mechanical obstruction of airflow to the sensation of fullness in the midface [1152]. Generally the subjective sensation of nasal obstruction and rhinomanometric or nasal peak flow evaluations show a good intra-individual correlation in a number of studies considering normal controls, patients with structural abnormalities, hyper-reactivity or infective rhinitis [1153-1158]. However, there are also some studies where this correlation is not seen [1159] or the correlation was poor [1160-1162].
The inter-patient variation in subjective scoring suggests that every nose is "individually calibrated", which makes inter-patient comparisons less reliable but still significant [1153, 1155].

Subjective nasal obstruction correlates better with objective functional measurements of nasal airflow resistance (rinomanometry, peak flow) than with measurements of nasal cavity width, such as acoustic rhinometry [1158, 1163].
Rhinomanometry has been shown to correlate with subjective symptom scoring with and without decongestion [1164]. In healthy individuals there is a poor correlation between acoustic rhinometry and subjective nasal obstruction scores, though these are better in congested subjects [1165].
Nasal obstruction can also be assessed objectively by tests using personal nasal peak flow instruments, inspiratory or expiratory, which patients can take home or to their work place and do measurements at any desired time intervals.
Subjective assessment of nasal obstruction is a well-validated criterion.

4.3.10.2. Nasal discharge

Techniques for objective assessment of nasal discharge are not as good as for nasal obstruction: counting the nose blowings in a diary card or using a new handkerchief from a counted reservoir for each blow and possibly collecting the used handkerchieves in plastic bags for weighing have been used in acute infective rhinitis [1166] and in "autonomic (previously termed vasomotor) rhinitis" [1167].
Validating correlation studies between "objective" discharge measures (collecting and measuring amount or weight of nasal secretion as drops, by suction, or using hygroscopic paper strips etc) and subjective scoring of nasal discharge or postnasal drip has not been done.

4.3.10.3. Smell abnormalities

Fluctuations in the sense of smell are associated with chronic rhinosinusitis. This may be due to mucosal obstruction of the olfactory niche (conductive loss) and/or degenerative alterations in the olfactory mucosa due to the disease or its treatment eg repeated nasal surgery.
Subjective scoring of olfaction is a commonly used assessment method. In validating clinical settings subjective scores have been found to correlate significantly to objective olfactory threshold and qualitative tests in normal population, rhinosinusitis with and without nasal polyps and other disease conditions [243-245, 1168-1172].

4.3.10.4. Facial pain and pressure

Facial or dental pain, especially unilateral, have been found to be predictors of acute maxillary sinusitis with fluid retention in patients with a suspicion of infection, when validated by maxillary antral aspiration [236] or paranasal sinus radiographs [1173]. The importance of facial pain as a cardinal sign of chronic rhinosinusitis has also been called into question (See section 4.4) [1174] where the symptoms are more diffuse and fluctuate rendering the clinical correlation of facial pain and pressure scorings against objective assessments unconvincing. In a study correlating symptoms with CT Lund-Mackay scores, patients presenting with facial pain as a primary symptom were more likely with a score of 0 or 1 (ie normal) on CT [1175, 1176]. Poor correlation between facial pain localisation and the affected paranasal sinus CT pathology in patients with supposed infection, both acute and chronic, has been reported [1177].
However, rhinosinusitis disease specific quality of life studies also include facial pain-related parameters, which have been validated [1178].

4.3.10. Correlation between patient-reported symptoms and objective measures

Several publications have demonstrated the lack of correlation between patient rates measures of symptom severity in chronic rhinosinusitis and objective measures, such as the radiological Lund-Mackay scoring system [1179-1182]. Similarly a recent systematic review has demonstrated no correlation between

sensation of nasal obstruction and measurements of cross-sectional airflow using rhinometry [1183].

The relationship between the biological burden of disease and symptoms is complex. Physiological variables can be profoundly abnormal in some asymptomatic patients, while others may report severe symptoms in the absence of change in biological markers of disease – for example a patient may present with severe symptoms of CRS in the face of minimal disease on cross-sectional imaging, while another may be virtually asymptomatic despite pansinusitis on CT. Studies in many other medical specialties demonstrate that patient reported measures of symptoms are poorly correlated with clinical measures. In studies of benign prostatic hypertrophy there was only a modest association between urodynamic indices of obstruction and obstructive symptoms [1184]. Studies of asthma and COPD have found little or no correlation between subjective dyspnoea and FEV1 [1185].

It is proposed that patients' symptoms and quality of life are the result of an interaction between many factors, in which biological or physiological variables are only a piece of the final jigsaw [1186]. Disease severity is modified by the interactions between many patient factors. For example, studies have shown the gender appears to modify symptom severity in sinonasal disease, with women reporting higher SNOT-20 [1187] scores than men for the same level of disease severity on cross sectional imaging. AERD, depression [1188] and ethnicity [1189] have also be shown to worsen baseline QOL in CRS. Cultural expectations, age, socio-economic status and additional co-morbidities are amongst other factors that may modify the impact of disease.
Clinicians probably overestimate the impact that measurable biological variables have on symptoms and functioning. It is perhaps not surprising that there should be little correlation between a patient-based symptom severity-scoring systems. The absence of correlation does not suggest that either patient rated or objective scores are invalid, but that they are measuring different aspects of the disease process, and therefore are useful adjuncts in outcome measurement.

For the majority of rhinological complaints where reducing the impact of symptoms on the quality of life of the patient is the primary aim of treatment, patient-rated measures are usually more useful in guiding treatment and measuring the resulting outcome. Clinician-rated measures may however provide more useful feedback to the surgeon in terms of technique. There are also occasions when clinician-rated measures are important to guide whether treatment is likely to be successful; and to confirm if the clinical aim is achieved.

4.4. Facial Pain

4.4.1. Summary

The majority of patients who present with facial pain and headaches believe they have 'sinus trouble'. There is an increasing awareness that neurological causes are responsible for a large proportion of patient's headache and facial pain. The vast majority of patients who present with a symmetrical frontal or temporal headache, sometimes with an occipital component, have tension type headache. Unilateral, episodic headaches are often vascular in origin. Rhinosinusitis rarely causes headache, let alone facial pain, except when there is an acute bacterial infection when the sinus in question cannot drain - and it is usually unilateral and severe. These patients usually have a history of a viral upper respiratory infection immediately before this and they have pyrexia with unilateral nasal obstruction. The vast majority of patients with acute rhinosinusitis respond to antibiotics. More than two episodes of genuine bacterial rhinosinusitis in one year should be investigated for evidence of poor immunity. Patients with chronic bacterial rhinosinusitis rarely have any pain unless the sinus ostia are blocked and their symptoms are similar to acute rhinosinusitis.

With the advent of nasal endoscopy and computerised tomography, along with the finding that many patients' symptoms of headache or facial pain persist after sinus surgery it has become apparent that many patient's symptoms are not due to their sinuses. It is also relevant that over 80% of patients with purulent secretions visible at nasal endoscopy have no headache or facial pain. Even if patients with intermittent symptoms of headache or facial pain, and who believe that it is due to infection, are asked to attend the clinic when they are symptomatic the majority are found not to have any evidence of infection and a neurological cause is responsible.
Over 90% of self-diagnosed and doctor-diagnosed sinus headaches meet the International Headache Society criteria for migraines and yet 60% receive an antibiotic prescription. Over 40% of migraine sufferers had at least one unilateral nasal symptom of congestion or rhinorrhoea or ocular lacrimation, redness or swelling during an attack, which can confuse the picture but these episodes do not last longer than 72 hours.
In cases of headache or facial pain secondary to genuine rhinosinusitis, there are usually endoscopic signs of disease, and these patients almost invariably have coexisting symptoms of nasal obstruction, hyposmia and/or a purulent nasal discharge. An interdisciplinary consensus group recently agreed that "the majority of sinus headaches can actually be classified as migraines" and that "unnecessary diagnostic studies, surgical interventions, and medical treatments are often the result of the inappropriate diagnosis of sinus headache".
Other unilateral, episodic headaches are also vascular in origin,

being hemicrania continua, cluster headache or paroxysmal hemicrania – although the latter two comprise more periorbital pain than headache. A relatively recently described condition, which affects about a third of patients with facial pain seen in ENT clinics, is midfacial segment pain. This is a version of tension-type headache that affects the midface and its features include a symmetrical sensation of pressure or tightness that can involve the areas of the nasion, under the bridge of the nose, either side of the nose, the peri- or retro-orbital regions, or across the cheeks. The symptoms of tension type headache often coexist. There may be hyperaesthesia of the skin and soft tissues over the affected area. There are no consistent exacerbating or relieving factors. There are no nasal symptoms (note that approximately 20% of most populations have intermittent or persistent allergic rhinitis, which may occur incidentally in this condition). The majority of patients with this condition respond to low dose amitriptyline, but usually require up to 6 weeks of 10 mg (occasionally 20 mg) at night before it works. Amitriptyline should then be continued for 6 months before stopping it, and the 20% whose symptoms return when they stop it need to restart it if the pain returns.
Patients with facial pain who have no objective evidence of sinus disease (endoscopy negative) are very unlikely to be helped by nasal medical or surgical treatment. In these patients, other diagnoses should be considered and an appropriate medical treatment tried.
A comprehensive examination including nasendoscopy is highly desirable if medical nasal treatment directed at sinusitis has failed in order to confirm or refute the diagnosis of sinusitis.

4.4.2.Introduction

Otorhinolaryngologists see many patients with facial pain. They have the equipment to help diagnose whose facial pain is due to paranasal sinus disease or, as important, whose is not. This is vital as so many patients and their physicians mistakenly attribute their pain as being due to rhinosinusitis, when this is not the case. In the group of people who are referred to an ORL surgeon with a presumptive diagnosis of rhinosinusitis as the cause for their facial pain, only 1 in 8 patients are found to have pain attributable to their sinus disease [1076]. "Significant caution is needed when considering surgery in those patients (with facial pain) because of high long-term failure rates and the eventual identification of other causes of the pain in many cases" [1190]. This does not mean that rhinosinusitis does not cause facial pain, rather that caution is needed before making the link to this diagnosis.

Facial pain without any other nasal symptoms is unlikely to be due to rhinosinusitis.

4.4.3. Sinogenic facial pain

Before describing the characteristics of facial pain secondary to sinusitis it is worthy of note that over 80% of patients with purulent secretions visible at nasal endoscopy have no facial pain and those that do have it during an acute exacerbation [1191] and the majority of patients with nasal polyposis do not have pain [1192]. Children with chronic rhinosinusitis very rarely complain of facial pain, even in the presence of florid purulent secretions. Also of note is the fact that a significant proportion of patients in several series have persisting facial pain after endoscopic sinus surgery [1174, 1193]. In other words not only does chronic rhinosinusitis not usually cause facial pain but facial pain is not synonymous with rhinosinusitis. Interestingly the IHS (International Headache Society) classification says "chronic rhinosinusitis is not validated as a cause of headache or facial pain unless relapsing into an acute stage" [1194].

4.4.3.1. Bacterial rhinosinusitis

Acute bacterial rhinosinusitis usually follows an acute viral upper respiratory tract infection and if there is pain it is usually unilateral, severe, associated with pyrexia in about 50% and they have nasal obstruction. In maxillary sinusitis unilateral facial and dental pain are good predictors of true infection and this has been validated in studies using maxillary sinus aspiration [236] (Evidence Level III). This differs from chronic rhinosinusitis where there is a poor correlation between the site of facial pain and evidence of sinus pathology [1177, 1195] (Evidence Level III). An increase in the severity of pain on bending forward has traditionally been thought to be diagnostic of sinusitis but this is non-specific and it can occur in many other types of facial pain.

Coexisting nasal obstruction and/or clear rhinorrhoea can occur along with various types of vascular facial pain but these are normally short lived and rarely last longer than 48 hours.

The key points in the history of sinus related pain are an exacerbation of pain during an upper respiratory tract infection, an association with rhinological symptoms, worse when flying or skiing and a response to antibiotic medical treatment. It is important to realise that many types of facial pain are vascular in origin and last less than 72 hours so that a patient with this type of pain might presume that their pain has responded to an antibiotic when it would have resolved within this time frame in any event. A good history is vital in arriving at a correct diagnosis. There is no diagnostic investigation that can make a diagnosis in most neurological causes of facial pain other than analysing the patients' symptom complex in the light of their examination and response to treatment. "When patients present

with a headache and that they believe to be related to allergies and sinus problems, the clinical interview is often orientated by them in a way that supports their assumption" [1196].

Normal nasal endoscopy makes it very unlikely that a person's facial pain is due to rhinosinusitis

4.4.3.2. Examination

In acute frontal sinusitis the patient is often pyrexial and has tenderness on the medial side of the orbital floor under the supraorbital ridge where the frontal sinus is thinnest. Endoscopic examination shows marked hyperaemia of the nasal mucosa and purulent secretions are often visible. Acute sphenoiditis is uncommon and said to cause pain at the vertex of the head but pain can be referred to the temporal region or whole head. Facial swelling other than that caused by periorbital cellulitis, cavernous sinus thrombosis or subgaleal infection usually results from dental sepsis [440, 455, 1197] (Evidence level III). A normal nasal cavity, showing no evidence of middle meatal mucopus or inflammatory changes makes a diagnosis of sinogenic pain most unlikely, particularly if the patient is currently in pain or has had pain within the past few days. If the patient or surgeon are in doubt because the patient is asymptomatic on the day they are seen and their nasal endoscopy is normal in the clinic, it is often useful to review them and repeat the nasendoscopy when they have pain in order to clarify the diagnosis.

If a patient complains of constant symmetrical facial pain then midfacial segment pain should be excluded.

It is extremely rare for patients to have endoscopic evidence of inflammation or infection when they return with their pain. Even the presence of inflammatory changes or infection does not indicate with any certainty that the pain is sinogenic as it can occasionally be incidental [1076] (Evidence level III). If it is incidental this will become apparent as the patients pain will persist after their sinusitis has resolved.

Nasal endoscopy has better specificity than CT in diagnosing whether someone has rhinosinusitis.

4.4.3.3. Investigations

Plain sinus x-rays are very insensitive and non-specific in diagnosing chronic sinusitis The interpretation of changes on the sinuses with computerised tomography (CT) scans must also be treated with caution. Approximately 30% of asymptomatic patients will demonstrate mucosal thickening in one or more sinuses on CT scanning. The presence of this finding is certainly not an indication that pain is sinogenic in origin [277, 570, 1177, 1195, 1198, 1199] (Evidence level III) However, a clear CT makes it very unlikely there is any rhinosinusitis. In one study of 305 patients who met the American Academy Taskforce clinical criteria for chronic rhinosinusitis, of whom 154 had facial pain, they found that 60% had normal sinuses thereby questioning the diagnosis and selection criteria. More recent guidelines include endoscopic findings +/- CT changes to confirm the diagnosis [5, 1175] (Evidence level III). Care should be taken in making the diagnosis of recurrent acute sinusitis as this is very unusual and patients who have two or more bacterial sinus infections within 12 months should be investigated for an immune deficiency [560, 1200, 1201].

If a patient complains of recurrent acute rhinosinusitis, yet they are clear when you see them, ask them to return when they are symptomatic. Recurrent bacterial rhinosinusitis is rare. Most of these patients with recurrent facial pain have a vascular aetiology for their pain

4.4.3.4. Medical treatment

The majority of patients with bacterial sinusitis respond to treatment with antibiotics. The common pathogens are streptococcus pneumoniae and haemophilus influenzae and less commonly *S. aureus* and *M. catarrhalis* [296, 1202-1204] (Evidence level III), various streptococci, and a minority have anaerobes such as bacteroides and anaerobic streptococci. In chronic bacterial rhinosinusitis, defined by its persistence over 12 weeks [1205], anaerobes [1206] and staphylococci [639] (Evidence level III) are more prevalent.

4.4.3.5. Surgery

Surgery is normally effective in helping many symptoms in patients with genuine rhinosinusitis unresponsive to medical treatment but specific care is needed when the symptom of facial pain is concerned.An analysis of 10 series of endoscopic sinus surgery of 1,713 patients showed a mean improvement rate of 91%, taking a range of symptoms into account [1207] but this series does not specifically address the issue of facial pain. Many studies have looked at quality of life, or encompass a range of nasal symptoms and pathologies and do not provide a sufficient breakdown of the different symptoms to analyze the effect of surgery on facial pain [1208-1217]. Studies that have looked at symptoms of facial pain and pressure in sinusitis show that between 56-77% of patients who have facial pain are better after sinus surgery [1217, 1218] (Evidence level IIb). However, these studies they do not claim very good results in the complete resolution of facial pain. One study with a validated outcome score showed an improvement in facial pain and headache after endoscopic sinus surgery in patients with facial pain caused by sinusitis [1219] (Evidence level III). It is important to ensure that

the diagnosis of rhinosinusitis is correct before embarking on surgery.

4.4.3.6. Facial pain and CRS with nasal polyps (CRSwNP).

Chronic rhinosinusitis with or without clear evidence of a bacterial infection is often painless, except during an acute exacerbation precipitated by an upper respiratory tract infection or induced by barotrauma. CRSwNP patients rarely have facial pain, even with opaque sinuses on CT, unless there is an acute exacerbation with obstruction of the sinus ostia [1192] (Evidence level III).

4.4.3.7. Other diseases of the nose or paranasal sinuses that cause facial pain

Although tumours rarely present with facial pain, constant, progressive pain, particularly if associated with other suspicious symptoms or neurological signs should alert the clinician. A thorough examination and appropriate imaging is mandatory to exclude the possibility of a tumour.

Stretching of the arterial tree which, supplies the proximal portions of the cranial nerves and the dura within 1 cm of any venous sinus induces a headache but can cause facial pain. The supratentorial vessels and dura refer pain to the ophthalmic division of the trigeminal nerve. Infratentorial structures refer pain to the distribution of the glossopharyngeal nerve and vagus, along with the upper three cervical nerve dermatomes. Space-occupying lesions such as meningiomas, angiomas and intracerebral metastases can induce facial pain by irritation of the trigeminal nerve along its intracerebral course. Syringobulbia, syphilis and multiple sclerosis are rarer causes of central lesions, which may cause facial pain. Raised intracranial pressure produces a bursting headache, which is worse on coughing or straining and is associated with effortless vomiting. The fundi can show papilloedema in around a third of patients. Lesions in the posterior cranial fossa produce occipital and upper neck pain, while supratentorial lesions with raised intracranial pressure produce pain at the vertex or over the frontal and temporal region. Cerebrovascular accidents can cause such pain, but these symptoms may only present when the other more distressing signs and symptoms of a stroke are resolving. They are particularly severe when part of the thalamus has been infracted.

Carcinoma of the maxilla is uncommon. Patients unfortunately often present late when the disease has spread beyond the confines of the sinuses. Unilateral serosanguinous nasal discharge and obstruction is the most frequent presentation. Less common symptoms are infraorbital paraesthesiae, loose teeth or ill-fitting dentures, proptosis, deformity of the cheek, epiphora, nasal obstruction or epistaxis. Pain is usually a late feature. Occasionally adenoid cystic carcinoma can present with pain in the distribution of the trigeminal ganglion or its branches.

4.4.4. Non-sinogenic facial pain

4.4.4.1. General comments on the main categories of non-sinogenic facial pain

Only about 1 in 8 patients attending a rhinology clinic have pain that is attributable to rhinosinusitis [1076, 1289,1204]. (Evidence level III). The remainder of patients who have non-sinogenic pain have migraine or its variations, tension type headache/ midfacial segment pain, trigeminal-autonomic cephalgias, neuropathic pain or other specific neurological conditions. Clinical examination and diagnostic tests rarely help to make a diagnosis (rare exceptions include an MRI in multiple sclerosis or brainstem tumours, and PET scans can shown abnormalities in the hypothalamus in cluster headache). In facial pain a diagnosis is primarily made on the basis of the history and response to treatment. The following broad characteristics are used to categorise the main types of facial pain:

4.4.4.2. Migraine, Trigeminal-autonomic cephalgias, Cluster headache, Paroxysmal Hemicrania, SUNCT syndrome (short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)

Vascular pain of various types can be associated with autonomic rhinological symptoms such as nasal congestion and rhinorrhoea and this has lead to confusion in arriving at

Table 4.4.4. Characteristics of migraine without aura [1194].

Migraine without aura	
A	At least 5 attacks fulfilling B-D
B	Headache lasting 4-72 hours (untreated or unsuccessfully treated)
C	Headache has at least two of the following characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate to severe pain intensity 4. Aggravation by or causing avoidance of routine physical activity (eg walking or climbing stairs)
D	During headache, at least one of the following 1. Nausea and/or vomiting 2. Photophobia or phonophobia
E	Not attributable to another disorser
Migraine with aura	
A	At least two attacks fulfilling B
B	Migraine aura fulfilling criteria B and C for one of the subforms (1.2.1-1.2.6 or migraine without aura, childhood periodic syndromes that are commonly precursors of migraine, retinal migraine, complications of migraine, probable migraine).

a correct diagnosis as many patients understandably believe that these symptoms are synonymous with rhinosinusitis. The prevalence of trigeminal autonomic symptoms is approximately 27% [1220] (Evidence level III). Other causes of facial pain include atypical forms of migraine [1221-1224] cluster headache, paroxysmal hemicrania and atypical facial pain.

Migraine has been defined by the IHS [1194] as an episodic headache lasting 4-72 hours with certain distinguishing features. The diagnostic criteria for migraine are shown in Table 4.4.4. These include throbbing head pain in attacks, often with a prodromal state and usually preceeded by an aura, which frequently contains visual phenomena. Migraine is occasionally isolated to the face and a minority can have pain confined to the periorbital area, and rarely affect the cheek and nose alone. [1225]. The pain is typically unilateral but may be bilateral. Nausea, vomiting, photophobia and phonophobia often accompany the pain. The prevalence of migraine that involves the face is approximately 9% of the whole migraine population and occasionally it can be isolated to the face [1226, 1227]. Patients who have migraine that involves the face have more trigemino-autonomic symptoms than other migraine patients [1226].
The condition has 2 main forms. One type, migraine without aura (previously called common migraine) affects almost 75% of migraine sufferers. It is characterised by a headache, which can be severe and is typically unilateral, sharp, pulsating and often accompanied by nausea, photophobia or phonophobia. Symptoms last 4 to72 hours. There is no premonition. The second type, migraine with aura (previously called classic migraine) affects 25% of migraine sufferers. The attacks are preceded by neurological symptoms such as visual disturbances or numbness. It is three times more common in women and there is often a family history. Stress release, diet, the premenstrual state and barometric pressure can induce attacks. This system of classification is conservative, and it is recognised that many patients fall outside these criteria yet have migraine [1228]. Thus, the diagnostic criteria are highly specific but less sensitive. Other conditions have some migrainous features such as cluster headache and paroxysmal hemicrania. These however, have cohesive groups of symptoms that allow them to be categorised separately. However, many patients with facial pain do not neatly fit any diagnostic criteria. Some have migrainous features such as nausea, an aura, or facial flushing. The proposed theories of the cause of migraine have swung between being a primarily vascular or neural mechanism. Griggs and Nutt suggested migraine may be part of the spectrum of diseases known as channelopathies - disorders involving voltage-gated channels [1228]. The genetic component of migraine may be explained by the identification of migraine genes in familial hemiplegic migraine that affect the Ca2+ channei [1229].
In recent years, neuroimaging of the primary headache syndromes, such as migraine and cluster headaches, has begun to provide a glimpse of the neuroanatomical and physiological basis of these conditions. Functional imaging with positron emission tomography and magnetic resonance angiography (MRA) have documented activation in the midbrain, pons [1230] and hypothalamic grey matter in cluster headache [1231, 1232]. Work by Goadsby and colleagues suggest activation of the trigeminal innervation of the cranial circulation due to vasoactive peptides such as calcium gene related peptide [1233-1235].

A primary dysfunction of the mid-brain endogenous anti-nociceptive system (periaqueductal grey and dorsal raphe nucleus and the neural control of cerebral blood flow) seems to be responsible [1236]. Neuroimaging has reconciled previous theories that migraine was solely vascular and they now suggest that it is a neurovascular headache and an epiphenomenon of trigeminal activation.

It appears that whilst vascular input predominates in migraine and myofascial nociception prevails in tension type pain, but there is a great deal of overlap. The pioneering work by Olesen and colleagues suggests a neurovascular mechanism [1237] and this is supported by the finding that approximately 50% of patients with tension type headache also have migraine. They proposed a vascular-supraspinal-myogenic model that integrates the effects of pericranial myofascial afferents, activation of peripheral nociceptors from cephalic arteries, and convergence on the caudal nucleus of the trigeminal, along with qualitative changes in the central nervous system. A recent study showed an increase in functional MRI blood oxygen dependant levels in the thalamus during migraine attacks with allodynia, the experience of ordinarily nonpainful stimuli as painful, or hyperaesthesia [1238].

The management of migraine begins with providing

Table 4.4.3. Treatment options for acute migraine attacks.

Treatment options for acute migraine attacks.
The Triptans (e.g. Sumatriptan, Naratriptan, Rizatriptan, Zolmatriptan)
Ergotamine or dihydroergotamine
Aspirin, paracetamol, codeine phosphate, ibuprofen, naproxen, with or without metoclopramide.
Treatment options for preventative therapy.
Pizotifen (weight gain is a common side-effect and reduces its acceptability)
Propranolol
Amitriptyline
Sodium valproate

information to the patient, the identification and avoidance of aggravating factors. Regular sleep, exercise and a diet that avoids aggravating factors will help many patients although there is no objective data to support this assertion. An assessment must be made on the severity based on a frequency diary, intensity of pain and degree of disability. Pharmacological treatment consists of the management of acute attacks and preventative treatment. Current literature suggests preventative treatment should be considered if symptoms occur more than three times a month with a duration of symptoms more than 48 hours, and if there is a prolonged aura or failure to reduce acute symptoms [1239-1241] (Evidence level III). The options available for medication are shown in Table 4.4.3.

Acute anti-migraine therapy is most likely to be beneficial if started early in an attack and prophylactic anti-migrainous medication may need to be continued for up to 6 weeks before its beneficial effects occur. Treatment can be divided into non-specific and specific. The former consists of analgesia, such as paracetamol, codeine and aspirin, or non-steroidal anti-inflammatory drugs. An anti-emetic may be added if there is associated nausea or vomiting. If headaches are severe, specific anti-migrainous medications can be used. These include the triptans. Ergotamine has to be carefully prescribed as its overuse can cause severe headaches. The 5-HT1B/D receptor agonists, or triptans, are shown to be effective after the headache begins as long as they are given early (1242) (Evidence level Ib).
These constrict blood vessels, block neurogenic inflammation and neuropeptide release by a neuronal mechanism of action. Triptans should be prescribed with caution to patients with ischaemic heart disease, a history of myocardial infarction, uncontrolled hypertension or cerebrovascular disease. Pizotifen is a 5-hydroxytriptamine antagonist that is very effective in the prophylaxis of migraine but its side effects include weight gain and drowsiness [1243] (Evidence level Ib). Propranolol, a beta-receptor antagonist, also has some subclass of 5-HT2 effect [1243] (Evidence level Ib). Patients with asthma should not be given beta-blockers. Topiramate is preferred to sodium valproate as a second line drug in the treatment of migraine [1244] (Evidence level Ib).

4.4.4.3. Cluster Headache

Cluster headaches are defined as a primary neurovascular headache that is both severe and uncommon. It is characterised by recurrent, strictly unilateral attacks of headache that typically wake the patient and are retro-orbital or centred at the medial aspect of the orbit, of great intensity and last up to one hour (not in my experience but feel free to change it). The pain is also accompanied by ipsilateral signs of autonomic dysfunction such as the ipsilateral parasympathetic signs of rhinorrhoea, lacrimation, impaired sweating and sympathetic signs of miosis and ptosis [1245]. The most salient feature is its periodicity, which could be circadian or in terms of active or inactive bouts lasting 6-10 weeks annually, separated by clinical remission when the patient is completely pain free for at least 2 weeks between attacks. About 15% to 20% of patients suffer from chronic CH and have no significant remissions. Treatment includes sumatriptan injections, oxygen, and prophylactic treatment includes verapamil, gabapentin, and Pizotifen [1246] (Evidence level IIb).

4.4.4.4. Paroxysmal Hemicrania

Paroxysmal Hemicrania has been described as an excruciating unilateral pain, which is usually ocular, and frontotemporal with short-lasting (2-45 minutes), frequent attacks (usually more than 5 a day). By definition, at least one of the following autonomic symptoms should be present; nasal congestion (42%), rhinorrhoea (36%), lacrimation (62%), conjuctival injection (36%), or rarely ptosis, eyelid oedema, heart rate changes (bradycardia, tachycardia and extrasystoles), increased local sweating, salivation and facial flushing [1247, 1248]. Attacks may occur bilaterally even though they are usually more pronounced in the symptomatic side. These last between 5 to 45 minutes on each occasion, and they recur many times, between 7-22 times daily. Remission varied between 3 months to 3 years. Rarely do these headaches develop into the chronic form. The ratio is said to be 4:1 for CPH to episodic PH [1249]. Overall, the average age of the onset of PH is usually 30-40 years, but the spectrum range from 6 years old to 81 years old. The episodic form tends to have an earlier age onset [1250].

The condition's complete or rapid response to indomethacin is said to differentiate paroxysmal hemicrania from cluster headache [1251] (Evidence level III). However, recently the inclusion of this 'absolute' response to make it a criterion has been questioned [1252-1254] (Evidence level IV). The majority of patients with PH respond to indomethacin within 24 hours. If not, a trial, which entails increasing the dose to 75 mg daily after 3 days, followed by 150 mg daily after another 3 days has been recommended [1255]. Another study by Antonaci et al., recommended the 'Indotest', with an intramuscular injection of 50 mg indomethacin, and the response is monitored to differentiate paroxysmal hemicrania, hemicrania continua (HC) and other headache disorders with which they can be confused [1256]. They also noted that this test is a useful tool in the clinical assessment of unilateral headaches by establishing the interval between indomethacin administration and the clinical response.
A need for a persistently high dose may imply a sinister underlying pathology [1257]. In cases where indomethacin fails to work, other drugs that have been sugested, include calcium-channel blockers [1253, 1258] naproxen, carbamezapine [1259], and sumatriptan [1260] (Evidence level IV). The main features of PH and CH are listed in Table 4.4.1.

Table 4.4.1. Salient features to differentiate Cluster Headache from Paroxysmal Hemicrania.

Parameters	Cluster headache	Paroxysmal hemicrania
Age of onset female	25-50 /5:1	30-40/1:2
Age of onset male	25-50 /5:1	30-40/1:2
Laterality	Unilateral	Unilateral
Changes sides	Sometimes	Rarely
Duration	15 mins-2 hours	2-45 mins
Location	Occular, fronto-temporal and facial	Occular, frontotempo-ral, and facial
Wakes subject from sleep	+	+
Waking time	Night (50%)	Night (30%)
Attack frequency	1 per day, after several days	5/day
Remission	For days-weeks	Unusual
Autonomic (lacrima-tion, nasal conges-tion, facial flushing, injection of eye)	+	+
Non-narcotic anal-gesics	Little help	Little help
Prophylactic re-sponse	Indomethacin occasional Pizotifen helps	Indomethacin good Calcium channel blockers some help

4.4.4.5. Hemicrania Continua

Chronic Paroxysmal Hemicrania and Hemicrania Continua (HC) are two strictly unilateral headache disorders characterised by an absolute response to indomethacin. HC, first described by Sjaastad and Spiering, is a unilateral headache which is moderately severe without side shift, continuous but with fluctuations, with complete resolution of pain with indomethacin, and exacerbations that may be associated with autonomic features such as conjuctival injection, lacrimation, and photophobia to the affected side [1261, 1262] (Evidence level IV).

SUNCT (Short-lasting neuralgiform pain with conjunctival injection and tearing) SUNCT is one of the rarest idiopathic headache syndromes. This is a form of primary headache, marked by trigeminal pain, particularly orbital or periorbital area, associated with autonomic symptoms, in which conjunctival injection and tearing is the most prominent feature. Attacks last between 15 to 60 seconds and recur between 5-30 times an hour. These attacks may be precipitated by chewing movements and ingesting certain foods such as citrus fruits. Treatment is difficult with lamotrigine, carbamezapine or topiramate [1263] (Evidence level IV)

4.4.4.6. Indomethacin-responsive headaches. (Episodic and Chronic Paroxysmal Hemicrania, Remitting and Unremitting Hemicrania Continua, and Benign Cough Headache, Benign Exertional Headache, and sharp short-lived headache pain syndrome)

Indomethacin-responsive headaches are defined as those responding to doses of 25 mg twice daily to 75 mg three times daily, usually having an effect in less than 72 hours from the start of the effective dose. These rare syndromes include Episodic and Chronic Paroxysmal Hemicrania, Remitting and Unremitting Hemicrania Continua, and Benign Cough Headache, Benign Exertional Headache, and sharp short-lived headache pain syndrome. Most of these headaches are provoked by physical stimulation, for example exertion, cough, flexion or extension of the neck [1263].

How indomethacin works for these headaches is unclear. Currently, it is thought that indomethacin reduces the cerebral blood flow [1264], thereby decreasing the load on the presumed phlebotic cavernous sinus which chould be the origin of the pain in CPH attacks [1236] and is results in a decline in cerebral permeability [1265] and cerebrospinal pressure [1266]. The anti-inflammatory effect of indomethacin on these vessels may also have a role in aborting pain in CPH [1259] (Evidence level IV).

4.4.4.7. Persistent idiopathic facial pain

This is defined as persistent, unilateral facial pain not associated with sensory or physical signs. One study showed that with voxel-based morphometry there was a decrease in grey matter volume in the left anterior cingulated gyrus and left temporo-insular region as well as bilateral motor and sensory areas projecting to the areas that represent the face [1267] (Evidence level IV).

4.4.4.8. Chronic oro-facial pain

A small proportion of patients go on to have chronic pain and a prospective study supports the hypothesis that psychological factors such as anxiety, depression, illness behaviour, somatic symptoms are markers for chronic pain [1268]. A multi-disciplinary facial pain clinic supported by a clinical psychologist is very helpful in treating these patients as it not only stops them from "shopping around" but it helps to check that no treatment strategy has been overlooked and after that coping mechanisms can be put in place. Comprehensive pain programmes have been shown to be both therapeutically efficacious and cost-effective in an evidence-based review of the subject [1269]. Functional restoration, often through cognitive behaviour therapy, is central to the rehabilitation of most patients with chronic pain, almost whatever the cause. Psychological therapies are similarly helpful in children and adolescents with chronic pain [1270] (Evidence level Ib).

4.4.4.9. "Sinus Headaches".

Headaches that are due to rhinosinusitis are very uncommon and confined to a minority of patients who have acute frontal sinusitis or sphenoiditis. The vast majority of people who present with a symmetrical frontal or temporal headache, sometimes with an occipital component, have tension type headache. Unilateral, episodic headaches are often vascular in origin. The idea that rhinosinusitis can trigger migraine is misplaced as the whole symptom complex is vascular and coexisting nasal congestion is due to vasodilation of the nasal mucosa that is sometimes part of the vascular event. The use of nasal endoscopy and imaging of the paranasal sinuses have advanced our appreciation that these patients are suffering from a vascular event.

Over 90% of self-diagnosed and doctor-diagnosed sinus headaches meet the International Headache Society criteria for migraines and yet 61% receive an antibiotic prescription [1271]. One study of 100 patients who believed that they suffered from sinus headache found that 52% had migraine, 11% had chronic migraine associated with medication overuse, 23% had probable migraine, 1% cluster headache, 1% hemicrania continua, 3% secondary to rhinosinusitis, 9% were nonclassifiable [1272]. Seventy-six percent of migraine subjects reported pain in the distribution of the second division of the trigeminal nerve (either unilateral or bilateral), 62% experienced bilateral forehead and maxillary pain with their headaches and the most common associated feature was nasal congestion in 56% and rhinorrhoea in 25% [1272]. Another study of 1000 patients with headache has as the diagnostic causes migraine, tension-type headache, trigeminal autonomic cephalalgias, cranial neuralgias, trauma, drugs but that sinusitis is very, very rarely the cause [1273]. In another study 46% of migraine sufferers attending a tertiary referral centre had at least one unilateral nasal symptom of congestion or rhinorrhoea or ocular lacrimation, redness or swelling during an attack due to the trigeminal-autonomic reflex [1222]. Another study found that in self-reported sinus headaches 82% of patients had a significant response to empiric treatment with triptans [1223] (Evidence level IIb). Cady and Schreiber comment that "The concept of sinus disease as a common cause of headache is deeply engrained in the American public, but there is little evidence to support the sinuses as a common cause of disabling headache." [1274]. They reported that nearly 90% of participants with self-diagnosed or physician-diagnosed sinus headache met the IHS criteria for migraine-type headache and responded to triptans. They note that during a migrainous episode there is engorgement and erythema of the nasal mucosa along with rhinorrhoea and after subcutaneous sumatriptan both the symptoms and endoscopic signs resolve. Others have found that migraine often affects the face and can be misinterpreted as being due to rhinosinusitis, particularly as symptoms can last 72 hours and that vascular changes in the lining of the nose can also produce nasal obstruction through vasodilatation of the vascular turbinate tissue [1223, 1275]. An interdisciplinary consensus group recently agreed that "the majority of sinus headaches can actually be classified as migraines" and that "unnecessary diagnostic studies, surgical interventions, and medical treatments are often the result of the inappropriate diagnosis of sinus headache" [1276]. (Table 4.4.2.)

Table 4.4.2. Headache attributed to rhinosinusitis from so called "sinus headaches". Diagnostic criteria Section 11.5. of [1194].

A	Frontal headache accompanied by pain in one or more regions of the face, ears or teeth and fulfilling criteria C and D.
B	Clinical, nasal endoscopic, CT and/or MRI imaging and/or laboratory evidence of acute or acute-on-chronic rhinosiusitis.
C	Headache has at least two of the following characteris- Headache and facial pain developing simultaneously with onset or acute exacerbation of rhinosinusitis.
D	Headache and/or facial pain resolve within 7 days after remission or successful treatment of acute or acute-on-chronic rhinosinusitis
Notes:	
1	Clinical evidence may include purulence in the nasal cavity, nasal obstruction, hyposmia/anosmia and/or fever.
2	Chronic sinusitis is not validated as a cause of headache or facial pain unless relapsing into an acute stage.

Other conditions that are often considered to induce headache are not sufficiently validated as causes of headache. These include deviation of nasal septum, hypertrophy of turbinates, atrophy of sinus membranes and mucosal contact

4.4.4.10 Tension type headache

Seventy to eighty percent of the population has headaches every year and 50% have at least one a month, 15% once a week and 5% daily [1277, 1278]. The main quality of the pain is one of symmetrical pressure that may be confined to a small area just above the nasion or extend across the whole forehead. There is often an occipital component. There are often no exacerbating or relieving factors although bending forwards can sometimes aggravate them, a symptom often incorrectly said to mean the patient must have rhinosinusitis. There is often some hyperaesthesia of the soft tissues in the area. Patients are often taking many analgesics although they say they do little to help. Analgesic dependant headache can complicate the picture. Withdrawal from analgesics for several weeks alone may be sufficient in this group but is rarely tolerated without starting other treatment for their headache but this is an option. The prevalence of headache increases sharply during the second

decade then levels off until the age of 40-50, after which it reduces. The ideas from the Copenhagen group on tension-type headache [1279, 1280] postulate that central sensitisation of the trigeminal nucleus from either prolonged nociceptive input from a peripheral injury, surgery, inflammation, myofascial nociceptive input, along with psychological or neurological factors that can reduce supraspinal inhibition can contribute to tension-type headache. This concept offers a broader perspective and is a more inclusive method of interpreting. Amitriptyline should be given for six weeks before judging its effect, and should be continued for six months if it has helped [1281, 1282] (Evidence level Ib). The starting dose is 10 mg, and after six weeks if pain is not controlled this can be increased to 20mg (and rarely 50mg are needed). Patients need to be warned of the sedative effects of even at this low dose, but they can be reassured that tolerance usually develops after the first few days. It is our practice to inform patients that amitriptyline is also used in higher doses for other conditions such depression, but that it is not being given for this reason and its effect is unrelated to its analgesic properties, that would take effect much more quickly and normally require 75mgs. It is often reassuring for patients to know that the dose used for depression is some 7 or more times the dose used in tension-type headache and that other antidepressants do not help this condition.

4.4.4.11. Midfacial segment pain

Over the last decade, studies on facial pain have shown that there is a distinct group of patients who have a form of facial neuralgia that has all the characteristics of tension type headache with the exception that it affects the midface [1283]. The criteria that comprise midfacial segment pain is:

- A symmetrical sensation of pressure or tightness. Some patients may say that their nose feels blocked even though they have no nasal airway obstruction.
- Involves the areas of the nasion, under the bridge of the nose, either side of the nose, the peri- or retro-orbital regions, or across the cheeks. The symptoms of tension type headache often coexist.
- There may be hyperaesthesia of the skin and soft tissues over the affected area. - Nasal endoscopy is normal.
- Computerised tomography of the paranasal sinuses is normal (note a third of asymptomatic patients have incidental mucosal changes on CT).
- There are no consistent exacerbating or relieving factors.
- There are no nasal symptoms (note that approximately 20% of most populations have intermittent or persistent allergic rhinitis, which may occur incidentally in this condition).

The aetiology of this type of pain is uncertain but Olesen's theory, which integrates the effects of myofascial afferents, the activation of peripheral nocioceptors and their convergence on the caudal nucleus of trigeminal, along with qualitative changes in the central nervous system, provides one of the best models [1237]. Downregulation of central inhibition from supraspinal impulses due to psychological stress and emotional disturbances may also play a role. A higher proportion of these patients have myofascial pain, irritable bowel and fatigue than is found in the normal population, although many appear to be healthy individuals in all other respects.

The majority of patients with this condition respond to low dose amitriptyline, but usually require up to 6 weeks of 10 mg at night and occasionally 20 mg before it works [1076] ((Evidence level III). Amitriptyline should then be continued for 6 months before stopping it, and in the 20% whose symptoms return when they stop it they need to restart it if the pain returns. Other antidepressants are not effective; again this is akin to tension-type headache. If amitriptyline fails, then relief may be obtained from gabapentin or pregabalin.

4.4.4.12. Analgesic dependant headache

This entity is all too often unrecognised and mismanaged. As has already been mentioned, patients with tension type headache or midfacial segment pain often take a great number of analgesics in spite of the fact that they have little effect. Similarly migraine sufferers can get into a cycle of using an excessive amount of analgesics. Drug-induced headache is usually described as dull, diffuse, and band-like, and usually starts in the early morning. The original headache (migraine or tension headache) has often been present for many years and the regular intake of drugs often started several years before people present. Patients take on average 30 or more tablets per week often containing several different substances. The drugs most often used are caffeine, ergotalkaloids, paracetamol, and pyrazolone derivates. Withdrawal is problematic as patients' symptoms take several weeks to resolve. However, chronic headache disappears or decreases by more than 50% in two-thirds of the patients. Positive predictors for successful treatment are migraine as primary headache, chronic headache lasting less than 10 years, and the regular intake of ergotamine. It is well worth considering if this might be the patient's problem before adding to it with more tablets!

4.4.5. How surgery can influence pain

It is interesting to note that a proportion of patients who mistakenly undergo surgery for non-sinogenic pain experience temporary relief from their symptoms, although their pain returns within a few weeks and nearly always within 9 months. It is hypothesised that the reason for a temporary or partial reduction in their pain is either the effect of cognitive dissonance or the effect of surgical trauma on the afferent fibres going to the trigeminal nucleus, which alters its threshold for spontaneous activity in the short term. In about a third of

patients surgery does not significantly affect the pain and in a third the pain is made far worse [1284]. Patients whose pain is made worse by surgery may develop a more unpleasant quality to the pain such as burning.The criteria for diagnosing chronic rhinosinusitis vary, but most studies quote more than three nasal symptoms for more than 3 months [490]. It is important to note that the inclusion of facial pain/pressure "on its own does not constitute a suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign" [1205]. The evidence that a vacuum within a blocked sinus can causes protracted pain is poor. Transient facial pain in patients with other symptoms and signs of rhinosinusitis can occur with acute pressure changes when flying, diving or skiing but this resolves as the pressure within the sinuses equalises within hours through perfusion with the surrounding vasculature. Patients who repeatedly suffer these intermittent symptoms whilst there is a pressure change are often helped by surgery to open the ostia. Persistent blockage of the sinus ostia rarely causes continuous pain for example silent sinus syndrome that is due to a blocked sinus with resorbtion of its contents to the extent that the orbital floor prolapses into the maxillary sinus causes no pain [1285]. Endoscopic sinus surgery (ESS) has been advocated by a few workers for facial pain in the absence of endoscopic or CT evidence of sinus disease or anatomical variations Cook et al. advocated ESS on patients with facial pain, which also occurred 'independently' of episodes of rhinosinusitis, with no CT evidence of sinus pathology [1286]. Twelve of the 18 patients who underwent surgery in their series had a significant reduction in their pain severity, yet it is significant that, "complete elimination of symptoms was not accomplished in any patient". They had no evidence of ostiomeatal obstruction. If the cause of their pain was due to ostial obstruction then it might be anticipated that surgery would cure their symptoms of pain. This was not the case as they all had residual pain. Similarly Parsons et al. retrospectively described 34 patients with headaches who had contact points removed and found that whilst there was a 91% decrease in intensity and 84% decrease in frequency, 65% had persisting symptoms [1287]. One possible reason for a temporary or partial reduction in their pain is either the effect of cognitive dissonance or the effect of surgical trauma on the afferent fibres going to the trigeminal nucleus and this might alter the nucleus and its threshold for spontaneous activity for up to several months as has been found when patients with midfacial segment pain undergo surgery [1174].

4.4.5.1. Post surgical pain/Neuropathic pain

Neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system [1288]. Neuropathic pain is often spontaneous or it can be an abnormal response to a non-painful stimulus. The pain is often deep, burning, gnawing, occasionally stabbing or like an electric shock. It may start after a relatively minor injury or surgical procedure. There may be an altered sensation in the area affected. Acquadro et al. noted that in those patients with preoperative pain who underwent endoscopic sinus surgery, 7% developed new pain, and 2% reported a worsening of their facial pain but none developed de novo pain if they had had no pre-operative pain [1289]. Indeed to date, there has been few reported cases of facial pain following ESS in previously pain-free patients although it may be under-reported [1174, 1284]. This fact is surprising given that open sinus surgery, in particular the Caldwell-Luc procedure has long been known to cause de novo facial pain. One study noted this complication in 46% of all patients who had undergone a Caldwell Luc procedure, including some who had no prior facial pain though this may be due to direct trauma to the infraorbital nerve [1290].
Trauma causes pain that is mediated by myelinated A delta and unmyelinated C fibres. Prolonged stimulation of these can activate N-methyl-D-aspartate (NMDA) and cause central sensitisation. An alteration in central processing can then lead to an alteration in pain thresholds producing hyperalgesia or even lead to spontaneous firing of neurones and may produce reverberating circuits. It is also possible that antidromic flow in C fibres can cause the release of substance P or that efferent sympathetic flow can release noradrenaline; both these mechanisms have the potential to sensitise peripheral receptors [1291]. Trauma can be an initiating factor by either altering the fibres within the trigeminal nucleus or by altering its somatosensory input, thereby altering nocioceptive fibres to or within the caudal nucleus of the trigeminal nerve. These mechanisms, by altering the neuroplasticity of the nerves to and within the trigeminal nucleus, result in neuropathic pain.

Amitriptyline has been shown to be effective in relieving post-traumatic neuralgia [1292] in doses of 75 mg or alternatively gabapentin or pregabalin [1284] (Evidence level III). Duloxetine may help, particularly if there is coexisting anxiety. These need to be given for 6 to 8 weeks before judging if they have helped. A local anaesthetic nerve block can sometimes be successful in blocking localised pain and having a more prolonged benefit. Lignocaine patches over the area can help as can transcutaneous electrical nerve stimulation. The management of patients with pain unresponsive to medical treatment should involve pain coping strategies that involve a pain management team and psychologist and cognitive behaviour therapy. Physical activity, treated depression and anxiety, as well as establishing work or other activities can play an important role. Opiates can help but care is needed in prescribing these as they can lead to tolerance and dependency, which is a further obstacle to recovery.

4.4.5.2. Contact points

The theories that implicate contact points within the nose as a cause of headache or facial pain originate from McAuliffe who described stimulating various points within the nasal cavity and paranasal sinuses in five individuals in whom he said that both touch and faradic current caused referred pain to areas of the face [1293]. He illustrated this paper with diagrams that have been reproduced in many texts. These findings have been used to support the idea that mucosal contact points within the nasal cavity can cause referred pain, even though McAuliffe's studies did not describe contact point induced headache or facial pain [1294]. McAuliffe's work has recently been repeated in a controlled study and was found not to produce the referred pain that he described [1295]. The prevalence of a contact point has not only been found to be the same in an asymptomatic population as in a symptomatic population but, when a contact point was present in symptomatic patients with unilateral pain, it was found in the contralateral side to the pain in 50% [1296]. Stammberger and Wolf postulated that variations in the anatomy of the nasal cavity result in mucus stasis, infection and ultimately facial pain [1297]. They also stated that mucosal contact points might result in the release of the neurotransmitter peptide substance P, a recognised neurotransmitter in nociceptive fibres but there has been no in vitro or vivo work to substantiate this. For contact points to be credible as a cause of facial pain or headache they should also be a predictor of facial pain in the whole population [1298]. Another observation is that nowhere else in the body does mucosa-mucosa contact cause pain.

Other authors have embraced these concepts to explain how pain might be induced by anatomical variants such as a concha bullosa [1299-1302], or a pneumatised superior turbinate touching the septum [1303]. The description of the presence of anatomical 'abnormalities' such as a concha bullosa, a paradoxical middle turbinate, a superior turbinate touching the septum, or a large ethmoid bulla is a misnomer as these are variations that occur in asymptomatic populations. Case-controlled studies examining the prevalence of anatomical variations in patients with rhinosinusitis and asymptomatic control groups have shown no significant differences [277, 570, 571, 576, 578-580, 1177, 1199, 1303-1310]. It seems probable that the majority of the case series in the literature that describe surgery for anatomical variations in patients with facial pain that responded to surgery, that is more often partial than complete and relatively short lived, result from the effect of cognitive dissonance [1311], or from surgery altering neuroplasticity within the brainstem sensory nuclear complex [1237, 1279, 1280, 1312].

The IHS classification [1194] has entered mucosal contact point headache as a new entry but says the evidence for it is limited. "Controlled trials are recommended to validate it, using the selection criteria:

A. Intermittent pain localised to the periorbital or medial canthal or temporozygomatic regions fulfilling criteria C and D.

B. Linical, nasal endoscopic and/or CT imaging evidence of mucosal contact points without acute sinusitis.

C. Evidence that the pain can be attributed to mucosal contact based on at least one of the following:

1. pain corresponds to gravitational variations in mucosal congestion as the patient moves between upright and recumbent positions.
2. abolition of pain within 5 minutes after diagnostic topical application of local anaesthesia to the middle turbinate using placebo or other controls.

D. Pain resolves within 7 days, and does not recur, after surgical removal of mucosal contact points (abolition of pain is indicated by a score of zero on the visual analogue scale).

At present reports that support the removal of contact points are notable by their retrospective nature, the lack of any controlled study, ability to explain the prevalence of these findings in many asymptomatic people in the population [1313] and a failure to meet the criteria in the HIS classification [1194].

4.4.6. Specific neurological conditions

4.4.6.1. Trigeminal neuralgia

The characteristic presentation of trigeminal neuralgia with paroxysms of severe lanciolating pain induced by a specific trigger point is well recognised. In more than one third of sufferers the pain occurs in both the maxillary and mandibular divisions, while in one fifth it is confined to the maxillary division. In a small number of patients only the ophthalmic division is affected (3%). Typical trigger points are the lips and naso-labial folds, but pain may also be triggered by touching the gingivae. A flush may be seen over the face but there are no sensory disturbances in primary trigeminal neuralgia. Remissions are common but the condition can also increase in severity. Younger patients should undergo MR imaging to exclude other pathology such as disseminating sclerosis that is identified in 2-4% of patients with trigeminal neuralgia. Tumours such as posterior fossa meningiomas or neuromas are found in 2% of patients presenting with trigeminal neuralgia reinforcing the need for imaging to exclude such pathology. Carbamazepine remains the first line medical treatment, with gabapentin, Lamotrigine [1314] (Evidence level IIb) and Topiramate [1315] (Evidence level IIb) being employed more frequentlyIn cases refractory to medical treatment, referral to specialist centres for consideration of other treatment modalities such as micro-vascular decompression or stereotactic radiotherapy may be appropriate.

4.4.6.2. Post-herpetic Neuralgia

This is pain following a herpes zoster infection, and is defined as pain recurring or continuing at the site of shingles after the onset of the rash. Up to 50% of elderly patients who have had shingles may develop post-herpetic neuralgia, though fortunately most recover during the first year. Antiviral agents help curtail the pain of acute shingles, and there is some evidence that they reduce the risk of subsequent post-herpetic neuralgia. Various medical treatments may be helpful particularly carbamazepine or gabapentin with or without a tricyclic antidepressants [1316] (Category of evidence IV).

4.4.6.3. Atypical Facial Pain

This is very much a diagnosis of exclusion and care must be taken in reaching this conclusion, even when the patient has received previous opinions and no pathology has been identified. The history is often vague and inconsistent with widespread pain extending from the face onto other areas of the head and neck. The pain may move from one part of the face to another between different consultations and other symptoms such as 'mucus moving' in the sinuses are often described. A number of patients have such completely fixed ideas about their condition that they will not be convinced otherwise whatever the weight of evidence to the contrary. Pain is often described in dramatic terms in conjunction with an excess of other unpleasant life events. Many of these patients have a history of other pain syndromes and their extensive records show minimal progress despite various medications. They have often undergone previous sinus or dental surgery and may be resentful about their treatment. It is not uncommon for such patients to give a history of nasal trauma. Many patients with atypical facial pain exhibit significant psychological disturbance or a history of depression and are unable to function normally as a result of their pain. Some project a pessimistic view of treatment, almost giving the impression they do not wish to be rid of the pain that plays such a central role in their lives. A comprehensive examination (including nasendoscopy) is essential and imaging such as MRI is advisable to exclude pathology before the patient is labelled as having atypical pain. The management of such patients is challenging and confrontation is nearly always counterproductive. A good starting point is to reassure the patient that you recognise that they have genuine pain and an empathetic consultation with an explanation should be conducted. Drug treatment revolves around a gradual build-up to the higher analgesic and antidepressant levels of amitriptyline (75-100 mgs) at night [1317] (Evidence level II). The second line treatment includes gabapentin and carbamazepine. Patients should sympathetically be made aware that psychological factors may play a role in their condition and referral to a clinical psychologist or psychiatrist may be helpful [1318] (Evidence level IV). Referral to a pain clinic is often appropriate.

4.4.6.4. Myofascial pain

Myofascial pain causes a widespread, poorly defined aching in the neck, jaw or ear. It is five times more common in women and worse when the patient is tired or stressed. Tender points may be found in the sternomastoid or trapezius muscles and initiating factors include malocclusion or poor deltopectoral posture. This syndrome overlaps to a large degree with temporomandibular joint dysfunction. Reassurance, local heat treatment, ultrasound and massage help.

4.4.6.5. Ophthalmological

Uncorrected optical refractive errors can cause headaches, but their importance is exaggerated. Visual acuity is tested ideally with a Snellen chart and if there is a refractive problem this can be overcome by testing vision through a pinhole. Disease involving the optic nerve results in reduced acuity and colour vision. Pain on ocular movement is suggestive of optic neuritis or scleritis. It is vital to recognise acute glaucoma, which may cause severe orbital pain and headache. The patient may see haloes around lights, and circumcorneal injection can occur as well as systemic upset, especially vomiting. This condition requires urgent treatment as vision is rapidly lost. Pain is a feature of periorbital cellulitis, which may present with lid swelling and erythema if it is preseptal and with chemosis, proptosis and reduced mobility if it arises posterior to the septum. Orbital pain can also be caused by uveitis, keratitis, dry eye syndrome and convergence insufficiency.Orbital haemorrhage can cause sudden pain, proptosis, nausea and vomiting, along with ecchymosis, reduced mobility and oedema of the optic disc. It may be secondary to an orbital varix, blood dyscrasias, hypertension or trauma.
The term 'Inflammatory Orbital Pseudotumour' should not be used for disorders whose aetiology is known (polyarteritis nodosa and vasculitis). This condition probably has an immunological basis is often a precursor of lymphona and it can produce pain, proptosis, reduced mobility, lid swelling and injection of the eye. Some individuals have recurring bouts and are pain free, whereas others have pain with upper respiratory tract infections and these can mistakenly be held responsible. The majority of other causes of proptosis are painless, such as hyperthyroidism and tumours of the orbit or of adjacent structures.

4.4.7. Conclusion

The key message in this evidence based review on facial pain is that contrary to the preconceptions of many patients and their primary care physicians, the majority of patients with facial pain or headache do not have rhinosinusitis. It is very

important to ensure that the surgeon has the correct diagnosis in a patient with facial pain before embarking on any surgical treatment. Not only do the vast majority of patients with facial pain have a neurological cause, but in the small proportion that have paranasal sinus disease, the majority respond to medical treatment. We describe the prevalence and characteristics of the different causes of facial pain and headache and the symptoms and signs that are found in acute and chronic rhinosinusitis in order to help differentiate this group from other diagnoses.

4.5. Genetics of CRS with and without nasal polyps

4.5.1. Summary

Chronic rhinosinusitis (CRS) is a complex disease, with a pathophysiology that is likely to be affected by multiple genetic and environmental factors. There are several studies that linked different chromosomal associations and single nucleotides polymorphism to CRS. Although genetic studies will probably not answer all questions, it should provide new information to redirect basic science studies to disease-related pathophysiological pathways. In the future we hope to be able to improve diagnostics and treatments for patients with CRS using the subclassification of the disease on the basis of genetics. Additionally, identification of environmental factors that may interact with subject's genome may also help to avoid these risk factors and potentially prevent disease expression.

Chronic rhinosinusitis (CRS) is a complex disease, with a pathophysiology that is likely to be affected by multiple genetic and environmental factors.

4.5.2. Introduction

Genetic studies to identify genes that could be responsible for certain disease can be performed with different techniques. These include candidate gene studies, linkage studies, or genome-wide association studies (GWAS). However, in genetic studies the GWA approach is rapidly replacing the more traditional candidate gene studies and microsatellite-based linkage mapping studies. The GWA approach would be useful to identify causal genes related to complex diseases such as CRS, due to its comprehensive and unbiased strategy. This progress was made possible by key developments in human genomics over the last decade and the completion of human genome DNA sequence analysis (HapMap) [1319]. A molecular pathway based approach has been recently developed to facilitate more powerful analysis of GWA study data sets. In GWAS the basic principal is to compare the frequency of a genetic variant between cases and controls. Many genetic variants (SNPs) are tested (usually 300,000 to 1 million) and therefore adjustment for multiple testing is required. For example for NIH catalog of GWAS p values of 5x 10-8 or less are required (www.genome.gov/GWAS) [615]. For any gene variant to be considered possibly significant for a given disease, it has to be replicated in at least two different, independent patient cohorts.

In addition to the direct effect of differences between genotypes we must also consider inter-individual and inter-tissue variations in gene transcript levels. These differences can be important in mediating disease susceptibility and may be caused by either genetic or epigenetic variation. Genetic variants influencing transcription include large-scale structural changes in the genome such as gene duplications and deletions; equally they can arise due to polymorphisms in a gene's regulatory elements.

4.5.3.Chronic rhinosinusitis with and without nasal polyps. (CRSw and CRSsNP)

4.5.3.1. Family and twin studies

An interesting observation is that chronic rhinosinusitis with nasal polyps (CRSwNP) is frequently found to run in families, suggesting a hereditary or with shared environmental factor. Alexiou et al. [1320] studied 100 patients with NP and 102 controls from the general population and showed that 13.3% of the patients and none of the controls had a history of polyps in the family. In the study by Rugina et al. [508], more than half of 224 CRSwNP patients (52%) had a positive family history of NP. The presence of CRSwNP was considered when NP had been diagnosed by an ENT practitioner or the patients had undergone sinus surgery for CRSwNP. A lower percentage (14%) of familial occurrence of CRSwNP was reported earlier by Greisner et al. [1321] in smaller group (n = 50) of adult patients with CRSwNP. Thus, these results strongly suggest the existence of a hereditary factor in the pathogenesis of CRSwNP. However, studies of monozygotic twins have not shown that both siblings always develop polyps, indicating that environmental factors are likely to influence the occurrence of NP [1322, 1323]. CRSwNPs have been described in identical twins, but given the prevalence of nasal polyps it might be expected that there would be more than a rare report of this finding [1324].

Studies of monozygotic twins have not shown that both siblings always develop polyps, indicating that environmental factors are likely to influence the occurrence of CRSwNP.

4.5.3.2. Linkage analysis and association studies

Most genetic studies of CRS to date are candidate gene or candidate pathway approach studies. The focus in these studies has been the role of innate immunity in the pathophysiology of CRS. Large-scale genome wide associations studies (GWAS) of CRS are still lacking. For GWAS to have sufficient statistical

power, larger patient cohorts are needed than that have been used up to now. There is one study in CRS using a DNA pool-based GWA, a technique that was developed to reduce costs of GWAS by replacing individual DNA genotyping by pooled genomic DNA [1325]. The technique uses separate pools of DNA from patients and controls and hybridizes these pools on high-density single nucleotide polymorphisms (SNPs) microarrays to determine the allele frequencies in each pool [1326]. In this study with 210 CRS patients and 189 controls, the authors identified 600 SNPs from 445 genes that were potentially associated with CRS. Authors stated that validation in a bigger cohort is needed to separate true positive results from the false positive.

Several affected genes and enriched SNPs have been published for patients with CRS with polyposis (CRSwNP) or without polyposis (CRSsNP). Three SNPs related to CRSwNP have been replicated this far and they are genes IL1A, TNF , and AOAH.

In the near future, due to the decreasing cost of GWAS technology, it is expected that large-scale GWAS studies of CRS will soon be performed as well.

Several affected genes and enriched SNPs have been published for patients with CRSw and sNP Three SNPs related to CRSwNP have been replicated this far. These are for the genes IL1α [1327, 1328]. TNF [1329], and AOAH [1321, 1328]. The original study of association of IL1α, IL1β and TNF in CRSwNP in a Turkish population was published 2007 [1330]. Association of IL1A to the development of severe CRS was reported in a replication study of 206 patients [1328]. Patients had had at least one endoscopic sinus surgery and their symptoms persisted. Nasal polyps was the initial diagnosis in 74,8% of the patients in this study. The TNFA association to nasal polyps was replicated in study of 170 CRSwNP patients compared to 153 non-polyposis controls [1329].
Several other polymorphisms associated with CRS have been published but have not been replicated, including polymorphism in IL-22 [1331], and the heterozygote status for the alpha-1-antitrypsin (AAT) gene (SERAPINA1) [1332] in severe CRSwNP, as well as for the IL-1 receptor-associated kinase 4 (IRAK4) [1333] and MET gene [1334] in a Canadian population. Two SNPs in Toll-like receptor 2 (TLR2) were associated with increased risk of CRS in the Korean population [1335] suggesting that these SNPs may affect the susceptibility to bacterial infections leading to development of CRS. In another study, polymorphism of IL-4 (IL-4/-590 C-T), a potential determinant of IgE mediated allergic disease, was found to be associated with a protective mechanism against NPs in the Korean populations [1336]. The role of IL-33 pathway in development of pathogenesis of NP was studied in 284 NP-patients from Belgium. Thiss tudy found two SNPs in the IL-33 ILIRL1 pathway to increase susceptibility for NP [840].

Several other polymorphisms associated with CRS have been published but not been replicated.

A population based genome-wide screen for CRS among 291 Hutterites (isolated religious community in US and Canada) linked a locus on chromosome 7q to the disease, suggesting CFTR (cystic fibrosis transmembrane conductance regulator) gene influencing disease susceptibility [1337]. Reduced expression of several epithelial genes, like S100A7, S100A8 and SPINK5 has been reported in CRSwNP and CRSsNP. These finding suggest alterations in epithelial barrier function and host defense in CRS [782].
A number of genetic association studies found a significant correlation between certain HLA (human leukocyte antigen) alleles and NP. HLA is the general name of a group of genes in the human major histocompatibility complex (MHC) region on the human chromosome 6 that encodes the cell-surface antigen-presenting proteins. Luxenberger et al. [1338] reported an association between HLA-A74 and NPs, whereas Molnar-Gabor et al. [1339] reported that subjects carrying HLA-DR7-DQA1*0201 and HLA-DR7¬DQB1*0202 haplotype had a 2 to 3 times odds ratio of developing NP. The risk of developing NP can be as high as 5.53 times in subjects with HLA¬DQA1*0201-DQB1*0201 haplotype [1340]. Although several HLA alleles were found to be associated with NP, such susceptibility can be influenced by ethnicity. In the Mexican Mestizo population, increased frequency of the HLA¬DRB1*03 allele and of the HLA-DRB1*04 allele were found in patients with NP as compared to healthy controls [1341]. Fruth et al. [1342] studied Glutathione S-Transferases (GST) as one of major group of antioxidative active enzymes involved in cellular detoxification. The authors analyzed 170 nasal tissue samples (CRS without nasal polyps=49, CRS with nasal polyps=69 and healthy tissue controls of the inferior turbinate=52) and concluded that there is no correlation between any GST-polymorphism and CRS with and without nasal polyps or allergies or asthma or aspirin-intolerance.

4.5.3.3. Multiple gene expressions in nasal polyps

No single gene has been shown to be uniquely related to CRS.

The development and persistence of mucosal inflammation in NPs have been reported to be associated with numerous genes and potential single nucleotide polymorphisms (SNPs). The products of these genes determine various disease processes,

such as immune modulation or immuno-pathogenesis, inflammatory cells (e.g., lymphocytes, eosinophils, neutrophils) development, activation, migration and life span, adhesion molecule expression, cytokine synthesis, cell-surface receptor display, and processes governing fibrosis and epithelial remodelling. In the literature, gene expression profiles in nasal polyp have been performed by many studies, including the major repertoire of disease-related susceptibility genes or genotypic markers. With the advance of microassay technique, expression profiles of over 10,000 of known and novel genes can be detected. A recent study showed that in NP tissues, 192 genes were upregulated by at least 2-fold, and 156 genes were downregulated by at least 50% in NP tissues as compared to sphenoid sinuses mucosa [1059]. In another study [1065], microarray analysis was used to investigate the expression profile of 491 immune-associated genes in nasal polyps. The results showed that 87 genes were differentially expressed in the immune-associated gene profile of nasal polyps, and 15 genes showed differential expression in both NP and controls (turbinate). These seemingly conflicting results are likely due to the heterogeneity of inflammatory cells within nasal polyps and the differences in study designs and analytic approaches. In addition, in most of the published studies, the functional significance of aberrant gene expression with respective to the pathogenesis of NP is yet to be determined. The expression of gene products is regulated at multiple levels, such as during transcription, mRNA processing, translation, phosphorylation and degradation. Although some studies were able to show certain NP associated polymorphisms and genotypes, the present data is still fragmented. In common with many common human diseases, inherited genetic variation appears to be critical but yet still largely unexplained. Future studies are needed to identify the key genes underlying the development or formation of NP and to investigate the interactions between genetic and environmental factors that influence the complex traits of this disease. Identifying the causal genes and variants in NP is important in the path towards improved prevention, diagnosis and treatment of NPs.

A subset of CRSwNp patients has Samter's triad (ASA) characterized by presence of aspirin sensitivity, CRSwNP and asthma. Five different genes were reported to be associated in this group of 30 patients. The gene most characteristic of the ASA phenotype was periostin (POSTN) that was upregulated compared to controls. Also the proto-oncogene MET and protein phosphate 1 regulatory subunit (PP1R9B) were upregulated, whereas prolactin induced protein (PIP) and zinc alpha2 glycoprotein (Azgp1) were down-regulated [1029].

A PubMed literature research (Jan1950-July 2010) was performed to identify candidate molecular markers associated with CRSwNP by Platt et al. [1343]. Pathway analysis of molecular markers in CRSwNP included 554 genes that had fold change more than 3 and False Discovery Rate of less than 0.1 selected from the group's previous genome-wide expression study [1029]. From these genes 365 were up-regulated and 189 were down-regulated. The most common affected pathways for these genes were: inflammatory response, cellular movement, hematological system development and function, immune cell trafficking, and respiratory disease pathways. Gene network pathway analysis generated from the literature of this data showed tumor necrosis factor (TNF) as a central nodal molecule of the highest scoring network ($p = 1 \times 10^{-41}$) related to these pathways.

4.5.3.4. CRS and cystic fibrosis

The role of genetic factors in CRS has been implicated in patients with cystic fibrosis (CF) and primary ciliary dyskinesia (Kartagener's syndrome). CF is one of the most frequent autosomal recessive disorders of the Caucasian population, caused by mutations of the CFTR gene on chromosome 7 [564]. The most common mutation, F508, is found in 70 to 80% of all CFTR genes in Northern Europe [1344, 1345]. Upper airway manifestations of CF patients include CRS and nasal polyps, which are found in 25 to 40 % of CF patients above the age of 5 [1346-1349]. Interestingly, Jorissen et al. [1350] reported that F508 homozygosity represents a risk factor for paranasal sinus disease in CF and Wang reported that mutations in the gene responsible for CF may be associated with the development of CRS in the general population [1351].

Conclusion

No single gene has been shown to be uniquely related to CRS. This is unlikely to change in the future due to a complexity of the disease and its pathophysiology. Only when CRS can be phenotyped into subgroups with similar pathophysiological features could we hope to detect the genes behind these subgroups more accurately.

European Position Paper on Rhinosinusitis and Nasal Polyps 2012.

5. Special items in CRS

5.1. Complications of Chronic Rhinosinusitis

Summary

Complications associated with CRSwNP and CRSsNP are less dramatic and rarer than those that can occur in ARS but may be difficult to manage

Complications of CRSwNP & CRSsNP are rare and are largely due to effects on the surrounding bone. They include bone erosion and expansion due to mucocoeles or polyps, osteitis and metaplastic bone formation and occasionally optic neuropathy.
Generally these are far less documented in the literature than those associated with acute infection and inflammation. In some cases, they may be considered as simply a manifestation of the natural history of the condition.
The following may be included:

1. Mucocoele formation
2. Osteitis
3. Bone erosion and expansion
4. Metaplastic bone formation
5. Optic neuropathy

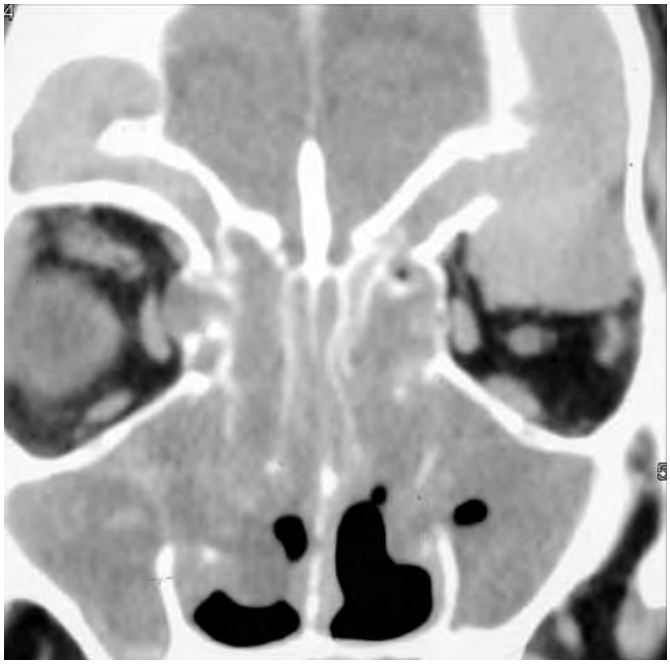
There is no evidence that CRS is associated with neoplastic change, either benign or malignant. A few case reports refer to orbital, intracranial and osseous complications typical of ARS can occur in CRS but are almost always secondary to a superimposed acute infective episode.

Complications in CRS generally result from an imbalance in the normal process of bone resorption, regeneration and remodelling.

5.1.2. Mucocoele formation

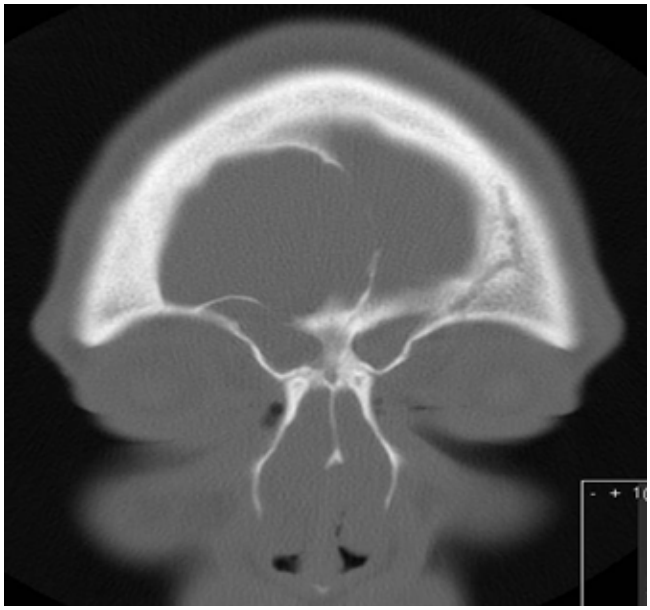
A mucocoele is an epithelial-lined sac completely filling the paranasal sinus and capable of expansion as opposed to an obstructed sinus which simply contains mucus [1369]. Mucocoeles are relatively rare and usually uni-locular (92%) and unilateral (90%). The exact pathogenesis is unknown though is often associated with obstruction of sinus outflow and some form of chronic inflammation or infection. Studies of inflammatory markers suggest an active process analogous to that seen in odontogenic cysts at the mucocoele bone interface [1370]. However, in one third of cases, no obvious cause for the initiation of this process can be found [1371]. Where an associated pathology can be identified, it is most often chronic rhinosinusitis with or without nasal polyposis, cystic fibrosis or allergic/eosinophilic fungal rhinosinusitis, in either case with or without surgical intervention. The time interval from potential initiating event to clinical presentation varies from 22 months to 23 years [1371]. Growth is generally slow unless an acute bacterial infection produces a pyocoele. (Figures 5.1-5.2)

Fig. 5.1. Mucocoele expansion of lateral compartments of frontal sinuses associated with nasal polyposis with associated expansion of ethmoids, erosion of the lamina papyracea and pseudohyperteliorism .



The distribution of mucocoeles within the sinuses is interesting, occurring most often in the fronto-ethmoid region (86%). The maxillary sinus is least often affected. Consequently the patients most often present with orbital symptoms and signs (axial proptosis, lateral and inferior displacement of the globe, diplopia).

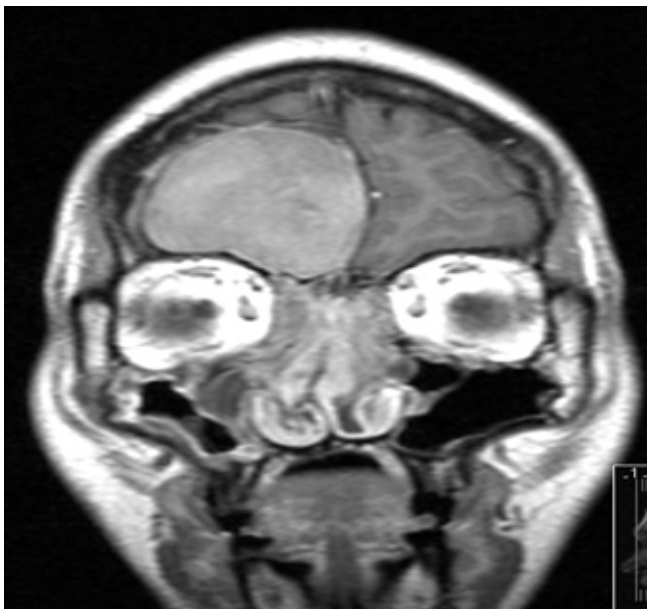
Fig. 5.2a. Coronal CT showing asymptomatic intracranial extradural chronic collection of insipissated mucus in patient with nasal polyposis.



A mucocoele is an epithelial-lined sac completely filling the paranasal sinus and capable of expansion as opposed to an obstructed sinus which simply contains mucus which sometimes occurs in CRS, though not exclusively and which is managed surgically

In fronto-ethmoidal mucocoeles, visual acuity is rarely at risk unless a pyocoele develops whereas visual loss may be the presenting clinical feature with sphenoidal mucocoeles.

Fig. 5.2b. Coronal MRI (T1 with gadolinium) in same patient.



Large mucocoeles can extend into the anterior cranial cavity where they may eventually have a mass effect. Age at presentation varies from 23 months to 79 years, though they are generally rare in children and affect men and women fairly equally. It is not possible to predict who will develop a mucocoele.

Diagnosis is confirmed with CT scanning which shows a smooth walled lesion filling an expanded sinus, with areas of thinned or dehiscent bone, usually between the mucocoele and the orbit or anterior cranial fossa [1372]. MRI may be used if there is doubt about the diagnosis e.g. a carotid aneurysm involving the sphenoid. The usual signal characteristics are low T1 and high T2 but any permutation can occur depending on the water and protein content.

The histology of the mucocoele lining is also variable, but is generally composed of pseudostratified columnar epithelium with some squamous metaplasia, goblet cell hyperplasia and a cellular infiltrate dependant on the degree and type of chronic (and acute) inflammation i.e. neutrophils, eosinophils, macrophages, monocytes and plasma cells [1373].

Treatment is by marsupialisation, which can be undertaken endoscopically in the majority of cases. No repair of the dehiscent bone is required as long as the lining mucosa is undisturbed and remodelling of the expanded bone can be anticipated with time. A review of the literature shows an overall success rate of >90%, particularly in those undergoing endoscopic surgery alone. Recurrence is higher in those who have undergone previous surgery, have CRS with nasal polyposis, fistulas to the upper eyelid and who have had the more complex disease, which may require combined external and endoscopic surgical approaches. (Table 5.1.1) [1374-1380].

5.1.3. Osteitis

This process has often been reported in association with CRS and might be regarded as part of the pathophysiological process rather than a complication. Animal experiments in rabbits by Kennedy, Senior and others in the late 1990's suggested that the presence of osteitis acted as a stimulant to persistent mucosal inflammation with osteoclastic resorption of bone within and adjacent to infected sinuses [1023, 1382]. These pathological changes in the bone were observed in 92% of rabbit models on the infected side and even in 52% on the contralateral non-inoculated side suggesting a route of spread via the enlarged Haversian canal systems [1383].

Osteitis can be associated with CRS but its role, if any, in the pathogenesis of CRS remains unclear

Bone remodelling with accompanying neo-osteogenesis

Table 5.1.1. Endoscopic Management of Mucocoeles.

		Site				Age (yrs)		Female: Male	Previous surgery	Follow up		Recurrence
	n	F	E	S	M	Range	Mean			Range	Mean	
Kennedy et al 1989 (1374)	16	9	5	2	-	10-76	44.7	8:10	5 (31%)	2m-42m	17.6m	0%
Moriyama et al 1992 (1375)	49 (47pt)	-	41	8	-	20-69	46.2	14:33	37 (78%)	2yr-10yr	?	?
Beasley & Jones 1995 (1381)	34 (25pt)	21	10	1	2	23-76	51	7:18	18 (72%)	6m-3yr	2yr	6% (both had previous external surgery)
Benninger et al 1995 (1376)	15	-	7	8	-	?	?	10:5	5 (33%)	5m-40m	20m	13%
Lund 1998 (1377)	20 (ESS)	12	6	2	-	4-89	42.6	10:10	0	7m-61m	34m	0%
	28 (Combined ESS & external)	28				25-83	59	11:17	9 (42%)	10m-76m	44m	11%
Conboy and Jones 2003 (1378)	68 (59pts; 44 ESS 14 EFE 9 Comb)	42	16	4	6	14-90	56	?	21 (31%)	3m-10.2yr	6.2yr	13% (9% post-ESS; 26% post-external ops)
Khong et al 2004 (1379)	41 (28pts)	32	3	1	5	15-83	52	11:17	At least 18 (64%)	1-42m	18m	0%
Bockmuhl et al 2006 (1380)	290 (255 pts; 185 ESS)	148	41	29	72	10-80	52	85:170	168 (66%)	4-21 yr	?	2%

F: frontal or fronto-ethmoidal. E: ethmoid. S: sphenoid. M: maxilla

has been demonstrated histologically in the ethmoid bone of patients with CRS (1384). The extent of bone remodelling correlated with severity of disease as evidenced by the Lund-Mackay CT score. Radionucleotide scintigraphy has been used to show increased bone turnover consistent with osteitis in CRS as compared to normal controls (1385). Interestingly this was greatest in the maxilla and ethmoid whereas clinically it is more often observed and problematic in the frontal and sphenoid. A prospective study of 121 patients undergoing endoscopic sinus surgery for CRS was assessed for radiological and histological evidence of osteitis (1022). CT showed neo-osteogenesis in 36% whereas osteitis was confirmed histologically in 53%. (Figure 5.4)

A thorough review of the literature by Videler et al. (1030) confirmed an association of osteitis with CRS but its role, if any, in the pathogenesis of CRS remains unclear. A variety of grading systems have been used to classify the osteitis, usually based on CT appearances(Table 5.1.2) (1022, 1386, 1387).

An earlier prospective case-control study by Georgalas et al. (1388) of 102 patients undergoing CT for CRS were compared with a cohort of age and gender matched non-CRS controls using a variety of parameters including a Global Osteitis Scoring Scale. The severity of osteitis correlated with extent of mucosal disease (as assessed by the Lund-Mackay score)($p<0.001$), duration of symptoms ($p<0.01$) and previous surgery ($p<0.001$) but there was no correlation between osteitis and symptoms including facial pain and headache. There are no studies at present on management.

Figure 5.3. Coronal CT showing heterogeneous change in left antroethmoid region typical of non-invasive eosinophilic fungal rhinosinusitis.

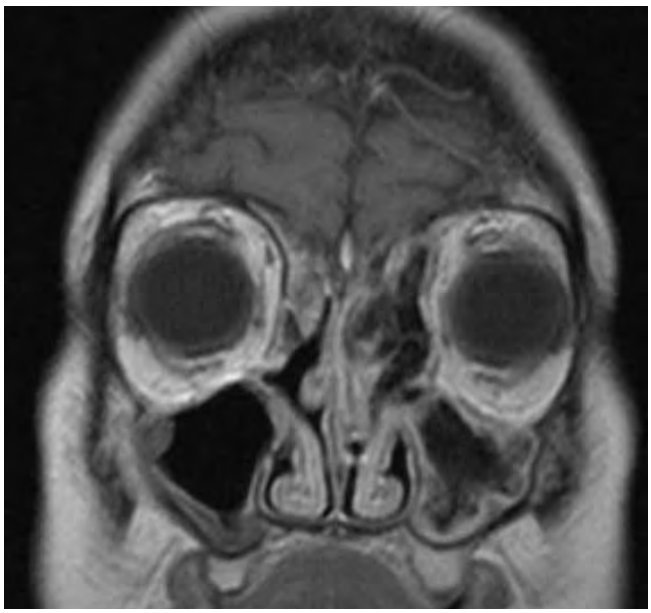


Table 5.1.2. Examples of CT grading systems for severity of osteitis.

Biedlingmaier et al. [1386].
Osteitis is defined as rarefaction and/or demineralization; loss of trabeculae; cortical destruction; focal sclerosis; loss of expected structures or landmarks
1= normal
2= findings suggestive of osteitis, but polyps make osteitis indeterminate
3= interpretation limited due to dental artifact
4 = osteitis
Lee et al. [1022]
Osteitis thickness measurement
Mild: 3 mm
Moderate: 4-5 mm
Severe: >5 mm

5.1.4. Bone erosion and expansion

The converse process to bone sclerosis associated with osteitis is the bone thinning and erosion seen in the more aggressive forms of CRS with nasal polyposis (CRSwNP) (Fig. 5.1.) This is distinct from true mucocoele formation and most often affects the ethmoids where the lamina papyracea may become even thinner than normal and bow into the orbit [1389]. This is accompanied by expansion of the opacified ethmoid cells and is usually a bilateral process, resulting in displacement of the orbital contents. Ultimately the lamina becomes dehiscent, most often anteriorly, adjacent to the nasolacrimal system and may be associated with epiphora.

Bone erosion and expansion is the converse process to osteitis seen in the more aggressive forms of CRSwNP

In severe cases a marked pseudohyperteliorism can result. An early study looking at plain x-rays of patients with CRSwNP [1390] showed that widening of the ethmoids was found in 20% of cases and that this correlated with the age at onset of symptoms rather than length of symptoms. The skull base may also be affected, simulating a neoplastic process [1391]. Both thickening and thinning of the walls of the paranasal sinuses can occur in the same patient. Foreknowledge of these changes from CT scanning is a pre-requisite to safe surgery. They are particularly marked in cases of allergic (eosinophilic) fungal rhinosinusitis where 80% of cases show evidence of bone erosion [1392] (Fig. 5.3).

5.1.5. Osseous metaplasia

Rarely osseous metaplasia can be found in the upper aerodigestive tract in response to chronic inflammation with or without polyposis and/or previous surgery. New bone formation occurs with a well-developed Haversian system and bone marrow where one would not expect to encounter it i.e. within the lumen of the paranasal sinuses or nasal cavity in contradistinction to the osteitis seen in the walls of paranasal sinuses. This can achieve impressive proportions, obstructing the nose and impacting on the orbit, producing a benign looking mass on CT composed of bone hyperdensities and soft-tissue which may require surgical removal, if only to exclude a neoplastic process [1393-1395] (Figure 5.5).

Fig. 5.4. Coronal CT showing unilateral osteitis affecting walls of left sphenoid sinus with associated mucosal thickening.

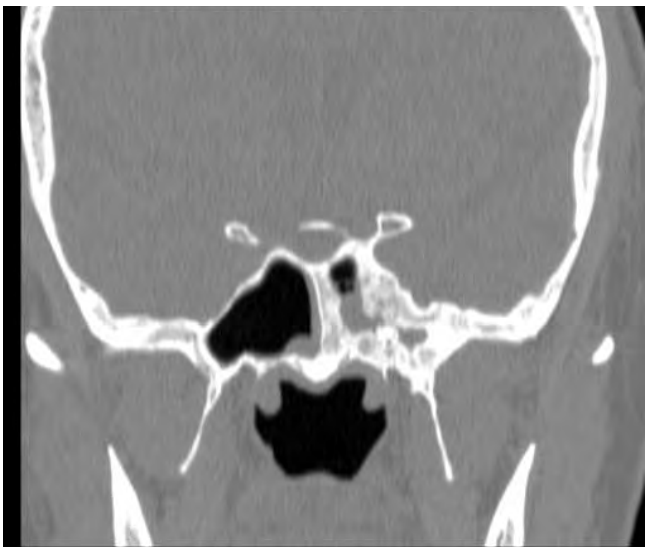
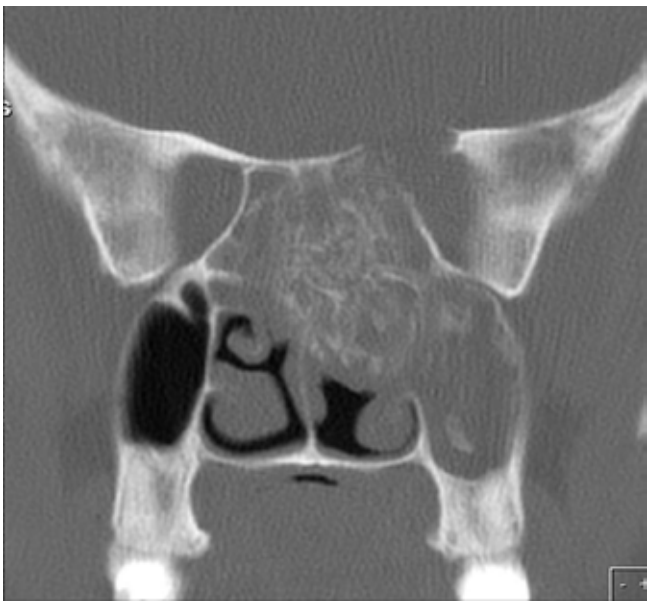


Figure 5.5. Coronal CT showing bilateral osseous metaplasia with associated mucosal swelling affecting ethmoids, maxillary sinus and expansion of posterior ethmoid cell into right orbital roof with bone erosion.



5.1.6. Optic neuropathy

Optic neuropathy has been reported in association with CRS principally affecting the sphenoid or posterior ethmoid region, even without expansion as in a mucocoele but usually in the presence of bone erosion between the sinus and orbital apex. This may occur with eosinophilic fungal rhinosinusitis [1396]. Visual improvement can be anticipated when emergency decompression is undertaken if the visual loss was partial but in patients with pre-operative blindness, recovery is rare [1397]. Endoscopic approaches are most often recommended usually in combination with systemic steroids though no trials have been performed due to the rarity and heterogeneous presentation of the cases.

5.2 CRS with and without NP in relation to the lower airways

5.2.1. Introduction

Due to its strategic position at the entry of the airway, the nose plays a crucial role in airway homeostasis. By warming up, humidifying and filtering incoming air, the nose is essential in the protection and homeostasis of the lower airways [1398]. The nose and bronchi are linked anatomically, are both lined with a pseudo-stratified respiratory epithelium and equipped with an arsenal of innate and acquired immune defence mechanisms. It is not hard to imagine that nasal conditions causing nasal obstruction may become a trigger for lower airway pathology in susceptible individuals. In chronic sinus disease with nasal polyps (NP), total blockage of nasal breathing may occur, hence bypassing nasal functions that may be relevant in preventing lower airway disease. It is however evident that the nasobronchial interaction is not restricted to bronchial repercussions of hampered nasal air conditioning. Nose and bronchi seem to communicate via mechanisms such as neural reflexes and systemic pathways. Bronchoconstriction following exposure of the nose to cold air suggests that neural reflexes connect nose and lung [1399]. However, Koskela et al. [1400] reported on facial cooling rather than nasal cold dry air being responsible for bronchoconstriction in COPD. The neural interaction linking the release of inflammatory mediators in the bronchi following a nasal inflammatory stimulus has recently been shown by bronchial release of neural mediators after selective nasal allergen provocation [1401]. However, the precise neural pathways linking nose and bronchi still remain incompletely understood [1401]. Recently, the systemic nature of the interaction between nose and bronchi has received more attention. Indeed, many inflammatory diseases of the upper airways show a systemic immunologic component involving the blood stream and bone marrow [1402]. In addition to the systemic and neural interaction, genetic factors may as well play a role in the manifestation of nasal and/or bronchial disease [1403]. In spite of the fact that aspiration of nasal contents may take place in neurologically impaired individuals, it is not clear whether micro-aspiration of nasal contents plays a role in the development or severity of bronchial disease [1404].

5.2.2. Asthma and Chronic Rhinosinusitis

CRS with/without NP and asthma / COPD are diseases that often occur together

Bronchial asthma is considered a comorbid condition of CRS. In a recent large-scale European survey, the strong association between CRS and asthma was confirmed [13]. CRS in the absence of nasal allergies was associated with late-onset asthma [13]. In some centres, around 50% of patients with CRS have clinical asthma [1405, 1406]. Interestingly, most patients with CRS who do not report to have asthma show bronchial hyperresponsiveness when given a metacholine challenge test [1405]. In the studies mentioned above, the differentiation of CRS with/without NP was not possible [13] or made [1405, 1406].

Radiologic imaging of the sinuses has demonstrated sinonasal inflammatory opacification in the majority of patients with severe asthma [1406, 1407]. However, these epidemiologic and radiologic data should be interpreted with caution as they may reflect a large referral bias.

Histopathologic features of CRS and asthma largely overlap. Heterogeneous eosinophilic inflammation and features of airway remodelling like epithelial shedding and basement membrane thickening are found in the mucosa of CRS and asthma [1405]. Cytokine patterns in sinus tissue of CRS highly resemble those of bronchial tissue in asthma [524], explaining the presence of eosinophils in both conditions. Therefore, eosinophil degranulation proteins may cause damage to the surrounding structures and induce symptoms at their location in the airway. Finally, lavages from CRS patients show that eosinophils were the dominant cell type in both nasal and broncho-alveolar lavages in the subgroup of patients with CRS with asthma [1086].

Beside the similarities in pathophysiology, sinusitis has been etiologically linked to bronchial asthma, and vice versa. As is the case in allergic airway inflammation, sinusitis and asthma can affect and amplify each other via the systemic route, involving interleukin IL-5 and the bone marrow. In both CRS and allergic asthma, similar pro-inflammatory markers are found in the blood. Recently, nasal application of Staphylococcus aureus enterotoxin B has been shown to aggravate the allergen-induced bronchial eosinophilia in a mouse model [1408]. However, the interaction between both rhinosinusitis and asthma is not always clinically present, as Ragab et al. [1086] found no correlation between rhinosinusitis and asthma severity. However, patients with asthma showed more CT scan abnormalities than non-asthmatic patients [1409], and CT scan abnormalities in severe

asthmatic patients correlated with sputum eosinophilia and pulmonary function [1407].

The interaction between chronic upper and lower airway inflammation has primarily been studied in allergy and not in CRS

Endoscopic sinus surgery (ESS) for CRS aims at alleviating sinonasal symptoms but also improves bronchial symptoms and reduces medication use for bronchial asthma [1410-1413]. After a mean follow-up period of 6.5 years, 90% of asthmatic patients reported their asthma was better than it had been before the ESS, with a reduction of the number of asthma attacks and medication use for asthma [1414]. Also in children with chronic rhinosinusitis and asthma, sinus surgery improves the clinical course of asthma, reflected by a reduced number of asthma hospitalizations and schooldays missed [1415]. Lung function in asthma patients with CRS was reported to benefit from ESS by some authors [1413, 1416, 1417], but denied by others [1410, 1412, 1415]. Of note, not all studies show beneficial effects of ESS on asthma [1418]. The reason for the inconsistency in study results between studies relates to the heterogeneity and small number of patients included in these studies, and difference in outcome parameters studied. Interestingly, the presence of lower airway disease may have a negative impact on the outcome after ESS. Outcomes after ESS were significantly worse in the asthma compared to the non-asthma group [1411, 1417]. Poor outcomes after ESS have also been reported in patients with aspirin-intolerant asthma [1215, 1419, 1420]. On the other hand, other authors report that asthma does not represent a predictor of poor symptomatic outcome after primary [1219, 1421] or revision ESS [1409]. In a series of 120 patients undergoing ESS, Kennedy [762] reports that asthma did not affect the outcome after ESS when comparing patients with equally severe sinus disease, except for the worst patients, in which asthma did adversely affect the outcome.
Interestingly, Ragab et al. [1422] published the first randomized prospective study of surgical compared to medical therapy of 43 patients with CRS with/without NP and asthma. Medical therapy consisted of a 12 weeks course of erythromycin, alkaline nasal douches and intranasal corticosteroid preparation, followed by intranasal corticosteroid preparation tailored to the patients' clinical course. The surgical treatment group underwent ESS followed by a 2-week course of erythromycin, alkaline nasal douches and intranasal corticosteroid preparation, 3 months of alkaline nasal douches and intranasal corticosteroid, followed by intranasal corticosteroid preparation tailored to the patients' clinical course. Both medical as well as surgical treatment regimens for CRS were associated with subjective and objective improvements in asthma state. Interestingly, improvement in upper airway symptoms correlated with improvement in asthma symptoms and control.

The presence of asthma is a negative predictor of outcome after ESS for CRS w/s NP

5.2.3. Asthma and Chronic Rhinosinusitis with NP

Seven percent of asthma patients have NP compared to lower percentages in the non-asthma population [505]. In non-atopic asthma and late onset asthma, NP are diagnosed more frequently (10-15%). Alternatively, up to 60 % of patients with NP have lower airway involvement, assessed by history, pulmonary function and histamine provocation tests [1423]. Aspirin-induced asthma is a distinct clinical syndrome characterized by the triad aspirin sensitivity, asthma and NP and has an estimated prevalence of one percent in the general population and ten percent among asthmatics [1424].

Increased nasal colonization by Staphylococcus aureus and presence of specific IgE directed against Staphylococcus aureus enterotoxins were found in NP patients [661]. Interestingly, rates of colonization and IgE presence in NP tissue were increased in subjects with NP and co-morbid asthma or aspirin sensitivity. By their super-antigenic activity, enterotoxins may activate inflammatory cells in an antigen-unspecific way. Indeed, nasal application of Staphylococcus aureus enterotoxin B is capable of aggravating experimental allergic asthma [1408].
No well-conducted trials on the effects of medical therapy for NP on asthma have been conducted so far. After ESS for NP in patients with concomitant asthma, a significant improvement in lung function and a reduction of systemic steroid use was noted, whereas this was not the case in aspirin intolerant asthma patients [1420]. In a small series of patients with NP, endoscopic sinus surgery did not affect the asthma state [1425]. However, nasal breathing and quality of life improved in most patients.
Data on effects of surgery for NP on asthma mostly point towards a beneficial effect of surgery on different parameters of asthma. Ehnhage et al. investigated the effects of FESS followed by fluticasone proprionate nasal drops 400 µg twice daily on nasal and lower airway parameters in 68 asthmatics with NP. It was conducted over 21 weeks and the effects of FESS on nasal and lower airway parameters were examined. FESS significantly improved mean asthma symptom scores and daily PEFR and all the nasal parameters measured [1426]. Batra et al. [1420] reported a significant improvement in lung function (FEV1) and a reduction in OCS use after FESS in 17 patients with NP and oral corticosteroid dependent asthma. In a series of 13 patients with nasal polyposis and asthma, Uri et al. [1425] reported that FESS did not improve the asthma state in patients with massive nasal polyposis. However, there was a significant decrease

in oral corticosteroid and bronchodilator inhaler usage. In a subgroup of 35 patients with NP and asthma, Ragab et al. [1427] reported that FESS had a subjective and objective tendency for asthma improvement. Although the study results are not always consistent, overall it would appear that FESS has a positive effect on asthma in nasal polyposis.

5.2.4. Cystic fibrosis and rhinosinusitis

Bilateral NP in children are often a clinical sign of CF [1428]. Sinonasal inflammation is found in most CF patients, with NP being present in 1/3 of CF patients. Rhinosinusitis may often be a presenting symptom of the so-called atypical CF patient with normal or borderline sweat test result and carrying only one mild mutation of the CFTR gene [1428].

A significant association exists between broncho-alveolar lavage and sinus cultures in cystic fibrosis patients [1429]. Children with CF undergoing sinus surgery may experience some improvement of lung function parameters, although this change may not be uniform [1430]. Large-scale prospective studies on the effects of FESS on lower airway function in CF are lacking.

5.2.5. COPD and rhinosinusitis

The upper airways of COPD patients remain less studied than in asthma in spite of the fact that a majority of COPD patients presenting at an academic unit of respiratory disease do experience sinonasal symptoms [1431, 1432]. Several pro-inflammatory mediators have been found in nasal lavages of COPD patients [1432] and nasal symptoms corresponded with the overall impairment of the quality of life [1431]. Recently, a high number of patients with bronchiectasis have shown to present with rhinosinusitis symptoms, radiologic abnormalities on CT scans [1433] and have a reduced smell capacity [1434]. The impact of upper airway treatment in patients with COPD and bronchiectasis still needs to be properly investigated.

5.3. Cystic Fibrosis

5.3.1. Summary

There is increasing evidence that multiple genetic and protein expression differences in CF patients may contribute to their tendency to develop CRS. Future studies may identify genome- and proteome-level therapeutic targets, which may be used to prevent or lessen the severity of CRS in CF patients. Topical nasal dornase alfa, nasally inhaled or irrigated antibiotics, and saline irrigations have all been shown to improve outcomes in CF patients with CRS, both as monotherapy or combined with ESS. ESS also improves outcomes in CF patients with CRS. Future prospective studies are needed to further elucidate the role of medical and surgical therapy in CF patients with CRS.

5.3.2. Introduction

Cystic fibrosis (CF) is the most common lethal recessive disorder in Caucasians. It is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CTFR) gene on chromosome 7, which leads to production of a defective chloride channel. This in turn causes improper salt balance and thick tenacious secretions in CF patients. Since Bulgarelliet al. [1435] and others reported sinusitis in patients with pulmonary and pancreatic manifestations of cystic fibrosis, it has been recognized that patients with cystic fibrosis are prone to the development of early and refractory chronic rhinosinusitis (CRS). While mucous stasis and impaired mucociliary transport play a significant role, the full range of factors at play in this association have yet to be elucidated. Chronic bacterial infections and host inflammatory response cause stasis and damage in the sinuses, lungs, and gastrointestinal system, and it is thought that high mucus viscosity leads to obstruction of sinus ostia, dysfunction of ciliary clearance, and recurrent polyposis and paranasal sinus infections.

5.3.3. Anatomic, histopathologic, and physiologic factors in Cystic Fibrosis patients with Chronic Rhinosinusitis

Histopathologic studies have found several differences in expressed proteins found in CF and control patients, particularly proteins involved in the various inflammatory pathways. Additionally, studies have found altered glandular structure in CF patient sinonasal mucosa. Studies have examined anatomic differences in CF patients, such as hypoplasia or decreased aeration in the sinus cavities of CF patient. The prevalence of heterozygous CFTR gene mutations in patients with chronic rhinosinusitis has also been examined.

5.3.3.1. Bacteriology/Mycology

The bacteriology and the association between pathogenic bacteria found in bronchoalveolar lavages (BAL) and paranasal cavity cultures in patients with cystic fibrosis (CF) has recently been the subject of investigation [1429]. In CF patients who underwent functional endonasal endoscopic sinus surgery (FESS) culture samples obtained from bronchoalveolar lavages and paranasal cavities most frequently demonstrated Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus viridans. Statistical analysis revealed a statistically significant association between paranasal cavity cultures and lower airway bronchoalveolar lavage cultures for P. aeruginosa and S. aureus. Another study reviewed 30 consecutive CF patients undergoing ESS for the presence of sinus fungal isolates [1436]. Thirty-three percent of fungal cultures were positive, with two patients newly diagnosed with allergic fungal sinusitis. The opportunistic pathogen Pseudomonas aeruginosa is a frequent colonizer of the airways of patients suffering from

cystic fibrosis (CF). In a study it was observed in several children that the paranasal sinuses constitute an important niche for the colonizing bacteria in many patients. The paranasal sinuses often harbor distinct bacterial subpopulations, and in the early colonization phases there seems to be a migration from the sinuses to the lower airways, suggesting that independent adaptation and evolution take place in the sinuses. Importantly, before the onset of chronic lung infection, lineages with mutations and antibiotic-resistant clones are part of the sinus populations. Thus, the paranasal sinuses potentially constitute a protected niche of adapted clones of P. aeruginosa, which can intermittently seed the lungs and pave the way for subsequent chronic lung infections [1437]. It has been suggested that P. aeruginosa can adapt or acclimate to the environment in the lungs, during growth in anoxic parts of the paranasal sinuses [1438].

5.3.3.2. Arachidonic Acid Metabolism

Patients with CF are known to have increased pro-inflammatory cytokine, leukotriene, and prostaglandin production. The staining patterns of cyclooxygenase 1 and 2 (COX-1 and -2) and 12-Lipoxygenase lipoxygenase (12-LO) in the sinonasal epithelium and submucosal glands of CF and non-CF patients with chronic rhinosinusitis (CRS) demonstrates a significant elevation in the staining of columnar epithelium and submucosal glands for COX-2 and 12-LO in CF patients compared to control CRS patients [1439]. No significant differences were noted for the staining intensity of COX-1, 5-LO, or 15-LO. The upregulation of COX-1 and COX-2 in nasal polyps in patients with cystic fibrosis has also been examined [1440]. The degree of mRNA and protein expression of COX-1 and COX-2 in the nasal mucosa of patients with CF was examined using RT-PCR and Western blot analysis. COX-1 and COX-2

Table 5.3.1. CF Histological, immunohistochemical, and immunological markers.

Study	Marker	Tissue	Method	Conclusion
Owens et al. 2008 [1439]	COX-1, COX-2, 5-LO, 12-LO, and 15-LO	sinonasal epithelium and submucosal glands	IHC	significant elevation in epithelial COX-2 (cytoplasm) and 12-LO (cytoplasm and nucleus) and submucosal glands for COX-2 (cytoplasm) and 12-LO (cytoplasm) in CF patients compared to controls. No difference in COX-1, 5-LO, or 15-LO
Roca-Ferrer 2006 et al. [1440]	COX-1, COX-2	nasal polyps and nasal mucosa	RT-PCR and Western blot	COX-1and COX-2 mRNA significantly higher in CF NP versus control nasal mucosa, COX-1 and COX-2 protein levels significantly higher in CF NP versus nasal mucosa and non-CF NP
Schraven et al 2011 [1441]	mucous ducts and glands	sinus mucosa	histology and IHC	CF showed dilated glandular ducts, predominance of mucous glands, elevated plasma cells and mast cells but not eosinophils
Wu et al 2001 [1442]	goblet cells (GCs), submucosal glands and mucin gene (MUC) expressing cells	sinonasal mucosa	histology and IHC	significantly increased area of submucosal glands in CRS/CF increased glandular MUC5B expression in CRS/CF vs. non-CF CRS
Knipping et al.2007 [1443]	glands, goblet cells	inferior turbinates and nasal polyps	histology and IHC	CF tissue with high proportion of goblet cells, abnormal seromucous glands with cystic dilatation. glandular cells with inhomogeneous heterogeneous glandular droplets in the supranuclear cell portion.
Sobol et al. 2002 [862]	CD3, CD25, CD68, CD20, MPO, CD138, eotaxin, IL-1beta, IL-2sRalpha, IL-5, IFN-gamma, IL-8, TGF-beta1, and TNF-alpha	sinonasal mucosal tissue	IHC	NP and CF-NP showed increased numbers/activation of T cells, NP patients displayed increase in plasma cells. NP significantly higher levels of eosinophils, eotaxin, and eosinophil cationic protein (ECP)] compared with CRS, controls and CF-NP. CRS characterized by Th1 polarization with high levels of IFN-gamma and TGF-beta, NP showed Th2 polarization/high IL-5 and IgE.
Ebbens et al. 2010 [18]	CD34, sialylated Lewis X Antigen	nasal mucosa	IHC	CRSwNP patients-decreased CD34+ vessels, increased eosinophils and percentage of vessels expressing [sLe(x)]. Tissue eosinophilia but not % of endothelial sLe(x) increased in NP/aspirin intolerance. CF NP similar to simple NP. Antro-choanal polyps-low tissue eosinophils and endothelial sLe(x) + vessels.
Woodworth et al 2007 [1444]	surfactant gene expression (SPA1, A2, and D	sinonasal tissue	RT-PCR	CF patients significantly increased SPA1, SPA2, and SPD mRNA vs. controls. CRS-NP demonstrated elevated SPA1, SPA2, and SPD, but lower levels than CF patients. AFS patients non-significant increase in SPA1, SPA2, SPD vs. controls.

mRNA levels were significantly higher in CF nasal polyps versus control nasal mucosa, but no significant difference was found between CF nasal polyps and non-CF nasal polyps. COX-1 and COX-2 protein levels were significantly higher in CF nasal polyps versus both nasal mucosa controls and non-CF nasal polyps, suggesting that upregulation in the expression of COX-1 and COX-2 might be related to the high production of prostanoids reported in CF patients.

CF patients with CRS show upregulation in COX, MUC/mucin, and surfactant gene expression, as well as increased L-selectin mediated lymphocyte localization and adhesion. Paranasal sinus development is often decreased in CF patients.

5.3.3.3. Mucous Production and Glandular Histology

A study of paediatric CF patients and non-CF patients with CRS with polyps who underwent sinus surgery examined surgically obtained sinus specimens of each group using conventional histology and immunohistochemistry [1441]. CF patients showed dilated glandular ducts and a predominance of mucous glands with a significantly elevated number of plasma cells and mast cells, but not eosinophils, compared to non-CF patients. Another study examined the histologic and morphometric characteristics of paranasal sinus mucosa of paediatric CRS controls and paediatric CF patients with CRS [1442]. The number of goblet cells (GCs) and mucin-expressing cells and the submucosal gland (SMG) area was determined, as well as the cellular localization and expression of MUC5AC and MUC5B mucins. A significantly increased area (4.4-fold) of submucosal glands (SMGs) was detected in the sinus mucosa of patients with CRS/CF compared with controls. Neither GC hyperplasia nor increased expression of MUC5AC was observed in the CRS/CF group, but there was a positive trend toward increased glandular MUC5B expression in the CRS/CF cohort. Colocalization of MUC5AC and MUC5B expression was observed in a subset of GCs. A study examined the microscopic ultrastructural mucosal changes in paediatric CF patients, comparing the nasal mucosa of patients without chronic inflammation as controls and specimens of duodenal mucosa of patients with CF [1443]. The mucosa of CF patients showed seromucous glands displaying abnormal morphological structures with wide mucous cells and cystic dilatation under a thick layer of respiratory epithelium with a high proportion of goblet cells. The glandular cells showed inhomogeneous heterogeneous glandular droplets in the supranuclear cell portion. The nuclei contained dispersed chromatin as a sign of increased activity and the structures of the Golgi apparatus were clearly detectable. Alterations in surfactant gene expression (SPA1, A2, and D) in various forms of inflammatory CRS, including CF, has been examined [1444]. Patients with CF showed significantly increased SPA1, SPA2, and SPD mRNA when compared with controls. Patients with CRS with nasal polyposis also demonstrated elevated SPA1, SPA2, and SPD, but lower levels than CF patients. Patients with allergic fungal sinusitis (AFS) had increased SPA1, SPA2, and SPD, but the increases were not significant versus healthy controls.

5.3.3.4. Inflammatory Mediators

The alteration in various inflammatory pathways in CF patients has been examined. A study compared the inflammatory-cell and cytokine profiles of CRS patients with CF, adults with, and control patients with no allergies or sinus disease [862]. Immunohistochemical analysis found a higher number of neutrophils, macrophages, and cells expressing messenger RNA for interferon gamma and interleukin-8 in patients with CF vs. non-CF patients with CRS or in controls. The number of eosinophils and cells expressing messenger RNA for IL-4, IL-5, and IL-10 was higher in patients with CRS versus those with CF and controls. Subgroups of patients with CRS were identified by inflammatory mediator profile in another study [620]. Sinonasal mucosal tissue from nasal polyp (NP) patients, CF patients with nasal polyps (CF-NP), CRSsNP patients and control patients were stained for CD3, CD25, CD68, CD20, myeloperoxidase (MPO), CD138, eotaxin, interleukin IL-1beta, IL-2sRalpha, IL-5, interferon IFN-gamma, IL-8, transforming growth factor TGF-beta1, and tumour necrosis factor-alpha. NP and CF-NP patients showed increased numbers and activation of T cells, while only NP patients displayed an increase in plasma cells. NP patients had significantly higher levels of eosinophilic markers (eosinophils, eotaxin, and eosinophil cationic protein (ECP)) compared with CRS, controls and CF-NP. CRS was characterized by a Th1 polarization with high levels of IFN-gamma and TGF-beta, while NP showed a Th2 polarization with high IL-5 and IgE concentrations. NP and CF-NP were discriminated by oedema from CRS and controls, with CF-NP displaying a very prominent neutrophilic inflammation. The expression of the endothelial L-selectin ligand was examined in patients with nasal polyps, including CF patients [18]. Selectins are a family of glycoproteins essential for leukocyte recruitment, and L-selectin is expressed by most circulating leukocytes. L-selectins on leukocytes and their counter-receptors on endothelial cells (such as CD34) have been shown to be involved in leukocyte recruitment in chronic rhinosinusitis without nasal polyps. CD34 is a cell-cell adhesion molecule also required for T cells to enter lymph nodes, and binds to L-selectin. CD34 is expressed on lymph node endothelia whereas the L-selectin to which it binds is on the T cell. The sialylated Lewis X Antigen (sLe(x)) is another reported selectin ligand. Patients with NP showed a decrease in the number of CD34+ vessels while the number of eosinophils and the percentage of vessels expressing endothelial sulfated (sLe(x)) tetrasaccharide epitopes was upregulated in all groups of simple NP. Tissue eosinophilia but not the percentage of

endothelial sulfated sLe(x) epitopes was also increased in NP patients with aspirin intolerance. Results in CF NP patients were similar to those observed for simple NP. Antro-choanal polyps were characterized by low numbers of tissue eosinophils and relatively few vessels expressing endothelial sulfated sLe(x) epitopes.

5.3.3.5. Anatomic Variations

Variations in temporal bone pneumatization (TBP) and paranasal sinus pneumatization (PSP) in CF patients were assessed by computed tomography [1445]. Genotype data for patients with CF was determined. TBP did not differ between CF, CRS and controls. PSP was less developed in the CF group than the CRS and control groups. CRS and controls did not differ in PSP. The DeltaF508 status correlated with poorer PSP, but greater TBP. PSP was impaired in CF, and DeltaF508 homozygosity was related to poor PSP. TBP was well preserved in the CF population and DeltaF508 homozygosity correlated with greater TBP.

5.3.4. Heterozygous and Homozygous CTFR Mutations and CRS

Evidence suggests that even CFTR-mutation heterozygotes may be more likely to experience CRS when compared to the normal wild-type CFTR population.

Several studies have examined the prevalence of mutations in the cystic fibrosis transmembrane regulator (CFTR) gene in the CRS population, and whether heterozygous mutations predispose patients to CRS [1446]. One study examined the DNA of CRS patients and controls for 16 mutations accounting for 85% of CF alleles in the general population [1351]. Chronic rhinosinusitis patients with 1 CF mutation were evaluated for a CF diagnosis by sweat chloride testing, nasal potential difference measurement, and DNA analysis for additional mutations. Of 147 patients with CRS and 123 CRS-free control volunteers 11 CRS patients were found to have a CF mutation (DeltaF508, n = 9; G542X, n = 1; and N1303K, n = 1). Diagnostic testing excluded CF in 10 of these patients and led to CF diagnosis in one patient. The proportion of CRS patients who were found to have a CF mutation (7%) was significantly higher than in the control group (2%). Nine of the 10 CF carriers had the CTFR gene polymorphism M470V, and M470V homozygotes were significantly overrepresented in the remaining 136 CRS patients. Another study surveyed 261 obligate CFTR heterozygotes and a control group of 201 individuals negative for a standard mutation panel for possible CF-related conditions such as asthma, bronchiectasis, pneumothorax, allergic bronchopulmonary aspergillosis, sinusitis, nasal polyps, gallstones, liver cirrhosis, diabetes, pancreatitis, bone fractures, and hypertension [1447]. There was no difference between heterozygotes and controls, with the exception of hypertension (carriers 28/261, controls 7/201, p = 0.004), and, in males, nasal polyps (carriers 7/126, controls 0/102, p value = 0.0178), and, again, hypertension (carriers 17/126, controls 5/102, p value = 0.0407). The investigated CF-related conditions were no more frequent in CF heterozygotes than in control subjects, with the exception of a higher rate of hypertension overall in heterozygotes and a higher rate of nasal polyposis in male CF heterozygotes. When age-matched carriers and controls were compared these differences disappeared, suggesting that age differences in the groups with significant differences in nasal polyps and hypertension may have contributed. A study in an isolated population practicing a communal lifestyle with common environmental exposures examined genetic variation underlying susceptibility to CRS using linkage analysis [1337]. Using physical examination, medical interviews, and a review of medical records, eight individuals with CRS were identified from 291 screened. These eight individuals were related to each other in a single 60 member, nine-generation pedigree. A genome-wide screen for loci influencing susceptibility to CRS using 1123 genome-wide markers was conducted and the largest linkage peak was on chromosome 7q31.1-7q32.1, 7q31 and included the CFTR locus again indicating that CTFR mutations may be a marker for CRS. Genotyping of 38 mutations in the CFTR gene did not reveal variation accounting for this linkage signal.
In the paediatric population a study examined 58 white children who had chronic rhinosinusitis, none of whom satisfied diagnostic criteria for CF, who underwent sweat testing and genotyping for CFTR mutations using an assay that detects 90% of mutations seen in this ethnic group [1448]. Of the patients tested 12.1% harboured CFTR mutations as compared with the expected rate of 3% to 4% in this ethnic group. The mutations included DeltaF508, R117H, and I148T. Only 1 child had a borderline abnormal sweat test. Two of the patients experienced recurrent Pseudomonas aeruginosa rhinosinusitis, and both were DeltaF508 heterozygotes. Three other children with no detectable CFTR mutation had borderline elevated sweat-test results. A related study examined the prevalence of chronic rhinosinusitis in known cystic fibrosis carriers [1449]. Obligate CF carriers (parents of patients with CF) were assessed by a sinus disease questionnaire and a subgroup of participants was evaluated by a physician for signs and symptoms of CRS. Of 147 obligate CF carriers 36% had self-reported CRS. Twenty-three CF carriers (14 with and 9 without CRS based on self-reporting in the questionnaire) were clinically evaluated and of these7 were diagnosed as having CRS (all 7 with self-reported CRS), while another 6 had allergic rhinitis or recurrent acute rhinosinusitis (all 6 with self-reported CRS), and 10 had no evidence of active sinus disease (1 with self-reported CRS).
Another study examined 126 cystic fibrosis patients, 90 with

typical clinical features and 36 with atypical phenotypes [1450]. Genetic tests were carried out to determine the genotype of CFTR gene. Cytological examination of nasal mucosa was carried out in all the patients. In 71.5% of patients with cystic fibrosis, infectious chronic non-specific rhinosinusitis was found. Other types of rhinosinusitis such as acute infectious, chronic allergic and non-allergic with eosinophilia were found in 21.4% of patients, whereas in 7.1% of patients no clinical symptoms of rhinosinusitis were found. Nasal polyps were found in 18.3% of patients with cystic fibrosis: in 21 patients with a typical form and in 2 patients with an atypical form. Nasal polyps were more frequent in groups with the genotype consisting of both "strong" mutations than in the group with unknown or "mild" mutations.

Conclusion: There is Level II and III evidence that significant immunologic differences exist in the CF population with CRS versus non-CF CRS patients. COX-1 and COX-2 are upregulated in CF patients with CRS, leading to increased prostaglandin levels. Level III data also suggests an increase in mucous gland proliferation, surfactant gene expression, and MUC mucin gene expression is also seen in CF patients with CRS, and L-selectin receptors involved in lymphocyte localization and adhesion are also increased in CF patients with CRS. There are conflicting level II and III reports on whether CFTR-mutation heterozygotes are more likely to experience CRS, but the predominance of level II and III data suggests that patients who are heterozygous carriers of CF mutations are more predisposed to CRS when compared to the normal wild-type CFTR population. Level II and III data suggests that the bacteriology of bronchial cultures in CF patients often correlates with the bacteriology of sinonasal cultures.

There is Level IB evidence to support the use of nasally inhaled dornase alfa in CF patients with CRS, and level II and III evidence supporting the use of nebulized or irrigated topical antibiotics in CF patients with CRS.

5.3.5. Medical Therapy in Cystic Fibrosis and Chronic Rhinosinusitis

5.3.5.1. Dornase Alfa

Two studies have examined the use of dornase alfa (the mucolytic agent Pulmozyme) in CF patients with CRS. One study reported on the efficacy of dornase alfa as a postoperative adjunct in CF patients with CRS in a double-blind placebo-controlled trial on 24 patients with cystic fibrosis and chronic sinusitis [1451]. The patients underwent sinonasal surgery during a 3-year period and received once-daily doses of either dornase alfa (2.5 mg) or hypotonic saline solution (5 mL of 0.876% w/v NaCl solution) beginning 1 month after surgery and for a 12-month period. Primary outcomes were nasal-related symptoms and nasal endoscopic appearance; secondary outcomes were forced expiratory volume in 1 second, nasal computed tomography findings, and saccharine clearance test results. Patients were evaluated before and after treatment. All postoperative outcomes were significantly improved for both treatments at 1 month ($P<.05$); primary outcomes were improved at 24 and 48 weeks in the group receiving dornase alfa ($P<.05$), and at 12 weeks in the group receiving placebo. Secondary outcomes were better in the dornase alfa group ($P<.01$) than in the placebo group at 12 months except for the saccharine clearance test results. In particular, median relative difference in forced expiratory volume in 1 second between dornase alfa and placebo was significantly improved in the dornase alfa group ($P<.01$). Nasally inhaled dornase alfa was superior to hypotonic saline for improving forced expiratory volume in 1 second, nasal computed tomography findings, and saccharine clearance test results. Another double-blinded placebo-controlled crossover trial examined sinonasal inhalation of dornase alfa in CF patients [1452]. Primary outcome parameters were assessed by the Sino-Nasal Outcome Test (SNOT-20) and ventilated volume as measured by magnetic resonance imaging. Five CF patients were randomized to inhale either dornase alfa or 0.9% NaCl for 28 days and, after a wash-out period of 28 days, crossed over to the alternative treatment. Normal saline was not associated with relevant changes in SNOT-20 scores while dornase alfa significantly improved quality of life as measured by the SNOT-20. MRI results showed no definite trend.

5.3.5.2. Topical Antimicrobial Therapy in CF Patients with CRS

One systematic review examined the evidence for topical antimicrobial therapy in CRS, including some data specifically looking at cystic fibrosis patients with CRS [1453]. A search of the MEDLINE, EMBASE, and CINAHL databases; Cochrane Central Register of Controlled Trials (3rd Quarter 2007); and Cochrane Database of Systemic Reviews (3rd Quarter 2007) databases yielded seven controlled trials with five of these double blinded and randomized. Only one of the randomized trials showed a positive outcome. Overall, there was low-level corroborative evidence for the use of topical anti-bacterials. They found evidence for the use of nasal irrigation or nebulization rather than delivery by nasal spray. For the antibacterial studies, the highest level of evidence was for studies that used postsurgical patients and culture-directed therapy. Both stable and acute exacerbations of CRS appeared to benefit from topical antimicrobials. The evidence in the subgroup of cystic fibrosis patients with CRS seemed to indicate that topical antibiotics should not be first-line management for Cruet were useful in patients refractory to topical steroids and oral antibiotics.

5.3.5.3. Gene Therapy

A single phase II, randomized double blind placebo-controlled trial of tgAAVCF, an adeno-associated cystic fibrosis transmembrane conductance regulator (CFTR) viral vector/gene construct, was identified [1454]. TgAAVCF was given to 23 patients with a dose of 100,000 replication units of tgAAVCF administered to one maxillary sinus, while the contralateral maxillary sinus received a placebo treatment as a control. Neither the primary efficacy endpoint (the rate of relapse of recurrent sinusitis) nor secondary endpoints (sinus transepithelial potential difference (TEPD), histopathology, sinus fluid interleukin IL-8 measurements) achieved statistical significance when comparing treated to control sinuses within patients. One secondary endpoint, measurements of IL-10 in sinus fluid, was significantly increased in the tgAAVCF-treated sinus relative to the placebo-treated sinus at day 90 after vector instillation. The tgAAVCF administration was well tolerated, without adverse respiratory events or enhanced inflammation in sinus histopathology and the Phase II trial confirmed the safety of tgAAVCF but provided little support of its efficacy in the within-patient controlled sinus study.

Conclusion: There is Level IB evidence to support the use of nasally inhaled dornase alfa in CF patients with CRS, with dornase alfa demonstrating an improvement in nasal-related symptoms, nasal endoscopic appearance, FEV1, and CT findings vs. inhaled hypo- and isotonic saline. There is level II and III evidence supporting the use of nebulized or irrigated topical antibiotics as a second-line therapy for CF patients with CRS. There is level IB data demonstrating the safety of tgAAVCF, an adeno-associated cystic fibrosis transmembrane conductance regulator (CFTR) viral vector/gene construct, but no therapeutic benefit vs. control vector in reducing frequency of sinusitis, decreasing IL-8 levels, or decreasing histopathological evidence of inflammation. Further randomized controlled trials on oral and topical steroids and antimicrobials in CF patients with CRS are needed.

5.3.6. Surgical Therapy in Cystic Fibrosis and Chronic Rhinosinusitis

Data on surgical therapy for CF patients with CRS is primarily level III but supports the safety and efficacy of endoscopic sinus surgery in CF patients.

5.3.6.1. ESS in the Adult CF Population

Several retrospective studies and case series have examined the efficacy of endoscopic sinus surgery in the CF population, but no randomized controlled trials specifically on CF and CRS were identified. One prospective, non-randomized study examining ESS in CF patients was identified [1455]. One study used a retrospective medical record review of the extent of nasal polyposis endoscopically in a cystic fibrosis population before the first surgical intervention and the effect of the severity of preoperative polyposis on the need for revision ESS in the CF population [1456]. Patients with a clinical preoperative diagnosis of cystic fibrosis and sinusitis were graded preoperatively with the extent of polyps prospectively graded into 3 groups before the first surgical intervention [no polyps (grade A), mild polyposis (grade B), and extensive polyposis (grade C)]. The number of patients needing revision ESS and the mean time to revision ESS were compared among the 3 groups: 14 patients required revision surgery: 3 with mild polyps and 11 with extensive polyps. Mean time to revision surgery was 39.7 months for those with grade B and 23.8 months for those with grade C and the rate of revision ESS was significantly different among the 3 groups. A nested case-control study examined the outcomes following endoscopic sinus surgery in adult patients with cystic fibrosis compared matched controls without CF [1456]. Preoperative CT and preoperative/postoperative endoscopic findings and changes in two disease-specific quality-of-life (QoL) instruments were evaluated both preoperatively and postoperatively. Preoperative CT scores and endoscopy scores were significantly worse in CF patients. Postoperative endoscopy scores were significantly worse for CRS patients with CF, although the degree of improvement on endoscopy within each group was no different and both groups experienced similar improvement in QoL after ESS.

The benefit of endoscopic mega-antrostomy for recalcitrant maxillary sinusitis in CRS patients including CF patients was examined in a retrospective review of patients who underwent endoscopic maxillary mega-antrostomy (EMMA) for recalcitrant maxillary sinusitis [1457]. Relevant comorbid factors included prior Caldwell-Luc or maxillofacial surgery (16/42), cystic fibrosis (11/42), asthma (11/42), and IgG deficiency (3/42). Seventy-four percent of patients reported complete resolution of symptoms while 26% reported partial symptomatic improvement. EMMA appeared to be effective and safe for the management of recalcitrant maxillary sinus disease, including the CF subset of patients.

A prospective trial examined the efficacy of endoscopic surgery with serial antimicrobial lavage (ESSAL) in CF patients, comparing ESSAL in 32 patients to conventional sinus surgery without serial antimicrobial lavage in 19 controls [1455]. Conventionally treated patients underwent nasal polypectomy, ethmoidectomy, antrostomy, or Caldwell-Luc operation while the ESSAL approach incorporated preoperative rhinosinuscopy and computed tomography, endoscopic surgery, a postoperative course of antral antimicrobial lavage, and monthly maintenance antimicrobial lavage via brief antral catheterization. The main outcome measure was intensity

and frequency of sinus surgery after initial presentation. The two groups were similar in clinical presentation, including the presence of nasal polyposis. The ESSAL group had fewer operations per patient, fewer Caldwell-Luc procedures, and a decrease in repeated surgery at 1-year and 2-year follow-ups.

CF patients tend to have worse preoperative CT and endoscopy scores than non-CF CRS patients, but the degree of improvement on endoscopy and the improvement in QoL after ESS tends to be similar in CF and non-CF patients. ESS with serial antimicrobial lavage has been shown to be superior to surgery alone in CF patients, and CF patients may benefit from mega-antrostomies for recalcitrant disease.

Several other retrospective, Level III studies examined the safety and efficacy of ESS in the CF population. A retrospective study on the effect of ESS on CF with nasal polyposis found that the patients had a 50% chance either of their symptoms returning to preoperative severity or of undergoing a second endoscopic sinus procedure, by 18 to 24 months of postoperative follow-up [1458]. Patients with predominantly infective symptoms of mucopurulent rhinorrhoea and pain had a significantly better outcome than patients with predominantly nasal blockage. The chance of the infective symptom group of patients suffering symptom deterioration back to the preoperative state or undergoing a second endoscopic sinus operation was 37% of that of the nasal blockage symptom group. A retrospective study on functional endoscopic ethmoidectomy (FEE) in patients with CF found that symptoms improved or disappeared in 9/12 cases between 1 and 3 years of follow-up and in 5/7 cases after 3 years of follow-up with a good or mild anatomical result recorded in 6/12 cases between 1 and 3 years of follow-up and in 5/7 cases after 3 years of follow-up. During follow-up, a new surgical procedure (limited in 8 patients and complete in 3 patients) was often necessary. A retrospective review of complications of ESS in patients with demonstrated a complication rate of 11.5%, which compared favourably with the non-CF ESS complication rates of 0-17% reported in the literature. A related study on the effectiveness of sinus surgery in CF patients status post lung transplant reviewed ESS in 37 patients with cystic fibrosis after lung transplantation and found ESS to be successful in 54% and partially successful in 27% of patients [1459]. A significant correlation was found between negative sinus aspirates and negative BAL and between positive sinus aspirates and positive BAL. Successful sinus management led to a significantly lower incidence of tracheobronchitis and pneumonia.

5.3.6.2. ESS in the Paediatric CF Population

A retrospective review of paediatric patients with CF treated for recurrent sinusitis Duplechain et al. [1460] examined the role of ESS in. The charts of 32 children were retrospectively reviewed. All children underwent surgery performed by one of two physicians. The presence of polyps in the population with cystic fibrosis was significant; 86% of patients (12 of 14) in the CF group demonstrated polyps at the time of surgery, whereas polyps were detected in only 16% of the patients (3 of 18) with non-CF CRS. Eighty-nine percent (eight of nine) of intraoperative sinus culture samples were culture positive for Pseudomonas species in the CF group, while none of the samples taken from the group with non-CF showed Pseudomonas organisms. ESS was safe, well-tolerated, and effective in the paediatric CF and non-CF populations. Another retrospective study examined the relationship between CF and ESS [1461]. Sixteen paediatric and 1 adult patients with previously diagnosed CF, documented chronic sinus disease and nasal polyposis that had failed long-term maximal medical management underwent ESS. The patients or their parents rated the pre- and postoperative severity and frequency of their symptoms associated with chronic sinus disease. There was no change in the relative health of patients as measured by the number of hospitalizations but there was a significant improvement in the quality of life. There was a marked decline in the frequency of nasal obstruction, nasal discharge and postnasal drip and a high level of patient satisfaction following FESS.

Conclusion

Data on surgical therapy for CF patients with CRS is primarily level III. The available data supports the use of ESS in CF-related CRS, and supports its safety and efficacy in retrospective studies. The level III data also suggested that the rate of complications is similar to non-CF patients, that ESS is safe in paediatric CF patients, and that patients with more severe polyposis tended to require repeat surgery more frequently. Two level IIA studies were identified. One prospective case control study demonstrated that while CF patients tended to have worse preoperative CT scores and endoscopy scores and worse postoperative endoscopy scores, the degree of improvement on endoscopy and the improvement in QoL after ESS tended to be similar in CF and non-CF patients. Another level IIA, prospective trial demonstrated that endoscopic surgery with serial antimicrobial lavage (ESSAL) was superior to surgery alone in CF patients, with the ESSAL group having fewer operations per patient, fewer Caldwell-Luc procedures, and a decrease in repeated surgery at 1-year and 2-year follow-ups. Randomized controlled trials are lacking.

5.4 Aspirin exacerbated respiratory disease

5.4.1. Summary

The presence of aspirin sensitivity in a patient with rhinosinusitis/asthma is associated with severe and protracted eosinophylic airway disease requiring comprehensive management of all components of the syndrome. The diagnosis of ASA-hypersensitivity initially based on a history should be confirmed/excluded with oral, nasal or bronchial provocation testing with aspirin. Avoidance of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) should be recommended and the airway disease management should follow general guidelines, with emphasis on adequate dose of topical steroids. If sinus surgery is performed the beneficial effects may extend to bronchial asthma. Desensitization and maintenance treatment with aspirin may be valuable alternative for some patients.

5.4.2. Introduction

Presence of hypersensitivity to aspirin/NSAID's in a patient with chronic rhinosinusitis heralds severe, hyperplastic sinus disease with high polyps recurrence after sinus surgery

The presence of hypersensitivity to aspirin or other NSAIDs in a patient with rhinosinusitis and nasal polyposis is associated with a particularly persistent and treatment-resistant form of the disease, coexisting usually with severe asthma and referred to as the "aspirin triad" [1462]. Since the chronicity of the upper and lower airway inflammation is not related to NSAIDs intake or avoidance, and NSAIDs only occasionally may exacerbate symptoms the term Aspirin Exacerbate Respiratory Disease (AERD) has been recently propose to describe this syndrome [1463, 1464]. The prevalence of nasal polyposis in aspirin-sensitive asthmatics may be as high as 60-70%, as compared to less than 10 % in the population of aspirin-tolerant asthmatics [1465]. The unusual severity of the upper airway disease in these patients is reflected by high recurrence of nasal polyps, and frequent need for endoscopic sinus surgery [1466, 1467]. Rhinosinusitis in aspirin hypersensitive patients with nasal polyposis is characterized by involvement of all sinuses and nasal passages and the thickness of hypertrophic mucosa is significantly higher in AERD patients as documented with computer tomography [1468].

5.4.3. Pathomechanism of acute ASA-induced reactions

In ASA-sensitive patients acute nasal symptoms (sneezing, rhinorrhoea and congestion) may be induced by challenge with oral or intranasal aspirin but also with other cross-reacting NSAIDs .The mechanism of these acute adverse reactions has been attributed to inhibition by NSAIDs of an enzyme cyclooxygenase-1, with subsequent inflammatory cell activation and release of both lipid and non-lipid mediators [1469, 1470]. The ASA-induced nasal reaction is accompanied by an increase in both glandular (lactoferrin, lysozyme) and plasma (albumin) proteins in nasal secretions indicating a mixed response, involving both glandular and vascular sources [1471]. Concomitant release of both mast cell (tryptase, histamine) and eosinophil (ECP) specific mediators into nasal washes clearly indicate activation of both types of cells [1472-1474]. Increased concentration of cysteinyl leukotrienes in nasal secretion was also observed within minutes after ASA-challenge although the cellular source of leukotrienes has not been determined [1475]. In parallel with inflammatory mediator release an influx of leucocytes into nasal secretions occurred with significant enrichment in eosinophils [1474].

The mechanisms of hypersensitivity to aspirin/NSAID's is not immunological, but is related to cyclooxygenase inhibition and involves several abnormalities of the arachidonic acid metabolism

5.4.4. Pathomechanism of chronic rhinosinusitis and nasal polyposis in patients with AERD

Although the pathogenesis of chronic eosinophilic inflammation of the airway mucosa and nasal polyposis in ASA-sensitive patients, does not seem to be related to intake of aspirin or other NSAIDs it has been speculated that the pathomechanism underlying rhinosinusitis and nasal polyposis in aspirin-sensitive patients may be different from that in aspirin tolerant patients [1467, 1476].

Cells and cytokine profile

A marked tissue eosinophilia is a prominent feature of rhinosinusitis and nasal polyposis in ASA-hypersensitive patients and accordingly significantly more ECP was released from non-stimulated or stimulated nasal polyp dispersed cells from ASA-sensitive patients [1477, 1478]. An increased number of eosinophils in the tissue has been linked to distinctive profile of cytokine expression with upregulation of several cytokines related to eosinophil activation and survival (e.g. IL-5, GMC-SF, RANTES, eotaxin) [902, 1479, 1480]. It has been suggested that overproduction of IL-5 might be a major factor responsible for an increased survival of eosinophils in the nasal polyps resulting in increased intensity of the eosinophilic inflammation particularly in aspirin-sensitive patients [1481]. In fact decreased apoptosis was documented in polyps from aspirin-sensitive patients, and increased infiltration with eosinophils was associated with prominent expression of CD45RO+ activated/memory cells and this cellular pattern was related to clinical features of rhinosinusitis [1482]. Bachert at al [542] demonstrated, that IgE-antibodies to Staphylococcal

enterotoxins (SAEs) were present in nasal polyp tissue and their concentration correlated with the levels of ECP, eotaxin and IL-5. These relations seemed to be particularly evident in ASA-sensitive patients suggesting that an increased expression of IL-5 and ECP in polyp tissue from ASA-sensitive patients may be related to the presence of SAE that can exert direct effects on eosinophil proliferation and survival or may act as a superantigen to trigger a T-cell mediated inflammatory reaction [1483-1485].

Not only activated eosinophils but also mast cells are abundant in the nasal polyps tissue from ASA-sensitive patients [824, 1486]. The density of mast cells was correlated with the number of polypectomies, implicating an important role for these cells in the pathogenesis of nasal polyposis. Stem cell factor (SCF) also called c-kit ligand is a multi-potent cytokine generated by nasal polyp epithelial cells and critical for differentiation, survival, chemotaxis and activation and of human mast cells but also involved in eosinophil activation and degranulation. SCF expression in nasal polyp epithelial cells in culture correlated closely with the density of mast cells in nasal polyp tissue and was significantly higher in asthmatic patients with aspirin hypersensitivity as compared to aspirin tolerant patients [1483].

In the nasal polyp tissue from AERD patients expression of metalloproteinase TIMP-1 was found to be significantly reduced and the MMP-9/TIMP-1 ratio was significantly increased in the compared with both aspirin tolerant and patients without nasal polyps, indicating for the importance of metalloproteinases expression in polyps remodelling and inflammatory changes [1487].

Recently, microarray technology was used to examine gene expression in nasal polyps of aspirin sensitive patients. It has been demonstrated that nasal polyps from AERD patients have distinct transcriptional and methylation signatures [1029, 1488, 1489]. Furthermore , using proteomics based approaches several proteins that exhibited differential expression between ATA and AERD patients were identify , although at present pathophysiological and functional significance of these findings is not clear yet [1490, 1491].

5.4.5. Abnormalities in arachidonic acid metabolism

Since Szczeklik et al. [1492] reported an increased susceptibility of nasal polyps cells from ASA-sensitive patients to the inhibitory action of aspirin , arachidonic aid metabolism abnormalities have been considered a distinctive feature of nasal polyps in this subpopulation of patients. A significantly lower generation of PGE2 by nasal polyps and, nasal polyp epithelial cells as well as a decreased expression of COX-2 in nasal polyps of these patients were reported [1055, 1493]. Low expression of COX-2 mRNA in nasal polyps from ASA-sensitive patients was in turn linked to a downregulation of NF-KB activity and to abnormal regulation of COX-2 expression mechanisms at the transcriptional level [1494, 1495]. Since PGE2 has significant anti-inflammatory activity, including inhibitory effect on eosinophil chemotaxis and activation, it has been speculated that an intrinsic defect in local generation of PGE2 or abnormal balance between PGD2/PGE2 could contribute to development of more severe eosinophilic inflammation in aspirin-sensitive patients [1496]. Although a significant deficit of PGE2 was demonstrated in polyp tissue of ASA-sensitive as compared to ASA-tolerant patients, decreased expression of COX-2mRNA seem to be a feature of nasal polyposis also in patients without ASA-sensitivity representing more general mechanism involved in the growth of nasal polyps (595). On the other hand the percentages of neutrophils, mast cells, eosinophils, and T cells expressing prostaglandin EP2, but not EP1, EP3, or EP4 receptors , were significantly reduced in the aspirin-sensitive compared with non aspirin-sensitive patients suggesting a potential regulatory abnormality of inflammatory cells at the receptor level [1497].

Cysteinyl leukotrienes have been implicated in the pathogenesis of chronic mucosal inflammation in ASA-sensitive patients and some studies demonstrated an increased production of cysteinyl leukotrienes in nasal polyps of ASA-sensitive asthmatics as compared to aspirin tolerant patients in vitro [1498, 1499] but these observations could not be reproduced in vivo when nasal washes were analysed [1471, 1475]. Similarly when nasal polyp dispersed cells were cultured basal and stimulated release of LTC4 was found to be similar in nasal polyp cells from ASA-sensitive and ASA-tolerant patients [902]. More recently an increased expression of enzymes involved in production of leukotrienes (5-LOX and LTC4 synthase) and an increased generation of LTC4/D4/E4 in nasal polyp tissue from ASA-sensitive patients were found [1500-1502]. Cysteinyl leukotriene production correlated with tissue ECP concentration both in ASA-sensitive and ASA-tolerant polyps suggesting that these mediators may be linked to tissue eosinophilia rather that to aspirin-sensitivity . On the other hand an increased expression of leukotriene LT1 receptors was found in the nasal mucosa of ASA-sensitive patients, suggesting local hyper-responsiveness to leukotrienes in this subpopulation of patients [1496, 1503]. More recently other arachidonic acid metabolites generated on 15-LOX pathway have been associated with nasal polyposis in AA-sensitive patients. In nasal polyp epithelial cells from ASA-sensitive but not ASA-tolerant patients aspirin triggers 15-HETE generation, suggesting the presence of a specific abnormality of 15-LO pathway in these patients [1493]. Upregulation of 15-lipoxygenase and decreased production of the anti-inflammatory 15-LO metabolite lipoxin A4 found in nasal polyp tissue from ASA-sensitive patients further points to a distinctive but not yet understood role for 15-LO metabolites in nasal polyps.

In summary, presence of hypersensitivity to aspirin or other NSAID heralds not only more severe and protracted clinical

course of chronic rhinosinusitis/nasal polyps by is also associated with distinct pattern of cellular, biochemical and molecular markers of inflammation.

5.4.6. Natural history

A history of chronic rhinosinusitis and or asthma usually precedes the development of hypersensitivity to aspirin. In some patients the beginning of the disease is associated with flu-like infection, which is followed by development of chronic intractable rhinosinusitis with nasal polyps and appearance of asthma [515] Rhinosinusitis and asthma once developed run protracted course which is independent of avoidance of aspirin and other NSAIDs [1463]. Although patients usually report nasal symptoms typical for non-allergic rhinitis, exacerbations of symptoms on exposure to both seasonal and perennial inhalant allergens are reported by significant proportion of patients [1466]. Rhinosinusitis in patients with AERD is complicated by mucosal hypertrophy and polyps formation : the prevalence of nasal polyposis varies from 60% to 90% if diagnosed by rhinoscopy. On computer tomography polypoid mucosal hypertrophy is present in up to 100 % of patients and is more extensive in ASA-sensitive as compared to ASA-tolerant patients with nasal polyposis [1468]. Nasal polyposis has a high tendency to recurrence after surgery ; the recurrence rate in ASA-sensitive patients is several times higher even after ESS [1504].
A subgroup of ASA-sensitive patients manifests a reaction exclusively in the upper respiratory tract; they do not have asthma, but clinical picture of the nasal disease (hyperthrophic rhinosinusitis) in these patients is similar to that observed in patients with ASA-triad [1505]. Although some of these patients may evolve with time to a full aspirin triad, their risk of developing asthma in the future is not known.

5.4.7. Diagnosis of AERD

Oral challenge with aspirin or nasal / bronchial provocation with lysine aspirin are reliable tools to confirm/exclude hypersensitivity to aspirin/ NSAID's

The diagnosis of ASA-hypersensitivity is based on a history of adverse reaction precipitated with ASA or other non-steroidal anti-inflammatory drug. In asthmatic patients with negative history and /or those who have never been exposed to NSAIDs, but have additional risk factors (rhinosinusitis, nasal polyposis, history of near fatal reactions), the risk of adverse reaction is further increased and provocation testing my be required [1506]. Oral challenge is the reference standard for the diagnosis of hypersensitivity to aspirin and other NSAIDs and several protocols for oral aspirin provocation have been developed and described [1507, 1508]. Inhalation challenge with lysine-aspirin (a soluble form of acetylsalicylic acid) has been introduced by Bianco et al. in 1977 [1509] and in Europe is often used to confirm/ exclude aspirin sensitivity in patients with bronchial asthma. Inhalation test is faster and safer to perform than oral challenge (the reaction is usually easily reversible by with nebulized beta2 agonists) and both tests have similar sensitivity and specificity [1510, 1511]. Nasal provocation test with lysine aspirin is also a possible tool to diagnose hypersensitivity to aspirin providing that the clinical symptoms are combined with the objective and standardized technique of airflow measurement for assessment of the results [1512]. The test is rapid and safe and can be performed in an outpatients setting even in asthmatic patients with low pulmonary function not suitable for bronchial provocation. In experienced hands the sensitivity of intranasal aspirin provocation is approaching performance of bronchial challenge [1512, 1513].
More recently in vitro tests measuring aspirin-specific peripheral blood leukocytes activation have been proposed for the diagnosis of aspirin sensitivity.
The newly developed in vitro tests (FLOW CAST and ASPITest) seem to demonstrated promising performance , but require further investigations and validation before becoming routine tools for confirming the presence of aspirin hypersensitivity [1477].

5.4.8. Management of patients with AERD

Selective COX-2 inhibitors (celecoxib) are well tolerated by aspirin sensitive asthmatics and are good alternative NSAID's for patients with aspirin triad

Patient education and careful avoidance of ASA and other NSAIDs in sensitive patients seem to be of high importance, since aspirin may be a cause of severe asthmatic attack [1510].
In most patients acetaminophen in low or moderate doses (below 1000 mg) can be recommended as an alternative antipyretic or analgesic drug. Preferential COX-2 inhibitors (nimesulide, meloxicam) are also tolerated by the majority, but not all, hypersensitive patients and can be recommended in an individual patient after tolerability is proved by oral challenge. Selective COX-2 inhibitors (celecoxib) are well tolerated by aspirin sensitive asthmatics and could be ideal alternative NSAIDs for patients with aspirin triad [1514].

Antileukotrienes are not more effective in aspirin-sensitive as compared to aspirin-tolerant patients

The presence of aspirin sensitivity in a patient with asthma/ rhinosinusitis heralds severe and protracted disease of the respiratory tract, characterized with eosinophilic inflammation

and requiring comprehensive management of all components of the syndrome . Management of asthma and rhinosinusitis in AERD patient should follow general guidelines, but several specific measures for AERD should be considered. Standard treatment for rhinosinusitis includes high doses of topical steroids, antibiotics and occasional bursts of oral corticosteroids to control symptoms and slow down nasal polyps recurrence. Although antileukotriene drugs may also be effective in in AERD patients, they are not more effective than in ASA-tolerant [1515, 1516]. At certain stage of the disease surgical procedures (polypectomy, functional endoscopic sinus surgery or ethmoidectomy) are usually needed to relieve symptoms of CRS and to remove polypoid tissue from sinuses [1517]. Beneficial effects of sinus surgery may extend to bronchial asthma [1518], although patients with AERD seem to respond less well to surgical intervention [1419, 1420, 1519-1521].

Nasal/sinus surgery (polypectomy, functional endoscopic sinus surgery or ethmoidectomy) may be less effective in patients with AERD

In order to control asthma symptoms and lower airway inflammation inhaled glucocorticosteroids in relevant doses, often in combination with long acting beta-2 agonists, are recommended but in about 50% of patients chronic treatment with oral prednisone may be necessary to control the disease. There is some indication that by giving repeated doses of ASA after the initial adverse reaction a desensitization can be achieved [1522-1526] (Evidence level D).

Desensitization and maintenance treatment with aspirin alleviate upper airway symptoms and decrease rate of polyp recurrence in some patients

An alternative, but not well documented approach is intranasal desensitization and prolonged treatment with soluble lysine aspirin, which may reduce recurrence rate for nasal polyps in AERD patients [1527-1530].

5.5. Immunodeficiencies and Chronic Rhinosinusitis

5.5.1. Primary Immunodeficiencies

The association between rhinosinusitis and primary immunodeficiencies (PID) can be examined in one of two ways:
1. Those patients presenting to their primary care physicians or otorhinolaryngologists with recurrent acute rhinosinusitis (RARS) or chronic rhinosinusitis (CRS) who may have an underlying PID contributing to their clinical symptoms or
2. Patients presenting to immunologists with a variety of infections who may have RARS/CRS as one aspect of their clinical picture.

In the first situation, among CRS patients who are referred for immune evaluation, up to half may have T lymphocyte dysfunction [560], while roughly 20% have decreased IgG, IgA or IgM [560, 1531]. In addition, nearly 10% have common variable immune deficiency (CVID) [560,1532]. Among CRS patients who underwent FESS and had immune workup, 72% had low baseline pneumococcal titres, while 11-67% had an inadequate functional response to pneumococcal vaccine [1531,1533] and these patients had lower serum IgA [1533]. These studies were conducted at tertiary institutions, thus it is possible that there is significant selection bias.

In the second situation, when examining patients with PIDs, CVID is the most frequent symptomatic primary immunodeficiency in North America and Europe, with an incidence between 1:25,000 and 1:66,000 [1534]. Among CVID patients, 36 to 78% present with CRS [1534,1535]. In another large cohort of multiple forms of PID [1536], the most common diagnosis was IgA deficiency (30%), followed by IgG subclass deficiency (26%) and hypogammaglobulinemia (23%), with CVID being present in 15%. Less common were combined B and T cell defects (11%), phagocytic defects (8%) and complement defects (3%). RARS was present in 41% of this cohort and CRS in 40% [1537]. In patients with decreased response to pneumococcal vaccine, thus a functional antibody deficiency, 77% have rhinosinusitis [1538].

5.5.1.1 Diagnosis

The diagnosis of PID can be difficult. Up to 20% of the population may have an IgG subclass deficiency but be clinically asymptomatic. Up to 90% of IgA deficient patients are asymptomatic [1539]. Thus a clinically significant diagnosis requires both a defect in antibody responsiveness, as well as recurrent infections. The diagnostic delay between presentation with symptoms and definitive diagnosis ranges from 4.7 to 15 years [1534, 1536, 1540]. Between 53 and 90% of adult and paediatric patients with agammaglobulinemia or CVID present with CT findings of CRS [1541]. These upper airway findings do not correlate with pulmonary imaging and most commonly include mucosal thickening. Bone sclerosis and polyposis are less common [1542].

5.5.1.2 Treatment

Treatment for IgG deficiency is typically intravenous immunoglobulin (IVIG) and/or prophylactic antibiotics. While these treatments may improve overall survival and decrease the rate of serious life threatening infections, they do not appear to prevent radiographic development of CRS [1542] and their clinical benefit in CRS is not proven [1534]. During clinical follow

up of CVID patients, 54 to 63% develop CRS in spite of IVIG [1535, 1540]. Patients with CVID have persistent inflammation in sinus mucosa and positive bacterial and viral cultures despite IVIG [1541]. Those with selective IgA deficiencies have increased IgG and IgM and the increase in inflammatory mediators is not as significant [1543]. Most authors do not recommend IVIG routinely for clinically asymptomatic IgG deficiency patients and this is typically used in less than 10% of patients [1539]. Surgery for patients with PID has not been thoroughly studied. Limited series examining a variety of patients with immune dysfunction contained only a select number of patient with immunoglobulin deficiency, thus are inconclusive [1544].

5.5.1.3. Referral

The question of when the otorhinolaryngologist should perform an immunologic evaluation or refer to an immunologist for a patient with CRS or RARS is not well established. It would seem prudent to conduct such an evaluation in children with recurrent respiratory tract infections in order to identify PIDs as early as possible and initiate treatment that will impact overall survival. It would also seem prudent to conduct such investigations in adults with multiple system infections, such as otitis media, bronchitis or pneumonias or those that fail standard medical and surgical treatments for CRS. However, widespread immunologic screening in all adult CRS patients who respond to routine therapies, would likely uncover laboratory abnormalities that are clinically insignificant and do not require treatment [1539].

5.5.2. Acquired immunodeficiencies

In contrast to patients with PIDs who typically present with viral or bacterial rhinosinusitis, patients with acquired immunodeficiencies can develop rhinosinusitis in a variety of forms, including non-fungal acute rhinosinusitis (ARS), chronic rhinosinusitis (CRS), or fungal forms, most often acute invasive fungal rhinosinusitis (AIFRS) or even described more recently, fungus balls. Acquired immunodeficiencies that may predispose patients to rhinosinusitis include immunosuppression due to transplant, diabetes mellitus, medications or malignancies or human immunodeficiency virus (HIV).

Organ transplants: Solid organ transplant patients often have hepatic or renal failure prior to transplant and thus are immunocompromised from their primary disease state, but even after transplant they remain at risk for development of rhinosinusitis due to immunosuppressive medications. Prior to transplant, Moon [1545] found CRS was present in 28 of 996 (2.8%) pre-liver transplant patients. Twenty-two of these patients had no treatment for CRS prior to transplantation. This untreated CRS was associated with aggravated symptoms after transplantation, but no increase in infectious or overall mortality. Similarly, another study found that preoperative CT of patients awaiting organ transplant demonstrated 64% had radiographic abnormalities, however 77% of these patients were asymptomatic with normal endoscopy, thus routine CT scans prior to transplant is not indicated [1546].

One retrospective review of ESS in 7 patients awaiting liver transplant reported that operative blood loss was an average of 495 mL and 2 cases were stopped due to excessive bleeding. Higher blood loss was associated with more severe liver disease. Four of seven patients subsequently underwent transplant [1547]. Thus ESS is feasible in these patients, however it is not without risk and the benefits are not established.

Post-transplant acute invasive fungal rhinosinusitis (AIFRS) becomes a major concern. Sun [1548] reported an overall mortality of 52% in ninety solid organ transplant patients with rhino-orbital-cerebral zygomycosis. Central nervous system (CNS) involvement was present in 56% with isolated CNS involvement in only 2%. Sinus disease was most frequent in maxillary sinus (80%), followed by ethmoid (65%), sphenoid (45%) and frontal sinus (22%). Compared to diabetes mellitus (DM) patients, transplant patients had a lower likelihood of orbital and sinonasal involvement, but higher likelihood of CNS invasion. Lipid formulations of amphotericin B correlated with lower mortality in transplant patients.

5.5.2.1. Hematopoietic stem cell transplantation (HSCT)

Similar to solid organ transplant, patients undergoing hematopoietic stem cell transplantation (HSCT), are at risk of developing rhinosinusitis prior to transplant due to their underlying malignancy, as well as post-transplant from their immunosuppression. A number of studies have looked at pre-HSCT screening for rhinosinusitis, and have generally concluded they are not useful in asymptomatic patients.

A retrospective review of 100 patients who underwent HSCT found that there was no increased risk of developing CRS post-HSCT for patients with disease on pre-HSCT screening CT, sinus symptoms at time of transplant, tobacco use, asthma, allergies, low IgG or prior history of CRS. Patients with graft versus host disease (GVHD) were 4.3 times more likely to develop CRS post-HSCT [1549].

Ortiz [1550] found no evidence of disease on 77% of pre-HSCT scans and 61% of post-HSCT scans, thus concluding CT staging prior to HSCT is not useful in predicting post-HSCT CRS. This was corroborated by Moeller [1551]. Prior to HSCT, 71 patients underwent evaluation for rhinosinusitis. Sixty-five percent were asymptomatic. All patients who required medical or surgical treatment had symptoms and positive endoscopy and/or CT. Won [1552] evaluated 252 HSCT patients. Nine percent had sinusitis prior to HSCT and this increased to nearly 16% post-HSCT. Patients with pre-HSCT rhinosinusitis had a high occurrence of post-HSCT rhinosinusitis (34 vs. 14%), but again,

CT scans alone were not predictive of post-HSCT rhinosinusitis. However, in pre-HSCT patients who are clinically symptomatic and have CT evidence of CRS, medical or surgical intervention for CRS prior to HSCT reduced the rate of post-HSCT CRS. Routine CT scans and clinical evaluation in asymptomatic patients was not useful.

When examining clinical symptoms, Arulrajah [1553] found that children who are status post HSCT had more severe sinus disease on CT associated with symptoms of rhinorrhoea, nasal congestion or cough when compared to immunocompetent children, however the immunocompetent children still had significant symptoms.

5.5.2.2. Hematologic malignancies

Acute invasive fungal rhinosinusitis (AIFRS) can be a life threatening infection in patients with hematologic malignancies that requires aggressive medical and surgical intervention. A retrospective review of 46 patients with AIFRS found Aspergillus was the most common pathogen and AIFRS developed more commonly in patients with acute myeloid leukaemia (AML) and prolonged neutropenia > 10 days. Bony erosion and extra sinus infiltration was found in 33% of patients and 41% patients died within 6 weeks [1554]. Zappasodi [1555] reported on seven cases of AIFS in patients with acute leukaemia with neutropenia. Facial pain was the initial symptom in all cases, associated with fever in 6 of 7. CT demonstrated unilateral involvement, endoscopy and biopsy confirmed diagnosis. Resolution required improvement in neutropenia, as well as surgical debridement and antifungals. There is controversy over the benefits of antifungal prophylaxis in these patients [1556]. One study found that patients with invasive zygomycosis infections were more likely to have sinus involvement and be on voriconazole prophylaxis than those patients who developed invasive aspergillus infections [1557].

5.5.2.3. HIV

The prevalence of CRS in HIV infected adults ranges from 12-14.5% [1558, 1559]. The presence of sinusitis was not associated with an increased risk of death [1559]. In adults with AIDS, there is a higher incidence of fever, postnasal discharge and more severe CT findings [1558]. In a retrospective review of 471 HIV-infected children, 7.8% had CRS and 6.5% had ARS. Lower CD4 lymphocytes were seen in children with CRS, while those over 6 years of age with ARS had higher CD4 counts. Children less than 6 years old who were taking protease inhibitors presented with a higher prevalence of ARS [1560].

5.5.2.4. Diabetes Mellitus (DM)

Uncontrolled DM is among the leading causes of AIFRS in most series. AIFRS in DM patients may more commonly involve the orbit or sinuses and less commonly involve the CNS when compared to transplant patients [1548]. Mortality appears to be higher in AIFRS associated with DM when compared to that associated with hematologic malignancies [1561].

5.5.2.5. Diagnosis

The diagnosis of AIFRS depends upon maintaining a high clinical suspicion in the immunocompromised patient population. Symptoms and radiographic findings can often be subtle, as these infections appear to begin in the nasal cavity [1562] and prompt biopsy is required to establish the diagnosis. Unilateral nasal cavity thickening has been reported as the most common finding in AIFRS [1563]. The most sensitive imaging study for detecting early changes of AIFRS is extrasinus invasion on MRI [1564].

5.5.2.6. Treatment and outcomes

A retrospective review of 45 cases of AIFRS included patients with hematologic malignancy (28 patients), DM (10 patients), solid organ transplant (3 patients), chronic steroid use (3 patients) and HIV (1 patient). The overall mortality was 18%. Twenty five percent of patients with hematologic malignancy died and had no recovery of their neutrophil count. Forty percent of DM patients died of AIFRS. The mortality rate for Mucor was 29% and for Aspergillus it was 11% [1561]. AIFRS can be treated surgically with endoscopic or open approaches with similar outcomes. Overall survival in a retrospective review was 57% in open surgery group (7 patients) and 47% in endoscopic group (19 patients) [260]. Ruping [1565] reported on 41 patients with invasive zygomycosis, including those with malignancy (63%), DM (17%) and solid organ transplant (9.8%). Sites of infection included the lungs (58%), soft tissues (19%), sino-orbital region (19%), and CNS (15%). Overall survival was 51%. Antifungal prophylaxis did not prevent development of invasive zygomycosis, however, treatment with liposomal amphotericin

Evidence based recommendations

Statement	Grade of Recommendation
Among tertiary CRS patients who undergo immune evaluation, a variety of PIDs are common	C
Among PID patients, clinical symptoms of CRS are found in approximately half	C
PID patients often have CT findings consistent with CRS	C
IVIG therapies improve survival and decrease serious infections in PID patients, but do not provide clinical benefit, prevent radiographic development of CRS or decrease bacterial culture rate from the sinuses	C
Screening CTs in asymptomatic patients prior to solid organ transplant or HSCT are not indicated	C
Successful treatment of AIFRS involves surgery, antifungal therapy and reversal of the immune compromised state	C

B was associated with improved response and survival. Early detection and reversal of the underlying disease process and immunosuppression is as important as the surgical and antifungal therapies [1566].

5.5.2.7. Fungus ball

In addition to AIFRS, immunocompromised patients can develop non-invasive fungus balls that present differently than fungus balls in immunocompetent patients [1567]. In a retrospective review of 24 patients, 11 of 24 had some degree of immunocompromise. These immunocompromised patients (organ transplant or DM) were more likely to have aspergillus and non-dilated sinus ostia.

5.6. Allergic fungal rhinosinusitis

5.6.1. Introduction

There is much debate regarding the role of fungi in CRSwNP and whether the diagnostic group of AFRS truly represents a unique disease. In spite of our limited knowledge regarding the pathophysiology of CRSwNP, there is a subset of patients as defined by the classic Bent-Kuhn criteria for AFRS who demonstrate some phenotypic differences when compared to other CRSwNP patients. The original Bent-Kuhn diagnostic criteria [721] consist of the following:

1) Nasal polyposis,
2) Fungi on staining,
3) Eosinophilic mucin without fungal invasion into sinus tissue,
4) Type I hypersensitivity to fungi and
5) Characteristic radiological findings with soft tissue differential densities on CT scanning.

Although used widely since their inception, many of these criteria are not unique to AFRS patients. All CRSwNP patients have nasal polyposis by definition, with a large proportion of them also demonstrating eosinophilic mucin without fungal invasion. Furthermore, as fungal detection techniques improve, so does the sensitivity to detect them, with some studies demonstrating fungal presence in almost 100% of patients, both controls and CRS patients [592, 1568]. Consequently it appears that type I hypersensitivity and characteristic CT findings are the only unique factors in Bent and Kuhn's criteria for AFRS that allow it be distinguished from other forms of sinus disease. Subsequently, a number of authors have found other factors particular to AFRS. Demographically, AFRS patients are younger, more likely to be African American and present with more significant bone erosion/expansion than other CRSwNP patients [728,1569,1570]. While some have reported immunologic differences, with AFRS demonstrating increased mean serum total IgE and IgG anti-Alternaria antibodies when compared to CRSwNP [723], this has not been conclusively demonstrated as others report no significant differences [727-729, 1571]. Many questions remain unanswered: Are there any significant underlying immunologic differences between AFRS and other forms of CRSwNP? What is the relevance of fungi or fungal specific IgE to the pathophysiology of AFRS? Do these factors truly play a role in the immunologic response or are they simply a defining marker of the disease state?

5.6.2. Medical therapy

Most reports on treatment options for AFRS are combined into larger series addressing CRSwNP patients and this issue is covered elsewhere in this document. It is therefore difficult to discern if there are varying effects in the AFRS population as opposed to the entire CRSwNP population. In general, medical therapies have been divided into oral and topical steroids, oral and topical anti-fungals, leukotriene antagonists and immunotherapy. In all but the mildest cases of AFRS, it is felt that medical therapy alone without surgical intervention, is not effective in the long term, thus most efficacy studies examining medical treatments have been performed post operatively.

5.6.2.1. Oral steroids

Oral steroid studies specific to AFRS patients have generally been conducted in the postoperative setting where benefit has been demonstrated. In a prospective, randomized double-blinded, placebo-controlled (DBPC) trial in AFRS patients examining the effectiveness of postoperative oral steroids, as well as the side effects of such treatments, patients received oral prednisolone (50 mg qd x 6 weeks, then additional 6 week taper) or placebo for two weeks after surgery [1572]. All patients received fluticasone nasal spray and oral itraconazole for 12 weeks. At 12 week follow up, symptoms and endoscopy were improved in the oral steroid group. All 12 patients in the steroid group suffered from weight gain, 5 developed Cushinoid features, 2 developed acne and 1 developed steroid induced diabetes mellitus. At 18 months of follow up, patients who stopped all treatment, including topical steroids, developed recurrent disease. It is unclear if postoperative oral steroids for 12 weeks had an impact at 18 months.

A number of other non-placebo controlled case series have been reported with highly variable dosing protocols and durations, but generally reporting a positive effect when using postoperative oral steroids [1573-1578].

5.6.2.2. Topical steroids

It does not appear that prospective studies on the effects of topical steroids alone have been conducted in the AFRS population. A case controlled study of surgery alone vs. surgery plus the combination of postoperative oral and topical steroid spray in AFRS patients demonstrated benefits of the combined therapy at a minimum of 2 year follow up, as 50% of the no steroid group recurred, while only 15% of the combined steroid group recurred [1579].

5.6.2.3. Subcutaneous Immunotherapy (SCIT)

SCIT may have efficacy in the short term (3-4 years), however, its long-term efficacy is unclear. Fortunately, there are a number of reports of both high dose and low dose subcutaneous immunotherapy that have all demonstrated safety [1580].

A large retrospective, series reported that compliance with immunotherapy for all fungal and non-fungal antigens was beneficial in preventing recurrence of disease. A 3-4 year course of subcutaneous immunotherapy (SCIT) demonstrated benefit 12-26 months after discontinuation [1581] and prolonged courses of systemic steroids were not used in these patients [1582]. However a subsequent study by the same group on a smaller subset of patients with longer term follow up ranging from 46 to 138 months failed to demonstrate any benefit of SCIT with 60% of SCIT patients having normal mucosa or only mild oedema on endoscopy, while 100% of non-SCIT patients having normal mucosa or mild oedema [1583]. This study was not randomized and obviously has the potential for bias in selecting treatment arms.

5.6.2. 4. Anti-fungal therapy

It is unclear if such therapies have a differing effect in the AFRS subset of patients. Limited non-placebo controlled case series have reported benefits of systemic anti-fungal therapies in patients with AFRS [28, 1584]. This is in contrast to a Cochrane review of topical and systemic anti-fungal therapies in all CRS patients, which failed to demonstrate any benefit [1585].

5.6.2.5. Leukotriene antagonist

One case report of improvement on leukotriene antagonist therapy has been reported [1586].

5.6.2.6. Manuka honey

A randomized, single-blind, prospective study of AFRS patients, who failed surgery and maximal postoperative medical management, used Manuka honey in one nostril. Overall, the group failed to demonstrate improvement [1587].

5.6.2.7. Surgical therapy

Most clinical series describe surgical therapy to remove polyps and eosinophilic fungal mucin followed by aggressive medical therapies described above. Generally from the literature it appears that surgery both alone and in combination with other medical treatments leads to improved outcomes.

A retrospective review reported that incomplete removal of all fungal and eosinophilic mucin contributed to disease recurrence and the need for revision surgery [1588].

Champagne et al. [1589] demonstrated that in AFRS patients, African American patients had higher CT and endoscopy scores, but similar SNOT20 scores. At 12 months postoperatively, SNOT20 and endoscopy scores improved in all patient groups with significantly greater improvement in women. In this series, all patients were treated postoperatively with saline irrigations, topical nasal steroid spray, oral antibiotics and a one-month oral steroid taper. Their maintenance treatment consisted of topical nasal steroid spray, nasal saline, montelukast, budesonide irrigations and month long bursts of oral steroids for exacerbations. Thus it is difficult to isolate the impact of surgery alone.

The placebo arm of the Rupa study [1572] was treated with nasal steroid spray and oral itraconazole during the postoperative period. At 6 weeks, 5 of 12 patients had endoscopic recurrence of their disease severe enough to withdraw from the study. At 12 weeks, 4 of the remaining 7 patients had complete or partial relief of symptoms with only 1 of those patients having normal endoscopy, thus their recurrence rate at 12 weeks with surgery plus nasal steroids and oral intraconazole was 11/12 (92%). The recurrence rate in the placebo arm of the Ikram study that did not receive oral or topical steroids [1579] was lower at 50% at 2 years. Overall recurrence rates after surgery has been reported from 10% to 100% [1590].

Evidence based recommendations

Statement	Grade of Recommendation
AFRS demonstrates immunologic differences when compared to CRSwNP	D (conflicting reports)
AFRS demonstrates clinical differences when compared to CRSwNP	C
Oral steroids lead to short term postoperative improvement in symptoms and endoscopy in AFRS, but can have significant side effects	A
SCIT improves short term outcomes in AFRS, but long term benefits are unclear	C
Anti-fungal therapy improves outcomes in AFRS	D
Surgery with postoperative medical therapy improves AFRS outcomes	C

5.7. Paediatric Chronic Rhinosinusitis

5.7.1. Summary

CRS in children is not as well studied as the same entity in adults. Multiple factors contribute to the disease including bacteriologic and inflammatory factors. The adenoids are a prominent contributor to this entity in the pediatric age group. The mainstay of therapy is medical with surgical therapy reserved for the minority of patients who do not respond to medical treatment.

5.7.2. Classification and Diagnosis

CRS in children is defined similar to adults as an inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure,
± cough;
and either endoscopic signs of disease and/or relevant changes on the CT scan of the sinus.

The clinical diagnosis of CRS in children is challenging related to the overlap of symptoms with other common childhood nasal diseases such as viral upper respiratory tract infections, adenoid hypertrophy/adenoiditis and allergic rhinitis as well as the challenges related to physical examination. The EPOS2012 group felt that it was impossible to differentiate CRS from adenoid hypertrophy/adenoiditis in young children. Furthermore, studies examining the incidence of abnormalities in the paranasal sinuses on CT scans obtained for clinical reasons not related to CRS in children have shown a percentage of sinus radiographic abnormalities ranging from 18% [1591] to 45% [1592] with one study actually showing a Lund McKay score average of 2.8 in a similar pediatric population without symptoms of rhinosinusitis [1593]. It has also been suggested that only a Lund-Mackay score over 5 is indicative for CRS in children [1594]. Adding to the challenge in making the diagnosis is the fact that symptoms consistent with the diagnosis of CRS such as purulent rhinorrhea and cough are very common in the pediatric age group, and the symptoms of CRS are often subtle and the history is limited to the observations and subjective evaluation by the child's parent. Because some younger children might not tolerate nasal endoscopy, clinicians are sometimes hindered in their physical examination and have to rely on history and or imaging studies for appropriate diagnosis.

Studies examining clinical characteristics of pediatric patients with CRS suggest that the four most common clinical symptoms are cough, rhinorrhea, nasal congestion, and post nasal drip with a slightly higher predominance of chronic cough [527, 1595]. Tatli et al found that 66% of children undergoing evaluation for chronic cough (>4 weeks duration, excluding recent upper respiratory tract infections) had CT scan abnormalities in the paranasal sinuses which were mild in 14%, moderate in 19%, and severe in 33% of the patients [480]. In those children, the most frequent symptoms reported, other than cough, included rhinorrhea, sniffling, and halitosis.

A thorough history of the timing of symptoms is critical to attempt to understand the category of disease that best applies to each patient. A very common clinical scenario in children presenting to the otorhinolaryngologist's office is that of chronic rhinosinusitis with upper respiratory tract infection-induced acute exacerbations. In this document, we characterize CRS as symptoms lasting 12 weeks or longer without symptom free periods.

5.7.3. Prevalence

The exact prevalence of chronic rhinosinusitis (CRS) in children is difficult to determine as only a small percentage of cases present to the physician's office. Many studies that address prevalence have been performed in select populations typically in children who have upper respiratory complaints. In one such study, CT scans were obtained in 196 children 3-14 years of age presenting with chronic rhinorrhoea, nasal congestion and cough [1596]. Maxillary involvement was noted in 63%, ethmoid involvement in 58% and sphenoidal sinus involvement in 29% of the children of the youngest age groups. The incidence of abnormalities decreased to 10% of the ethmoids, 0% of sphenoids, but 65% of the maxillaries being involved in the older, 13-14 year old, age group. In a prospective study, all new patients (ages 2-18 years) presenting to 2 allergy practices with upper respiratory tract symptoms for at least 3 months were investigated with a CT scan to determine sinus abnormalities [1597]. In 91 eligible patients, 63% had chronic sinusitis with clinical signs and positive CT findings and 36% had no sinus disease. The best association between symptoms and CT scan abnormalities was noted when the symptoms of rhinorrhoea, cough, and the absence of sneezing were combined. Furthermore, age was the single most important risk factor associated with chronic sinusitis, with 73% of 2-6 year olds, and 74% of 6-10 year olds having sinus CT abnormalities as opposed to the low incidence of sinus abnormalities detected in only 38% of children over 10 years of age.

There are few studies that follow the prevalence over time and they suggest a decrease in the prevalence of rhinosinusitis after age 6-8 years [8, 1598, 1599]. There is also evidence to suggest that children with a family history of atopy or asthma who attend daycare in the first year of life have 2.2 times higher odds of having doctor-diagnosed sinusitis than children who do not attend daycare [1600].

5.7.4. Effects on Quality of life

CRS has a negative impact on quality of life

CRS in children leads to impaired quality of life. In a study of children with recurrent and CRS failing medical treatment and requiring surgical intervention, Cunningham and colleagues administered generic parental and childhood quality of life questionnaires [1601]. The results showed significant impairment

of the quality of life of these children and, surprisingly, significantly lower quality of life scores than that of children with other common chronic childhood diseases such as asthma, attention deficit hyperactivity disorder, juvenile rheumatoid arthritis, and epilepsy. The differences were most marked in the physical domains of the quality of life questionnaires such as bodily pain and limitation in physical activity. The SN-5 survey, a disease specific tool was validated as a measure of change over time in sinonasal symptoms [1602]. It consists of 5 domains, which include sinus infection, nasal obstruction, allergy symptoms, medication use, emotional distress, and activity limitations, and is filled by the parents reflective of the previous 4 weeks. The survey's reproducibility, validity, and responsiveness to change was ascertained in a study of 85 children aged 2-12 years suffering from sinonasal symptoms for 1 month or longer, and it has been shown to correlate with CT scan scores in patients with CRS suggesting that it can be used as a substitute for repeated CT scans in clinical follow up [1603]. There is also limited evidence showing improvement of quality of life (using the SN-5 tool) in patients with CRS after surgical intervention (adenoidectomy or endoscopic sinus surgery) [1604].

5.7.5. Anatomical factors

It is not clear whether anatomic abnormalities have any contribution to CRS in children

Similar to adults, the ostiomeatal complex (OMC) is believed to be the critical anatomic structure in rhinosinusitis and is entirely present, though not at full size, in newborns. Changes occurring in the anterior ethmoids are known to impair drainage through the OMC, resulting in chronic maxillary sinusitis and, occasionally, frontal sinusitis. Sivalsi et al studied the anatomical variations of the paranasal sinuses in paediatric patients with CRS [1605]. A pneumatized middle concha was the most common anatomic variation, followed by pneumatisation of the superior concha, Haller cell, and agger nasi cell. Compared with adults, nasal septal deformities tended to be less common. In another study, Al-Qudah examined the CT scans of 65 children with persistent symptoms of CRS (>3months) after maximal medical treatment and identified anatomical abnormalities and correlated those to extent of disease in the paranasal sinuses (1606). In his population, the most common abnormality was an agger nasi cell, followed by concha bullosa, paradoxical middle turbinate and Haller's cell. In addition to listing the abnormalities, this study actually performed correlation analyses between the anatomical abnormalities and the extent of sinusitis and found no significant correlation. The limitation of both studies is that they did not include a control group without rhinosinusitis making it difficult to assess the importance of these changes in the genesis of chronic sinus inflammation. Actually, the second study and studies in adults suggest that despite the common occurrence of these anatomical factors, they do not seem to correlate with the degree and existence of CRS.

5.7.6. Pathophysiology

5.7.6.1. Bacteriology.

The pathogens involved in CRS are difficult to identify due to low bacterial concentration rates, inconsistent data, and because most cultures are obtained at the time of surgery after patients have been treated with antibiotic therapy. Muntz and Lusk reported bacteriologic findings in 105 children with CRS when they obtained cultures from the anterior ethmoid cell at the time of endoscopic sinus surgery [1607]. The most common bacterial species recovered were alpha hemolytic streptococci and Staphylococcus aureus, followed by S. pneumoniae, H. influenzae, and M. catarrhalis. Anaerobic organisms were grown from 6% of specimens. Brook et al also reported that the incidence of anaerobic organisms recovered increased with chronic infections [477]. In 1981, his group obtained sinus cultures from 37 of 40 children with CRS and isolated anaerobic organisms from all specimens [1608]. The most common organisms were anaerobic gram-positive cocci, followed by other anaerobic organisms including Bacteroides species and Fusobacteria. Aerobes were recovered in 38% of these cultures and included Streptococci, Staphylococci and few Hemophilus species.

Hsin and colleagues performed maxillary sinus taps for irrigation in 165 children with symptoms of CRS for≥12 weeks and abnormal radiographs [1609]. Of the 295 sinuses tapped, the most commonly isolated organisms were α-hemolytic Streptococcus (21%), Hemophilus influenza (20%), Streptococcus pneumonia (14%), coagulase negative Staphylococcus (13%), and Staphylococcus aureus (9%). Anaerobes were identified in 8% of the isolates. When examining the susceptibility of the organisms over time, an increase rate of resistance of Hemophilus influenza to ampicillin was noted. In a study evaluating the effect of the introduction of the heptavalent pneumococcal conjugate vaccine on the bacteriology of rhinosinusitis in children, McNeil and colleagues evaluated all cultures of the paranasal sinuses that yielded Streptococcus pneumonia at Texas Children's hospital between 2007 and 2008 [1610]. These were all obtained from children with the diagnosis of chronic or recurrent rhinosinusitis and out of the 24 cultures, 23 were non vaccine serotypes, with serotype 19A accounting for 50% of the isolates and exhibiting high rates of antimicrobial resistance.

5.7.6.2. Biofilms

Biofilms are complex aggregations of bacteria distinguished by a protective and adhesive matrix and have recently been

implicated in CRS. They form when planktonic bacteria adhere and coalesce to various surfaces via glycoconjugate moieties and form well organized ecosystems within the human host. These ecosystems are well suited for conditions of environmental stress and altered oxygen tension, and it is thought that 99% of bacteria exist in biofilm form. Biofilms are also characterized by surface attachment, structural heterogeneity, genetic diversity, complex community interactions, and an extracellular matrix of polymeric substances, which all contribute to their resistance to antibiotic treatment [1611]. Intermittently, planktonic bacteria shed from the biofilm, migrate, and colonize other surfaces. It is therefore hypothesized that biofilms may provide a chronic reservoir for bacteria and may be responsible for the resistance to antibiotics seen in pediatric patients with CRS. Sanclement and colleagues evaluated sinus mucosa obtained at the time of surgery for CRS for the presence of biofilms and, in a mixed adult and pediatric population, demonstrated the presence of biofilms in 24 out of 30 (80%) specimens [1611]. Although the existence of biofilms is now well documented in adults with rhinosinusitis, more research is needed to clearly characterize their contribution to the pathophysiology of CRS in children.

5.7.6.3. Role of adenoids

The adenoids are in close proximity to the paranasal sinuses and adenoidectomy has been shown to be effective in resolving the symptoms in a proportion of children with CRS (see below). In an attempt to explain these findings, Zuliani et al. collected adenoid specimens obtained from children with CRS and obstructive sleep apnea and examined them for the presence of biofilms using electron microscopy [1612]. They found that a large percentage (88-99%) of the mucosal surface area of all the specimens from children with CRS was covered with a dense biofilm. This was in contrast with the adenoids obtained from patients with sleep apnea where modest percentages (0-6.5%) of the surface area were found to be covered by biofilm. Although the number of specimens in this study was small, the work provides a potential explanation for the improvement seen with adenoidectomy in antibiotic-resistant CRS.

In a study comparing middle meatal swabs and adenoid core cultures in children with hypertrophied adenoids and chronic or recurrent sinusitis, Elwany and colleagues found that the bacteria were very similar in both locations and included coagulase-negative staphylococci, Staphylococcus aureus, Streptococcus pneumonia, Haemophilus influenza and group A streptococci [1613]. They also found that adenoid core culture had a positive predictive value of 91.5 in forecasting the middle meatal culture results and a negative predictive value of 84.3, suggesting that the bacterial reservoir in the adenoids mirrors the bacteriology isolated close to the paranasal sinuses in these children. Another line of evidence to support the role of the adenoids as a bacterial reservoir in CRS in children comes from the observation that bacterial isolation rates from adenoids of children undergoing adenoidectomy increased significantly according to sinusitis grade on radiographs [1614]. This was especially true of Hemophilus influenza and Streptococcus pneumonia. In contrast, children with nasal discharge who had a CT scan of the sinuses and underwent adenoidectomy were investigated and the results showed no correlation between the size of the adenoids and the severity of disease on CT scan as gauged by the Lund McKay score [1615]. This suggests that the nasal discharge could be due to adenoiditis alone and that the bacterial reservoir of the adenoids more than their size was important in the relationship between CRS and the adenoids.

There is also some evidence that supports a contribution of the adenoids as an immunological organ in children with CRS. One study compared immunoglobulin expression in adenoid tissues of patients with adenoid hyperplasia compared to those with CRS and showed a significantly lower expression of IgA in the adenoids of children with CRS with no difference in expression of the other immunoglobulins [1616]. This could suggest that the adenoids of patients with CRS are not able to mount the local immune response expected of them. Obviously whether this is a primary or secondary occurrence (related to chronic infection) cannot be elucidated from this study which only evaluated adenoids at one point in time. Shin and colleagues examined adenoids obtained from children with and without CRS and showed higher levels of tissue-remodeling cytokines, transforming growh factor TGF-β1, matrix metalloprotease MMP-2, MMP-9, and tissue inhibitor of metalloprotease TIMP-1 in the CRS patients, again supporting a relationship between the adenoids and the status of the sinuses in children with CRS [1617].

In summary, data related to the role of adenoids in CRS is emerging but the studies are small and mostly evaluate the adenoids after their removal from the site. They do suggest a role for the adenoids in patients with CRS, both from a bacteriologic and immunologic perspective. Most of these studies however, do not really shed light on the relative contribution of adenoiditis proper vs CRS in chronic nasal symptomatology in children.

5.7.6.4. Cellular Studies

Studies of the cellular response in pediatric CRS indicate that eosinophils and CD4+ lymphocytes play a significant role in tissue inflammation. Baroody and colleagues found higher numbers of eosinophils in the sinus mucosa of older children (Median age = 7 years, range: 3-16 years) obtained at the time of surgery for CRS as compared to sphenoid sinus mucosal specimens of adults with no previous history of sinusitis [1618].

The inflammatory reaction in the sinus tissues of children with CRS is rich in lymphocytes and exhibits less eosinophilia and epithelial disruption compared to adults

Lymphocytes, particularly the CD4+ population, were also increased in the sinus mucosa of children with CRS irrespective of allergic status [1619]. In similar studies performed in younger children with CRS (median age= 3.9 yrs) Chan and colleagues compared maxillary sinus biopsies from these children to archival adult maxillary sinus tissues [1620]. The pediatric mucosa had more neutrophils, and significantly more lymphocytes, while the adult mucosa was richer in eosinophils and major basic protein positive cells. They also noted less epithelial disruption and thickening of the basement membrane in children compared to the adults. In a similar study using immunohistochemistry to evaluate different inflammatory cells, the same group showed higher numbers of CD8+ cells, neutrophils, macrophages, B lymphocytes, and plasma cells in younger children with CRS compared to adults [1621]. In a similar study, Berger and colleagues compared sinus specimens obtained from children with CRS to tissues obtained from adults [1622]. The children were older (mean age=11.6±2.9 years) and their tissues had fewer eosinophils and lesser epithelial disruption than the adult specimens. There were large numbers of T lymphocytes, and extensive fibrosis in the lamina propria in half the specimens, findings comparable to the adult specimens. In children with nasal polyps, vascular endothelial growth factor-expressing cells and intra-polyp blood-vessel density were higher in polyp specimens as compared to the chronically inflamed tissue of children without nasal polyposis [1008]. In general these limited studies suggest fewer eosinophils and less epithelial disruption in the tissues of children with CRS compared to their adult counterparts.

5.7.7. Comorbid Diseases

5.7.7.1. Allergic Rhinitis

Allergic rhinitis is a common coexisting disease in pediatric patients with CRS. The data about the association between the 2 diseases in children is variable. In a series of 42 patients with CRS refractory to medical treatment on which a RAST test as well as a CT scan was available, 40% of the patients were atopic and 60% were nonatopic [1623]. In the same study, patients with a positive RAST test were found to have a significantly higher CT score compared to the patients with negative RAST testing. While this study supports the relationship of a positive allergy test to CRS, the population was mixed children and adults with a mean age of 28 years and a range from 2-61 years. In a study of 100 children with a clinical diagnosis of sinusitis and abnormal plain sinus radiographs in Thailand, the authors report a positive skin test to common aeroallergens in 53% of the patients again suggesting a correlation between the 2 diseases [1624].

In contrast, a study from Belgium evaluated CT scans from allergic children and adults and noted the presence of sinus opacification in 61% of allergic children and 58% of adults [1625]. This data was compared to previous studies of nonallergic children and adults showing the incidence of sinusitis changes on CT to be similar (64% in children and 57.5% in adults) suggesting the lack of an important role of allergy in sinus abnormalities on CT scan. In their study of children with chronic respiratory symptoms who underwent allergy evaluation and CT scanning, Nguyen and colleagues found no correlation between atopic status and sinus abnormality and the prevalence of sinus disease was essentially similar in the atopic patients (63%) versus the nonatopics (75%) [1597]. Finally, a more recent study showed positive allergy tests in 30% of 351 Italian children with CRS, a prevalence that was not much different than that of allergy in the general population (32%) [1626]. When age was examined, the incidence of positive allergy testing was significantly higher in children older than 6 years as compared to those younger than 3 years of age. Thus the causal relationship between allergies and CRS in children is still controversial but probably non-existent.

5.7.7.2. Asthma

Asthma is another disease that is commonly associated with CRS in the pediatric age group. Rachelefsky and colleagues reported on treatment outcomes in 48 nonrandomized children with moderate to severe asthma and co-morbid CRS [1627]. After pharmacologic or surgical intervention for sinusitis, 80% of these children were able to discontinue asthma medications. Furthermore, asthma recurred when sinusitis subsequently relapsed. In another study, Tosca and colleagues identified 18 children, 5-12 yrs of age, with poorly controlled asthma and co-morbid CRS [1628]. The patients were treated for 14 days with antibiotics, intranasal and systemic steroids, and were evaluated at baseline, after treatment, and 1 month later. In addition to improvement in their nasal symptoms, patients had a significant improvement in spirometry, wheezing, and inflammatory markers in nasal lavage. These and other studies support the concept that clinical control of CRS may be important in optimizing the control of difficult-to-treat asthma. However, the limitations of most available studies include the lack of good controls or randomization to different treatment modalities and therefore, the relationship between CRS and asthma in children remains largely descriptive.

5.7.7.3. Gastroesophageal Reflux Disease (GERD)

GERD has also been associated with rhinosinusitis in several studies. Phipps et al conducted a prospective study of 30 pediatric patients with chronic rhinosinusitis who underwent 24-hour pH probe and found that 63% of children with CRS had GE reflux [1629]. In addition, 79% of children experienced

improvement in rhinosinusitis symptoms after medical treatment of GERD. In a large case control study at Texas Children's hospital, 1,980 children with gastroesophageal reflux disease and 7,920 controls (ages 2-18 yrs) were identified based on ICD-9 codes [1630]. The number of cases with a concomitant diagnosis of sinusitis was significantly higher in the children with GERD (4.19%) compared to the control group (1.35%). Another retrospective study by Bothwell showed that treatment for GERD in patients with CRS (no placebo control) allowed many patients to improve and to obviate planned surgical procedures [1631]. The differential diagnosis between GERD and post nasal drip can be difficult. Although some evidence supports an association between GERD and CRS, more controlled studies are required to strengthen this association and validate it and routine anti-reflux treatment of children with CRS is not warranted.

5.7.7.4. Immunodeficiency

Shapiro et al prospectively evaluated the immune function of children referred to their offices over a 1-year period with recurrent rhinosinusitis despite maximal medical therapy [1632]. Of 61 patients (2-13 yrs of age), 34 showed some abnormality in immune studies with depressed IgG3 levels and poor response to pneumococcal antigen 7 being most common. Sethi and colleagues reported the following immune deficits in 20 patients (ranging from 3 to 51 years) with recurrent/chronic rhinosinusitis: isolated IgA and IgG1 deficiency, low immunoglobulin levels with poor response to pneumococcal vaccine, and low immunoglobulin levels with normal vaccine responses [1633]. Costa Carvalho and colleagues evaluated the humoral immune response in 27 children (7-15 years) with chronic or recurrent sinusitis [292]. One patient had IgA and IgG2 deficiency, and another had IgG3 deficiency. Eight and 12 of 27 patients had IgG2 and IgG3 serum levels below 2.5th percentile, respectively and no patient had an abnormal response to vaccination. In an open label, pilot, study, Ramesh and colleagues treated 6 patients with CRS refractory to medical management with IVIG for 1 year and compared their response during treatment to the 1 year before therapy [1634]. Treatment resulted in a decrease in antibiotic intake (183 to 84 days) and episodes of sinusitis (9 to 4 per year), and CT scans showed significant improvement. Based on the above evidence, it seems prudent to evaluate immune function in the child with chronic/recurrent rhinosinusitis with an immunoglobulin quantitation and titers to tetanus and diphtheria as well as pneumococcal titers. If responses are abnormal, a repeat set of titers post pneumococcal vaccination is appropriate.

5.7.7.5. Primary Ciliary Dyskinesia

The normal movement of mucus by mucociliary transport toward the natural ostia of the sinuses and eventually to the nasopharynx can be disrupted by any ciliary dysfunction or mucosal inflammation. The most common cause of ciliary dysfunction is primary ciliary dyskinesia (PCD), an autosomal recessive disorder involving dysfunction of cilia and present in 1 of 15,000 of the population [1635]. Half the children with PCD also have situs inversus, bronchiectasis, and CRS and are known as Kartagener's syndrome. The diagnosis should be suspected in a child with atypical asthma, bronchiectasis, chronic wet cough and mucus production, rhinosinusitis, chronic and severe otitis media (especially with chronic drainage in children with ear tubes) [8]. Screening tests for PCD include nasal nitric oxide (lower levels than controls) and in vivo tests such as the saccharin test, which documents slower mucociliary transit time. Specific diagnosis requires examination of cilia by light and electron microscopy, which is usually available in specialized centers. The most commonly described structural abnormality involves lack of outer dynein arms, or a combined lack of both inner and outer dynein arms [86]. Contrary to some thoughts that the prolonged inflammation associated with PCD would lead to nasal polyposis in adults, a review of 30 children with PCD in one center showed none with nasal polyposis despite the fact that the children were debilitated by CRS as documented by SNOT-20 scores [1636].

5.7.7.6. Cystic fibrosis

Cystic fibrosis is a genetic disease with autosomal recessive inheritance that affects approximately 1 in 3500 newborns. It is caused by a mutation in the CFTR gene on chromosome 7, which leads to disruption in cAMP-mediated chloride secretion in epithelial cells and exocrine glands. This leads to increased viscosity of secretions resulting in bronchiectasis, pancreatic insufficiency, CRS and nasal polyposis. The prevalence of chronic sinusitis is very high and nasal polyps occur in between 7 and 50 % of affected patients [1450, 1637]. In fact, this is one of the few causes of nasal polyposis in children. A lengthier discussion of this disorder is presented in the chapter devoted to this entity.

5.7.8. Diagnostic Workup

A complete physical exam should follow a carefully obtained medical and family history. The nasal exam in children should begin with anterior rhinoscopy examining the middle meatus, inferior turbinates, mucosal character and presence of purulent drainage. This is often feasible in younger children using the larger speculum of the otoscope. Topical decongestion may improve visualization but may not always be tolerated in younger children. Nasal endoscopy which will allow superior visualization of the middle meatus, adenoid bed and nasopharynx is strongly recommended in children who are able to tolerate the examination. An oral cavity exam may reveal purulent drainage, cobblestoning of the posterior pharyngeal wall, or tonsillar hypertrophy. The finding of nasal

polyps in children is unusual and, if seen on exam, should raise the suspicion for cystic fibrosis or allergic fungal sinusitis. Although there is no supportive data, nasal polyps might be more common in children than previously appreciated as evidenced by a report from Taiwan [1008] and anecdotal personal communications from Europe. Obviously, antrochoanal polyps occur in children but those are usually unilateral and the rest of the sinuses are clear, which would help differentiate that entity from CF or bilateral nasal polyposis. Allergic fungal sinusitis also presents with a rather unique clinical picture which includes expansile nasal polyps and characteristic CT and MRI findings [1638].

Following the history and physical examination, appropriate diagnostic tests should be considered. Allergy skin testing or serologic testing should be considered in children with CRS. Immunodeficiency testing should be pursued in children with recurrent or chronic disease, poor response to medical treatment, history of other infectious diseases (such as recurrent pneumonia or otitis media) or when unusual organisms are cultured from the sinus contents.

In patients who have not responded to conventional medical treatment, obtaining a culture may be useful in directing further therapy. In children, data regarding the usefulness of this approach are limited. Orobello and colleagues cultured the middle meatus at the time of endoscopic sinus surgery in children with chronic rhinosinusitis and then obtained cultures from the maxillary antrum and the ethmoids during the procedure [1639]. They reported a strong association between cultures of the middle meatus and cultures of the maxillary (83%) and ethmoid sinuses (80%). In a recent study, Hsin and colleagues obtained middle meatal cultures and maxillary sinus aspirates under general anesthesia from children with rhinosinusitis unresponsive to medical treatment [1640]. Endoscopic sampling provided a sensitivity of 75%, a specificity of 88.9%, a positive predictive value of 96%, a negative predictive value of 50%, and an accuracy of 50%, making it a little less favorable compared to results from adult studies. In a more recent study by the same group, the correlation between maxillary sinus taps and middle meatal cultures improved when the middle meatal sample was obtained by suction aspiration (correlation 87%) as opposed to swabs (correlation 66%) [1609]. We reserve this technique for the older children who have a complicated course and who are likely to tolerate rigid endoscopy in the office setting. If general anesthesia is needed, one should revert to the gold standard, which is obtaining a culture from the maxillary sinus itself by antral puncture, a technique that also allows the potential benefit of sinus irrigation.

Interdisciplinary consultations are useful in evaluating the pediatric patient with medically refractory disease. Consultants may include those in the disciplines of allergy-immunology, infectious disease, pulmonary or genetics to aid in further workup.

Not any CT scan abnormality indicates relevant clinical CRS in children

While the diagnosis of chronic rhinosinusitis in the pediatric population is generally made on clinical grounds, computed tomography (CT) is the imaging modality of choice [279]. Findings on plain radiographs have been shown not to correlate well with those from CT scans in the context of chronic/recurrent sinus disease [281]. In a prospective study where children with chronic sinus symptoms were imaged using both modalities, the findings on plain radiographs did not correlate with those on CT scans in 75% of the 70 patients studied [281]. About 45% of the patients had normal findings on plain radiographs of at least one sinus with an abnormality of that sinus shown on CT scan, and almost 35% of the patients had an abnormality of at least one sinus on plain radiographs but that sinus was normal on CT scan. Thus, the most useful modality for the diagnosis of rhinosinusitis in children is the CT scan. A recent study compared CT scans obtained in 66 patients (mean age 8 years) satisfying the clinical criteria of CRS to those obtained in a group of 192 control children (mean age 9 years) for non-sinusitis reasons [1594]. The scans were graded using the Lund-Mackay system and the analysis showed that adopting a Lund cutoff score for diseased vs nondiseased patients of 5 offers a sensitivity and specificity of 86% and 85% respectively in making an appropriate diagnosis. Lund scores of 2 or less, have an excellent negative predictive value, whereas scores of 5 or more have an excellent positive predictive value.

In uncomplicated CRS, scanning is reserved to evaluate for residual disease and anatomic abnormalities after maximal medical therapy. Abnormalities in the CT scan are assessed in the context of their severity and correlation with the clinical picture and guide the plan for further management which might include surgical intervention. In children with the clinical diagnosis of rhinosinusitis, the most commonly involved sinus is the maxillary sinus (99%) followed by the ethmoid sinus (91%) [1595]. Magnetic resonance (MR) imaging of the sinuses, orbits, and brain should be performed whenever complications of rhinosinusitis are suspected.

Adenoidectomy is successful in improving CRS

in 50% of operated children. Whether this is due to the fact that the symptoms were related to adenoiditis per se or to the elimination of the contribution of the adenoids to sinus disease is not clear

CT scans provide an anatomic road map for surgical treatment and are also useful for identifying areas of bony erosion or attenuation [1641]. Two examples of sinonasal diseases with characteristic radiologic appearances are allergic fungal sinusitis (AFS) and cystic fibrosis. In AFS, expansile disease may attenuate the bony skull base or orbital wall on CT. In addition, a speckled pattern of high attenuation ("starry sky") on both soft tissue and bone window settings correlates with the presence of thick allergic mucin and associated calcifications that may be noted intra-operatively. MRI T1 images show low signal in areas of fungal mucin, and T2 images show central signal void in areas of fungal mucin with high signal in peripheral inflamed mucosa [1638]. In patients with cystic fibrosis, CT scans characteristically demonstrate pan-opacification of the sinuses and medial displacement of the lateral nasal wall, which may obstruct the nasal passages [1642].

Finally, it has to be emphasized that the physical exam and history alone do not help in differentiating between adenoiditis and CRS, especially in the younger child. As detailed above a high Lund-Mackay score on the CT scan (>5) might be more suggestive of CRS than adenoiditis but further studies are clearly required to help distinguish these 2 entities.

6. Management, reasons for failure of medical and surgical therapy in Chronic Rhinosinusitis

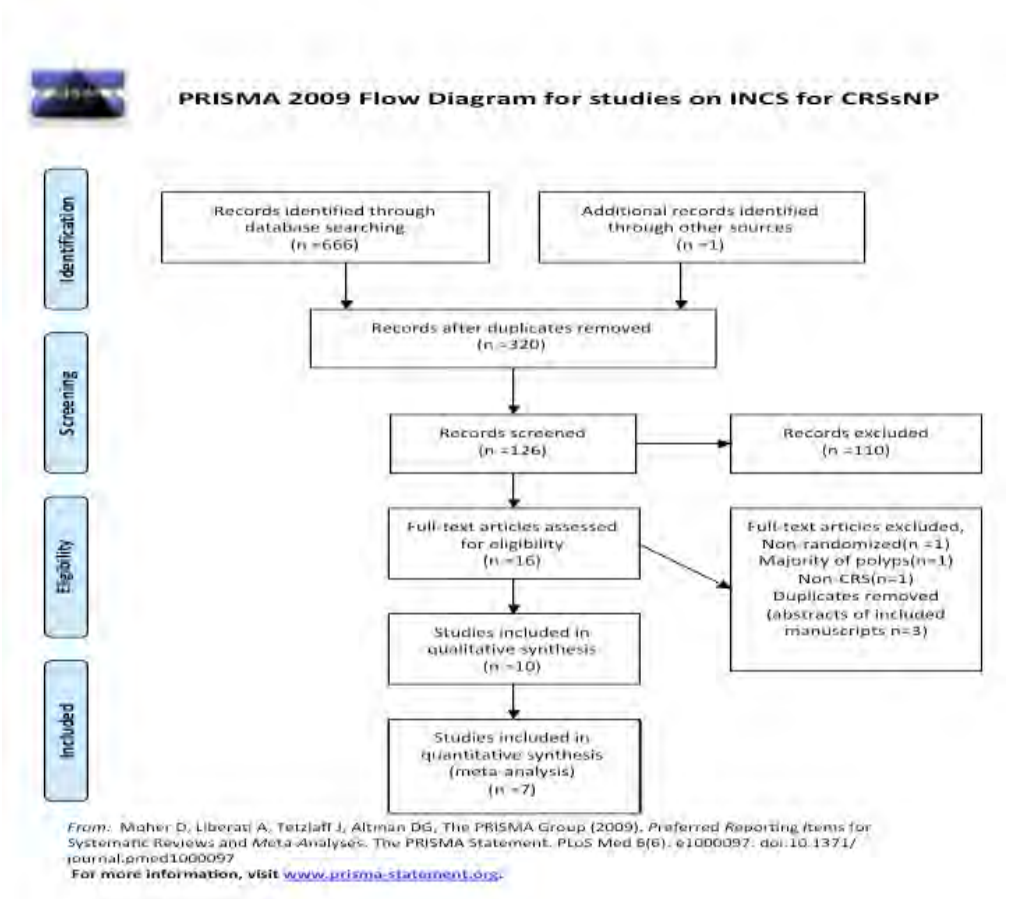
In this chapter a differentiation is made between CRSsNP and CRSwNP. Readers have to realize that often in studies no clear difference is made between these two patients groups. Sometimes for this reason studies are discussed in both the parts on CRSsNP as the parts of CRSwNP.

6.1. Treatment of CRSsNP with corticosteroids

6.1.1. Introduction

The introduction of topically administered glucocorticoids has improved the treatment of upper (rhinitis, nasal polyps) and lower (asthma) airway inflammatory disease. The clinical efficacy of glucocorticoids may depend in part on their ability to reduce airway eosinophil infiltration by preventing their increased viability and activation. Both topical and systemic glucocorticoids may affect the eosinophil function by both directly reducing eosinophil viability and activation [899, 1643-1645] or indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells [1646-1649]. The biological action of glucocorticoids is mediated through activation of intracellular glucocorticoid receptors (GR) [1650, 1651] expressed in many tissues and cells [1652]. Two human isoforms of GR have been identified, GRα and GRβ, which originate from the same gene by alternative splicing of the GR primary transcript [1653]. Upon hormone binding, GRα enhances anti-inflammatory or

Figure 6.1.1



represses pro-inflammatory gene transcription, and exerts most of the anti-inflammatory effects of glucocorticoids through protein-protein interactions between GR and transcription factors, such as AP-1 and NF-κB. The GRβ isoform does not bind steroids but may interfere with the GR function. There may be several mechanisms accounting for the resistance to the anti-inflammatory effects of glucocorticoids, including an overexpression of GRβ or a down-expression of GRα. Increased expression of GRβ has been reported in patients with nasal polyps [1654, 1655] while down-regulation of GR levels after treatment with glucocorticoids [1656, 1657] has also been postulated to be one of the possible explanations for the secondary glucocorticoid resistance phenomenon.

The ability of the drug to reach the appropriate anatomic region on the para-nasal system has been the subject of much research in the past 5 years. While systemic delivery is available, effective topical therapy relies on several factors. Delivery technique, surgical state of the sinus cavity, delivery device and fluid dynamics (volume, pressure, position) have a significant impact on the delivery of topical therapies to the sinus mucosa. Distribution of topical solution to the unoperated sinuses is

Table 6.1.1. Study characteristics of included publications on INCS in CRSsNP.

Study	Study type	Participants (diagnostic criteria)	Number of participants	Age (Mean)	Type of steroid	Steroid dose	Sinus Surgery Status	Delivery method of steroid	Duration of treatment (weeks)	Comparison
Hansen 2010 (1823)	RCT	CRSsNP (by symptoms, endoscopy and MRI	20	47,9	fluticasone propionate	400 mcg bid	with sinus surgery	with Optinose device	12	placebo
Jorissen 2009 (1674)	RCT	mixed CRS (by symptoms, endoscopy, CT)	99	47.4	mometasone furoate	200 mcg bid	with sinus surgery	spray	24	placebo
Furukido 2005 (1669)	RCT	CRSsNP (by AAO-HNS)	25	53.7	betamethasone	2ml solution (0.4 mg/ml) weekly	without sinus surgery	through YAMIK nasal catheter	4	placebo
Dijkstra 2004 (1668)	RCT	mixed CRS (by symptoms and CT)	162	41	fluticasone propionate	Arm1. 400µg bid Arm2.800µg bid	with sinus surgery	spray	52	placebo
Lund 2004 (1671)	RCT	CRSsNP (by symptoms)	167	40.6	budesonide	128 mcg bid	without sinus surgery	spray	20	placebo
Giger 2003 (1676)	RCT	allergic rhinitis or CRSsNP (by symptoms)	112	32.3	beclomethasone dipropionate	200 mcg bid	without sinus surgery	spray	12	beclomethasone dipropionate 400mcg od
Lavigne 2002 (1670)	RCT	CRSsNP (by symptoms)	26	46	budesonide	2ml solution (256 mcg) od	with sinus surgery	through maxillary sinus catheter	3	placebo
Parikh 2001 (1672)	RCT	CRSsNP (by symptoms, endoscopy and CT)	29	46.6	fluticasone propionate	200 mcg bid	mixed	spray	16	placebo
Qvarnberg 1992 (309)	RCT	CRSsNP (by symptoms)	40	45.4	budesonide	200mcg bid	without sinus surgery	aerosol	12	placebo
Cuenant 1986 (1675)	RCT	CRSsNP (by symptoms, endoscopy, radiograph and ventilometry)	60	39	tixocortol pivalate	5 ml solution of 50mg	without sinus surgery	through maxillary sinus catheter (plus neomycin)	11/7	neomycin only
Sykes 1986 (1673)	RCT	CRSsNP (by symptoms)	50	not stated	dexamethasone	20 mcg daily	without sinus surgery	spray	2	placebo

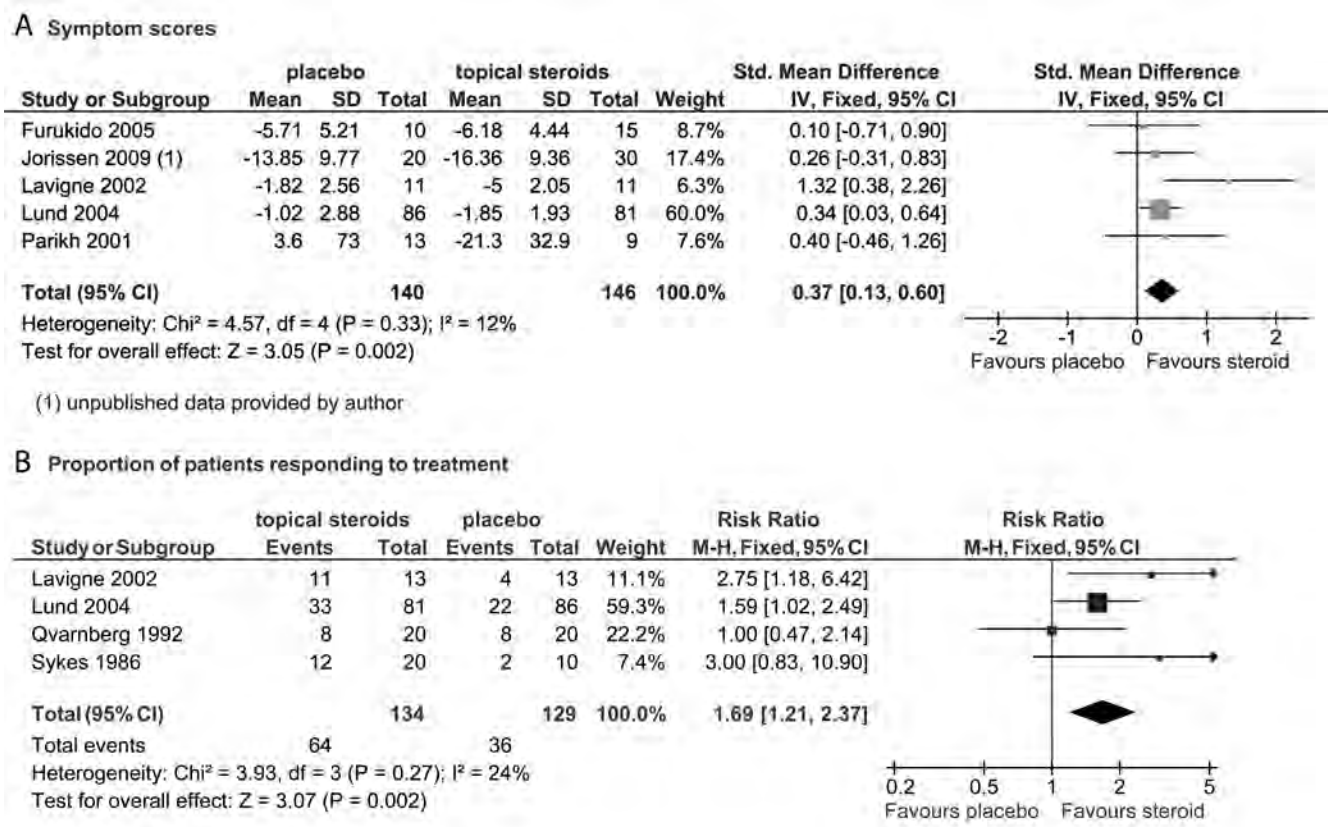
limited [1658] and in the setting of CRS with mucosal oedema it is probably only in the order of <2% of total irrigation volume [1659]. Nebulization is also ineffective with <3% sinus penetration [1660]. A fundamentally held belief amongst those treating CRS patients is that Endoscopic sinus surgery (ESS) improves the delivery of topical medications to the sino-nasal mucosa [1661, 1662], yet only recent evidence exists to support this claim [1658, 1663]. Endoscopic sinus surgery is essential to effectively allow topical distribution to the sinuses. The frontal and sphenoid sinus are essentially inaccessible prior to surgery [1658] and an ostial size of 4mm+ is required to even begin penetration to the maxillary sinus [1658]. For delivery, nebulizers poorly penetrate the sinuses even after maximal ESS [1664] and large volume squeeze bottles or passive flow devices appear to have the best efficacy post ESS [1658, 1661, 1662, 1664]. Pre-surgery, the distribution to the sinuses is extremely limited regardless of device [1658, 1659, 1663] and sprays are the least effective of all [1658]. Post-surgery distribution is superior with high volume positive pressure devices [1658, 1659, 1663]. Simple low volume sprays and drops have very poor distribution and should be considered a nasal cavity treatment only, especially prior to ESS [1658]. Although multiple devices and head positions have been trialled, less than 50% of most low volume applications will reach even the middle meatus [1665]. There is limited data on the exact volume required to allow complete distribution. Higher volumes do appear to penetrate both maxillary and frontal sinus with good coverage starting at about 100ml [1666]. The frontal and sphenoid sinuses are not accessed well by pressurized spray when compared to high volume devices such as squeeze bottles or neti pots [1658]. Higher volume and positive pressure irrigation is likely to result in the best distribution from current research.

The anti-inflammatory effect of corticosteroids could,

Table 6.1.2. Summary of outcomes from included studies of INCS on CRSsNP (studies with positive symptom outcomes are shaded. No study had placebeo favoured over INCS).

Study	Type of steroid	Steroid dose	Delivery method of steroid	Comparison	Patients report outcome measures (PROM) (scoring system and scale)	Summary PROM results	Endoscopic outcomes (scoring system and scale)	Summary endoscopic results
Hansen 2010 [1823]	fluticasone propionate	400 mcg bid	with Optinose device	placebo	symptom scores (3 symptoms; 0-3) total symptom VAS RSOM-3	favour steroid over placebo for combined symptom-score and nasal RSOM subscale	endoscopy scores (Lund-Kennedy;0-2)	favours steroid
Jorissen 2009 [1674]	mometasone furoate	200 mcg bid	spray	placebo	symptom VAS (5 symptoms)	no difference (p=0.09)	1.endoscopic score (8 variables;0-2) 2.post-hoc combination endoscopic score (3 variables;0-2)	1.no difference (p=0.34) 2.favor steroid (p=0.02)
Furukido 2005 [1669]	betamethasone	2ml solution (0.4 mg/ml) weekly	through YAMIK nasal catheter	placebo	symptom scores (4 symptoms;0-3)	comparison not reported	nil	nil
Dijkstra 2004 [1668]	fluticasone propionate	Arm1. 400µg bid Arm2.800µg bid	spray	placebo	symptom VAS (6 symptoms)	not reported at the endpoint	polyp recurrence	no difference (p-value not shown)
Lund 2004 [1671]	budesonide	128 mcg bid	spray	placebo	1. symptom scores (4 symptoms;0-3) 2. overall efficacy (0-4) 3. disease-specific quality of life (chronic sinusitis survey) 4. general health quality of life (SF-36)	1. favours steroid over placebo for all symptoms except facial pain and evening sense of smell 2. favour steroid (p=0.015) 3. no difference 4. favor steroid (p-value not shown)	nil	nil
Giger 2003 [1676]	beclomethasone dipropionate	200 mcg bid	spray	beclomethasone dipropionate 400mcg od	symptom scores (8 symptoms;0-3)	no difference between 2 regimes (p-value not shown)	nil	nil

Fig. 6.1.2 a en b



theoretically, be expected to benefit all forms of rhinosinusitis. Considering the abundance of publications on the use of corticosteroids in CRSsNP and CRSwNP, we present the findings from level 1 studies. Where no level 1 study exists, a summary of available evidence is presented. Data is presented separately on CRSsNP and CRSwNP along with local and systemic use.

6.1.2. Local corticosteroid (INCS) in CRSsNP

The use of local intranasal corticosteroid (INCS) has been widely published for many years and the following summary is based on a systematic search and summary of level 1 or randomized controlled trials for the evidence of benefit for symptoms in treating CRSsNP with INCS. However, not all studies demonstrate a benefit and a subgroup analysis is performed to help elucidate the reasons for some authors findings benefit over others.

6.1.2.1. Inclusion criteria and exclusion criteria Local corticosteroid (INCS) in CRSsNP

Inclusion criteria

Participants in the trials have to be defined as having chronic rhinosinusitis (CRS) by either:

- European Position Paper on Rhinosinusitis and Nasal Polyps 2007 [8];
- or Rhinosinusitis Task Force Report [523] and its revision [1667];
- or having chronic sino-nasal symptoms for longer than 12 weeks.
  - Trials which included participants of any age, who had any co-morbidity including asthma and aspirin sensitivity, were either allergic or non-allergic, and were followed for any duration.
  - Trials which included participants with CRS both with and without polyps if the majority of participants were without polyps. If possible, we only extracted data for participants with CRS without polyps.

Exclusion criteria

- Patients defined by the study authors as having acute or recurrent-acute sinusitis.
- Patients defined by the study authors as having CRS with polyps or nasal polyposis.
- Patients had CRS both with and without polyps and the majority of participants had polyps.

6.1.2.2. Types of interventions Local corticosteroid (INCS) in CRSsNP

- Any dose of topical steroid versus placebo.
- Any dose of topical steroid versus no treatment.
- Any dose of topical steroid versus alternative topical steroid.

6.1.2.3. Flow chart

A total of 666 references from the searches: 541 of these were removed in first-level screening (i.e. removal of duplicates and clearly irrelevant references), leaving 125 references for further consideration. We subsequently found one additional trial from a manual search guided by the identified references. A flow chart of study retrieval and selection is provided as Figure 6.1.1.

6.1.2.5. Included studies

Ten studies with a total of 590 patients met the inclusion criteria. The characteristics of included studies are listed as Table 6.1.1.

6.1.2.6. Summary of data

There were 11 included studies. Nine trials (80%) compared topical steroid against placebo (Hansen 2010; Dijkstra 2004; Furukido 2005; Jorissen 2009; Lavigne 2002; Lund 2004; Parikh 2001; Qvarnberg 1992; Sykes 1986) [309, 1668-1674, 1823].
One trial (10%) [1675] with 112 patients compared two treatment regimes of steroid administration without comparing to placebo. One (10%) trial [1676] with 60 patients compared topical steroid with antibiotic against antibiotic alone. We found no trials comparing topical steroid versus alternative topical steroid.

Five included studies were sponsored by pharmaceutical companies. Two were fully and three were partly supported as follows: Dijkstra 2004 [1668] (GlaxoSmithKline (GSK), Jorrisen 2009 [1674] (Schering-Plough Corp), Hansen 2010 [1823] (Optinose UK ltd), Lund 2004 [1671] (AstraZeneca and R&D Lund) and Lavigne 2002 [1670] (AstraZeneca Canada Inc and Fon de Recherche en Sante du Quebec). Medications were supplied by pharmaceutical companies in three studies: Parikh 2001 [1672] (Glaxo Wellcome Research), Sykes 1986 [1673] (Boehringer Ingelheim), Qvarnberg 1992 [309] (Suomen Astra OY). Furukido 2005 [1669] was not funded by pharmaceutical companies. Two studies did not state how they were funded (Cuenant 1986; Giger 2003) [1675, 1676]. A summary of outcomes is provided in Table 6.1.2. with the majority demonstrating a benefit to the use of INCS.

6.1.3.1. Meta-analysis

Of the eight studies comparing INCS to placebo, Five studies (Furukido 2005; Jorissen 2009; Lavigne 2002; Lund 2004; Parikh 2001); [1669-1672, 1674] and could be combined in the meta-analysis. Pooled data analyses of symptom scores and proportion of responding patients demonstrated significant benefit in the topical steroid group. The pooled results significantly favoured the topical steroid group (combined standardised mean difference (SMD -0.37; 95% confidence interval (CI) -0.60 to -0.13, p=0.002; five trials, 286 patients) The I2 was 12%, suggesting no heterogeneity (x2 = 4.57, degrees of freedom (df) = 4, p=0.33). This was true for both SMD and responder analysis (Figure 6.1.2a & 6.1.2b). The four studies that did not provide data for meta-analysis were [309, 1673, 1677, 1823] and only Dijkstra 2004 did not favour INCS.

Endoscopic scores were report in only 2 studies (Jorissen 2009 and Parikh 2001) [1672, 1674] and did not reach significant outcome on meta-analysis. Three studies used non-validated radiologic outcomes (Furukido 2005, Qvarnberg 1992, Sykes 1986) [309, 1669, 1673] and these all had no benefit favouring INCS but could not be combined for meta-analysis.

The standardised mean difference (SMD) and 95% CIs for continuous data such as post-intervention scores or change in symptom scores. The risk ratio (RR) and 95% CI of responsiveness was used at a specific time point for dichotomous data such as number of patients responding to treatment or number of patients having positive radiographs. The intervention effects were pooled when trials were sufficiently homogeneous. A fixed-effect model was used and assumed that each study was estimating the same quantity.

6.1.3.2. Subgroup analysis

Subgroup analysis was performed as follows.

- Topical delivery method
  - Nasal (drops, sprays, nebulisers) versus sinus (direct cannulation, irrigation post-surgery) delivery method.

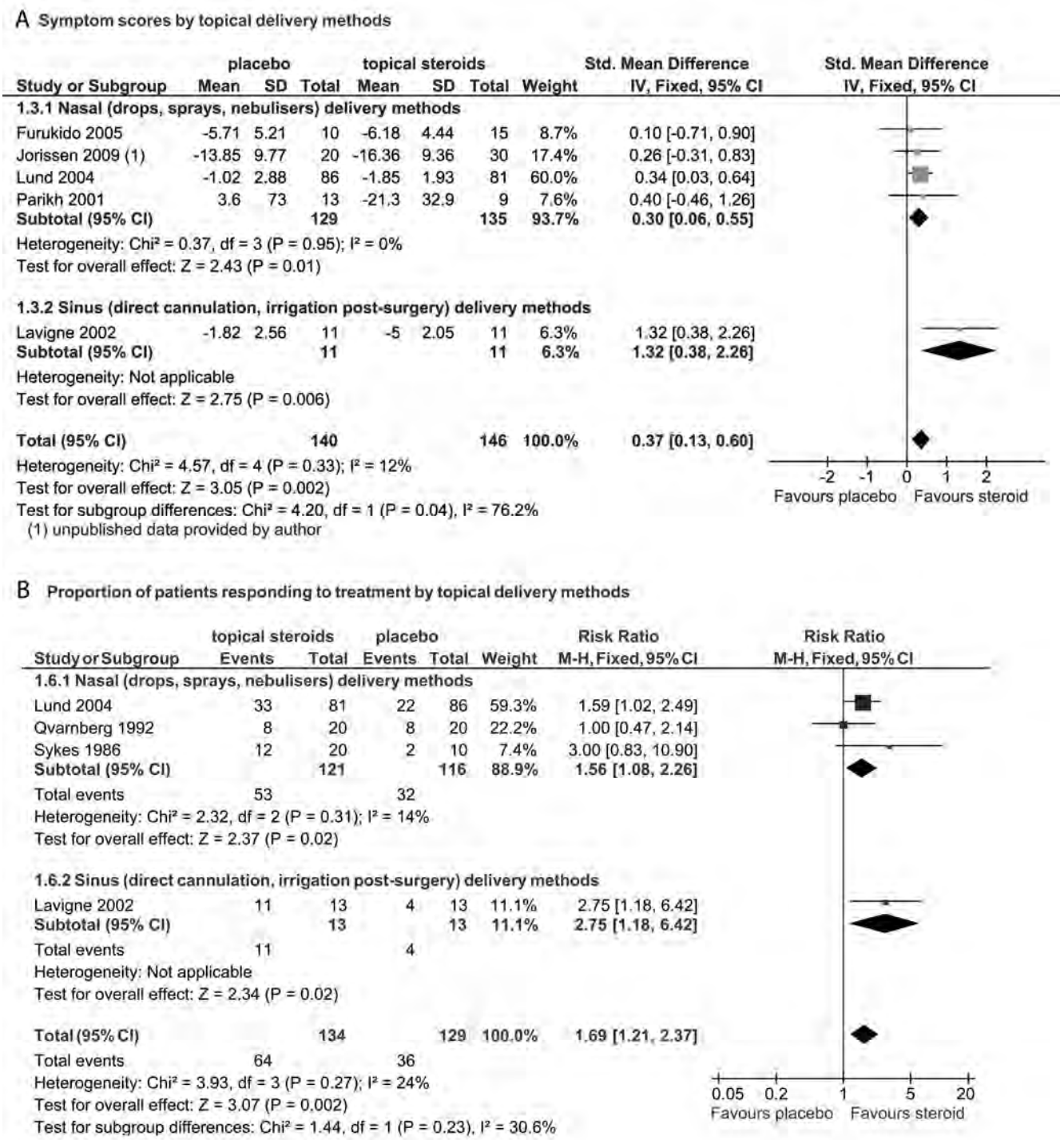
Low volume (defined as any simple spray volume approximating < 1 ml) versus large volume (defined as any significant volume > 60 ml - representing a simple irrigation syringe or smallest commercial irrigation device. We pre-defined low and large volume based on previous studies showing how the volume applied affects sinus delivery [1666]. Low pressure (including spray, nebulisers, instilled solution through a tube and non-pressure irrigation) versus high pressure (including positive pressure irrigation).

- Surgical status
  - Patients with prior sinus surgery versus those without sinus surgery.
- Corticosteroid type
  - Modern corticosteroids (mometasone, fluticasone, ciclesonide) v first-generation corticosteroids (budesonide, beclomethasone, betamethasone, triamcinolone, dexamethasone)

Differences between the two subgroups for fixed-effect analyses were based on the inverse-variance method in the case of continuous data and the Mantel-Haenszel method in the case of dichotomous data.

There was a benefit on subgroup analysis for INCS delivery method. This was significant when sinus delivery methods (SMD -1.32; 95% CI -2.26 to -0.38) were compared to nasal delivery

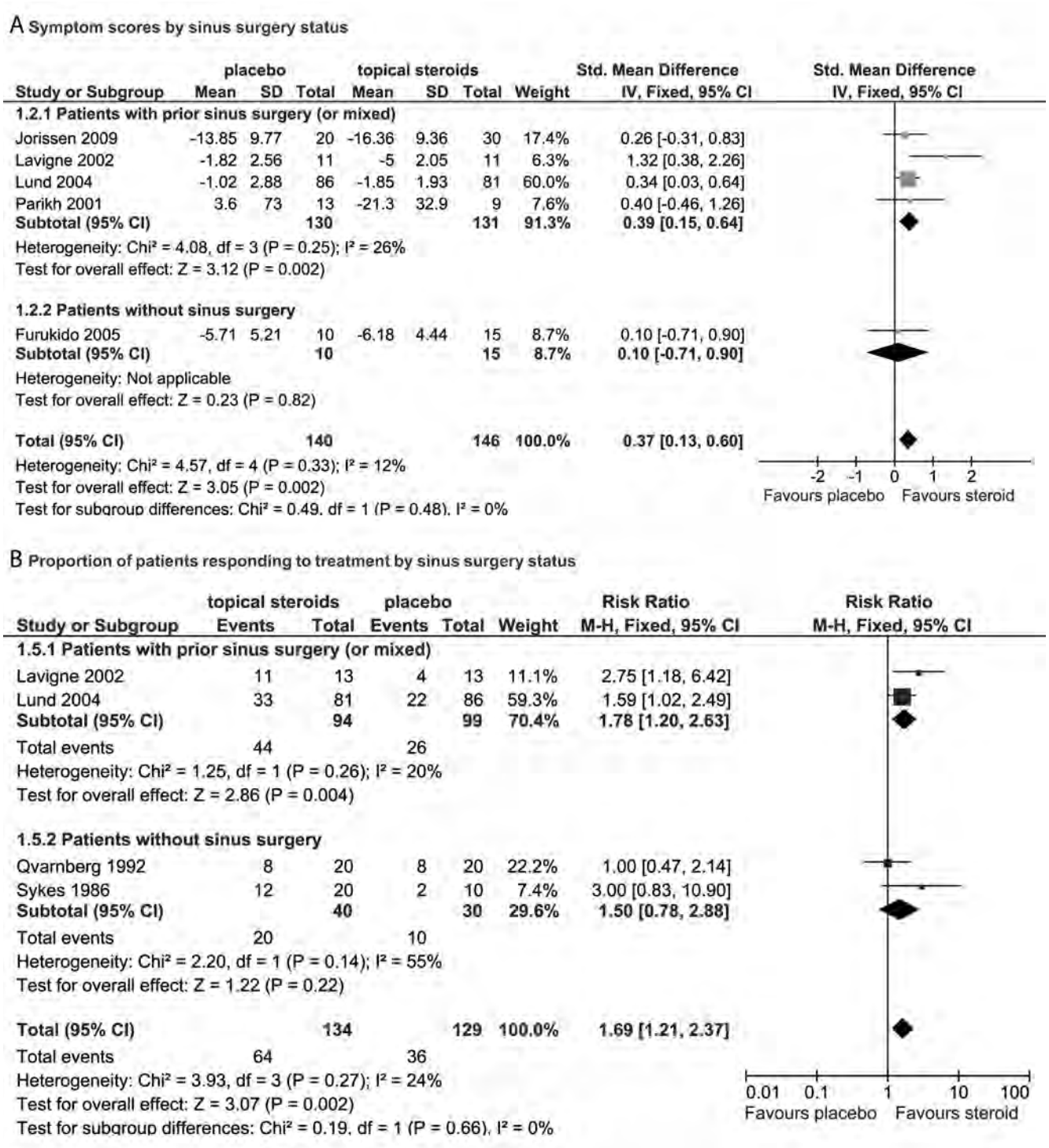
Figure 6.1.3. a en b



methods (SMD -0.30; 95% -0.55 to -0.06) (p=0.04). Similar findings were seen in responders as well as SMD analysis (Figure 6.1.3.a and 6.1.3.b). There were no studies using nasal drops and thus no comparison is made. No high volume and high pressure topical delivery techniques (i.e. irrigation or atomizer) were described.

When the surgical state of the patients was assessed on subgroup, only patients with prior surgery for CRSsNP had symptom improvement (SMD-0.54 CI -1.03, -0.06)) but there was no improvement for those patients without surgery (SMD -0.10, -0.90, 0.71). The comparative assessment between subgroups did not reach significance (p=0.23). This was true for responders as well as SMD (Figures 6.1.4.a and 6.1.4.b).

Figure 6.1.4. a en b



Finally, by corticosteroid type, there were 3 studies using modern corticosteroids [1674, 1668,1672] compared to 7 with older first-generation corticosteroid types. Only symptom scores were available for comparison with no significant difference between subgroups (p=0.75). Although, it may appear that the early generation INCS perform better than modern on the forest plot (Figure 6.1.5.a and 6.1.5.b) this difference is not significant and there are no data from modern INCS to use in the proportion of responders analysis.

6.1.4. Side-effects of local corticosteroid chronic rhinosinusitis without nasal polyps

Epistaxis, dry nose, nasal burning and nasal irritation are considered to be drug-related events. It is acknowledged that rare adverse events are possibly not detected in randomised controlled trials (RCTs). However, they were extremely low and there was no difference in adverse events between the study groups and control groups in any trial. Post-market adverse events for intranasal steroid sprays are very low. Minor adverse events from nasal steroid are well tolerated by patients. The amount of benefit clearly outweighs the risk. The reported adverse events from the included studies are summarized in Table 6.1.3.

6.1.5. Systemic corticosteroid chronic rhinosinusitis without nasal polyps

6.1.5.1. Introduction

There is limited data showing efficacy of oral corticosteroids in chronic rhinosinusitis without nasal polyps. A systematic review was performed by Lai et al [1678] in 2011. They found 27 clinical human publications on systemic corticosteroid use. Only 1 of these was a prospective trial (case series - level 4 evidence) and no RCTs or controlled cohorts. The remaining publications were 2 retrospective case series and 24 reviews or treatment guidelines. All studies used systemic corticosteroid in conjunction with antibiotics and INCS. Improved subjective and objective outcomes were seen in the 3 studies for CRSsNP [49, 1679, 1680]. In Tosca et al. the study population was children with asthma [49]. Subramamian et al. had both CRSwNP and CRSsNP and noted that the CRSsNP had better outcomes [1679]. Lal et al. noted that the CRSsNP had symptom resolution of 54.9% compared to 51% for the total CRS group [1680].

6.1.5.2. Side-effects of systemic corticosteroid chronic rhinosinusitis without nasal polyps

The side effect profile of corticosteroid use is likely to be similar between CRSsNP and CRSwNP, however, given the relative lack of clinical data (not data against) to support systemic corticosteroid use this risk-benefit ratio may be greater. Please refer to the description of side-effects of systemic corticosteroids from the section on CRSwNP.

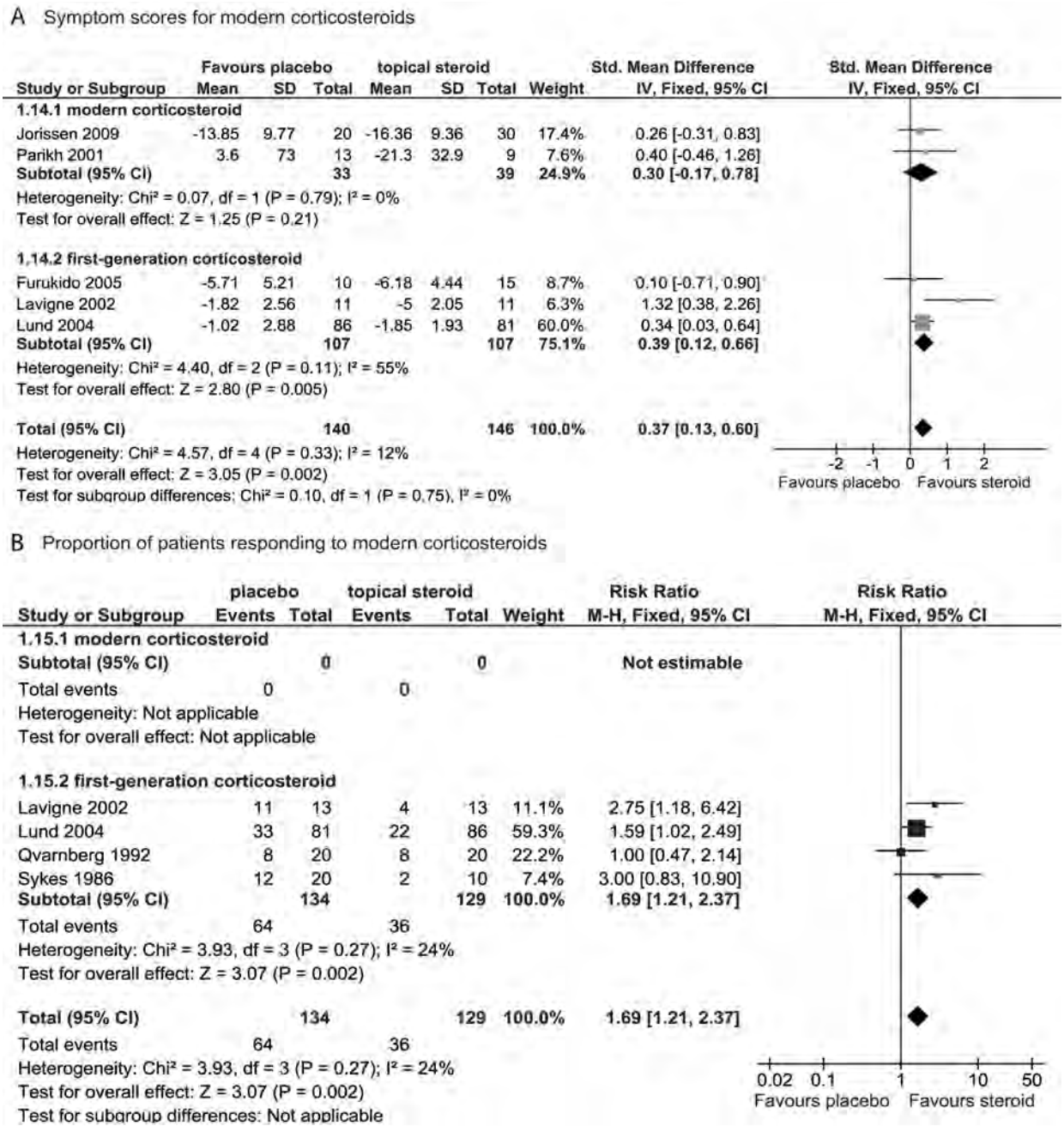
6.1.5.3. Evidence based recommendations

There is good evidence that INCS benefit CRSsNP. However, not all author demonstrate this finding. The surgical state of the sinuses treated (i.e. whether the sinuses have been opened and the ability of topical INCS to penetrate into the sinus cavity) appears to have a significant influence on response. The delivery device may be significant but there were not enough studies to come to a conclusion other than technique that deliver more effectively to sinuses are probably more beneficial.

Table 6.1.3. Reported adverse events in the included studies on INCS for CRSsNP (*low and ** high dose INCS compared, NR = not reported).

Study ID	Steroid group n(%)	Placebo group n(%)	Description of events reported	Remarks
Jorissen 2009 [1674]	29 (63)	28 (62)	Headache, sinusitis, cold	1. Most common headache 2. Few drug-related events 3. Rare serious events
Furukido 2005 [1669]	NR	NR	NR	NR
Dijkstra 2004 [1668]	NR	NR	Epistaxis	Epistaxis: not higher in steroids group
Lund 2004 [1671]	39 (48)	46 (53)	Respiratory infection, headache, blood-tinged secretion, viral infection, pharyngitis, sinusitis, flu-like, pain, rhinitis, external ear infection	1. Most events are mild or moderate 2. Regarding serious events, none were considered to be due to study medication 3. No difference of steroids with placebo 4. No increased incidence of infection
Giger 2003 [1676]	26* (47) 32** (56)		Epistaxis, dry nose, nasal burning, nasal itching, sinusitis, pharyngitis, otitis, change of taste, eczema, nausea/ diarrhoea, nasal irritation, common cold	1. Mild 61.6% moderate 4% severe; 3.8% 2. Most common epistaxis 3. No candidiasis 4. No difference between od and bid 5. No change in morning serum cortisol level
Lavigne 2002 [1670]	NR	NR	Tube fell out, epistaxis, diabetes with glycaemia, tube infection, asthma	No sinus irritation from steroid instillation
Parikh 2001 [1672]	NR	NR	NR	NR
Qvarnberg 1992 [309]	NR	NR	NR	NR
Cuenant 1986 [1675]	NR	NR	NR	NR
Sykes 1986 [1673]	NR	NR	NR	NR

Figure 6.1.5. a en b



Evidence based recommendations corticosteroids in CRSsNP.

Statement	Level of evidence	Grade of recommendation
Local		
INCS improve symptoms and patient reported outcomes in CRSsNP	1a	A
Delivery of INCS directly to sinuses brings about a greater effect	1a	A
Patients with prior sinus surgery have a positive effect of INCS compared to those without surgery	2a	B
INCS is associated with only minor side-effects	2a	B
Modern INCS do not have greater clinical efficacy (although potentially fewer sider-effects) compared to first-generation INCS	1a	A
Systemic		
Systemic corticosteroids benefit CRSsNP	4	C

6.2. Treatment of CRSsNP with antibiotics

6.2.1. Short-term treatment with antibiotics in CRSsNP

No placebo controlled trials exists in short-term systemic antibiotic treatment of CRSsNP

6.2.1.1. Summary of data

In this review short-term treatment with antibiotics is defined as treatment duration shorter than 4 weeks. There are no placebo-controlled trials available. However three randomised studies were identified, two double-blind and one open comparing the effect of 2 different antibiotics. In a multicentre, open parallel randomised clinical trial 206 adults with exacerbation of CRS were randomised to either amoxicillin/clavulanic acid (875 mg/125 mg b.i.d) or cefuroxime axetil (500 mg b.i.d). Clinical response rate was similar 95 and 88 % respectively. Bacteriological cure rate was 65 and 68 % respectively. Clinical relapse was significantly higher in the cefuroxime group, 8% compared to 0 % in amoxicillin/clavulanic acid group [1681]. In a double-blind study 251 CRS patients were randomised to either ciprofloxacin or amoxicillin/clavulanic acid. Clinical cure and bacteriological eradication rate was similar in both groups at approximately 60 % and 90 %. However, at 40 days after treatment cure rate was significantly higher in the ciprofloxacin group and there were more gastrointestinal side effects in the amoxicillin/clavulanic group [1682]. In the study by Huck et al comparing cefaclor with amoxicillin only 15 patients with CRS were included, too few to allow statistical analysis [1683].

6.2.1.2. Conclusion

In conclusion, no placebo-controlled studies are available. The 2 studies could not show any difference in short-term outcome comparing different antibiotics. Short-term treatment in CRSsNP is probably only relevant in exacerbations with a positive culture. The present level of evidence is level II. Recommendation B.

6.2.2. Long-term treatment with antibiotics in CRSsNP

6.2.2.1. Introduction to long-term treatment with systemic antibiotics in CRS

There has been an increasing interest in the use of macrolides in airway inflammatory disease since the publication of long-term, low-dose erythromycin treatment of diffuse panbronchiolitis (DPB). The treatment changed the 10 years survival rate from 25% to over 90 % and simultaneously cleared the CRS [1684, 1685]. Interesting to note is that the effect is seen at lower doses than used to treat infection and that the onset is slow and there is effect in the absence of common pathogens or in the presence of non-sensitive pathogens. Combined with the well-documented anti-inflammatory effects of macrolides in vitro it has led to the concept of macrolides being immune-modulatory rather than anti-bacterial.

6.2.2.2. Evidence for effect of long-term treatment with macrolides in the lower airways

From the literature it is evident that the pulmonary physicians have been much more successful than the ENT community to initiate Randomised Controlled Trials. In order to understand the potential of macrolide antibiotics to modify the inflammatory response in the airway it is therefore prudent to summarize present evidence from the lower airway.

The remarkable effect in diffuse panbronchiolitis patients have already been mentioned [1684, 1686]. In CF no less than eight RCTs have showed a beneficiary effect using clarithromycin,

Table 6.2.1. "Short Term" Antibiotics in CRSsNP.

Study	Drug	Number	Time/Dose	Effect on symptoms	Evidence
Huck 1993 [1683].	ceflaclor vs. amoxicillin	56 acute rhinosinusitis 25 recurrent rhinosinusitis 15 chronic maxillary sinusitis	2x 500mg 3x500mg for 10 days	clinical improvement: acute rhinosinusitis 86% recurrent rhinosinusitis 56% chronic maxillary sinusitis no statistics	1b (-)*
Legent 1994 [1682]	ciprofloxacin vs. amoxicillin clavulanate	251	9 days	nasal discharge disappeared: ciprofloxacin 60% amoxicillin clavulanate 56% clinical cure: ciproloxacin 59% amoxicillin clavulanate 51 clinical cure: ciproloxacin 59% amoxicillin clavulanate 51% bacterological eradication: ciprofloxacin 91% amoxicillin clavulanate 89%	1b (-)
Namyslowski 2002 [1681]	amoxicillin clavulanate vs. cefuroxime axetil	206	875/125mg for 14 days 500mg for 14 days	clinical cured: amoxicillin clavulanate 5% cefuroxime axetil 88% bacterial eradication: amoxicillin clavulanate 65% cefuroxime axetil 68% clinical relapse: amoxicillin clavulanate 0/ 98 cefuroxime axetil 7/89	1b (-)

* 1b (-): a level 1b study showing no difference between treatments

(one) or azithromycin, (seven). There are undisputed effects on inflammatory markers, such as IL-8, IL-4, interferon-gamma and TNF-α as well as reducing the rate of exacerbations and reducing decline in lung function [1687-1689]. Although not all studies have shown an overall improvement in quality of life it is now a recommended adjunctive treatment in CF.

In asthma, RCT studies using macrolides have shown to reduce airway hyperresponsiveness and to reduce inflammatory mediators in bronchoalvelar lavage such as IL-5, TNF-alpha and IL-12 [1690-1692]. More surprisingly roxithromycin therapy reduced markers for eosinophilic activity in aspirin sensitive asthmatics [1693]. A subgroup responding well to macrolides are the asthma patients with positive PCR for Chlamydophila pneumoniae or Mycoplasma pneumonia [1690].

Until recently in COPD there were two small (n<100) RCTs showing no effect on health status and exacerbation rate [1694, 1695]. However recently a large RCT in COPD (n=1577) using azithromycin for one year, showed a significant effect on time to exacerbation and number of exacerbation as well as improved functioning [1696].

In non-CF bronchiectasis, 3 RCTS have shown reduction in bronchial inflammation and sputum volume, individual studies have also demonstrated pulmonary function improvement and reduction in metacholine induced hyper responsiveness [1697-1699].

To sum up, the anti-inflammatory effects of macrolides in the lower airways is clearly demonstrated, especially in a neutrophilic inflammatory- infectious disease, such as CF. One has to bear in mind that a reduced dose was not always used and an added anti-bacterial effect is likely. In asthmatics PCR identification of Chlamydophila or Mycoplasma seems to be one way to identify the responsive phenotype. The case with COPD where 2 small studies showed little or no effect, whereas a large RCT showed effect, is an important reminder that a power analysis is paramount. A similar sized RCT in a defined CRS population would be of great consequence in constituting the care of CRS patients in the future.

6.2.2.3. Long-term treatment with systemic antibiotics in CRSsNP

In CRSsNP there is some evidence to use long-term, low-dose macrolide antibiotics for 12 weeks. Selecting patients with normal serum IgE could improve response rate.

In this review long-term treatment with antibiotics is defined as treatment duration longer than 4 weeks. Although antibiotic treatment is one of the mainstays of CRS treatment the number of placebo controlled trials are limited to two studies.

There are a number of open studies using macrolide antibiotics in varying doses, most often about half the daily dose compared to treating acute infections. All studies show a response rate (reduction in symptoms) that varies between 60 and 80 %. Most studies also show a reduction of inflammatory markers and some an increased ciliary beat frequency indicating less sticky secretions [1700-1706]. One study compared surgery with 12 weeks of erythromycin. Both treatment modalities improved symptoms significantly, except for nasal volume, which was better in the surgery group [16].

A recent review, June 2011, from the Cochrane Collaboration titled: Systemic antibiotics for chronic rhinosinusitis without nasal polyps [1707] identified only one prospective randomised placebo controlled trial [1708]. Recently and not included in the Cochrane review, another randomized controlled study has been published [1709]. These two studies represent the only placebo controlled randomised trials available in CRS. The studies investigated the effect of a macrolide antibiotic on the signs, symptoms and quality of life in patients suffering from chronic rhinosinusitis. In both studies the treatment period was 12 weeks. However, whereas the study of Wallwork and co-workers showed a clinical effect of roxithromycin with significant improvements in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid, the study by Videler and co-workers showed that azithromycin lacked

Table 6.2.2. Placebo controlled RCTs in long-term treatment with antibiotics in chronic rhinosinusitis without polyps [1708] and in a mixed population CRS [1709].

Study	Drug	N=	Time/dose	Effect symptoms	Level of evidence
Wallwork 2006 [1708]	Roxithromycin	64	12 weeks/150 mg daily	Significant effect on SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels. CRSsNP population. Improved or cured in treatment group was 67% vs 22% in placebo group. In a subgroup with normal IgE levels 93% were improved or cured in the treatment group.	1b
Videler 2011 [1709]	Azithromycin placebo controlled	60	12 weeks/500 mg week	No significant effect. Response rate was 44% in treatment group vs 22% in placebo group.	Ib (-)

* 1b (-): a level 1b study showing no difference between treatments

efficacy. In the Wallwork study the response rate overall in the treatment group was 67%, compared to 22% in the placebo group whereas in the Videler study it was 44% for azithromycin and 28% for placebo.
Both studies are about the same size 64 vs. 60 patients with CRS included. The inclusion criteria are however different. In the Wallwork study the patients were without polyps, whereas, the Videler study included patients both with and without nasal polyps, in fact a minimum CT score was required (CT scan score ≥5 at worst side according to Mackay-Lund), which suggest a polyposis or hyperplastic sinusitis. In the Wallwork study it was noted that a sub-population of patients with normal IgE levels had a higher response rate to the macrolide treatment than patients with elevated IgE, where most of the non-responders were found. Although not analysed, it is possible that the study population in the Videler study comprised of a higher number of patients with elevated IgE making them less suitable for macrolide treatment as previously described by Suzuki [1710]. Higher CT scores are also positively related to elevated IgE levels and eosinophilia [1711]. The discrepancy between these two studies highlights the need for matching the right patient with the right treatment. When considering long-term macrolide treatment, a serum IgE is helpful in trying to identify likely responders.
A retrospective analysis compared a mixed CRS population (both with and without polyps) treated with long-term macrolide, azithromycin or clarithromycin or trimethroprim-sulfamethoxazole. 76 patients were included, 53% had asthma and all had undergone sinus surgery. Severe nasal polyposis patients were excluded. The mean length of treatment was 189 and 232 day respectively. The response rate was 78% with no difference between the 2 treatment groups. Follow up for 4.7 months in mean after cessation of treatment showed that the improvement was sustained in 68% of patients. Interesting to note, smokers were less likely to respond and there were more allergic patients in the responding group [1712].

6.2.2.4. Conclusion

The majority of studies have used macrolide antibiotics. A number of open studies using macrolides have shown a response rate of 60-80%. One placebo controlled study using a roxithromycin showed efficacy in patients without polyps. The other placebo controlled azithromycin study had a mixed population of patients with or without polyps and although there were more responders in the treatment group it did not reach significance. Further larger placebo controlled studies in a defined CRS population are warranted. Concerning the open studies one has to be cautious, especially since an intervention is more likely to occur when the patient is suffering from an exacerbation, and as in any cyclic disease an improvement will eventually occur regardless of action taken. Thus, in a study lacking a placebo group, the risk of over-estimating efficacy of the intervention is high.
For now, long-term antibiotic treatment should be reserved for patients where nasal corticosteroids and saline irrigation has failed to reduce symptoms to an acceptable level. Data suggests that the population with high serum IgE are less likely to respond to macrolide treatment and the ones with normal IgE more likely to do so [1713]. Future phenotyping may also include PCR for Chlamydiophilia and Mycoplasma although this has not been explored in CRS.
Other choices such as long-term treatment with doxycycline or trimethroprim-sulfamethoxazole could turn out to be promising alternatives and further studies are warranted.
Level of evidence for macrolides in all patients with CRSsNP is Ib, and strength of recommendation C, because the two double blind placebo controlled studies are contradictory; indication exist for better efficacy in CRSsNP patients with normal IgE the recommendation A. No RCTs exist for other antibiotics.

6.2.2.5. Adverse events of antibiotic therapy of CRS

6.2.2.5.1. Effects on bacterial resistance.

A concern with long-term antibacterial treatment is the emergence of resistant bacterial strains. Especially when using a low dose not attaining minimal inhibitory concentrations. Data from primary care have shown that increased macrolide prescription in group A streptococci tonsillitis leads to a subsequent increase in resistance, which can reach alarmingly high levels [1714, 1715]. However in a tertiary setting, data is sketchy. The study by Videler at al. using azithromycin for 12 weeks, found 3 of 50 cultures with macrolide resistant strains before treatment, and after treatment 4 of 43 cultures with resistant strains [1709]. An emerging concern in cystic fibrosis patients is the increasing incidence of infection with the highly pathogenic Mycobacterium abscessus in azithromycin treated patients. The effect is probably due to azithromycin inhibition of autophagic and phagosomal degradation [1716-1718]. This has not been reported in CRS patients. In a placebo randomised, double-blind trial, studying the effect of exposure of oral streptococcal flora of healthy volunteers to azithromycin and clarithromycin, definitive proof that antibiotic use is the single most important driver of antibiotic-resistance was demonstrated. Physicians prescribing antibiotics should take into account these striking ecologic side-effects of antibiotics [1719].

6.2.2.5.2. Other side effects

Well-known side effects of antibiotics includes; gastrointestinal upset, skin rash reversible elevation of liver enzymes. In the study by Videler et al including 78 patients, the investigators found 1 case of muscle ache in the azithroprim group and 2 cases of mild skin rash in the clarithromycin treated patients and no adverse effects in the trimethroprim-sulfamethoxazole

group. The study comparing doxycycline treatment for 20 days with methylprednisolone and placebo reported no difference in adverse events in the different groups. However, rare side effects are not picked up in small clinical trials, but rather in national records on side effects. Hearing impairment due to macrolide treatment is a rare side effect but was recorded in a recent large trial in COPD [1696].

6.2.2.5.3. Conclusions on adverse events of antibiotic therapy of CRS

The safety of long-term antibiotic therapy, either azithromycin, clarithromycin or roxithromycin is recognised in patients with CRS, but also due to it's established long-term use in cystic fibrosis. As for doxycycline there is longstanding experience for long-term use in acne and rosacea patients. Trimethroprim-sulfamethoxazole has been used long-term in both the paediatric and adult population for treatment of infectious prone patients with certain immune deficiencies as well as urinary tract infections. Drawing on the experience from other areas than CRS, long-term treatment with the mentioned antibiotics is relatively safe. Although one has to bear in mind the interaction between macrolides and drugs such as dicumarol, antiepileptic drugs, terphenadine, methotrexate and antidepressant drugs.

To monitor the risk of the development of resistant bacterial strains, nasal swabs with culture every 3 months during treatment is advisable.

6.2.3. Treatment with topical antibiotics in CRSsNP

6.2.3.1. Summary of the data

There are three placebo-controlled studies with topical antibiotics and a number of open labelled studies. They open labelled studies show benefit in either signs and or symptoms ranging from 40 to 80% response rate [1455, 1720-1725]. A number of different topical solutions have been used with different treatment periods. Any general conclusions from these studies are difficult to draw.

There are 3 placebo-controlled trials with topical antibiotics in CRS. None of them showed any additive effect compared to saline.

However the three placebo-controlled studies are all negative. A study from 1986 where dexamethasone, neomycine and tramazoline were compared with dexamethasone without neomycine and a placebo group with vehicle alone showed no additive effect of neomycin both the group with dexamethasone alone and with the addition of neomycin were superior to placebo [1673]. Another placebo controlled trial by Desrosiers et al. investigated 20 patients in a randomized, double-blind trial of tobramycin-saline solution or saline-only, administered thrice daily by means of a nebulizer for 4 weeks, followed by a 4-week observation period. Both patient groups experienced improvement in signs and symptoms but the addition of tobramycin appears of no benefit [1726].

Thirdly a study by Videler et al investigated the effect of nasal irrigation with bacitracin/colimycin or placebo in a randomised, double blind, cross-over study in 14 patients with recalcitrant CRS in spite of surgery. Both groups improved and there was no difference in SF-36 and endoscopic appearance [1727]. Chiu et al showed in a rabbit model with Pseudomonas sinus infection that increasing concentrations of topical tobramycin resulted in the eradication of viable bacteria within the lumen of the sinus but did not eradicate Pseudomonas attached to the mucosa [1728].

6.2.3.2. Conclusion concerning the use of topical antibiotics in CRS

There is low level of evidence for the efficacy of topical antibacterial therapy in seven uncontrolled trials. However 3 placebo controlled trials failed to show any additive effect of topical antibiotics as compared to saline alone. Topical antibacterial therapy cannot be recommended in the treatment of CRS. Level of evidence Ib, grade of recommendation A.

Table 6.2.3. Placebo controlled RCTs in topical treatment with antibiotics in chronic rhinosinusitis without polyps

Study	Drug	N	Time/dose	Effect symptoms	Level of evidence
Sykes 1986 [1673]	Dexamethasone (D) neomycine (N) tramazoline (T) vs DT vs propellant alone	50	4x daily for 2 weeks	NDT 14/20 improved DT 12/20 improved Placebo 2/20 improved	1b (no effect of added antibiotic)
Desrosiers 2001 [1726]	Tobramycin double blind placebo controlled	20	80 mg x3 daily/4 weeks	Significant improvement in both groups in symptoms QoL and endoscopy	Ib (no effect of antibiotic)
Videler 2008 [1727]	Bacitracin/colimycin topical spray with systemic levofloxacin double-blind, randomized, placebo-controlled, cross-over	14	bacitracin/colimycin (830/640 µg/ml) x 2 daily / 8 weeks	Improvement in both groups, no significant difference in symptom score and SF-36	1b (no effect of antibiotic)

6.2.3.3. Adverse events of topical antibiotic spray

Not all studies mention side effects but the most common side effects seems to be intra-nasal stinging, burning sensation, moderate pain, throat irritation, cough and dry skin. Topical antibiotics not being registered as drugs makes reports on side effects sketchy.

6.3. Other medical management in CRSsNP

6.3.1. Summary

This chapter deals with medical therapies of CRSsNP in adults except antibiotics and glucocorticoids. For medical treatment of acute rhinosinusitis and in paediatric rhinosinusitis, please refer to the according chapters. No RCT for the treatment of CRSsNP in adults were identified for antihistamines, mucolytics and expectorants, homeopathic remedies, proton pump inhibitors, surfactants including baby shampoo or nasal decongestants. These treatment modalities are not recommended. No benefit was found in randomized controlled trials or systemic reviews for antimycotics, herbal medicines, or probiotics, which are also not recommended for the treatment of CRSsNP in adults. Based on the results of 1 RCT, bacterial lysate treatment may be considered as an adjunct to standard medical treatment in adults with CRSsNP. One Cochrane review and 2 RCTs indicate a beneficial effect of nasal douches in CRSsNP in adults.

6.3.2. Antimycotics

One trial with nasal amphotericin B treatment was explicitly performed in 64 CRS-patients without polyps [711]. Following inclusion, patients were randomized to either 20mg/day amphotericin B or a yellowish solution without amphotericin administered in 500 ml saline solution with a pulsatile irrigator. If the type of therapy was concealed to the investigators is not reported. Main outcome parameter was the sum score of the Rhinosinusitis Outcome Measures 31 questionnaire. Secondary endpoints included a nasal endoscopy score and pre- and post-treatment fungal cultures. Symptom scores were significantly lower in the amphotericin treated patients after 2 weeks treatment (p=0.018), but not after 4 weeks treatment (p=0.091). Endoscopy scores and fungal culture rates did not significantly differ between groups. Based on current data, nasal amphotericin B treatment in CRSsNP is not recommended (grade of recommendation A).

6.3.3. Bacterial Lysates

Bacterial lysates enhance Th1-skewed immune responses and dendritic cell maturation via activation of toll like receptors [1729, 1730]. Several trials on the preventive effect of immunostimulants including bacterial lysates on recurrent respiratory infections mainly in children were identified, however, only 1 bacterial lysate trial particularly assessed the effect on chronic rhinosinusitis in adults. In a multicentre randomized double-blind study, 284 patients with chronic purulent sinusitis were treated with the oral bacterial lysate Broncho Vaxom (OM-85 BV) or placebo in addition to standard therapy (antibiotics, mucolytics, inhalants). Treatment lasted for three ten-day periods in three consecutive months. At the start and during the therapy as well as after six months, symptoms were assessed on the basis of a scoring system and the X-rays of the nasal sinuses evaluated. During the course of therapy and the follow-up period, improvement of the major symptoms headache, purulent nasal discharge, cough, and expectoration was statistically significant in the immunostimulant group as compared with the placebo group, objective evidence being provided by the X-ray examinations and the number of reinfections during the period of observation [1731]. Based on the results of 1 RCT, oral OM-85 BV treatment may be considered as an adjunct to standard medical treatment in adults with CRSsNP (grade of recommendation A).

6.3.4. Herbal medicines and homeopathic drugs

Phytotherapy is the use of plants or herbs to treat diseases. A huge range of preparations, most of them not yet subjected to clinical trials and some with unknown ingredients, are marketed over the counter in Europe. Homeopathy is a system of therapeutics founded by Samuel Hahnemann [1755-1843], based on the Law of Similars where "like cures like". Diseases are treated by highly diluted substances that cause, in healthy persons, symptoms like those of the disease to be treated. Herbal and homeopathic drug use is subjected to great regional differences. Alternative treatment modalities are used by 15-50% of rhinosinusitis patients [1732-1734].

Guo and co-authors reviewed randomized clinical trials (RCTs) testing a herbal preparation, as sole or adjunctive treatment, administered systemically or topically, against a control intervention (placebo or no treatment), in patients with acute or chronic rhinosinusitis [1735]. The authors found no evidence that any herbal medicines are beneficial in the treatment of CRSsNP. Alcoholic extracts of pelargonii radix are marketed since decades as a treatment for upper and lower respiratory tract infections. In a recent Cochrane report on P. sidoides extracts and tablets, no trials on CRSsNP fulfilled the inclusion criteria [336].

No RCT on homeopathic treatment of CRSsNP could be identified. Based on current data, herbal medicines and homeopathic remedies are not recommended for the treatment of CRSsNP (grade of evidence D).

6.3.5. Nasal irrigation

Isotonic or hypertonic saline solutions delivered by bottle, spray, pump or nebuliser are frequently used in the treatment of sinus disease, mainly as a supplement to other therapies.

Sinus penetration of irrigation fluids differs in patients with and without previous sinus surgery [1663] and depends on the application mode [1661,1662].

Nasal saline irrigations were judged beneficial in the treatment of the symptoms of chronic rhinosinusitis when used as the sole modality of treatment in a Cochrane report [1736]. However, in this evaluation children were also included and no clear separation between CRSwNP and CRSsNP was reported. Moreover, it remained unclear, if patients had undergone previous sinus surgery.

In a community based, randomized, controled trial, Pynnonen and co-workers compared isotonic nasal saline spray and isotonic nasal saline douches in 127 adult patients with CRS without recent sinus surgery. Outcome parameters included change in symptom severity measured by mean 20-Item Sino-Nasal Outcome Test (SNOT-20) score; change in symptom frequency measured with a global question; and change in medication use. Outcomes were measured at 2, 4, and 8 weeks after randomization. All outcome parameters were significantly better in the nasal douches group than in the nasal spray group [1737].

The value of nasal douching following sinus surgery was assessed in an intra-individual, single blinded randomised controlled trial. Nasal douches were used by 22 patients following sinus surgery in one side of the nasal cavity, three times per day for 6 weeks. The opposite nasal cavity was not irrigated. Presence of adhesions, polyps, crusting, discharge or oedema was assessed 3 weeks and 3 months postoperatively. At 3 weeks, nasal saline douching improved the presence of discharge and oedema, but had no effect on adhesions or crusting. At 3 months, no significant differences between douched and non-douched nasal cavities were observed [1738].

Thorough cleaning of irrigation devices is required to prevent bacterial contamination, however, no sinus infection due to irrigation device contamination has yet been reported [1739-1741].

Based on current data, nasal douches are recommended for CRSsNP in adults without recent sinus surgery and in the post sinus surgery setting (grade of recommendation A).

6.3.6. Additions to nasal irrigation

Sodium hypochlorite (NaOCl) is a well-known bleaching and desinfecting agent that has been found to be effective against several organisms including *S. aureus* and *P. aeruginosa*. Nasal irrigation with 0.05% NaOCl solution in saline was significantly more effective than saline alone in the treatment of *S. aureus* positive CRS patients in a study where patients used saline irrigation for 3 months and afterwards saline irrigation with 0.05% NaOCl solution [1742] (Level of evidence IIb). Xylitol has been shown to effect ASL ionic composition in vitro and to reduce nasal bacterial carriage, otitis media, and dental caries in vivo. Xylitol in water is a well-tolerated agent for sinonasal irrigation. Xylitol irrigations result in greater improvement of symptoms of chronic rhinosinusitis as compared to saline irrigation [1743] (level of evidence 1b).

Biofilms are considered to play a pathophysiological role in CRS. Data on the impact of biofilms on sinus surgery outcomes are conflicting [693, 1744]. Surfactants reduce water surface tension and may help to dissolve biofilms [1745]. No RCT of surfactants in the treatment of CRSsNP was identified. Baby shampoo contains several surface active agents. Nasal irrigations containing Johnson's Baby Shampoo were tested in a non-randomized, open-label trial in 15 CRS patients for 4 weeks. Concomitant medications included antibiotics and oral prednisolone. Subjective improvement was observed in 46% of the patients [1746] (level of evidence III).

Current data do support the use of xylitol (recommendation A) or sodium hypochlorite nasal irrigations (grade of recommendations B) but not irrigations containing baby shampoo in CRS patients (grade of recommendation D).

6.3.7. Probiotics

Probiotics are living microorganisms that benefit the health of the host by conditioning the intestinal microenvironment. Supplementation with probiotics may alter intestinal microflora and promote Th1 responses by activating interferon gamma, interleukins 12 and 18. In a randomized, double-blinded, placebo-controlled trial, 77 patients with chronic rhinosinusitis received either oral probiotic Lactobacillus rhamnosus R0011 strain (500 million active cells/tablet twice daily, n=39) or oral placebo (n =38) for 4 weeks. The main study endpoint was the change in the SNOT-20 score. Secondary outcome parameters included a symptom frequency score and a medication score. No significant differences were found between the probiotic and the placebo group in their changes in SNOT-20 scores from baseline to 4 weeks (p=0.79) or from baseline to 8 weeks (p=0.23) [1747]. Current data do not support probiotic treatment in CRSsNP (grade of recommendation A).

6.3.8. Proton Pump inhibitors

Extraesophageal reflux has been supposed a possible cause of CRS [1748], however clinical data on the frequency of extra-oesophageal reflux in patients with rhinosinusitis do not support this link [1749, 1750]. No RCT on proton pump inhibitors in the treatment of CRSsNP in adults was identified. In one uncontrolled trial in 11 adult CRS patients with abnormal pH-monitoring, omeprazole 20mg daily for 12 weeks led to modest symptom improvement [1751].

Proton pump inhibitors frequently cause gastrointestinal symptoms and increase the risk to acquire pneumonia in children and respiratory infection in adults [1752, 1753]. Current data do not provide sufficient evidence for proton pump inhibitor treatment for CRSsNP in adults (grade of recommendation D).

6.4. Evidence based surgery for CRSsNP

6.4.1. Summary

Although trials providing high level evidence are missing, a number of large, well organised prospective studies has shown that endoscopic sinus surgery (ESS) is safe and effective in managing patients with CRS without NP when medical treatment has failed. ESS is more likely to be effective in managing nasal obstruction and facial pain than postnasal drip or Hyposmia and is associated in significant improvements in generic as well as disease specific quality of life outcomes. Middle meatal antrostomy as opposed to simple uncinectomy and (targeted) partial removal of the middle turbinate may be associated with improved endoscopic and radiological outcomes but not subjective improvements.

6.4.2. Introduction

Surgery is an imprecise art, and surgeons have traditionally had to make decisions with limited facts: Unfortunately, a look at the past will reveal a surgical landscape virtually "littered " with procedures and interventions that have now been abandoned and are deemed useless and even harmful. Evidence-based surgery emphasizes the need to evaluate adequately the efficacy of surgical interventions before accepting them as standard. Essential for evidence-based surgery is a clear definition of the disease and standardized outcome measures.

6.4.3. Evidence based surgical treatment of rhinosinusitis

Evidence based medicine does not always have to be based on randomized controlled trials (RCT). In surgery (just as in parachuting [1754]) it is often not ethical or possible to do RCTs; however, the fact remains that we need to evaluate the available evidence to prevent us from giving our patients ineffective or even harmful treatments. Evaluation of the available evidence is not always easy: There are a number of potential biases in all types of medical research (expectancy bias/patients expectations from treatment, variations between patients/ selection bias, co-intervention and timing bias, publication bias and withdrawal bias). Surgical studies introduce additional types of bias, including the lack of patient blinding to the surgical intervention and performance bias (procedures or interventions are not executed in a uniform way – any one surgeon may do the same procedure in a different way from day to day, and that is even more true between different surgeons). Despite these difficulties, studies are being performed, and sinus surgeons should critically evaluate published evidence and adjust their practices accordingly. We will attempt in this article to assess evidence on surgery for CRSsNP or CRSwNP, taking into account however, that many studies included patients with CRS with and without nasal polyps.

6.4.4. Functional endoscopic sinus surgery in CRSsNP

Large prospective studies and case series have shown that endoscopic sinus surgery is effective and safe for the management of patients of CRS without NP who have failed medical treatment

6.4.4.1. Randomised controlled trials

The "holy grail" of evidence-based medicine is the Randomised Controlled trial (RCT). However, the search for such studies is not always successful, and in the meanwhile, surgeons have to practice with the (best) available evidence. The Cochrane collaboration re-assessed and revised in 2009 [1755] the evidence for surgery in CRS: they screened 2323 studies and found 6 randomised control trials: Using strict methodological quality inclusion criteria they excluded 3 of these studies and examined the three remaining RCTs: the first one, a University of London thesis written by Fairley in 1993 [1153] compared 12 patients with CRS undergoing endoscopic middle meatal antrostomy with 17 patients who undergoing conventional intranasal inferior meatal antrostomy. The study found symptom improvement in both groups but no differences between groups; one year follow-up data were available for 11 patients and 9 patients respectively, a sample size the author acknowledges as being too small to exclude a type II error. The second study from 1997 [1756] assessed patients with isolated maxillary sinusitis and compared symptom improvement after ESS and after saline rinses among patients randomized before antibiotics were

Table 6.4.1. Randomised controlled studies comparing surgery with medical treatment in Chronic Rhinosinusitis without Nasal Polyps.

Author	N	Follow up	Inclusion criteria	Non ESS group	ESS group	Outcome
Hartog 1997 [1756]	89 (77)	12-52 wks	Rhinorhea /obstruction/headache and radiological evidence of maxillary opacification	Sinus irrigation + Loracarbef po 10 days	Sinus irrigation+ loracarbef po 10 days + ESS	No difference in overall cure rates, ESS group improved more in post-naasal discharge and hyposmia
Ragab 2004 [16]	90 (78)	52 wks	2 major or one major and 2 minor symptoms and CT evidence of CRS	3 months of erythromycin + nasal steroid + nasal douche	ESS+nasal steroid + nasal douche	No difference in total symptom scores, greater improvement in nasal volume in surgical group

administered. The third study by Ragab et al. from 2004 [16] was the most relevant of the three as it randomized 90 patients with CRS with and without NP in medical (long term antibiotics) or surgical (ESS) management and assessed both objective (endoscopic scores, nitric oxide, PNIF and saccharine clearance time) and patient reported outcomes (symptoms VAS, SF36 and SNOT 20 scores). It found that both treatments significantly improved almost all the subjective and objective parameters of CRS (P <.01), with no significant difference being found between the medical and surgical groups, except for the total nasal volume, in which the surgical treatment demonstrated greater changes. The effect of surgery was the same in both CRS groups (with and without NP). However, the surgical group received only 2 weeks of erythromycin after surgery while the medical group received 3 months of erythromycin after randomization. However, there was no placebo group, which somewhat reduces the importance of findings.

The Cochrane collaboration, using data from these 212 patients, stated that "(ESS) has not been demonstrated to confer additional benefit to that obtained by medical treatment with or without antral irrigation in relieving the symptoms of chronic rhinosinusitis". However, our impression is that there was simply insufficient evidence for any comment about the value of ESS compared with medical treatment based on these three studies. The first study included in the Cochrane review [1153] did not compare ESS with medical treatment, and the other two studies [16, 1756] did not analyse ESS results among patients who failed medical treatment, including antibiotic therapy. Indeed, current thinking precludes that sinus surgery must be always preceded and/or followed by various forms of medical treatment. This, together with the fact that surgery is often suggested for patients who fail medical therapy render comparisons of medical treatment with surgery difficult (Table 6.4.1).

6.4.4.2. Case series, case-control and cohort studies

RCTs in surgery are notoriously difficult to organise and (as in the case of truly blind "sham" studies), potentially unethical. If these are not available, it is appropriate to assess the available evidence, even if it is grade 2 or 3. Indeed, it seems counterintuitive to ignore high quality evidence collected from thousands of patients purely on the grounds that they did not form part of a randomised controlled trial.

In 2000 the Clinical Effectiveness Unit of the Royal College of Surgeons of England conducted a National Comparative Audit of the Surgery for Nasal Polyposis and Chronic Rhinosinusitis covering the work of 298 consultants working in 87 hospital sites in England and Wales [1757]. Patients undergoing sinus surgery were prospectively enrolled and followed up in this observational study at 3, 12 and 36 months post-operatively using the SNOT-22 as the main outcome measure. Two thirds [2176] of the 3128 patients participating in this study had CRS with nasal polyps. CRS patients with nasal polyps suffered more frequently from concomitant asthma and ASA-intolerance, had more previous sinonasal surgery, their mean CT score was higher and their mean SNOT-22 symptom score was slightly lower than that of CRS patients without polyps. All forms of sinus surgery were included though the majority were performed endoscopically. Overall there was a high level of satisfaction with the surgery and clinically significant improvement in the SNOT-22 scores was demonstrated at 3, 12 and 36 months [1757] (Figure 6.4.1.). Patients with chronic rhinosinusitis without polyps benefited less from surgery than polyp patients; surgery was indicated in 3.6% of patients at 12 months and 11.8% at 36 months. Major complications were very uncommon. Five year follow up results from almost half of the patients of this audit were published in 2009 [1758]: Nineteen percent of patients surveyed eventually underwent revision surgery during these five years, including 15% of patients with CRS without NP. The mean SNOT-22 score for all patients was 28.2, very similar to the results observed at 36 months (27.7), and represents a consistent 14-point improvement over the baseline score. Scores were better for polyp patients (mean = 26.2) than patients with CRS alone (mean = 33.3). (Evidence level IIc)

Long term revision rates in patients with CRSsNP have been shown to be above 10% (and as high as 15-20%)

6.4.4.3. Symptom-specific outcomes

A recent review by Chester et al [1759], screened 289 studies including only studies with 20 or more patients who used symptom severity scores to analyse at least 3 CRS symptoms (facial pressure, nasal obstruction, postnasal discharge, hyposmia and headache). They eventually included 21 studies and 2070 patients with CRS with or without NP a mean of 13 months after ESS: All symptoms improved compared with their preoperative scores by an overall Effect Size of 1.19 (95% confidence interval, 0.96 to 1.41). Nasal obstruction (Effect Size, 1.73) improved the most, with facial pain (ES, 1.13) and postnasal discharge (ES, 1.19) demonstrating moderate improvements. Hyposmia (ES, 0.97) and headache (ES, 0.98) improved the least (Evidence level IV).

6.4.4.4. Quality of life outcomes

6.4.4.4.1. Generic QOL

A number of studies have shown improvement in generic QOL outcome measures after surgery: Among others, a study published in 2010 [1760] included three hundred thirty-six patients assessed with Short Form 36 Health Survey (SF-36) four months after surgery: the SF36 scores that were significantly decreased before surgery improved and came very close to normal levels. Another study that used the SF-36 in 150 patients after

a mean follow-up of 3 years showed statistically significant improvements in QOL scores postoperatively. Importantly, the scores improved to the point of reaching general population levels.

6.4.4.4.2. Disease specific QOL

A variety of disease – specific instruments have been used to assess QOL changes after ESS: These included the Chronic Sinusitis Survey and the Rhinosinusitis Disability Index [1760, 1761], SNOT 20 [1757, 1762], SNOT 22 [1758] RSOM 31 [1763]. In all of these studies, evidence of improvement of generic and disease specific QOL with surgery was shown. Deal and Kountakis [1762] using SNOT 20 showed that patients with nasal polyps have worse nasal QOL compared to CRS without NP patients while the English National Comparative Audit using SNOT 22 showed the opposite. However, both studies confirmed that the improvement in QOL after surgery was more pronounced in patients with nasal polyps compared to CRS patients without polyps [1758] (Evidence level IIc).

6.4.4.5. Conclusion

It is fair to say that trials providing high level evidence of the efficacy of ESS for CRS are missing, as only a small percentage of the studies are RCTs, and those who are have inconsistent inclusion criteria, outcome measures and types of interventions making generalisations difficult. Additionally, intervention bias (the variability in surgical techniques and in experience between different surgeons) should not be underestimated. Having said that, there is a significant amount of well designed level II-level III evidence collected from tens of thousands of patients, that endoscopic sinus surgery is safe and is associated with improvements in symptoms scores (especially nasal obstruction and discharge), disease specific and generic QOL as well as objective measures.

6.4.5. Functional endoscopic sinus surgery versus conventional surgery

There have been no studies comparing open ethmoidectomy/ sphenoethmoidectomy with endoscopic sinus surgery for CRS. Lund [1764] examined retrospectively long term outcomes of inferior and middle meatal antrostomy and showed better outcomes in the endoscopic middle meatal antrostomy group. Penttila compared in a RCT ESS and Caldwell Luc and showed marked improvement in 50.7% of the C-L group and in 76.7% of the FESS group at one year [1765]. Venkatachalam compared in a RCT conventional surgery with ESS and found that ESS was associated with greater rates of complete relief of symptoms (76% versus 60%) and better overall outcomes [2064].

Conclusion

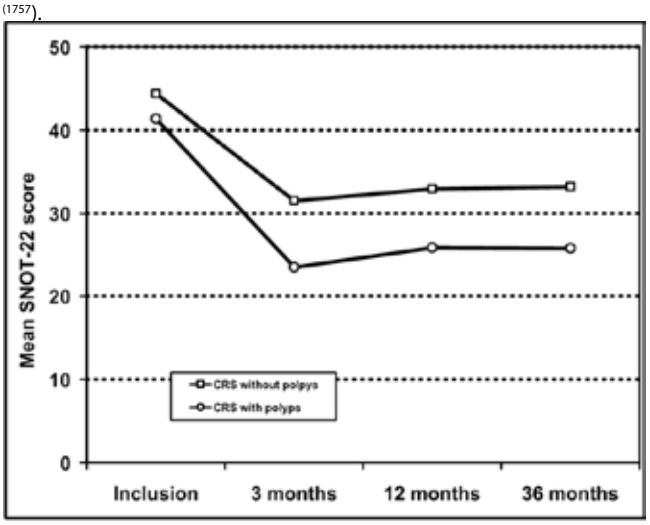
Functional endoscopic surgery is superior to conventional procedures including polypectomy, Caldwell-Luc, inferior meatal antrostomy and antral irrigations, but superiority to conventional sphenoethmoidectomy is not yet proven.

6.4.6. ESS modifications / extent of surgery

While there is some evidence that more extensive surgery (larger middle meatal antrostomy, widening of the frontal recess, more extensive sphenoithmoidectomy) may be associated with better objective outcomes, it is suggested to tailor the extent of surgery to the extent of disease.

Extent of surgery may vary from mere uncinectomy to radical sphenoethmoidectomy with middle turbinate resection.
In several studies, the extent of sinus surgery on various outcome parameters was investigated in CRS patients, not differentiating between CRS with and without polyps. In a prospective trial, 65 CRS patients with and without polyps were randomized to undergo limited endonasal functional surgery (uncinectomy) and a more extensive functional procedure including sphenoethmoidectomy and wide opening of the frontal recess. Disease extent was similar in both treatment arms. Outcome parameters included symptom scores, rhinoscopy scores and nasal saccharin transport time [1766]. Outcome parameters revealed no relevant differences after 3, 6 and 12 months, however, recall rates lower than 60% limit the usefulness of this study . Jankowski and co-authors retrospectively compared a case series of 37 CRS patients with extensive nasal polyps treated with FESS with a historical group of 36 patients with similar disease extent treated with radical sphenoethmoidectomy and middle turbinate resection [1767]. Outcome parameters assessed 5 years following surgery included a mailed questionnaire on nasal symptoms, the number of patients with revision surgery, and nasal endoscopy scores at a follow up visit. Recall was below 80% and differed significantly between the two groups. The radical surgical procedure yielded better symptom scores, less recurrences, and better endoscopic scores at the follow up visit (Evidence level IV).
In a randomized trial, 1,106 matched CRS patients with and without polyps, who underwent similar functional endonasal sinus surgery with (509 patients) or without (597 patients) partial middle turbinate resection [1768]. Partial middle turbinate resection was associated with less adhesion formation and less revision. Complications specific to partial middle turbinate resection were not observed (Evidence level Ib). In a study by Marchioni et al, 22 patients with middle turbinate resection and 34 patients with turbinate preservation were followed for three years. Patients without middle turbinate resection were shown to have earlier relapse of polyposis as judged by endoscopy

Figure 6.4.1 SNOT-22 scores in the National Comparative Audit in CRS patients with and without nasal polyps (adapted from Hopkins, 2006 [1757]).



examination [1769]. A recent non randomised prospective study compared patients on which 2/3 of the medial turbinate were removed (on medical reasons) with those where it was preserved [1770]. It is interesting to note that patients with MT resection were more likely to have asthma , aspirin intolerance, nasal polyposis, and prior sinus surgery, and higher baseline disease burden. Although there were no differences in generic or disease specific QOL measures, patients undergoing MT resection were more likely to show improvements in mean endoscopy and olfaction.

The patency rate after large middle meatal antrostomy and undisturbed maxillary ostium in endoscopic sinus surgery for CRS without nasal polyps was compared in a recent [2011] study: thirty patients with CRS without NP underwent randomized endoscopic sinus surgery [1771]. A large middle meatal antrostomy was performed on one side, whereas on the other side an uncinectomy preserving the natural maxillary ostium was done. The patency rates of the middle meatal antrostomy were significantly higher and the radiological Lund-McKay score was lower 9 months after surgery when compared to the side with the undisturbed maxillary ostium. This difference however did not translate to improved subjective outcomes (Evidence level Ib).

6.4.6.1. Balloon catheter

In a recent Cochrane review [2065] as well as in an evidence – based review published in 2011 [1772], Batra et al. assessed the evidence available for new ballon catheter systems for sinus surgery in CRS: There have not been any prospective comparative studies comparing it to standard FESS techniques. The one retrospective comparative study referred to patients with recurrent acute or mild CRS and the patients elected themselves the way of treatments, while follow up was 3 months, precluding any meaningful conclusions. On the other hand, a number of prospective multicentre studies assessing the balloon catheter systems have been published, which confirm a good safety profile (albeit not complication – free [1773]), but have unclear inclusion criteria, making their results difficult to generalise. Overall, the place of these systems in the sinus surgeon's armamentarium remains unclear (Evidence level IV).

Conclusion

Although not fully evidence based, the extent of surgery is frequently tailored to the extent of disease, which may appear as a reasonable approach. In primary paranasal sinus surgery, surgical conservatism is recommended. The decision to preserve or resect the middle turbinate can be left to the discretion of the surgeon based on its disease status. There is not enough data to support the use of balloon catheters as an alternative to standard endoscopic sinus surgery techniques.

6.4.8. Revision sinus surgery

Approximately 20% of operated patients respond unsatisfactorily to sinus surgery with concomitant medical therapy and eventually require a secondary surgical procedure [1758]. Middle turbinate lateralisation, adhesions and scar formation in the middle meatus, an incompletely resected uncinate process, and retained ethmoid cells are frequent findings in patients undergoing revision surgery [1778]. Previous revision surgery, extensive polyps, bronchial asthma, ASA-intolerance and cystic fibrosis are predictors of revision surgery [1762, 1775, 1779]. Inflammatory involvement of underlying bone may also be of significance [1388]. Technical issues of sinus revision surgery have be reported by Cohen and Kennedy [1780] and Javer more recently [1781]. A more extensive surgical procedure and also external approaches may be indicated [1767, 1782].

Success rates of revision endoscopic sinus surgery have been reported to range between 50 and 70% [762, 1783]. Complication rates of revision surgery are higher when compared with initial surgery and approximate 1%, but may be as high as 7% [1784, 1785], McMains and Kountakis also reported the results of 59 CRS patients with nasal polyps after revision surgery [1779]. Consistent with the results of the National Comparative Audit [1757] and the comparative study by Deal and co-workers [1762], CRS patients without polyps had higher SNOT scores preoperatively (more severe symptoms), less previous surgeries, and a lower CT score preoperatively than CRS patients with polyps. However, the improvement of outcome parameters after revision surgery was significant and comparable with the improvement in CRS patients without polyps, greater even after 5 years [1758] in the case of the English National Audit study. The same was found in, a recent comparative study [1786] that,

using Rhinosinusitis Disability Index (RSDI) and Chronic Sinusitis Survey (CSS) showed that the improvement in QOL is the same in patients undergoing revision or primary surgery, although the endoscopic improvement was CRS without NP patients undergoing revision surgery.
Schlosser [1787] and Ferguson [1788] looked at patients who underwent multiple failed procedures: such patients often harbour subtle humoral immunodeficiencies, systemic granulomatous or eosinophilic syndromes. There are a handful of observational studies suggesting that patients with aspirin exacerbated respiratory disease may benefit from aspirin desensitization, while dealing with allergy with antihistamines and desensitisation, as well as long term, culture driven antibiotics and an intensive program of nasal lavage may improve outcome.

Conclusion
Revision endonasal sinus surgery is only indicated, if medical treatment is not sufficiently effective. Substantial symptomatic improvement is generally observed in both, CRS with and without polyps, though the improvement maybe somewhat less than after primary surgery. Complication rates and particularly the risk of disease recurrence are higher than after primary surgery. Some patients still suffer from CRS symptoms after several extensive surgical procedures. CT scans frequently show mucosal alterations adjacent to osteitic bony margins in an extensively operated sinus system. As a rule, revision surgery is not indicated in these patients but radical surgery can be an option [1782].

6.5. Treatment with corticosteroids in CRSwNP

6.5.1. Introduction

In this chapter a differentiation is made between CRSsNP and CRSwNP. Readers have to realize that often in studies no clear difference is made between these two patients groups. Sometimes for this reason studies are discussed in both the parts on CRSsNP as the parts of CRSwNP.
In studies on the treatment of CRSwNP, it is of value to look separately at the effect on rhinitis symptoms associated with polyposis and the effect on the size of nasal polyps per se. There are many symptom aspects of CRSwNP and we have also included an objective measure of nasal obstruction, nasal peak inspiratory flow (PNIF), as this was the most commonly reported objective measure behind endoscopy.

6.5.2. Local corticosteroid (INCS) in chronic rhinosinusitis with nasal polyps

Considering the number of studies in the literature, only RCTs will be referred to in this summary. INCS for CRSwNP encompasses range of different treatment regimes. These have been carefully described in the Table of study characteristics (Table 6.5.1.).

6.5.2.1. Inclusion criteria and exclusion criteria

Inclusion criteria
Patients with benign nasal polyps diagnosed clinically with either:

- endoscopic evidence of nasal polyps; or/and
- radiological evidence of nasal polyps

Exclusion criteria

- Antrochoanal polyps (benign polyps originating from the mucosa of the maxillary sinus).
- Malignant polyps.
- Cystic fibrosis.
- Primary ciliary dyskinesia

6.5.2.2. Types of interventions

- Topical steroids versus no intervention.
- Topical steroids versus placebo.
- Topical and oral steroids versus oral steroids only

6.5.2.3. Flow chart

A total of 873 references were retrieved: three more records were identified from references of retrieved studies. 735 of these were removed in first-level screening (i.e. removal of duplicates and clearly irrelevant references), leaving 141 references for further consideration. Title and abstracts were screened and 93 studies were subsequently removed. Forty-eight full texts were assessed for eligibility. Three papers were abstracts of presentations at academic meetings of included studies. One paper pooled data from two included studies for reanalysis. Three non-randomized studies and neither two studies comparing topical steroid to neither placebo nor no intervention were excluded. Thirty-nine studies were included. A flow chart of study retrieval and selection is provided in Figure 6.5.1.

6.5.2.4. Included studies

There were 3,532 participants totally in 38 included studies. The mean age of patients was 48.2 years. The percentage of men was 66.6. The characteristics of included studies are listed as Table 6.5.1.

6.5.2.5. Summary of data

Thirtyfour trials (92%) compared topical steroid against placebo (Aukema 2005; Bross-Soriano 2004; Chalton 1985; Dingsor 1985; Djikstra 2004; Drettner 1982; Ehnhage 2009; Filiaci 2000; Hartwig 1988; Holmberg 1997; Holmstrom 1999; Holopainen 1982; Jankowski 2001; Jankowski 2009; Johansen 1993; Johansson 2002; Jorissen 2009; Keith 2000; Lang 1983; Lildholdt 1995; Lund

1998; Mastalerz 1997; Mygind 1975; Olsson 2010; Passali 2003; Penttila 2000; Rowe-Jones 2005; Ruhno1990; Small 2005; Stjarne 2006; Stjarne 2006b; Stjarne 2009; Tos 1998; Vlckova 2009) [1109, 1172, 1426, 1668, 1674, 1789-1816]. Among these, eight trials also compared low dose to high dose of topical steroid (Djikstra 2004; Filiaci 2000; Jankowski 2001; Lildholdt 1995; Penttila 2000; Small 2005; Stjarne 2006; Tos 1998) [1668, 1794, 1804, 1808, 1810, 1813, 1815-1817] and three trials also compared two steroid agents, fluticasone propionate and beclomethasone dipropionate (Bross-Soriano 2004; Holmberg 1997; Lund 1998) [1109, 1790, 1796].

Three trials (8%) compared topical steroid against no intervention (El Naggar 1995; Jurkiewicz 2004; Karlsson 1982) [1818-1820].

Twenty (55%) included studies were fully or partially sponsored by pharmaceutical companies; Glaxo (Aukema 2005; Djikstra 2004; Ehnhage 2009; Holmberg 1997; Keith 2000; Lund 1998; Mastalerz 1997; Mygind 1975; Olsson 2010; Penttila 2000; Rowe-Jones 2005) [1109, 1172, 1426, 1668, 1789, 1796, 1802, 1805, 1806, 1808, 1821]. Astra (Johansen 1993; Johansson 2002; Ruhno1990; Tos 1998) [1800, 1801, 1809, 1813] and Schering Plough (Jorissen 2009; Small 2005; Stjarne 2006; Stjarne 2006b; Stjarne 2009) [1674, 1810-1812, 1816].

The steroid agents used were differed across the studies:

1. Fluticasone propionate was studied in 15 trials (Aukema 2005; Bross-Soriano 2004; Djikstra 2004; Ehnhage 2009; Holmberg 1997; Holmstrom 1999; Jankowski 2009; Jurkiewicz 2004; Keith 2000; Lund 1998; Mastalerz 1997; Olsson 2010; Penttila 2000; Rowe-Jones 2005; Vlckova 2009) [1109, 1172, 1426, 1668, 1789, 1790, 1796, 1797, 1799, 1802, 1805, 1808, 1814, 1819, 1821].
2. Beclomethasone dipropionate was studied in 7 trials (Bross-Soriano 2004; El Naggar 1995; Holmberg 1997; Lund 1998; Karlsson 1982; Lang 1983; Mygind 1975) [1109, 1790, 1796, 1803, 1806, 1818, 1820].
3. Betamethasone sodium phospate was studied in 1 trial (Chalton 1985) [1791].
4. Mometasone furoate was studied in 6 trials (Jorissen 2009; Passali 2003; Small 2005; Stjarne 2006; Stjarne 2006b; Stjarne 2009) [1674, 1807, 1810-1812, 1816, 1822-1825].
5. Flunisolide was studied in 2 trials (Dingsor 1985; Drettner 1982) [1792, 1793].
6. Budesonide was studied in 9 trials (Filiaci 2000; Hartwig 1988; Holopainen 1982; Jankowski 2001; Johansen 1993; Johansson 2002; Lildholdt 1995; Ruhno1990; Tos 1998) [1794, 1795, 1798, 1800, 1801, 1804, 1809, 1813, 1815].

Table 6.4.3. Factors associated with outcome after endoscopic sinus surgery.

	Outcome parameter	Recall/participants	Minimum follow up	Analysis	Age	Sex	Pre-operative score	Extent	Allergy	Asthma	Polyps	ASA-I
Kennedy, 1992 [762]	verbal rating, endoscopy	120		u[2]	-	-		yes	no	no	-	no
Chambers 1997 [1421]	questionnaire, endoscopy	182	12	u[1]	-	-		-	no	no	no	
Gliklich, 1997 [1774]	SF-36, CSS, endoscopy	108	6	m[3]	no	no		no[4]	-	no	no	
Marks, 1997 [1775]	improvement score	93	12	u	no	yes[5]	-	no	no	no	-	-
Marks, 1997 [1775]	endoscopy score	93	12	m	no	no	-	yes	no	no	-	-
Wang, 2002 [1776]	CSS	230	6	m	-	-	yes	yes	-	-	-	-
Wang, 2002 [1776]	endoscopy score	230	6	m			-	yes	-	-	-	-
Kim, 2005 [1777]	endoscopy score	98	12	m	no	no	-	no	no	yes	-	-
Smith, 2005 [1761]	endoscopy score	119	12	m	-	no	yes	0.09	no	no	no	yes
Smith, 2005 [1761]	CSS/RSDI	119	12	m	-	no	yes	no	no	no	no	yes
Smith, 2010 [1189]	CSS /RSDI	302	12				yes		no	no	no	

[1] stratified for disease severity

[2] univariate

[3] multivariate

[4] high preoperative CSS score was associated with worse outcome

[5] less symptomatic improvement in females (p=0.008)

A summary of outcomes is provided in Table 6.5.3. with the majority demonstrating a benefit to the use of INCS.

6.5.2.6. Meta-analysis

When compared to placebo, pooled data analyses of symptoms, polyp size, polyp recurrence and nasal airflow demonstrated significant benefit in the topical steroid group. Although these outcomes were reported in various ways across studies such as the final value, the change of value after intervention and the proportion of responders, all meta-analyses show the same results favouring topical steroid. Although 32, 29 and 22 studies reported symptoms, polyp size and nasal airflow, data from only 9, 13 and 9 studies respectively can be pooled for meta-analysis. Most studies do not provide numeric data of the outcomes or do not show any of standard deviation, standard error, 95%CI, range nor interquartile range. Data from only one study was analyzed for change in CT scan [1789], and quality of life [1172]. No difference from placebo was found in these 2 outcomes. Olfactory outcomes are mentioned in 22 studies [1426, 1797, 1800, 1802, 1804, 1808, 1810-1814, 1816, 1818] and with mixed benefit to INCS. More studies may be helpful to make conclusions for these three outcomes.

6.5.2.6.1. Symptom improvement (score or responders)

Data addressing the change in combined symptom scores was available from seven studies [1674, 1794, 1798, 1801, 1805, 1806, 1814] and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (SMD -0.46; 95% CI -0.65 to -0.27), p<0.00001; seven trials, 445 patients) (Figure 6.5.2.A). Data addressing the proportion of responders in symptoms was available from four studies [1794, 1796, 1806, 1808]. The pooled results significantly favoured the topical steroid group (RR (Non-event) 0.59; 95% CI 0.46 to 0.78), p=0.0001 (Figure 6.5.2.B).

6.5.2.6.2. Polyp size (score, change or responders on endoscopy)

Data addressing the final value of polyp score at the endpoint was available from three studies (Dingsor 1985; Hartwig 1988; Johansson 2002) [1792, 1795, 1801] and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (SMD -0.49; 95% CI -0.77 to -0.21), p=0.0007 (Figure 6.5.3.A). Data addressing the change in polyp score was available from three studies [1806, 1814, 1815]. and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (SMD -0.73; 95% CI -1.00 to -0.46), p<0.00001 (Figure 6.5.3.B). Data addressing the proportion of responders in polyp size was available from eight studies [1791, 1797, 1798, 1802, 1803, 1808, 1811, 1814] and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (RR (Non-event) 0.74; 95% CI 0.67 to 0.81), p<0.00001. (Figure 6.5.3.C)

6.5.2.6.3. Nasal breathing (score, change or responders on Peak Nasal Inspiratory Flow (PNIF))

Data addressing the peak nasal inspiratory flow was available from seven studies [1789, 1798, 1799, 1801, 1805, 1809, 1814] and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (MD 22.04; 95% CI 13.29 to 30.80), p<0.00001 (Figure 6.5.4a). Data addressing the change in nasal airflow was available from three studies (Ehnhage 2009; Holmstrom 1999; Ruhno1990) [1797, 1809, 1818] and could be combined in the meta-analysis. The pooled results significantly favoured the topical steroid group (SMD -0.57; 95% CI -0.85 to -0.29), p=0.0001 (Figure 6.5.4b). Data addressing the proportion of responders in nasal airflow was available from two studies (Chalton 1985; Ruhno1990) [1791, 1809] which significantly favoured the topical steroid group (RR (Non-event) 0.55; 95% CI 0.33 to 0.89), p=0.02 (Figure 6.5.4.c.).

The standardised mean difference (SMD) and 95% CIs for continuous data such as post-intervention scores or change in symptom scores. The risk ratio (RR) and 95% CI of responsiveness was used at a specific time point for dichotomous data such as number of patients responding to treatment. The intervention effects were pooled when trials were sufficiently homogeneous. The SDs were imputed from p values for Lund 1998 after assuming parametric data. A fixed-effect model was used and assumed that each study was estimating the same quantity.

6.5.2.7. Subgroup analysis

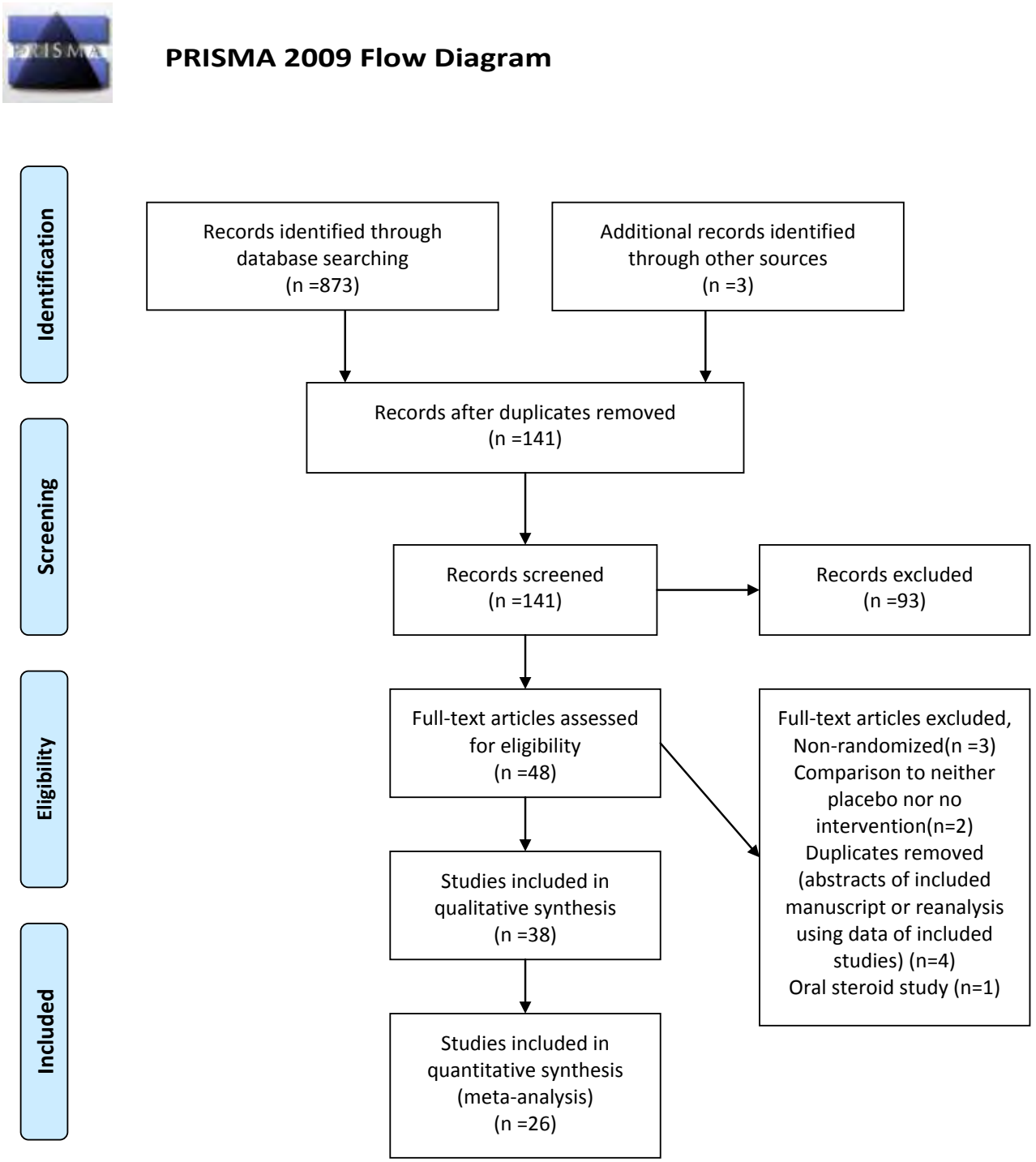
Subgroup analysis was performed as follows.

- Surgical status
- Patients with prior sinus surgery versus those without sinus surgery.
- Topical delivery method
- Nasal drops versus nasal sprays versus sinus (direct cannulation, irrigation post-surgery) delivery method.
- Corticosteroid type
- Modern corticosteroids (mometasone, fluticasone, ciclesonide) versus first-generation corticosteroids (budesonide, beclomethasone, betamethasone, triamcinolone, dexamethasone)

Differences between the two subgroups for fixed-effect analyses were based on the inverse-variance method in the case of continuous data and the Mantel-Haenszel method in the case of dichotomous data.

The 38 included studies were diverse, both clinically and methodologically. Variability included sinus surgery status, topical delivery methods, polyp severity, steroid agent used and regimes. Subgroup analyses were performed to investigate heterogeneity.

Figure 6.5.1.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 6.5.1. Characteristics of included studies on INCS for CRScNP.

Study	Study type	Participants (diagnostic criteria)	Number of participants	Age (Mean)	Type of steroid	Steroid dose	Sinus Surgery Status	Delivery method of steroid	Duration of treatment (weeks)	Comparison
Chur 2010 (1822)	RCT	CRSwNP (NS)	127	NS	mometasone furoate	100 mcg (ages 6-11y) 200 mcg (ages 12-17y) arm1. od arm2. bid	without sinus surgery	spray	16	placebo
Olsson 2010 (1172)	RCT	CRSwNP (by endoscopy)	68	51.6	fluticasone propionate	400mcg bid	with sinus surgery	nasal drop	10	placebo
Ehnhage 2009 (1426)	RCT	CRSwNP (by endoscopy)	68	51.6	fluticasone propionate	400 mcg bid	with sinus surgery	nasal drop	10	placebo
Jankowski 2009 (1799)	RCT	CRSwNP (by endoscopy)	242	51	fluticasone propionate	200mcg bid	without sinus surgery	spray	4	placebo
Jorissen 2009 (1674)	RCT	mixed CRS (by endoscopy)	99	47.4	mometasone furoate	200 mcg bid	with sinus surgery	spray	24	placebo
Stjarne 2009 (1812)	RCT	CRSwNP (by endoscopy)	159	48.5	mometasone furoate	200 mcg od	with sinus surgery	spray	24	placebo
Vlckova 2009 (1814)	RCT	CRSwNP, small to medium size (by endoscopy)	109	47.9	Fluticasone propionate	400mcg bid	mixed	spray	12	placebo
Stjarne 2006 (1816)	RCT	CRSwNP (by endoscopy)	310	48.6	mometasone furoate	arm 1. 200 mcg od arm 2. 200 mcg bid	without sinus surgery	spray	16	placebo
Stjarne 2006b (1811)	RCT	CRSwNP (by endoscopy)	298	53	mometasone furoate	200 mcg od	mixed	spray	16	placebo
Aukema 2005 (1109)	RCT	CRSwNP (by endoscopy and CT)	54	44	fluticasone propionate	400 mcg od	mixed	nasal drop	12	placebo
Rowe-Jones 2005 (1821)	RCT	CRSwNP (by endoscopy)	109	41	fluticasone propionate	200 mcg bid	with sinus surgery	spray	260	placebo
Small 2005 (1810)	RCT	CRSwNP (by endoscopy)	354	47.5	mometasone furoate	arm 1. 200 mcg od arm 2. 200 mcg bid	without sinus surgery	spray	16	placebo
Bross-Soriano 2004 (1109)	RCT	CRSwNP (NS)	142	40.4	Arm1.fluticasone propionate Arm2. beclomethasone dipropionate	arm1. FP 400 mcg od arm2. Beclo 600 mcg od	with sinus surgery	spray (after saline lavage)	72	saline lavage only
Dijkstra 2004 (1668)	RCT	mixed CRS (by endoscopy and CT)	162	41	fluticasone propionate	arm1. 400µg bid arm2.800µg bid	with sinus surgery	spray	52	placebo
Jurkiewickz 2004 (1819)	RCT	CRSwNP (NS)	86	NS	fluticasone propionate	400mcg bid	with sinus surgery	spray	52	no treatment

Table 6.5.1. continued.

Study	Study type	Participants (diagnostic criteria)	Number of participants	Age (Mean)	Type of steroid	Steroid dose	Sinus Surgery Status	Delivery method of steroid	Duration of treatment (weeks)	Comparison
Passali 2003 (1807)	RCT	CRSwNP, medium to large size (by endoscopy)	73	37.3	mometasone furoate	400mcg od	with sinus surgery	spray	52 (at least)	1.placebo 2.intranasal furosemide
Johansson 2002 (1801)	RCT	CRSwNP (by endoscopy)	98	56	budesonide	128 mcg bid	without sinus surgery	spray	2	placebo
Jankowski 2001 (1804)	RCT	CRSwNP (by endoscopy)	183	44	budesonide	arm1. 128mcg od arm2. 128mcg bid arm3. 256mcg od	without sinus surgery	spray	8	placebo
Filiaci 2000 (1794)	RCT	CRSwNP (by endoscopy and MRI)	157	47.9	budesonide	arm 1. 140mcg bid arm 2. 280mcg od arm 3. 140mcg od	without sinus surgery	turbuhaler	8	placebo
Keith 2000 (1802)	RCT	CRSwNP, small to medium size (by endoscopy)	104	48	fluticasone propionate	400 mcg od	mixed	nasal drop	12	placebo
Pentilla 2000 (1808)	RCT	CRSwNP, small to medium size (by endoscopy)	142	51	fluticasone propionate	arm 1. 400 mcg bid arm 2. 400mcg od	mixed	nasal drop	12	placebo
Holmstrom 1999 (1797)	RCT	CRSwNP, small to medium size (by endoscopy)	104	NS	fluticasone propionate	400 mcg od	without sinus surgery	nasal drop	12	placebo
Lund 1998 (1796)	RCT	CRSwNP (by endoscopy and CT)	29	49.3	1.fluticasone propionate 2.beclomethasone dipropionate	arm 1. FP 400 mcg bid arm 2. Beclo 400 mcg bid	mixed	spray	12	placebo
Tos 1998 (1813)	RCT	CRSwNP, medium to large size (by endoscopy)	138	NS	budesonide	arm1. spray64 mcg bid arm2. turbuhaler 100 mcg per nominal dose/170 mcg per delivered dose bid	with sinus surgery	spray or turbuhaler	6	placebo
Holmberg 1997 (1790)	RCT	CRSwNP (by endoscopy)	55	54	arm1. fluticasone propionate arm 2. beclomethasone dipropionate	arm1. FP200 mcg bid arm2. Beclo200 mcg bid	with sinus surgery	spray	26	placebo
Mastalerz 1997 (1805)	RCT cross-over	mixed CRS, with aspirin sensitivity (NS)	15	44.7	fluticasone propionate	400mcg od	without sinus surgery	spray	4	placebo

Table 6.5.1. continued.

Study	Study type	Participants (diagnostic criteria)	Number of participants	Age (Mean)	Type of steroid	Steroid dose	Sinus Surgery Status	Delivery method of steroid	Duration of treatment (weeks)	Comparison
El Naggar 1995 (1818)	RCT	CRSwNP (by endoscopy)	29	51.5	beclomethasone dipropionate	100mcg bid in one nostril	with sinus surgery	spray	6	no treatment in the other nostril
Lidlholdt 1995 (1804)	RCT	CRSwNP (by rhinoscopy)	126	51	budesonide	arm1. 200 mcg arm2. 400 mcg bid	without sinus surgery	turbuhaler	4	placebo
Johansen1993 (1800)	RCT	CRSwNP, small to medium size eosinophilic polyps (by pathology)	91	52	budesonide	200mcg bid	without sinus surgery	spray and aerosol	12	placebo
Ruhno1990 (1809)	RCT	CRSwNP (NS)	36	46.6	budesonide	400mcg bid	with sinus surgery	spray	4	placebo
Hartwig 1988 (1795)	RCT	CRSwNP (by endoscopy)	73	54.2	budesonide	200 mcg bid	with sinus surgery	aerosol	24	placebo
Chalton 1985 (1791)	RCT	CRSwNP (by endoscopy)	30	42	betamethasone	100mcg bid	without sinus surgery	nasal drop	4	placebo
Dingsor 1985 (1792)	RCT	CRSwNP (by rhinoscopy)	41	49	flunisolide	100mcg bid	with sinus surgery	spray	52	placebo
Land 1983 (1803)	RCT	CRSwNP, small to medium size (by endoscopy)	32	42	beclomethasone dipropionate	400 mcg bid	without sinus surgery	spray	104	placebo
Drettner 1982 (1793)	RCT	CRSwNP (NS)	25	43.8	flunisolide	100mcg bid	with sinus surgery	spray	12	placebo
Holopainen 1982 (1798)	RCT	CRSwNP, small to medium size (by rhinoscopy)	19	42	budesonide	200 mcg bid	with sinus surgery	spray	16	placebo
Karlsson 1982 (1820)	RCT	CRSwNP, medium to large size (NS)	40	49	beclomethasone dipropionate	400mcg od for1month then 200mcg od	with sinus surgery	intranasal	30	no treatment
Mygind 1975 (1172)	RCT	CRSwNP, medium to large size (NS)	35	51	beclomethasone dipropionate	100mcg qid	mixed	aerosol	3	placebo

Table 6.5.2. Outcome summary of studies using INCS for Chronic Rhinosinusitis with nasal polyps (No study had placebo favoured over INCS).

Study	Type of steroid	Steroid dose	Delivery method of steroid	Comparison	Patients report outcome measures (PROM) (scoring system and scale)	Summary PROM results	Endoscopic outcomes (scoring system and scale)	Summary endoscopic results
Chur 2010 (1822)	mometasone furoate	100 mcg (ages 6-11y) 200 mcg (ages 12-17y) Arm1. od Arm2. bid	spray	placebo	symptom scores (2 symptoms;0-4)	favour steroid bid (-40%) over od (-30%) and placebo (-28%)	polyp size reduction (NS)	favour steroid bid (-34%) over od (-26%) and placebo (-24%)
Olsson 2010 (1172)	fluticasone propionate	400mcg bid	nasal drop	placebo	general health quality of life (SF36;1-5)	favour steroid for mental component (p=0.01) but not physical component (p=0.08)	nil	nil
Ehnhage 2009 (1426)	fluticasone propionate	400 mcg bid	nasal drop	placebo	nasal and asthma symptom scores (5 symptoms;0-3)	no difference (p>0.05)	polyp score (0-3)	no difference (p-value not shown)
Jankowski 2009 (1799)	fluticasone propionate	200mcg bid	spray	placebo	symptom scores 1. overall score (Likert;0-3) 2.VAS (3 symptoms)	1.favour steroid (p=0.0001) 2.favour steroid (p-value not shown)	polyp grade (0-3)	favour steroid (p<0.01 for right nostrils, p<0.001 for left nostrils)
Jorissen 2009 (1674)	mometasone furoate	200 mcg bid	spray	placebo	symptom VAS (5 symptoms)	no difference (p=0.09)	1.endoscopic score (8 variables;0-2) 2.post-hoc combination endoscopic score (3 variables;0-2)	1.no difference (p=0.34) 2.favour steroid (p=0.02)
Stjarne 2009 (1812)	mometasone furoate	200 mcg od	spray	placebo	symptom scores (3 symptoms;0-3)	1. favour steroid for rhinoorhea (p=0.04) 2. no difference for congestion and sense of smell (p-value not shown)	polyp relapse 1. percentage of patients 2. time to relapse	1. favour steroid (33%) over placebo (44%) 2. favour steroid (175 days) over placebo (125 days)
Vlckova 2009 (1814)	Fluticasone propionate	400mcg bid	spray	placebo	symptom scores (7 symptoms;0-3)	favour steroid over placebo (p<0.001)	polyp score (0-3) 1. change in polyp score 2. proportion of responders	1. favour steroid over placebo (p<0.001) 2. favour steroid (57%) over placebo (9%) (p<0.001)

Table 6.5.2. continued.

Study	Type of steroid	Steroid dose	Delivery method of steroid	Comparison	Patients report outcome measures (PROM) (scoring system and scale)	Summary PROM results	Endoscopic outcomes (scoring system and scale)	Summary endoscopic results
Stjarne 2006 (1816)	mometasone furoate	Arm 1. 200 mcg od Arm 2. 200 mcg bid	spray	placebo	symptom scores (4 symptoms;0-3)	1.favour steroid od over placebo for obstruction and rhinoorhea (p<0.05 both). No difference for post nasal drip and loss of smell.2.favour steroid bid over placebo for obstruction (p<0.01), rhinorrhea (p<0.01) and post nasal drip (p<0.05). No difference for loss of smell.	polyp score (0-3)	favour steroid bid over placebo (p=0.04). No difference between steroid od and placebo.
Stjarne 2006b (1811)	mometasone furoate	200 mcg od	spray	placebo	symptom scores (3 symptoms;0-3)	favour steroid over placebo (p<0.005)	polyp score (0-3)	favour steroid in proportion of responders (41%) over placebo (27%), p=0.003
Aukema 2005 (1109)	fluticasone propionate	400 mcg od	nasal drop	placebo	symptom VAS (6 symptoms)	favour steroid over placebo for obstruction (p=0.0001), rhinorrhea (p=0.003), mucus in throat (p=0.03) and loss of smell (p=0.04). No difference for facial pain (p-value not shown) and headache (p=0.76).	polyp volume estimated by the investigator (NS)	favour steroid over placebo (p=0.038)
Rowe-Jones 2005 (1821)	fluticasone propionate	200 mcg bid	spray	placebo	symptom VAS (6 symptoms)	no difference (p=0.23 for "How do you feel overall" VAS, p=0.39 for toatal VAS)	endoscopic score (Lund Kennedy)	1. favour steroid over placebo for polyp score (p=0.02) 2. no difference for edema score (p=0.56) and discharge score (p=0.29)

Table 6.5.2. continued.

Study	Type of steroid	Steroid dose	Delivery method of steroid	Comparison	Patients report outcome measures (PROM) (scoring system and scale)	Summary PROM results	Endoscopic outcomes (scoring system and scale)	Summary endoscopic results
Small 2005 (1810)	mometasone furoate	arm 1. 200 mcg od arm 2. 200 mcg bid	spray	placebo	symptom scores (4 symptoms;0-3)	1.favour steroid od over placebo for obstruction (p<0.001), rhinorrhea (p<0.05) , post nasal drip (p<0.001) and loss of smell (p<0.01). 2.favour steroid bid over placebo for obstruction (p<0.001), rhinoorhea (p<0.001) , post nasal drip (p<0.01) and loss of smell (p<0.05)	polyp score (0-3)	favour steroid over placebo (p<0.001 for od and p=0.01 for bid)
Bross-Soriano 2004	arm1.fluticasone propionate Arm2. beclomethasone dipropionate	arm1. FP 400 mcg od arm2. Beclo 600 mcg od	spray (after saline lavage)	saline lavage only	nil	nil	polyp recurrence	favour steroid (fluticasone 14.8% and beclomethasone (25.9%) over placebo (44.4%)
Dijkstra 2004 (1668)	fluticasone propionate	arm1. 400µg bid Arm2.800µg bid	spray	placebo	symptom VAS (6 symptoms)	NR	polyp recurrence	no difference (p-value not shown)
Jurkiewickz 2004 (1819)	fluticasone propionate	400mcg bid	spray	no treatment	symptom scores (5 symptoms;0-10)	favour steroid over placebo (p<0.01)	endoscopy (presence of polyps)	favour steroid over placebo (p<0.01)
Passali 2003 (1807)	mometasone furoate	400mcg od	spray	1.placebo 2.intranasal furosemide	nil	nil	polyp recurrence	favour steroid (24.2%) over placebo (30%, p-value not shown)
Johansson 2002 (1801)	budesonide	128 mcg bid	spray	placebo	symptom VAS (1 symptom)	favour steroid over placebo (p=0.0017)	polyp score (Lildholdt;0-3)	no difference (p=0.12)
Jankowski 2001 (1804)	budesonide	arm1. 128mcg od arm2. 128mcg bid arm3. 256mcg od	spray	placebo	1. symptom scores (4 symptoms;0-3) 2. overall efficacy (0-4)	1. favour steroid (all doses) over placebo (p<0.01) 2. favour steroid (all doses) over placebo (p<0.001)	polyp score (0-3)	favour steroid (all doses) than placebo (p<0.01)

Table 6.5.2. continued.

Study	Type of steroid	Steroid dose	Delivery method of steroid	Comparison	Patients report outcome measures (PROM) (scoring system and scale)	Summary PROM results	Endoscopic outcomes (scoring system and scale)	Summary endoscopic results
Filiaci 2000 (1794)	budesonide	arm 1. 140mcg bid Arm 2. 280mcg od Arm 3. 140mcg od	turbuhaler	placebo	1. symptom scores (3 symptoms;0-3) 2. overall efficacy (0-4)	1. favour steroid (all doses) over placebo (p<0.01) 2. favour steroid (for 140mcg bid and 280mcg od) over placebo (p-value not shown).	polyp score (0-3)	favour steroid (140mcg bid;p<0.014 and 280mcg od;p=0.009) over placebo. No difference for 140mcg od and placebo (p-value not shown).
Keith 2000 (1802)	fluticasone propionate	400 mcg od	nasal drop	placebo	symptom scores (4 symptoms;0-3)	no difference (p-value not shown)	polyp score (0-3)	no difference (p-value not shown)
Pentilla 2000 (1808)	fluticasone propionate	arm 1. 400 mcg bid arm 2. 400mcg od	nasal drop	placebo	symptom scores (3 symptoms;0-3)	1. favour steroid bid over placebo for rhinitis (p<0.001) and nasal blockage (p<0.05) but not sense of smell (p-value not shown) 2. favour steroid od for rhinitis (p<0.05) but not nasal blockage and sense of smell (p-value not shown).	polyp score (0-3)	favour steroid bid in proportion of responders (41%) over placebo (15%) (p<0.01). No difference for steroid od (24%) and placebo (p-value not shown).
Holmstrom 1999 (1797)	fluticasone propionate	400 mcg od	nasal drop	placebo	nil	nil	polyp score (0-3)	no difference (p-value not shown)
Lund 1998 (1796)	1.fluticasone propionate 2.beclomethasone dipropionate	arm 1. FP 400 mcg bid arm 2. Beclo 400 mcg bid	spray	placebo	symptom scores (4 symptoms;0-4)	favour both steroids over placebo for nasal blockage (p-value not shown). No difference for rhinitis and sense of smell. Facial pain and headache not reported.	polyp score (0-3)	favour fluticasone over placebo (p=0.02). No difference between beclomethasone dipropionate and placebo (p-value not shown)
Tos 1998 (1813)	budesonide	arm1. spray64 mcg bid arm2. turbuhaler 100 mcg per nominal dose/170 mcg per delivered dose bid	spray or turbuhaler	placebo	1. symptom scores (3 symptoms;0-3) 2.sense of smell 3. overall efficacy (0-4)	1.favour steroid over placebo (both spray and turbuhaler, p<0.001) 2. favour steroid over placebo (both spray and turbuhaler, p=0.001 3.favour steroid over placebo (p=0.001 for spray and p=0.01 for turbuhaler)	1. polyp score (0-3) 2. number of polyps (0-4)	1.favour steroid over placebo (both spray and turbuhaler, p<0.001) 2. no difference from placebo

Table 6.5.2. continued.

Study	Type of steroid	Steroid dose	Delivery method of steroid	Comparison	Patients report outcome measures (PROM) (scoring system and scale)	Summary PROM results	Endoscopic outcomes (scoring system and scale)	Summary endoscopic results
Holmberg 1997 (1790)	arm1. fluticasone propionate Arm 2. beclomethasone dipropionate	arm1. FP200 mcg bid arm2. Beclo200 mcg bid	spray	placebo	symptom scores (5 symptoms;0-3)	favour fluticasone (86%) over placebo (0%) in the percentage of days with an overall scores of zero (p<0.05). No difference between bedomethasone (19%) and placebo.	nil	nil
Mastalerz 1997 (1805)	fluticasone propionate	400mcg od	spray	placebo	symptom scores (4 symptoms;0-3)	favour steroid over placebo (p<0.05)	nil	nil
El Naggar 1995 (1818)	beclomethasone dipropionate	100mcg bid in one nostril	spray	no treatment in the other nostril	nil	nil	nil	nil
Lidlholdt 1995 (1804)	budesonide	arm1. 200 mcg bid arm2. 400 mcg bid	turbuhaler	placebo	symptom scores (3 symptoms;0-3)	favour steroid over placebo (p<0.001 for both doses)	polyp score (0-3)	favour steroid over placebo (p<0.001 for 200 mcg bid and <0.05 for 400 mcg bid))
Johansen 1993 (1800)	budesonide	200mcg bid	spray and aerosol	placebo	1. symptom scores (3 symptoms;0-3) 2. sense of smell (0-3)	1.favour steroid over placebo for both spray and aerosol (p-value not given) 2. no difference (p-value not given)	polyp score (0-3)	favour steroid over placebo (p<0.01 for both spray and aerosol)
Hartwig 1988 (1795)	budesonide	200 mcg bid	aerosol	placebo	symptom scores (1 symptoms;0-3)	no difference (p-value not shown)	polyp score (0-3)	favour steroid over placebo (p-value not shown)
Chalton 1985 (1791)	betamethasone	100mcg bid	nasal drop	placebo	nil	nil	disappearnce of nasal polyps	favour steroid over placebo (p<0.05)
Dingsor 1985 (1792)	flunisolide	100mcg bid	spray	placebo	symptom scores (3 symptoms;0-2)	favour steroid over placebo (p<0.05) for obstruction. No difference for rhinorrhea and sneezing.	1.polyp number (NS) 2. polyp size (NS)	favour steroid over placebo 1.p<0.05and 2.p<0.03
Land 1983 (1803)	beclomethasone dipropionate	400 mcg bid	spray	placebo	symptom scores (3 symptoms;NS)	no difference (p-value not shown)	Polyp size (NS)	no difference (p-value not shown)

Table 6.5.2. continued.

Study	Type of steroid	Steroid dose	Delivery method of steroid	Comparison	Patients report outcome measures (PROM) (scoring system and scale)	Summary PROM results	Endoscopic outcomes (scoring system and scale)	Summary endoscopic results
Drettner 1982 (1793)	flunisolide	100mcg bid	spray	placebo	symptom scores (3 symptoms;0-3)	favour steroid over placebo ($p<0.05$)	Polyp size (NS)	no difference (p-value not shown)
Holopainen 1982 (1798)	budesonide	200 mcg bid	spray	placebo	symptom scores (4 symptoms;0-3)	no difference (p-value not shown)	1.polyp number (NS) 2. polyp size (0-3)	favour steroid over placebo for polyp number and size (p-value not shown)
Karlsson 1982 (1820)	bedomethasone dipropionate	400mcg od for1month then 200mcg od	intranasal	no treatment	nil	nil	polyp score (0-3)	favour steroid over placebo (p=0.003)
Mygind 1975 (1172)	bedomethasone dipropionate	100mcg qid	aerosol	placebo	1.symptom scores (3 symptoms;0-3) 2. change in symptoms (-3)-(+3)	1. favour steroid over placebo (p-value not shown) 2.no difference (p>0.1)	polyp size (NS)	no difference (p>0.1)

6.5.2.7.1. Effect of prior surgery

Patients with sinus surgery responded to topical steroid greater than patients without sinus surgery in polyp size reduction (Figure 6.5.5.). However improvement in symptoms and nasal airflow was not statistically different between the two subgroups (Figure 6.5.6.). It is difficult to make a complete assessment as not all studies could be pooled for meta-analysis. A summary of studies that showed a benefit with INCS by the surgical status of their patient population is shown in Table 6.5.3.

6.5.2.7.2. Effect of delivery of spray v drops

Nasal aerosols and turbuhaler were found more effective than nasal spray in symptom control (Figure 6.5.7.) but there was no difference in polyp size reduction and nasal airway across various types of topical delivery methods. Similar to assessing the surgical state, a complete assessment is difficult as not all studies could be pooled for meta-analysis. A summary of studies that showed a benefit with INCS by spray or drop is shown in Table 6.5.4. No study reported on direct sinus delivery methods or high volume, high pressure delivery in patient with prior sinus surgery.

6.5.2.7.3. Effect of modern corticosteroid v first generation

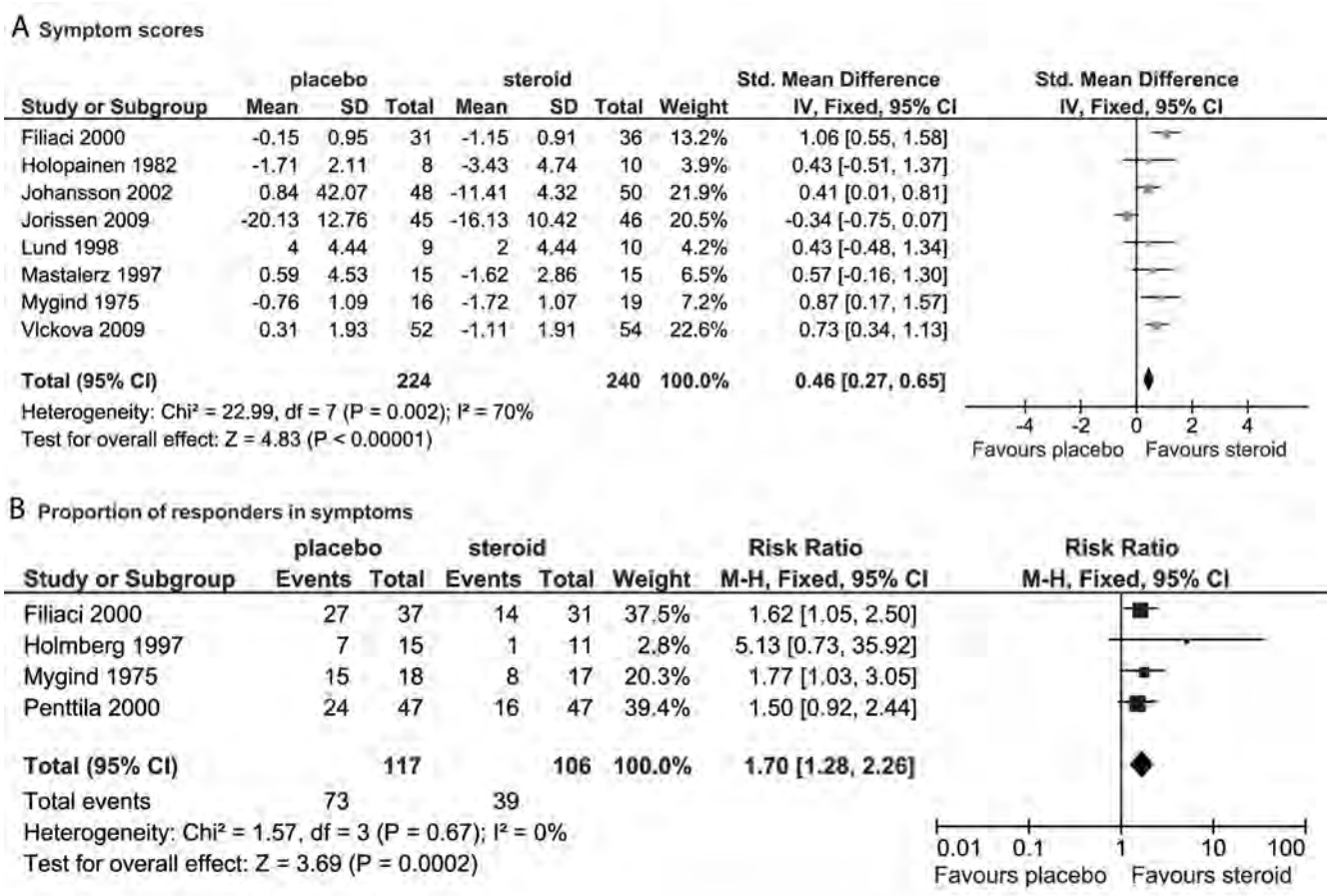
There does not appear to be a significant benefit of modern corticosteroid against first-generation for the final symptom score (Figure 6.5.8.a) or for responder with polyp reduction (Figure 6.5.8.b).

6.5.2.8. Side-effects of local corticosteroid chronic rhinosinusitis with nasal polyps

The most common events were epistaxis and nasal irritation including itching, sneeze, dry nose and rhinitis. Adverse events reported were possibly ambiguous. Rhinitis symptoms could be disease-related. It is acknowledge that rare adverse events are possibly not detected in randomised controlled trials (RCTs). However, they were extremely low and there was no difference in adverse events between the study groups and control groups in any trial. Post-market adverse events for intranasal steroid sprays are very low. However, we have not specifically sought adverse event data from non-RCT studies. Minor adverse events from nasal steroids are commonly tolerated by patients. The amount of benefit clearly outweighs the risk. The reported adverse events from the included studies are summarized in Table 6.5.5.

Reported epistaxis may be attributable to local effects of the INCS on septal mucosa and exacerbated by poor technique (1826) with significance preponderance of the side

Figure 6.5.2. CRScNP INCS for symptoms.

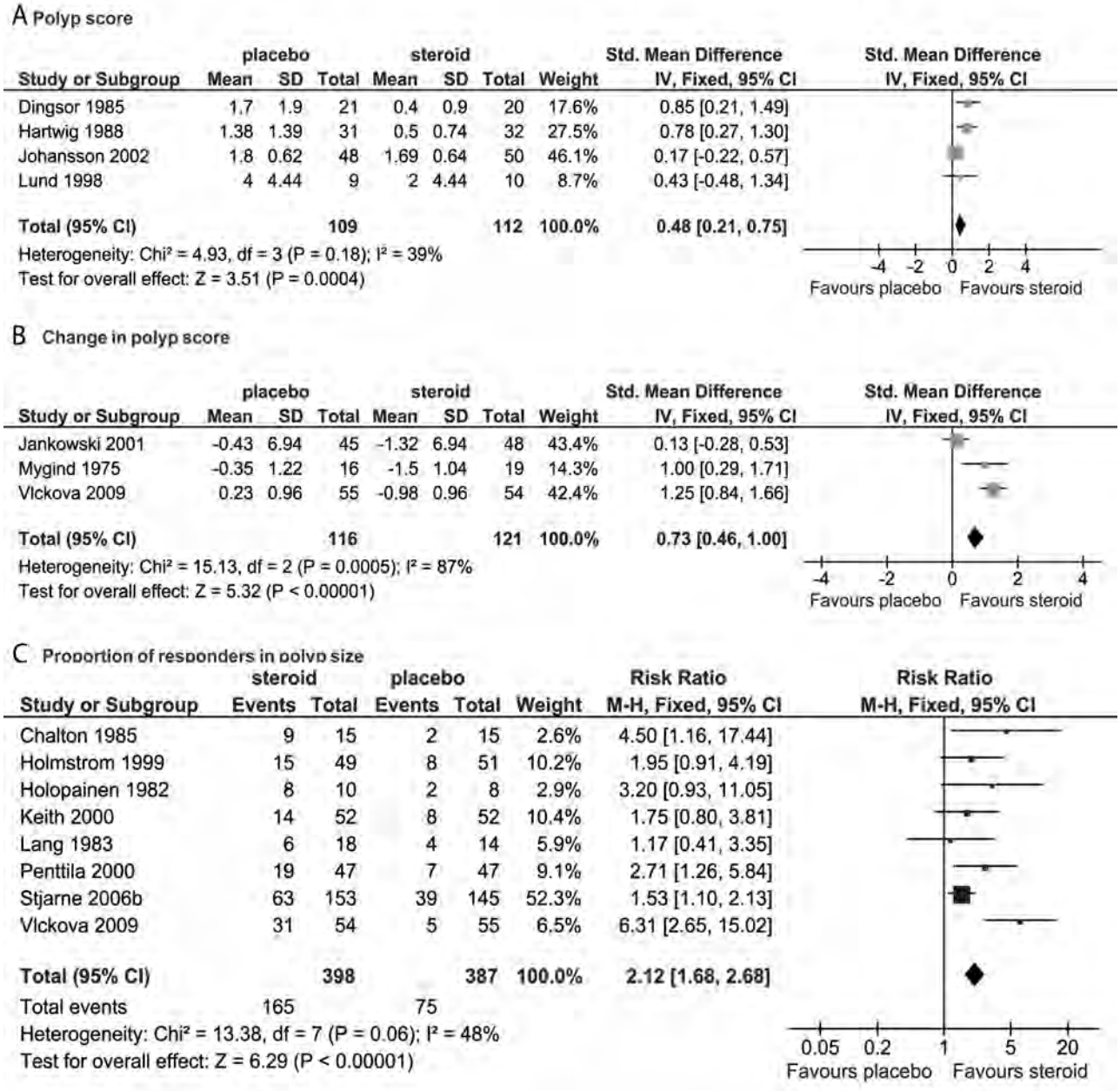


of epistaxis to handedness. Some have attributed epistaxis to the vasoconstrictor activity [1827] of the corticosteroid molecules, and postulated this as a mechanism for the very rare occurrence of nasal septal perforation [1828]. However, it should be remembered that minor nose bleeds are common in the population, occurring in 16.5% of 2197 women aged 50-64 years over a one year study [1829] and that spontaneous nasal perforation occurs within the community at a low rate [1830]. Nasal biopsy studies do not show any detrimental structural effects within the nasal mucosa with long-term administration of intranasal corticosteroids and atrophy does not occur as the mucosa is a single layer of epithelium compared to keratin producing multi-layered skin where atrophy is reported [1831-1838]. Much attention has focused on the systemic safety of intranasal application. The systemic bioavailability of intranasal corticosteroids varies from <1% to up to 40-50% and influences the risk of systemic adverse effects [1828, 1839]. Potential adverse events related to the administration of intranasal corticosteroids are effects on growth, ocular effects, effects on bone, and on the hypothalamic-pituitary-adrenal axis [1840]. Because the dose delivered topically is small, this is not a major consideration, and extensive studies have not identified significant effects on the hypothalamic-pituitary-adrenal axis with continued treatment. A small effect on growth has been reported in one study in children receiving a standard dosage over 1 year. However, this has not been found in prospective studies with the intranasal corticosteroids that have low systemic bioavailability and therefore the judicious choice of intranasal formulation, particularly if there is concurrent corticosteroid inhalation for asthma, is prudent [1841]. In summary, intranasal corticosteroids are highly effective; nevertheless, they are not completely devoid of systemic effects. Thus, care has to be taken, especially in children, when long-term treatments are prescribed. However the systemic effects of nasal corticosteroids are negligible compared to inhaled corticosteroids.

6.5.3. Systemic corticosteroid chronic rhinosinusitis with nasal polyps

Traditionally systemic steroids have been used in patients based on the significant effect on NP supported by open studies where a single injection of 14 mg betametasone have been compared with snare polypectomy surgery [1085, 1842]. In these studies effects are seen on nasal polyp size, nasal symptom score and nasal expiratory peak flow but it is difficult to differentiate the effect of systemic steroids from that of local treatment since both treatments were used at the same time. The control groups

Figure 6.5.3. CRScNP INCS for polyp reduction.

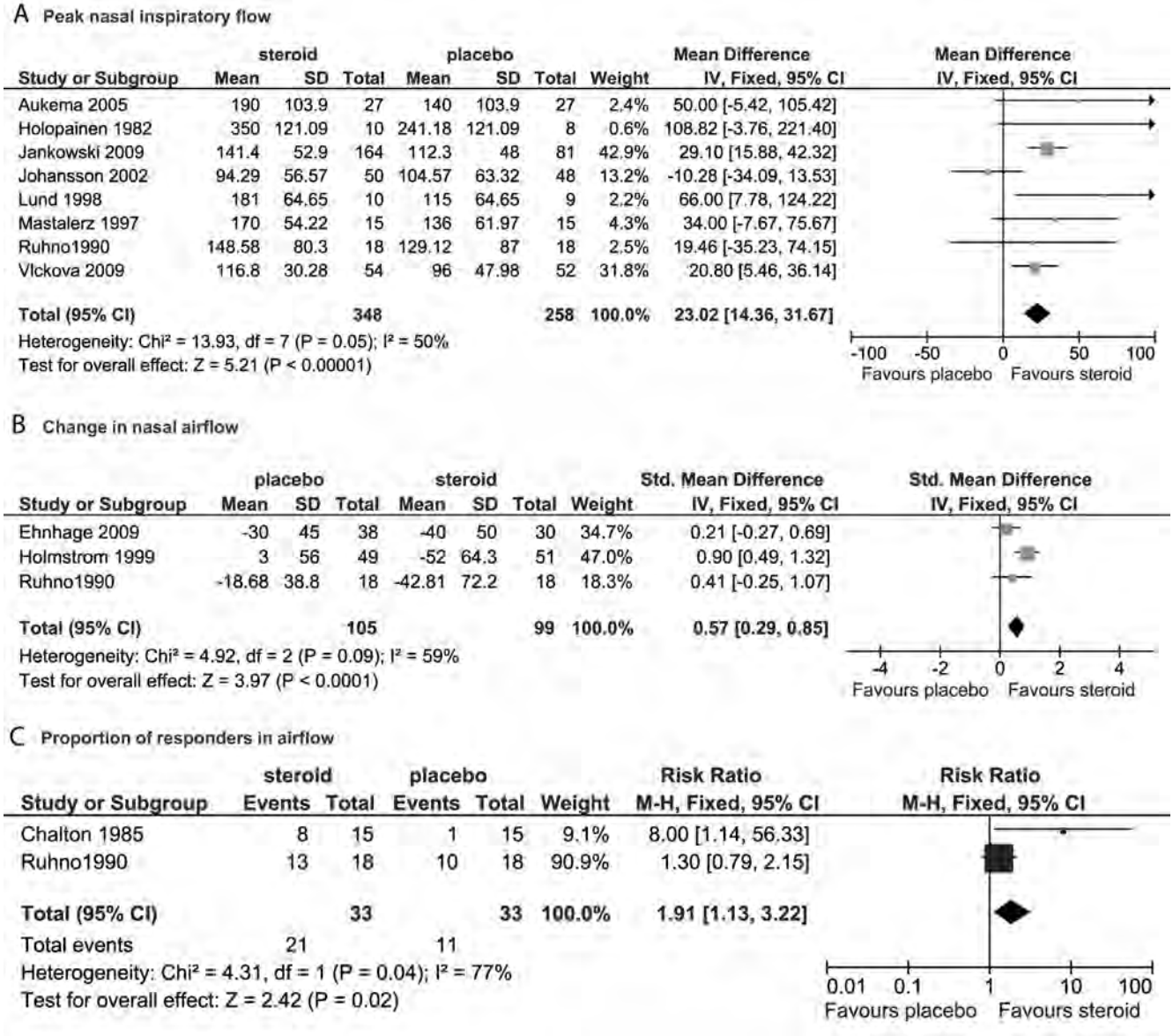


underwent surgery during the study period.
Since then a Cochrane review published in 2007 and its update in October 2010 has identified 3 level 1 studies (166 patients) to support the use of systemic corticosteroids in CRS with nasal polyps. The characteristics of these 3 included studies including the addition of 3 additional studies are described in Table 6.5.6.

Martinez-Anton 2008 [1843] and Benitez 2006 [1169] both contain the same data on the randomized component of these trials with oral corticosteroid (author correspondence).. The two other trials include a RCT in the allergic fungal sinusitis subtype of CRSwNP [1572] and a recent study of pre-treatment with and without systemic corticosteroid before ongoing INCS [1844]. There is definite intermediate effect that occurs with both symptoms and polyp size (Table 6.5.7.). However, given the inherent short period that this therapy is applied in a chronic condition, the treatment effects are short lived.

A combined oral followed by INCS protocol was described by Benitez et al.[1169] who performed a randomized placebo controlled study with prednisone for two weeks (30 mg 4 days followed by a 2-day reduction of 5 mg). After two weeks on prednisone or placebo, the prednisone group continued for ten weeks on intranasal BUD. After two weeks treatment

Figure 6.5.4. CRScNP INCS for nasal airflow.



a significant polyp reduction was seen, several symptoms improved and anterior rhinomanometry improved compared to the placebo group. After 12 weeks a significant reduction of CT-changes were seen in the steroid treated group.

6.5.3.1. Side-effects of systemic corticosteroid chronic rhinosinusitis with nasal polyps

The anti-inflammatory effects of corticosteroids cannot be separated from their metabolic effects as all cells use the same glucocorticoid receptor; therefore when corticosteroids are prescribed measures should be taken to minimize their side effects. Clearly, the chance of significant side effects increases with the dose and duration of treatment and so the minimum dose necessary to control the disease should be given. Patients on systemic corticosteroid therapy should be aware of impact on bone mineral density and regular calcium+vitamin D supplements are recommended. A bone density study every two years is commonly performed. There are changes to fat metabolism, catabolic muscle effects and appetite changes such that careful diet, exercise and weight management should be instituted. Additionally, the impact on glucose tolerance, early cataract formation and the pituitary-hypothalmic axis suppression need to be assessed and the patient educated on the impact of these.

6.5.4. Evidence based recommendations

There is good evidence that both INCS and systemic corticosteroids are effective for the management of CRSwNP. However, considering the evolving understanding of CRSwNP

Figure 6.5.5. CRScNP INCS influence of surgery for polyp reduction.

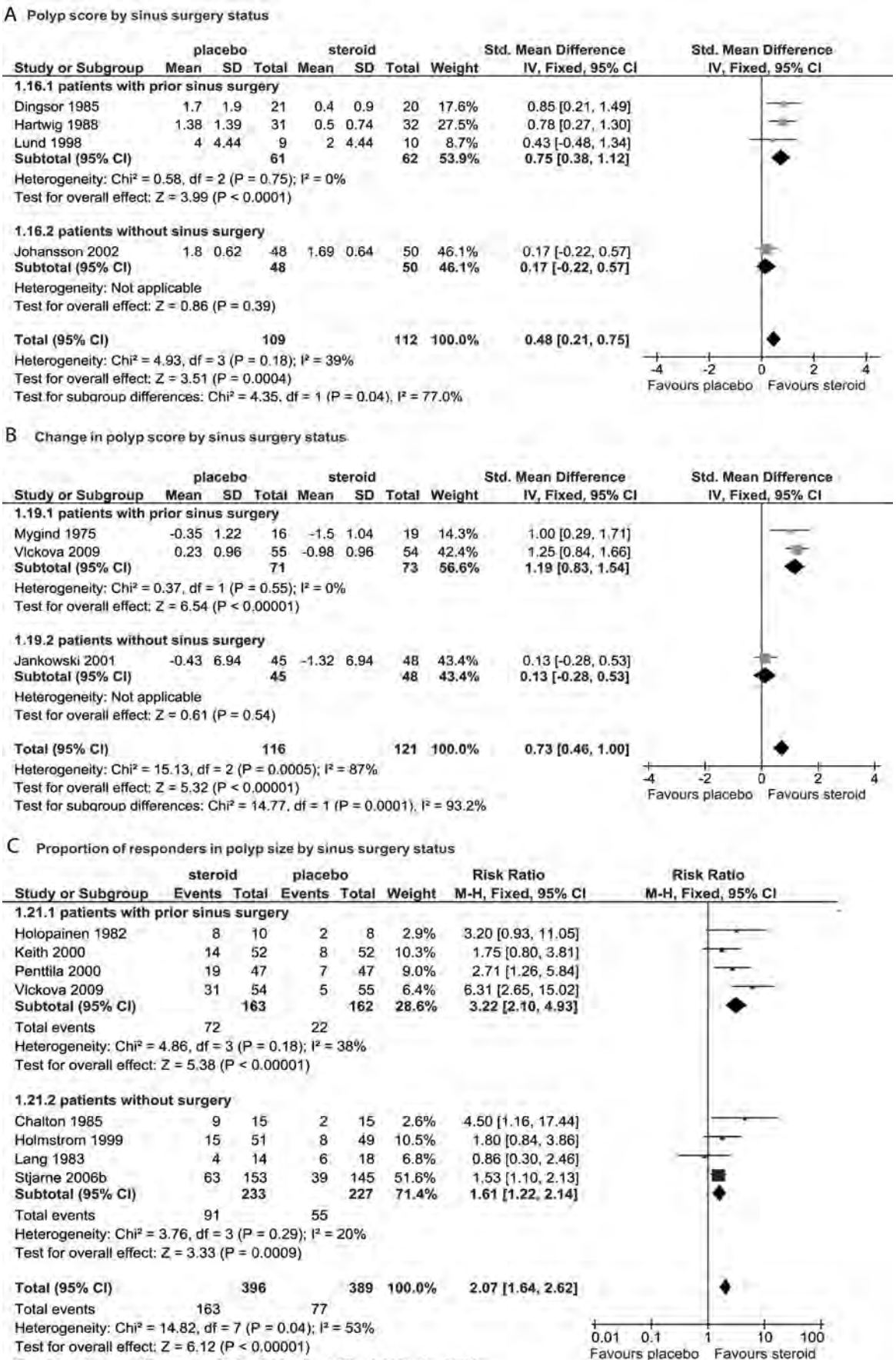


Table 6.5.3. Summary of outcomes comparing INCS versus placebo.

CRSwNP	Favours INCS	No effect or favours placebo
Without sinus surgery	Chalton 1985, Chur 2010, Filiaci 2000, Jankowski 2001, Jankowski 2009, Johansen 1993, Johansson 2002, Lildholdt 1995, Small 2005, Stjarne 2006, Stjarne 2006b (n=11)	Holmstrom 1999, Lang 1983, Mastalerz 1997 (n=3)
Mixed Populations	Aukema 2005, Keith 2000, Lund 1998, Mygind 1975, Ruhno1990, Vlckova 2009 (n=6)	Penttila 2000 (n=1)
Prior sinus surgery	Bross-Soriano 2004, Dingsor 1985, Drettner 1982, Hartwig 1988, Holmberg 1997, Jurkiewicz 2004, Karlsson 1982, Olsson 2010, Passali 2003, Rowe-Jones 2005, Stjarne 2009, Tos 1998 (n=12)	Dijkstra 2004, El Naggar 1995, Ehnhage 2009, Holopainen 1982, Jorissen 2009 (n=5)

Table 6.5.4 Study outcome comparing Drops v Sprays.

CRSwNP	Favours INCS	No effect or favours placebo
Drops	Aukema 2005, Pentilla 2000, Charlton 1985 (n=3)	Olsson 2010, Ehnhage 2009, Keith 2000, Holmstrom 1999 (n=4)
Sprays	Chur 2010, Jankowski 2009, Stjarne 2009, Vlckova 2009, , Stjarne 2006, Stjarne 2006b, Small 2005, Bross-Soriano 2004, Jurkiewickz 2004, Passiali 2003, Johansson 2002, Jankowksi 2001, Filiaci 2000, Lund 1998, Tos 1998, Holmberg 1997, Mastalerz 1997, Lidlholdt 1995, Johansen 1993, Dingsor 1985, Drettner 1982, Karlsson 1982, Mygind 1975 (n=23)	Jorissen 2009, Rowe-Jones2005, Dijkstra 2004, Hartwig 1998, Lang 1982, Holopainen 1982 (n=6)

Figure 6.5.6. CRScNP INCS for symptoms by surgery..

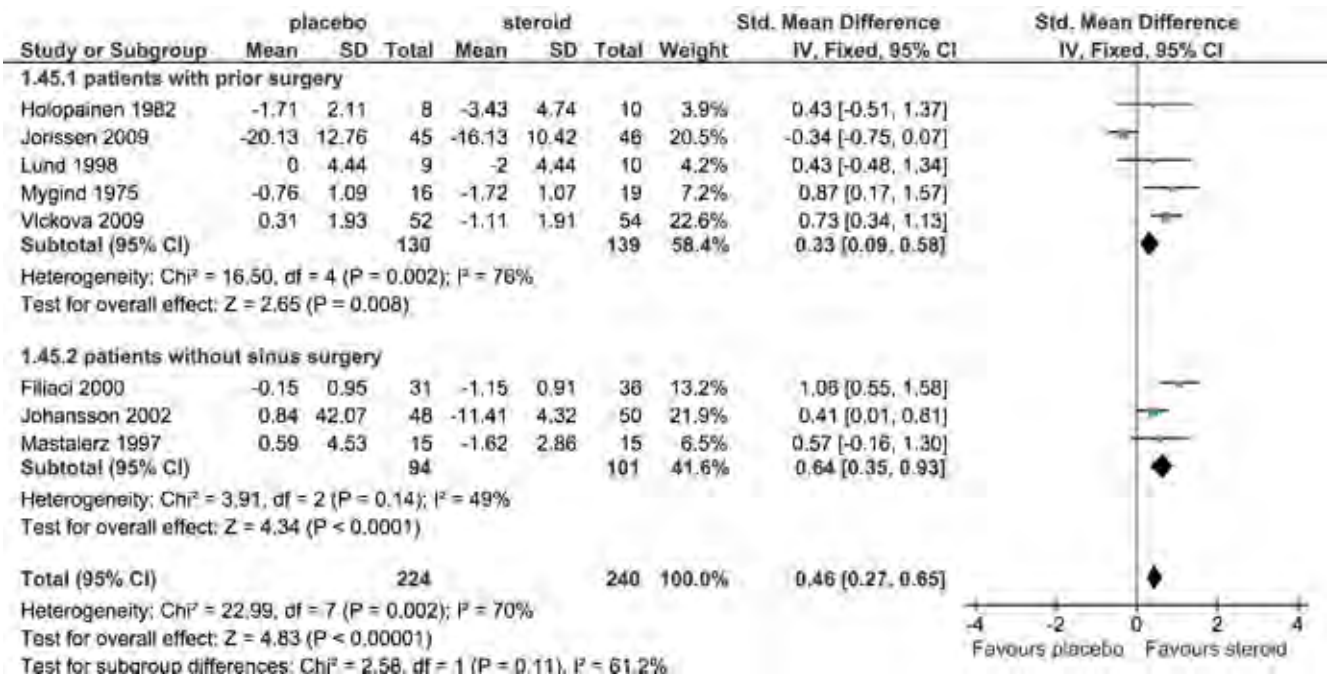


Figure 6.5.7. CRScNP INCS for symptoms by delivery.

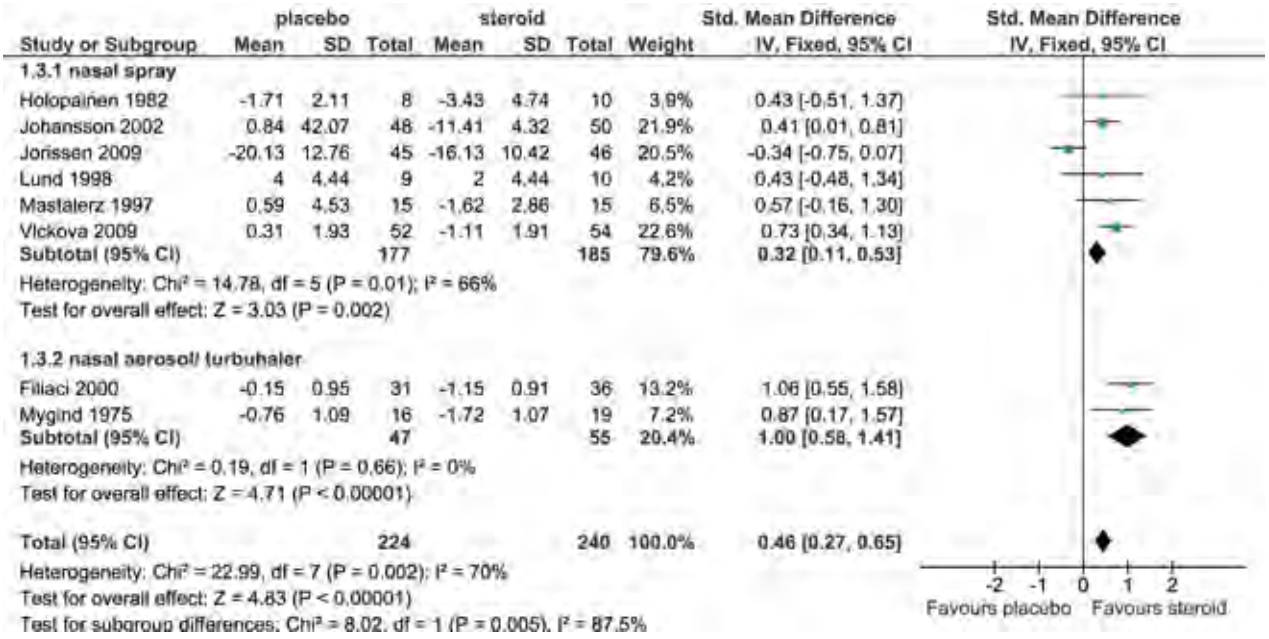


Figure 6.5.8. CRScNP INCS for symptoms for modern INCS..

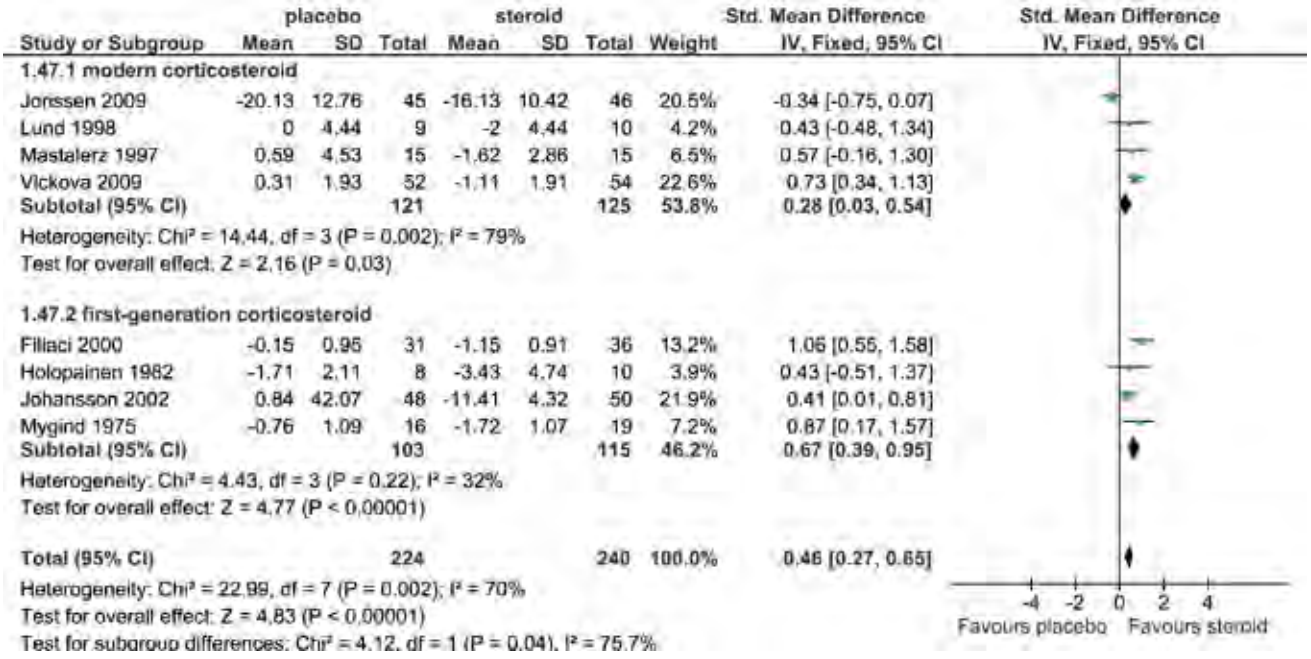


Table 6.5.5. Adverse events reported from included studies of INCS for CRSwNP.

Study	Steroid group n(%)	Placebo group n(%)	Description of events reported	Remarks
Chur 2010 (1822)				there was no difference in 24h urinary free cortisol change in all groups.
Ehnhage 2009 (1426)	22(73)	18(47)		70%mild23%moderate7%serious severity
Jankowski 2009 (1799)				the incidence of AEs was similar in all groups.
Jorissen 2009 (1674)	10(63)	16(62)	headache, sinusitis, cold	rare serious events
Stjarne 2009 (1812)	11(14)	9(11)	epistaxis, dyspepsia, obstruction, headache, sneezing, nausea, nasal congestion, rhinorrhea, skin irritation	Most AE are mild or moderate
Vlckova 2009 (1814)	13(24)	11(20)	epistaxis	no serious AE.Morning plasma cortisol was not changed.
Stjarne 2006 (1816)	54(53)	54(51)	respiratory infection, headache, epistaxis	most AE are mild or moderate.
Stjarne 2006b (1811)	93(61)	68(47)	epistaxis	most AE are mild or moderate.All epistaxis were mild.
Small 2005 (1810)	56(49)	64(55)	epistaxis and headache	most AE are mild or moderate and unrelated to study treatment.
Djikstra 2004 (1668)				the incidence of epistaxis was not higher in the steroid group.
Jankowski 2001 (1804)	16(33)	5(11)	blood tinged nasal secretion, headache, bronchospasm	most events are mild or moderate.
Filiaci 2000 (1794)			viral infection, abdominal pain, bronchitis, respiratory infection	80% are mild to moderate.
Keith 2000 (1802)	12(23)	9(17)	epistaxis, headache, viral respiratory infection	no serious events.No difference between groups in serum cortisol level.
Penttila 2000 (1808)	21(45)	27(57)	respiratory infection, epistaxis	no serious events. no difference in incidence of events between groups.
Holmstrom 1999 (1797)	14(14)	18(18)	epistaxis, throat irritation, nose dryness	there was no change in morning serum cortisol and no difference between treatment groups in the overall frequency of adverse events.
Lund 1998 (1796)	7(70)	3(33)	asthma, respiratory infection, headache	no serious events
Tos 1998 (1813)			respiratory infection, nasal mucosal blood, rhinitis, bronchospasm, headache	no serious events
Lildholdt 1995 (1804)			epistaxis, dryness	no serious events
Johansen 1993 (1800)			dry nose, headache, epistaxis	no differences between treatment groups.
Ruhno1990 (1809)	6(33.3)	5(27.8)	headache, epistaxis, dizziness	no serious events
Hartwig 1988 (1795)	9(25)	1(3)	nose bleed, nasal irritation	
Dingsor 1985 (1792)	6(30)	10(48)	itching, sore throat, sneeze, blood traces, nausea	no patients had abnormal plasma cortisol.
Drettner 1982 (1793)	4(36)	7(64)	nasal irritation, blood stain mucus, nasal crust, eye irritation, cataract, pharynx irritation	
Holopainen 1982 (1798)			transient nasal stinging and slight throat irritation.	mean morning plasma cortisol was not different between before and 4 months after treatment in both groups. Local SE were mild in both groups.
Mygind 1975 (1172)	8(44)	0(0)	nasal infection	

Table 6.5.6. Characteristics of included studies for systemic corticosteroid use in CRS with nasal polyps.

Study	Study type	Participants (diagnostic criteria)	number of participants	age (Mean)	Type of steroid	Steroid dose	Sinus Surgery Status	Delivery method of steroid	Duration of treatment (weeks)	Comparison
Vaidyanathan 2011 (1844)	RCT	CRSwNP (moderate to large)	58	49/52	prednisolone	25mg daily	23% in active and 30% in placebo	oral	2	placebo
Rupa 2010 (2066)	RCT	AFS	24	32/35	prednisolone	50mg daily for 6 weeks then tapered over 6 weeks	100% prior surgery	oral	12	placebo
Van Zele 2010 (928)	RCT	CRSwNP, recurrent after surgery or massive polyps (endoscopy)	47	53.2	methylprednisolone	32 mg daily for 5 days followed by a reducing dose to 16 mg daily for 5 days and 8 mg daily for 10 days	NS	oral	20/7	1.antibiotics group 2. placebo group
Martinez-Anton 2008/ Benitez 2006 (1843, 1169)	RCT	CRSwNP, medium to large size (by endoscopy and CT)	32	54.2	prednisone	30mg daily for 4 days then 5mg taper every 2 days	without surgery	oral	2	no treatment
Alobid 2006 (2067)	RCT	CRSwNP (endoscopy and CT)	78	50	prednisone	30 mg daily for 4 days followed by a dose reducing by 5mg every 2 days	15.4% of patients had previous sinus surgery	oral	10/7	no treatment
Hissaria 2006 (2068)	RCT	CRSwNP (endoscopy)	41	48.5	prednisone	50 mg daily	51.2% of patients had previous sinus surgery	oral	2	placebo

Table 6.5.7. Summary of outcomes from included studies of oral corticosteroid for CRS with NP.

Study	Type of steroid	Steroid dose	Delivery method of steroid	Comparison	Patients report outcome measures (PROM) (scoring system and scale)	Summary PROM results	Endoscopic outcomes (scoring system and scale)	Summary endoscopic results
Vaidyanathan 2011 (1844)	prednisolone	25mg daily for 2weeks	oral	placebo	total Nasal symptom score (VAS) and mRQLQ	mean difference 0.15 (0.02 to 0.40) p=0.001 favors steroid	polyp score (0-6)	mean difference favors steroid 1.8 (–2.4 to –1.2) p<0.001
Rupa 2010 (2066)	prednisolone	50mg daily for 6 weeks then tapered over 6 weeks	oral	placebo (all patients on INCS)	symptom score (8 questions)	steroid group had complete resolution of symptoms (p<0.0001)	kupferberg score	steroid group had complete resolution (p<0.0001)
Van Zele 2010 (928)	methylprednisolone	32mg daily for 5 days followed by a reducing dose to 16 mg daily for 5 days and 8 mg daily for 10 days	oral	placebo (additional arm of doxycycline)	symptom score (4symptoms)	improvement at 4wks then slow decline to no difference at 12 weeks for all symptoms	polyp score (0-4)	improvement up to 8wks then no difference at 12 weeks
Martinez-Anton 2008/Benitez 2006 (1843, 1169)	prednisone	30mg daily for 4 days then 5mg taper every 2 days (2weeks)	oral	no treatment	symptom scores (2 symptoms;0-3)	favor steroid over placebo (p<0.01)	nil	nil
Alobid 2006 (2067)	prednisone	30 mg daily for 4 days followed by a dose reducing by 5mg every 2 days	oral	no treatment	1. symptom score (2symptoms;0-3) 2. quality of life (SF-36)	1. favor steroid (p<0.05) 2. favor steroid (p<0.05)	polyp score (0-3)	favor steroid (p<0.05)
Hissaria 2006 (2068)	prednisone	50 mg daily	oral	placebo	1. symptom score (RSOM-31;6 nasal symptoms;1-5) 2.quality of life (total RSOM-31; 31symptoms;1-5)	1. favor steroid (p<0.005) 2. favor steroid (p<0.05)	polyp score (percentage reduction in polyp size) on: 1.endoscopy & 2. MRI	1. favor steroid (p<0.005) 2. favor steroid (p<0.05)

Statement	Grade of Recommendation	Level of evidence
Local		
INCS improve symptoms and patient reported outcomes in CRSwNP	A	1a
Delivery of INCS post surgery brings about a greater effect	A	1a
Objective measures of nasal breathing improve with INCS use in CRSwNP	A	1a
INCS is associated with only minor side-effects	B	2b
Modern INCS do not have greater clinical efficacy (although potentially fewer sider-effects) compared to first-generation INCS	A	1a
Systemic		
Systemic corticosteroids benefit CRSwNP but the effects are time limited post therapy	A	1a

and the chronicity of this condition (not from lack of treatment but natural history) many treatments will need to ongoing similar to local corticosteroid therapy in asthma. Thus the short-lived benefits of systemic corticosteroid therapy need to be balanced with the long-term potential side-effects. Local therapy appears to be effective but the ability to effectively deliver INCS to the paranasal sinuses may greatly influence the treatment response.

6.6. Treatment CRSwNP with antibiotics

Systemic doxycycline treatment for 3 weeks reduce polyp size and post-nasal discharge but not other symptoms compared to placebo in CRSwP.

6.6.1. Short-term treatment with antibiotics in CRSwNP

Short-term treatment with antibiotics in chronic rhinosinusitis with polyps

Two recent placebo controlled studies are available. It is the theory of endotoxin producing staphylococci as disease modifiers in CRSwNP that has prompted the interest. A placebo-controlled study by van Zele and co-workers, compared the effect of methylprednisolone in a 3 week course (32 mg for 1 w, 16 mg for 1 week and finally 8 mg for 1 week) with doxycycline (100 mg except for the first day of 200 mg) for 20 days with placebo.

Another placebo controlled study was performed by Schalek and co-authors [1845] 23 patients undergoing FESS, who tested positive for *S. Aureus* enterotoxin producing strains were randomized to oral anti-staphylococcal antibiotics (quinolone, amoxicillin/clavulanate or co-trimoxazole) for 3 weeks, or placebo. Both groups were compared pre-operatively and at 3 and 6 months using endoscopic score and SNOT-22. Slightly better results were found in the antibiotic group but it did not reach significance. Inflammatory markers were measured in both nasal secretions and blood, polyp size was estimated and symptoms were registered. Methylprednisolone had a short but dramatic effect on polyp size and symptoms. Doxycycline had a significant but small effect on polyp size compared to placebo, which was present for the length of the study, 12 weeks. Doxycycline showed a significant effect on postnasal discharge leaving other symptoms unchanged. Analysis of nasal secretions revealed that doxycycline reduced metallomatrix protein-9 (MMP-9) as well as myeoloperoxidase (MPO) and eosinophilic cationic protein (ECP). However quality of life measurements are lacking and one cannot deduce from the results whether the effect of doxycycline improved quality of life in the study population [928].

Table 6.6.1. Placebo controlled RCTs in short-term treatment with antibiotics in CRSwNP.

Study	Drug	N	Time/dose	Effect symptoms	Level of evidence
Schalek 2009 [1845]	anti staph antibiotic placebo controlled	23	3 weeks	no significant effect at 3 and 6 months, endoscopy, SNOT-22	1b (-)
Van Zele 2010 [928]	doxycycline placebo controlled	47	3 weeks/ 100 mg day	reduction of polyp size and postnasal secretion, reduction of pro-inflammatory markers	Ib

1b(-): 1b study with negative effect.

Conclusion

One RCT have shown that doxycycline for 3 weeks had a small effect on polyp size and post-nasal discharge but not other symptoms compared to placebo. The second study, where sample size was low, showed a trend towards effect (Level of evidence 1b) (Recommendation C).

6.6.2. Long-term treatment with antibiotics in CRSwNP

There are few studies where the study population has been properly defined into groups with, or without polyps. However one can identify at least 3 open studies where effect on polyp size is mentioned.

In an uncontrolled trial twenty patients with CRS and nasal polyps were treated for at least 3 months with clarithromycin 400 mg/day. In the group whose polyps were reduced in size, the IL-8 levels decreased and were initially significantly higher before macrolide treatment than those in the group whose polyps showed no change [1846]. In another uncontrolled trial 40 patients altogether were treated with either roxithromycin 150 mg alone or in combination with an antihistamine (azelastine) for at least 8 weeks. Smaller polyps were more likely to shrink and this happened in about half of the patients [1702]. A small, n=12, open study, using Roxithromycin 150 mg x1, also showed a reduction in IL-8 and improved aeration on CT [1704].

Conclusion

A few open studies have shown some effect on polyp size and patient symptoms. The effect seems to be moderate but may be more long lasting than systemic steroids, however quality of life data are missing and the clinical benefit for the patient is not fully investigated to date. Further studies are necessary to

evaluate this treatment option (Level of evidence III. Strength of recommendation C).

6.6.3. Treatment with topical antibiotics in CRSwNP

There are no data on the effect of topical antibitoics in CRSwNP.

6.6.4. Adverse events of antibiotic therapy of CRS

6.6.4.1. Effects on bacterial resistance.

A concern with long-term antibacterial treatment is the emergence of resistant bacterial strains. Especially when using a low dose not attaining minimal inhibitory concentrations. Data from primary care have shown that increased macrolide prescription in group A streptococci tonsillitis leads to a subsequent increase in resistance, which can reach alarmingly high levels [1714, 1715]. However in a tertiary setting, data is sketchy. The study by Videler at al. using azithromycin for 12 weeks, found 3 of 50 cultures with macrolide resistant strains before treatment, and after treatment 4 of 43 cultures with resistant strains [1709]. An emerging concern in cystic fibrosis patients is the increasing incidence of infection with the highly pathogenic Mycobacterium abscessus in azithromycin treated patients. The effect is probably due to azithromycin inhibition of autophagic and phagosomal degradation [1716-1718]. This has not been reported in CRS patients.

6.6.4.2. Other side effects

Well-known side effects of antibiotics includes: gastrointestinal upset, skin rash reversible elevation of liver enzymes. In the study by Videler et al. including 78 patients, the investigators found 1 case of muscle ache in the azithroprim group and 2 cases of mild skin rash in the clarithromycin treated patients and no adverse effects in the trimethroprim-sulfamethoxazole group. The study comparing doxycycline treatment for 20 days with methylprednisolone and placebo reported no difference in adverse events in the different groups. However, rare side effects are not picked up in small clinical trials, but rather in national records on side effects. Hearing impairment due to macrolide treatment is a rare side effect but was recorded in a recent large trial in COPD [1696].

6.6.4.3. Conclusions on adverse events of antibiotic therapy of CRS

The safety of long-term antibiotic therapy, either azithromycin, clarithromycin or roxithromycin is recognised in patients with CRS, but also due to it's established long-term use in cystic fibrosis. As for doxycycline there is longstanding experience for long-term use in acne and rosacea patients. Trimethroprim-sulfamethoxazole has been used long-term in both the pediatric and adult population for treatment of infectious prone patients with certain immune deficiencies as well as urinary tract infections. Drawing on the experience from other areas than CRS, long-term treatment with the mentioned antibiotics is relatively safe. Although one has to bear in mind the interaction between macrolides and drugs such as dicumarol, antiepileptic drugs, terphenadine, methotrexate and antidepressant drugs. To monitor the risk of the development of resistant bacterial strains, nasal swabs with culture every 3 months during treatment is advisable.

6.7. Other medical management in CRSwNP

6.7.1. Summary

Current data yield insufficient evidence to recommend anti-IgE, anti-IL5, antihistamines in non-allergic patients, antimycotics, immunosuppressants, furosemide, leukotriene antagonists, aspirin desensitisation, capsaicin and various other medical treatments for treatment of CRSwNP.

6.7.2. Introduction

In the EP^{3}OS 2007 publication [8], non-antibiotic and non-steroidal medical treatment of acute rhinosinusitis, CRSsNP and CRSwNP were discussed in one chapter. Due to differences in aetiology and pathophysiology, but also treatment principles, the authors decided to consider CRSwNP and CRSsNP in adults in separate chapters. Criteria to include publications in the current analysis were more restrictive, mainly focused on randomized controlled trials (RCT) and studies published after 2007. As a consequence, not all publications cited in the former version of EPOS were included. An analysis of publications on anti-IgE and anti-IL-5 antibodies was included. Moreover, a more in depth analysis of included publications was performed. The part on antihistamines was revised. The part on topical amphotericin B treatment was replaced due to the availability of a recent comprehensive Cochrane analysis. Tables were restricted to RCT, when at least two trials were available. A column was added indicating if patients with or without previous sinus surgery were included. For each substance group, most relevant adverse effects and levels of recommendation are provided.

6.7.3. Anti-IgE

In several investigations, total IgE-levels in nasal secretions, nasal polyp homogenisates and blood serum were higher in CRS-patients with nasal polyps than in controls. Omalizumab(R), a recombinant DNA-derived humanized IgG1k monoclonal antibody that selectively binds to human IgE, reduces serum and tissue IgE-levels. Omalizumab(R) is approved for patients with moderate-to-severe or severe allergic asthma. Two anecdotal reports [1847, 1848], 1 pilot study in 8 patients [1849] and 1 case series [1850] showed beneficial effects of omalizumab(R) in

CRS patients with nasal polyps. Pinto and co-workers conducted a randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis in 14 patients (12/14 with nasal polyps) with severe CRS refractory to standard treatment including sinus surgery [963]. Pretreatment serum total IgE-levels between 30 - 700 IU/ml were required for inclusion. All patients received omalizumab(R) 0.016 mg/kg per IU total serum IgE/mL subcutaneously or placebo injections all 4 weeks for 6 months on top og other medical treatment. The main outcome parameter was pre- and post-treatment sinus opacification in coronal CT scans. The median change of sinus opacification in omalizumab(R) treated patients was 11.9% vs. 5.9% in placebo treated patients ($p<0.391$). No significant differences were also found in various secondary outcome parameters including SNOT-20 scores, olfactory test scores, endoscopy scores, eosinophils in nasal lavage, and peak nasal inspiratory flow values. This study is underpowered due to recruitment problems following FDA warnings on anaphylactic AE to omalizumab. Omalizumab may cause anaphylaxis in approximately 1 patient per 1,000 [1851]. Omalizumab may increase the risk of cardiovascular events, thrombocytopenia or cancer [1852]. Based on current data, omalizumab is not recommended for the treatment of CRS with nasal polyps (grade of recommendation: C). Mainly data on patients with previous sinus surgery are available.

6.7.4. Anti-IL-5

IL-5 is a key activator in eosinophil growth, recruitment and activation. High amounts of IL-5 were detected in polyp homogenisates, nasal secretions and blood serum of patients with NP. Mepolizumab (Glaxo Smith Kline) and reslizumab (Schering-Plough) are humanized anti–IL-5 mAb that reduce the number of eosinophils in blood and tissues [1853, 1854]. Both antibodies currently undergo Phase II and III trials. In 2004, orphan designation (EU/3/04/213) was granted by the European Commission for mepolizumab for the treatment of hypereosinophilic syndrome. Two clinical trials with anti-IL-5 antibodies in CRS patients with nasal polyps were identified.

In a double-blind, placebo-controlled, randomized, 2-center phase I/II trial, 24 subjects with bilateral nasal polyps were randomized to receive a single intravenous infusion of reslizumab 3mg/kg or 1mg/kg or placebo (i.e. 8 patients per treatment arm). The post-injection observation period was 36 weeks. Adverse events did not significantly differ between treatment groups. No pharmacokinetic data and no detailed data on drop outs are provided. Main outcome measure for efficacy was an endoscopic nasal polyp score repeatedly evaluated for each nostril. Secondary efficacy parameters included peak nasal inspiratory airflow and nasal symptom scores. At no individual time point, a significant difference in the symptom scores or in the nasal peak inspiratory flow values was observed in both treatment groups compared with those in the placebo group. The total nasal polyp score was significantly decreased in the 1mg/kg group at week 12 compared with baseline values, however apparently not with the values of the control group. No dose response relation was observed. Blood eosinophil counts dropped significantly in both active groups, followed by a steep increase above baseline values 8-19 weeks post injection suggesting a rebound hypereosinophilia. Patients with nasal secretion IL-5 levels >40pg/ml were more likely to reveal a reduction of at least 1 polyp score on an 8 point scale when treated with anti-IL-5 [931].

In a further randomized, double-blind, placebo-controlled study, CRS-patients with nasal polyps received 2 single intravenous injections (28 days apart) of 750 mg of mepolizumab (20 subjects) or placebo (10 subjects). Post-injection observation period was 48 weeks. The primary end point was the reduction in an endoscopic nasal polyp score on an 8 point scale at 8 weeks after the first dosing (4 weeks after the second dose). Secondary outcome parameter included sinus opacification in CT scans, peak nasal inspiratory flow and symptom scores. Last observation carried forward imputation was used to handle missing data. Number and severity of adverse events did not differ between treatment groups. In the treatment group, nasal polyp scores improved 1.30±1.72 (SD) score points while it remained unchanged (0.00±0.94) in the control group, resulting in a treatment difference of 1.30±1.51 score points ($p=0.028$, Mann-Whitney U test). Moreover, significantly less sinus opacification was observed in the treatment arm [932].

The results of these clinical trials suggest that anti-IL-5 antibodies could play a role in the treatment of selected CRS-patients with nasal polyps. In a recent reslizumab study in asthma patients, nasopharyngitis, fatigue, and pharyngolaryngeal pain were common adverse events [1855]. No data on patients without previous sinus surgery are available.

6.7.5. Antihistamines

One randomized placebo-controlled trial on antihistamines in CRS-patients with nasal polyps was identified. Forty-five surgically treated patients with residual or recurrent nasal polyps received either cetirizine 20mg b.i.d. (n=23) or placebo (n=22) for three months. Inhaled steroids for asthma treatment up to 800 µg per day were allowed as concomitant medication. Endoscopic polyp size, nasal symptom score at follow up visits and a nasal symptom daily diary cards served as outcome parameters. No primary study endpoint was defined and no power calculations are provided. In each group, 18 patients finished the study regularly, an IT analysis was performed. The method of missing value handling is not reported. Adverse

events were equally distributed among treatment arms. The number and size of polyps remained unchanged during the study period. Nasal symptom scores at follow up visits did not significantly differ between the two treatment arms. In the daily diary cards, significantly less days with a symptom score <= 1 were observed for nasal hypersecretion (weeks 1 to 4, 5 to 8 and 9 to 12), sneezing (weeks 1 to 4 and 5 to 8) and nasal obstruction (weeks 9 to 12). However, daily dairy scores above >1 were rare for nasal hypersecretion and sneezing in the whole study population. No adjustment for multiple testing is reported [1856].
Cetirizine is a safe antihistamine. Adverse effects include drowsiness; dry mouth and tiredness. Based on current data, cetirizine is not recommended for the treatment of CRS with nasal polyps (grade of recommendation: D). In patients with concomitant nasal allergies, antihistamines may be indicated. (grade of recommendation: C) No data on patients without previous sinus surgery are available.

6.7.6. Antimycotics

Eosinophilic rhinosinusitis is a non-invasive, chronic eosinophilic sinus inflammation frequently associated with nasal polyps. Viscid sinus secretions with eosinophil decay products, termed eosinophilic mucus by Bent and Kuhn [721], are characteristic for this condition. If fungal elements are detected by histology, fungal culture or molecular methods, the term eosinophilic fungal rhinosinusitis is appropriate. Eosinophilic fungal rhinosinusitis may be further divided in allergic fungal rhinosinusitis (AFRS) with a positive diagnostic test for IgE mediated allergy to the fungal elements detected within the sinus. It is considered an IgE mediated mucosal hypersensitivity directed against fungal antigens deposited on sinus mucosa [1857]. If Type I allergy tests to moulds are negative, but eosinophilic mucus with fungal elements is found, the term non-allergic fungal eosinophilic rhinosinusitis is used [2069]. Eosinophilic mucus may also occur in the absence of fungal elements and is categorized as non-fungal eosinophilic mucus rhinosinusitis.
Based on fungal detection and the presence of allergic mucus in almost all patients with chronic rhinosinusitis, Ponikau and coauthors proposed that CRS is generally caused by a dysregulated, but IgE independent immune response to fungal elements present on the mucosal surface [592, 702]. As a consequence, reduction of fungus load should influence disease severity in all subtypes of CRS. This hypothesis led to a series of investigations, which did rather serve to proof this concept than to treat fungal disease. In these studies, patients complying with the AAO-HNS or EPOS definitions of CRS were included [8, 1205], irrespective of the presence of eosinophilic mucus and/or fungus detection.

6.7.6.1. Topical amphotericin B

In most trials with antifungals in CRS, amphotericin B was applied topically, either as a nasal spray or as a nasal irrigation. The majority of patients included in these trials suffered from CRS with polyps. However, not in all trials, the presence of nasal polyps was explicitly reported. Topical amphotericin B trials were extensively discussed in the last EPOS version. Since then, topical amphotericin B treatment was reviewed in 2 review articles and 1 Cochrane analysis. The authors conclude that the use of topical amphotericin B in patients with CRS with polyps is not justified [1585, 1858, 1859].
Amphotericin B is not systemically available after oral intake. Adverse events after topical nasal application include local irritation and rarely unpleasant smell sensations. Based on current data, topical amphotericin B is not recommended for the treatment of CRS with nasal polyps (grade of recommendation: A).
One report on topical nasal treatment with another antifungal was identified. In an uncontrolled study, 16 patients with previously treated allergic fungal sinusitis and worsening clinical symptoms received nasal fluconazole spray in addition to systemic steroids and/or systemic itraconazole. Stable disease or improvement was observed in 12/16 patients [1860].

6.7.6.2. Systemic antifungal treatments

There is 1 controlled study and few reports of uncontrolled studies of postoperative systemic antifungal treatment in patients with confirmed fungal rhinosinusitis.

Kennedy and co-authors prospectively compared oral terbinafine with placebo in fungus positive and fungus negative CRS patients. Treatment with terbinafine failed to improve

Table 6.7.1. Anti-IL-5 in CRSwNP.

author	drug	study design	active (n)	control (n)	number of patients post sinus surgery	effect	evidence level
Gevaert et al. 2006 [931]	reslizumab 1 i.v injection; 1mg/kg or 3mg/kg	randomized, double blind, placebo controlled	16	8	all	negative	2
Gevaert et al. 2011 [932]	mepolizumab 2 i.v. injections 750mg	randomized, double blind, placebo controlled	20	10	all	positive	2

* Ib (-): Ib study with a negative outcome.

symptoms or radiographic appearance of chronic rhinosinusitis even when nasal irrigation samples were positive for fungus on culture [1861].

Seiberling and co-authors performed a retrospective chart review of 23 patients with AFRS and non-allergic eosinophilic fungal sinusitis, who had failed maximal medical and surgical therapy. Patients with recurrent disease received itraconazole at a dose of 100mg b.i.d. for a minimum period of 6 months. Three patients had to stop treatment due to hepatic side effects, 4 patients did not respond and 16 patients showed a varying degree of symptom improvement including a decrease in the use of oral steroids and fungal mucus/polyps on endoscopy [1584]. Rains and Mineck performed a chart review of 139 patients with allergic fungal rhinosinusitis and reported a benefit of high-dose systemic itraconazole treatment in patients with recurrent disease [1862]. Chan and co-authors treated 32 patients with fungal eosinophilic chronic rhinosinusitis who did not respond to surgery, oral cortisone and nasal amphotericin B spray with oral itraconazole for at least 3 months. Twelve patients has improved endoscopic findings following treatment, 15 showed no difference, and 5 were worse. Serum total IgE levels were not affected [1863]. Rupa and co-workers treated 12 patients with fungus positive eosinophilic rhinosinusitis following sinus surgery with nasal steroids and oral itraconazole 200 mg daily for 12 weeks. All patients but one patient relapsed within the study period [1572].

Long-term itraconazole treatment has considerable adverse effects including nausea and fatigue. The main problem is hepatic toxicity with increased serum alanine tranferase levels in 4% of patients. Congestive heart failure is an infrequent side effect of itraconazole treatment. Itraconazole interacts with various other drugs. Drug interactions may increase the risk of congestive heart failure.

Based on current data, systemic antifungal treatment is not recommended in CRS with nasal polyps (grade of recommendation A).

6.7.7. Furosemide

Aerosolized furosemide was used in the treatment of acute asthma attacks [1864]. Several mechanisms including induction of relaxant prostaglandins, blockade of mediator production from inflammatory cells, and regulation of ion exchange in the airway epithelium were proposed to explain its anti-asthmatic activity [1865].

In a controlled, open label study, 64 CRS-patients with nasal polyps received furosemide nasal spray (200 µg daily) following endonasal sinus surgery. A control group of 40 patients received no treatment. The mode of randomization is not detailed. After 6 years, 4 patients in the furosemide group and 12 patients in the control group had experienced recurrent disease ($p<0.01$). Drop out handling is not detailed in the report [1866]. In 2003, Passali and co-workers published long term results of topical furosemide treatment in 170 CRS patients with nasal polyps following endonasal surgery. From 1991 to 1997, patients were randomly assigned to furosemide or control treatment. It appears that patients included in the 2000 report were included also in this evaluation. Furosemide was 1:1 diluted 2 mL isotonic sodium chloride solution administered as nasal spray (100µg per nostril and day). One-month treatment alternated with 1 month without treatment. The intervals without treatment were then gradually extended. In the control group, no specific treatment was given. In 1998, control treatment was stopped and mometasone was given instead. Patients received 2 puffs mometasone spray per day per nostril with the same monthly interruptions used in the furosemide group. No adverse events were registered. Seventeen (17.5%) of 97 patients in the furosemide group, 12 (30.0%) of 40 patients in the control group, and 8 (24.2%) of 33 patients in the mometasone group experienced nasal polyposis relapses ($p>0.2$) [1807].
Mode of randomization, number of screened patients, drop out rate and missing data handling are not reported. As a consequence, the value of these two trials is difficult to interpret. In a randomised trial, 40 CRS-patients with nasal polyps were randomly allocated to treatment either with oral methylprednisolone (1 mg/kg/day) or inhalation of 6.6 mmol/l furosemide solution/10 min through a jet nebulizer (20 mg/day furosemide) for 7 days prior to endonasal sinus surgery. The mode of randomization is not detailed. Twelve patients had undergone previous sinus surgeries ('recurrences'). Study endpoints were a nasal symptom score and an endoscopic polyp score assessed before and after treatment. Serum potassium levels and blood pressure were monitored before and during 1 h after each inhalation in the furosemide group. No systemic diuretic effects were observed. Total symptom scores changed from 15.50±3.44 (mean ± SD) to 9.55±3.55 in the methylprednisolone group and from 15.60±3.91 to 9.80±3.69 in the furosemide group (both $p<0.01$). Nasal polyp scores changed from 2.38±0.67 to 1.95±0.78 in the methylprednisolone group and from 2.23±0.89 to 1.68±0.89 in the furosemide group (both $p<0.01$) [1867].
The bioavailability of furosemide after oral intake is approximately 60%. Data on nasal uptake are not available. Main side effects of oral furosemide are water and electrolyte imbalances. Based on current data, (postoperative) long-term nasal furosemide treatment is not recommended (grade of recommendation D). Further studies are needed to assess the possible benefit of preoperative short term, high dose nasal furosemide treatment.

6.7.8. Immunosuppressants

In glucocorticoid-dependent asthma, immunosuppressants including methotrexate may aid to reduce the steroid dose [1868]. There are two anecdotal reports that nasal polyps may substantially improve, if methotrexate is given in steroid-dependent asthma or malignant conditions with concomitant nasal polyps [2070,2071]. Based on current data, the use of immunosuppressants is not recommended in CRS with nasal polyps (grade of recommendation D).

6.7.9. Leukotriene antagonists

Ragab and co-authors evaluated the efficacy and tolerability of montelukast as an add-on therapy in the treatment of nasal polyposis in association with asthma. In 44 adult CRS-patients with nasal polyposis (24 with AERD) refractory to medical therapy with long-term intranasal corticosteroids; oral montelukast (10 mg/day) was given for three months as an add-on therapy to intranasal and inhaled corticosteroids. Main outcome parameter was a clinical score based on the results of clinical symptoms, examination, acoustic rhinometry, and peak nasal inspiratory flow. The majority of patients experienced clinical improvement. Improvement of nasal polyp score was significant, irrespective if the patients suffered from AERD or not [1515].

In a single-blind, randomized, placebo-controlled cross over trial, 24 patients with asthma and post-FESS CRS with nasal polyps were enrolled. One group started with a 4-week placebo phase and continued with 6 weeks of montelukast treatment (10 mg/day) while the other group started with montelukast treatment for 6 weeks and continued with placebo for 4 weeks. Statistical analysis did not account for the special problems of cross-over designs and the data presentation is not appropriate for this type of trial design. During montelukast treatment, the mean scores decreased from 1.8 to 0.6 for nasal blockage, from 1.5 to 0.6 for rhinorrhoea, and from 0.6 to 0.25 for itching. In a similar manner, the quality of smell improved from 2.0 to 0.3 and the total symptom score improved from 5.9 to 1.75 ($p<.001$). No significant changes in symptoms were observed during the placebo period. Significant improvements were also noted in nasal endoscopy scores. Various proinflammatory biomarkers in nasal lavages revealed significant improvements [1869].

In an uncontrolled, open label study 26 CRS-patients with nasal polyps without AERD received 10 mg montelukast daily for 3 months on top on long-term nasal steroid therapy. Symptom scores were assessed before and after the 3-month treatment interval in 24 patients, who finished the study regularly. The symptoms improved in 17 patients (71%) and remained the same or worsened in 7 patients (29%). Patients with concomitant nasal allergy responded better than patients without allergy [1870].

In an uncontrolled open label study, 26 patients with nasal polyps received oral zafirlukast 10 mg bid or zileuton 600 mg qid on top of systemic steroid therapy. Nasal symptom scores were assessed before and after a treatment period of 7 months. Concomitant asthma was present in 14 patients, 2 patients suffered from AERD. Overall, 26 of the 36 patients (72%) experienced improvement in their symptomatology after starting antileukotriene therapy. No patient experienced a worsening of symptoms. The remaining 10 patients (28%) experienced no change [1871].

In an uncontrolled open label study, 20 patients with nasal polyps and bronchial asthma received oral montelukast 10 mg/day on top of nasal and inhaled steroid therapy for 1 year. Study endpoints included nasal polyp scores and sinus opacification on pre- and post treatment CT scans. Nasal allergy was present in 11 patients and 8 were judged to suffer from AERD on the basis of their history. Nasal polyp and CT scores improved significantly during treatment [1872].

Table 6.7.2. Systemic antifungal treatment in CRSwNP.

author	drug	study design	active drug (n)	control (n)	number of patients post sinus surgery	effect	evidence level
Kennedy 2005 [1861]	terbinafine 625 mg/day	randomized, double blind, placebo controlled	25	28	none with sinus surgery within 3 months before trial entry	negative	Ib(-)#
Rupa 2010 [1572]	itraconazole 200mg daily + oral prednisolone (active) vs. Itraconazole alone (control)	randomized, double blind, controlled	12	12	all	negative*	Ib(-)#

*All patients but 1 in the itraconazole only group had disease recurrences within the observation period.

Ib (-): Ib study with a negative outcome.

Following endoscopic sinus surgery, Mostafa and co-workers randomly assigned 40 patients with nasal polyps without asthma either to 10 mg montelukast daily or 400 µg beclomethasone nasal spray daily for 1 year. Study endpoints included disease relapse and nasal symptom scores. No differences in disease relapse frequency were noted. Nasal beclomethasone was superior to montelukast controlling nasal obstruction, rhinorrhoea, sense of smell and sneezing. The onset of montelukast action was prolonged, with the maximum therapeutic effect seen after 6 months of treatment [1873]. In a randomized, placebo-controlled trial, 20 patients with nasal polyps were treated with montelukast 10 mg/day and 10 patients received placebo treatment for 4 weeks. Nasal polyp scores, eosinophila cationic protein levels in nasal secretions and HRQL employing a modified Juniper score were assessed before and after treatment. No significant changes in polyp scores and nasal ECP levels were observed. In some HRQL parameters, better scores were observed in the treatment group [1874] In a randomized, controlled trial without allocation concealment, 38 consecutive adult patients with bilateral nasal polyps were treated with oral prednisolone for 14 days and budenoside nasal spray for 8 weeks (n=18). Twenty subjects received similar treatment with additional oral montelukast 10 mg/day for 8 weeks. Concomitant nasal allergy was more frequent among montelukast treated patients. Outcome measures included nasal symptom scores and the SF-36 HRQL questionnaire. When compared with subjects treated with steroid alone, subjects treated with montelukast showed a significant reduction in symptom scores at eight weeks with respect to headache, facial pain, and sneezing. However, montelukast therapy did not have a significant effect on the overall symptom score or on symptoms of nasal blockage, hyposmia, or nasal discharge [1875].

Adverse effects of leukotriene antagonists include skin rash, mood or behavior changes, tremors or shaking and occasional worsening of sinus symptoms and asthma. Current data do not support anti-leukotriene therapy in CRS-patients with polyps. Leukotriene antagonists are not recommended for the treatment of CRSwNP (Grade of recommendation A).

6.7.10. Aspirin desensitisation

Aspirin-exacerbated respiratory disease (AERD) is characterized by chronic rhinosinusitis with nasal polyps, bronchial asthma and hypersensitivity to inhibitors of cyclooxygenase-1 (Cox-1) including aspirin and other non-steroidal anti-inflammatory drugs [1525]. The diagnosis is mainly based on patient history and aspirin provocation tests [1506]. In AERD patients, aspirin may induce a period lasting 24 to 72 hours, in which patients are refractory to repeated aspirin challenges and experience clinical improvement [1876]. Based on this observation, several oral and nasal aspirin desensitisation protocols were developed. Most widely used is the Scripps-clinics oral aspirin desensitisation protocol, in which, following a stepwise dose increase, 625 mg aspirin is orally administered twice daily [1525].
Several case series suggest albeit weak clinical benefit from oral aspirin desensitisation [1526, 1877], but no randomized placebo-controlled trial on oral aspirin desensitisation in patients with AERD could be identified. In a cross-over trial, 25 AERD patients were treated with oral aspirin in 3 different dosages or with placebo for 3 months, separated by a 1 month wash out phase. Symptom scores and concomitant medication use in the two trial phases were compared with 1-sided t-test. The mode of randomization is not detailed in the publication. In the aspirin phase, less nasal symptoms and less nasal steroid use was observed. Lower respiratory tract symptoms, values of FEV1, and the use of anti-asthmatic medications including prednisone were not better during ASA treatment [1825].
In one clinical trial, 14 patients who reacted positively in an aspirin provocation test were alternately allocated to take 100 mg aspirin or 300 mg aspirin daily and were followed for at least 1 year. After 1 year of aspirin therapy, all patients of the 100mg group (100%; 95%CI, 59–100%) had developed recurrent nasal polyps. No patient of the 300mg group showed recurrent nasal polyps in endoscopic examination (0%; 95% CI, 0–41%) [1878].
Nasal administration of lysine-aspirin reduces the risk of severe hypersensitivity reactions and the frequency of gastrointestinal side effects associated with oral aspirin desensitisation. Some retrospective studies reported clinical benefit from nasal lysine-aspirin treatment [1824, 1529]. In a randomized, double-blind placebo-controlled cross over trial, AERD patients with positive nasal lysine-aspirin challenge received either 16mg nasal lysine aspirin or placebo every 48 hrs. for 6 months. Of 22 patients entering the trial, 11 were eligible for analysis. Multivariate analysis of measured parameters did not reveal a significant clinical benefit to patients receiving topical lysine-aspirin compared with placebo [1528].
Oral aspirin desensitisation is associated with the risk of severe hypersensitivity reactions and gastrointestinal side effects. Based on current data, the benefit of oral or nasal aspirin desensitisation in patients AERD remains elusive. Aspirin desensitisation is currently not recommended outside clinical trials (grade of recommendation D).

6.7.11. Capsaicin

Two case series and 1 RCT on nasal capsaicin treatment following sinus surgery were identified [1879-1881]. In the RCT, 29 patients capsaicin soaked cotton pellets were brought into the middle meatus of both nostrils for 20 min once a week for 5 weeks. An age and gender matched control group of 22 patients were treated with the capsaicin vehicle alone (70% ethanol). Nasal symptom scores and a nasal endoscopy score were the main outcome parameters. Patients treated with capsaicin

showed a significant smaller staging of their nasal polyposis compared with the control group (p<0.001) [1879] (grade of recommendation: C).

6.7.12. Various other medical treatments

Single studies and anecdotal reports on various topical and systemic treatments do not allow to recommend their use in CRSwNP including nasal decongestants [1882], mucolytics [1883], postoperative saline douches [1738] or spray [1884], manuka honey [1587], proton pump inhibitors or phytopreparations (no data available for CRSwNP).

6.8. Evidence based Surgery for CRSwNP

6.8.1. Introduction

Nasal polyps affect approximately 20% of patients with CRS. From a clinical, radiological and histological perspective the mucosal inflammatory response is more florid in CRS patients with nasal polyps than in those without, and the rate of relapse after surgery for nasal polyps tends to be higher [1885].

Surgical intervention in the treatment of nasal polyps is considered in patients who fail to improve after a trial of maximal medical treatment. Functional endoscopic sinus surgery involves the clearance of polyps and polypoid mucosa and opening of the sinus ostia. The removal of inflammatory tissue and reduction of the load of antigens inciting that inflammation, as well as the improvement of sinus ventilation and mucociliary clearance, are the probable mechanisms whereby FESS improves symptoms in nasal polyposis.

The optimal surgical management of nasal polyps has not yet been established. There are a number of factors contributing to the difficulty in gathering clinical data on which to base surgical management. A number of studies fail to distinguish between CRS with and without polyps. However in those studies that do, the distinction made on clinical grounds preoperatively (whether polyps are visible in the middle meatus) is itself imperfect. Many cases in which no polyps can be observed have impressively polypoid mucosa within the sinuses at the time of operation. There are very few RCT's which compare medical and surgical treatment with the extent of surgical resection required to optimize outcomes, hence this is largely unknown. Functional endoscopic sinus surgery describes an approach and not a standardized operation. The efficacy of procedures may well be dependent on their extent and so the specific details of the procedures performed need be considered carefully when assessing the reported efficacy.

The outcome post polyp surgery is influenced by whether the polyps are idiopathic or related to an underlying mucosal condition such as aspirin exacerbated respiratory disease, cystic fibrosis or primary ciliary dyskinaesia. However in both idiopathic and secondary nasal polyps, the long-term efficacy of surgery is almost certainly influenced by the regimen of medical treatment prescribed postoperatively and the subsequent compliance with this regimen.

In this chapter the evidence for efficacy of surgery will be reviewed, and compared to medical treatment alone. This is not an easy comparison to make as it is generally agreed that surgery is only indicated when medical therapy has failed. The issue of extent of surgery will be addressed, and the impact of underlying conditions and medical treatment have on surgical outcome will be summarized. Surgery for nasal polyps has been associated with a high rate of revision, and the role of second line procedures such as endoscopic modified Lothrop procedure will be discussed.

6.8.2. Efficacy of surgery for nasal polyposis

Endoscopic sinus surgery for nasal polyposis has been generally reported to be a safe and effective procedure.

A number of series have demonstrated that sinus surgery in

Table 6.7.3. Leukotrine antagonists in CRSwNP

Author	Drug	Study design	Active drug (n)	Control (n)	Effect	Evidence level
Schaper 2011 [1869]	montelukast (10 mg/day)	randomized, placebo controlled cross over	24	24	positive	Ib
Stewart 2008 [1875]	montelukast (10 mg/day)2)	randomized, unblinded	20	182	negative	Ib(-)*
Pauli 2007 [1874]	montelukast (10 mg/day)	randomized, double blind, placebo controlled	20	10	negative	Ib(-)
Mostafa 2005 [1873]	montelukast (10 mg/day)	randomized, double blind	20	201	negative	Ib(-)

* Ib (-): Ib study with a negative outcome.

patients with nasal polyps can result in a prolonged reduction of nasal symptoms and an improvement in quality of life. Dalziel et al. evaluated 33 articles published between 1978 and 2001 [1886]. The review included three studies comparing FESS with Caldwell–Luc or other endonasal procedures (n=240), three nonrandomized studies comparing different surgical approaches (n=2,699) and 27 case series (n=8,208). Seven studies included only patients with polyps and 26 had CRS had with and without polyps. Patients judged their symptoms to be 'improved' or 'greatly improved' in 75 to 95% of cases. The percentage of overall complications was low (1.4% for FESS compared and 0.8% for traditional procedures). The implications of this review are that FESS is safe and effective treatment for the great majority of patients.

Two-thirds [2176] of the 3,128 patients included in the National Comparative Audit had CRS with nasal polyps [1757]. In this prospective cohort study, a significant improvement in SNOT-22 scores was demonstrated at 3, 12 and 36 months with CRSwNP patients were found to benefit more from surgery than those with CRSsNP. Revision surgery was indicated in 3.6% of patients at 12 months and 11.8% at 36 months [1757].

6.8.3. Efficacy of surgery for nasal polyps compared to CRSsNP

The efficacy of FESS in patients with CRSwNP is at least as great as in patients with CRSsNP

There is some evidence that a significantly higher rate of recurrent surgery is required in patients with nasal polyposis than those without polyps [1887]. Despite the increased rates of revision, patients with polyps may have more improvement following sinus surgery than CRSsNP patients [1757]. In one large series, FESS was performed in 251 patients with medically refractory CRS (86 with polyps and 165 without), and the patients followed for at least 12 months. Symptom scores improved significantly in both groups ($p<0.001$). There were no significant differences between the groups except in oropharyngeal symptoms, which were improved more in the non-polyp patients [1888].

In another series, 43 patients with polyps were compared with 76 patients without polyps before and after ESS. Mean follow-up was 1.5 years. Patients were analysed prospectively based on CT scans, endoscopy, quality-of-life (QOL) assessment and visual analog symptom scales. Despite significantly worse objective scores, patients with polyps surprisingly reported significantly better QOL scores and less facial pain or headache both pre- and postoperatively [1885].

6.8.4. Efficacy of surgery for nasal polyps compared to medical therapy

The efficacy of FESS is equivalent to the efficacy of medical therapy (which includes systemic corticosterioid treatment) in CRSwNP patients randomized to receive one or other treatment.

As surgery for nasal polyposis is usually not considered until medical therapy has failed to provide adequate symptom relief, a clinically relevant comparison of the relative efficacies of medical and surgical treatment is difficult to make because the patient populations in whom these treatment modalities are indicated are different.

However, if untreated patients are randomized into either a medical treatment or surgical arm comparisons of the relative efficacies of these approaches can be made. In a randomized controlled trial comparing the effect of medical and surgical treatment of CRS on quality of life, 90 patients were evaluated before and after 6 and 12 months of follow up after either medical or surgical therapy [15]. Both medical and surgical treatment of CRS significantly improved almost all the domains of SNOT 20 and SF-36 ($p < 0.05$), with no significant difference being found between the medical and surgical groups ($p > 0.05$). The presence of nasal polyps did not adversely affect the outcome observed after either medical or surgical treatment. Another study included 109 patients with nasal polyps [1889]. A total of 53 patients were randomly allocated to receive oral prednisone for 2 weeks and 56 patients were allocated to undergo ESS. All patients were administered intranasal budesonide for 12 months. Patients were evaluated for nasal symptoms, polyp size and quality of life. At 6 and 12 months, a significant improvement in all SF-36 domains was observed after both medical and surgical treatment, reaching the levels seen in the general population. Nasal symptoms and polyp size improved after both medical and surgical treatment at 6 and 12 months. These results suggest that both medical and surgical treatment can lead to similar effects in improving quality of life.

Although these studies provide an interesting insight into the relative efficacies of medical and surgical therapy in unselected patients, neither reflects currently accepted practice guidelines in which surgery is performed in medically refractory patients.

6.8.5. Extent of treatment

The extent of surgery required to optimize outcomes in CRSwNP patients has not been established. Some reports suggest that outcomes may be improved after more extensive procedures.

A wide range of surgical procedures are undertaken to treat CRS and currently the vast majority of these are being performed endonasally. Although treatment by polypectomy alone effectively relieves symptoms of nasal blockage, it is associated with high recurrence rates [1887, 1890]. In 1997, Jankowski et al. prospectively compared patient satisfaction and recurrence rate of nasal polyps in a group of patients with severe nasal polyposis, 39 of whom had radical ethmoidectomy (nasalisation) and 37 of whom underwent functional ethmoidectomy performed by two different surgeons (reducing comparability between the groups) [1767]. It was found that the nasalisation group had a significantly lower recurrence rate of 22.7% versus 58.3% in the functional ethmoidectomy group. The overall functional benefit was also reported to be significantly higher in the nasalisation group, suggesting that treatment of nasal polyposis with complete ethmoidectomy leads to better long-term results than incomplete ethmoidectomy.

In a more recent study a retrospective review of revision rates and complications in 149 patients who underwent extensive FESS was performed [1891]. A comparison was made with patients from the UK National Comparative Audit who underwent polyp surgery limited to the anterior ethmoid cavity. At 36 months after surgery, five patients from the extensive surgery group had undergone a revision procedure, which was significantly less than the National Audit figure (4.0 vs. 12.3%, P = 0.006). The peri-operative adverse complication rate was similar (7.4 vs. 6.6%). There was a large improvement in SNOT-22 scores from the pre-operative period (mean 39) to the post-operative period (mean 8) in the extensive surgery group. This study provides some evidence that extensive sinus surgery performed by an experienced rhinologist can lead to a lower revision rate without compromising patient safety.

6.8.5.1. Surgery of the frontal recess

Mucosal thickening of the frontal recess easily leads to obstruction of the frontal sinus outflow tract. At the time of initial development of endoscopic surgery there was a reluctance to perform frontal recess dissection because of the ease with which the recess may stenose with postoperative scarring. However in recent years understanding of the anatomy of this region and instruments for its dissection have improved, and impressive patency rates have been reported. A recent review of the evidence of clinical efficacy of frontal sinus procedures for CRS found a generally high rate of success but some of the series were small and the follow up relatively short term [1892]. The review did not differentiate between CRS with and without polyps. Chan et al reported results from a group of 58 patients with eosinophilic CRS (most of whom presented clinically with nasal polyps) after frontal sinusotomy (Draf IIa) with an average follow-up of 61.6 months. A very high patency rate of 85% was achieved (although this was slightly lower than the 90% patency rate in non-eosinophilic CRS patients). This series demonstrates that frontal sinusotomy performed by experienced surgeons can produce excellent long-term patency rates [1893]. Friedman reported a slightly lower patency rate of 71.1% after a similarly long period of follow up in a group of 152 patients in whom frontal sinusotomy (Draf IIa) was performed [1894]. Many of these patients had nasal polyps, and recurrent polyps or scarring were the two most common causes of obstruction of the frontal sinus in this series.

6.8.5.2. Approaches to the maxillary sinus

In an effort to clear polypoid mucosa as completely as possible from the maxillary sinus, anterior antrotomies have been performed to allow access of powered instruments. The efficacy of this manoeuvre on the outcome after FESS has been the subject of a small number of studies. One such trial has compared the results of performing a canine fossa puncture with clearance of polyps via a middle meatal antrostomy [1895]. No benefit of the canine fossa procedure over conventional middle meatal antrostomy was seen after 12 months follow up, however the number in both groups is small. The authors concluded that although canine fossa puncture is a useful method for removing severe mucosal disease that cannot be reached through the MMA, it does not guarantee a better subjective or objective surgical outcome in patients with nasal polyposis. However, case control studies have found that patients who had a canine fossa puncture had a better outcome than those with similar disease severity who did not [1896, 1897].

Another approach to chronically diseased maxillary antra has been to lower the medial antral wall to the level of the hard palate. This procedure necessitates at least partial removal of the inferior turbinate and has been termed a mega-antrotomy. Cho and Hwang reported on a series of 28 patients who underwent 42 mega-antrostomies for recalcitrant maxillary sinusitis [1457]. All patients had previous maxillary sinus surgery (mean number of procedures 2.3). At the time of the most recent postoperative examination, 74% of patients reported complete resolution of symptoms while 26% reported partial symptomatic improvement. There were no complications and the revision rate was 0%.

6.8.6. Perioperative medical care

Prolonged postoperative medical treatment with topical corticosteroid sprays would appear to improve outcomes post FESS for CRSwNP

Although many studies have demonstrated the effectiveness of sinus surgery for patients who have nasal polyposis, it should not be thought of as the only treatment but rather as a modality used to manage patients to remove the disease burden and increase the efficacy of post-operative medical therapy. Surgically removed polyps have a high tendency for recurrence without aggressive postoperative medical management.

However, surgical management can be used to decrease the amount of inflammation so that the medical treatment may become more effective and the rate of recurrence may be reduced. In one study, 109 patients (77 of whom had nasal polyps) were randomized to receive postoperative fluticasone spray beginning six weeks after FESS. The change in the overall visual analogue score was significantly better in the fluticasone group at 5 years and significantly more prednisolone rescue medication courses were prescribed in the placebo group [(1821)].

There is evidence that administration of systemic steroids in the postoperative period for patients who have polyps may have a significant impact on their postoperative course. In a randomized placebo controlled study, those patients who received a course of perioperative prednisone (for five preoperative and 9 post operative days) had significantly healthier looking cavities at 6 month follow up than those patients who received the placebo [(1898)]. There was however no impact of perioperative prednisone on symptom scores.

6.8.7. Efficacy of revision surgery for nasal polyps

Revision surgery may be performed with good outcomes for recurrent nasal polyposis. Recalcitrant frontal sinus disease can be treated with good success rates and relatively little morbidity by performing the endoscopic modified Lothrop procedure.

Even after meticulous removal of polyps and polypoid mucosa, the opening of all sinus ostia to their anatomical limits and optimal postoperative medical care, some patients will present with recurrent disease. The frontal recess is the most common site of recurrence, probably because it is so easily stenosed postoperatively with scarring and recurrent inflammation.

Many studies have examined the prognostic factors affecting the success of endoscopic sinus surgery (ESS), and a history of previous ESS is often found to be a factor contributing to a poor surgical outcome. However this is not uniformly the case. In a recently reported study, the postoperative results between primary (101 cases) and revision (24 cases) FESS for chronic rhinosinusitis with nasal polyposis were compared using the SNOT-20 and nasal endoscopy scores at 6 and 12 months [(1895)]. Postoperatively the subjective and objective surgical outcomes of the 2 groups did not differ statistically. Also the need for additional medications during the follow-up period and the proportion of patients who required additional surgical intervention due to surgical failure was similar in both groups.

The extent of revision surgery is largely guided by postoperative CT scan results. If persisting sinus cells or septations are causing ongoing obstruction or stenosis of sinus ostia, then these require removal. However, in cases of severe nasal polyposis it is not uncommon for the frontal recess to have been completely cleared of cells, but for the soft tissue or neo-osteogenesis to have narrowed or occluded the recess. The implication is that the frontal recess needs to be enlarged beyond its anatomical limits. During the endoscopic modified Lothrop procedure the floor of the frontal sinuses and the intersinus septum are removed, creating a large common ostium [(1899)]. A very recently published series of 122 consecutive patients undergoing an endoscopic modified Lothrop procedure, reported a frontal patency rate of 90%[(1900)]. A meta-analysis of the 612 cases of endoscopic modified Lothrop procedures has been reported recently [(1901)]. Nearly 30% of these patients had nasal polyposis. In those patients with available data, patency was achieved in 95.9% and improvement of symptoms in 82.2%. The overall failure rate (requirement of further surgery) was 13.9%. The reported complication was low. This meta-analysis suggests that the endoscopic modified Lothrop procedure is a very good option if the frontal sinusitis persists after frontal sinusotomy has been performed. It would appear to offer a success rate similar to frontal sinus obliteration procedures but with much less morbidity.

6.8.8. Complications of surgical treatment of nasal polyps

The frequency of occurrence of severe orbital or skull base complications is very low in recently reported series

A number of significant complications have been reported after FESS for nasal polyps. Fortunately the frequency of occurrence of severe complications would appear to be reducing with time, and the risk of major orbital, intracranial or vascular injury

occurring is now very low.
A systematic review of safety and efficacy of FESS for removal of polyps by Dalziel et al. in 2006 reviewed three randomized control trials, four nonrandomized comparative studies and 35 case series studies [1902]. Major complications ranged from 0% to 1.5% and minor complications from 1.1% to 20.8%. Infection was reported in 16% of FESS procedures and 28% of conventional procedures. Disease recurrence ranged from 4% to 60% with a median of 20% across all studies reviewed. Recurrence following revision surgery ranged from 3% to 42% with a median of 6%.
The National Audit in England and Wales assessed the rate of complications of surgery for polyposis and chronic rhinosinusitis [1903]. A total of 3123 patients were included in the study of which 2176 (69.1%) had nasal polyps. Nearly 40% of patients underwent a simple polypectomy ± antral washout and the majority of operations were performed endoscopically. The microdebrider was used in 16.5% of operations. Major complications were observed in 0.4% of cases, minor complications in 6.6%. Statistical significance was found in complication rates between grades of polyposis, use of microdebrider, increasing Lund-Mackay score, increasing American Society of Anesthesiology score and patients with previous sinonasal surgery.
A retrospective study by Ecevit et al. compared the rate of microdebrider complications between 90 cases (177 sides) of chronic sinusitis with polyps to 49 cases (98 sides) of chronic sinusitis without polyps [1904]. The minor and major complication rate for the group with nasal polyps was 11.8 and 0.5% respectively. Only one major complication was reported, a cerebrospinal fistula which was repaired intra-operatively. The complication rate for chronic sinusitis without polyps was 4%. The difference between complication rates of the two groups was statistically significant (p=0.0001)
A retrospective medical record review by Devars du Mayne et al. assessed outcomes of patients with nasal polyps undergoing either radical ethmoidectomy (n=77) or polypectomy (n=50) [1905]. No severe complications were observed in either group although few complications were seen in the polypectomy group (8% vs 18.3%). Seven patients from the radical ethmoidectomy group required further surgery (four for polyp recurrence, two for ethmoidofrontal mucocoele and one for nasofrontal duct stenosis) and four from the polypectomy group required further surgery, all for polyp recurrence.
A retrospective case note review was performed by Bajaj et al. assessing the results of FESS as day-case surgery [1906]. Of the 105 procedures, 62.8% had both CRS and NP. The only reported complication of the study was bleeding, seen in 7 patients. Five patients had primary haemorrhage and were packed in theatre and 2 had reactionary bleeding, 1 of which required packing.

6.9. Influence of concomitant diseases on outcome of treatment in Chronic Rhinosinusitis with and without NP including reasons for failure of medical and surgical therapy

6.9.1. Summary

Many factors potentially outcome of treatment in CRS with and without nasal polyps. Extent of the disease, asthma, AERD, CF and biofilm formation have been proven to have a negative influence. For some factors, like allergy, smoking and , type of inflammation, studies contradict each other.
Gender does not seem to influence the results of treatment of CRS. Patients with higher age and fatigue may have a more pronounced improvement after FESS.

6.9.2. Sinus surgery in the elderly

In general no difference is found in symptomatology and QoL of CRS in the elderly [1187, 1907, 1908]. In a study comparing the objective endoscopic findings and subjective improvements in symptoms among the groups 6 months after the functional endoscopic sinus surgery (FESS) in three groups according to patient age: 20 paediatric (5-18 yr), 20 adult (19-65 yr), and 20 geriatric patients (over 65 yr.) no statistical differences in polyp extent or Lund-Mackay score were found before FESS between the three age groups and the subjective surgical outcome did not differ statistically between the groups, with the exception of olfactory disturbance. On the other hand the objective surgical outcome based on the endoscopic findings was worst in the paediatric group (45%), whereas the geriatric group showed the best results (90%). The differences in objective outcome among the three groups were significant, and patient age was a predictive variable for surgical result based on multiple logistic regression analysis [1907]. Also in the study of Sil et al. increasing age was significantly positively correlated with the objective signs improvement in endoscopic polyp scores and in nasal mucociliary clearance times, but not in symptomatology [1909]. This better objective outcome in the elderly could not be substantiated by Reh, however his elderly group comprised of only 18 patients [1908]. Analysis of recurrences was accomplished in a retrospective study on 192 patients operated for CRSwNP. No association of recurrence with age, gender, purulent nasal discharge, facial pain, anosmia, post nasal dripping, headache, nasal allergy, and asthma were observed [1910].
In a retrospective case control study, FESS outcome in 46 CRS patients > 65 years were compared with 522 CRS patients who were 18¬64 years old [1911]. In the elder patient group, complications occurred significantly more frequently than in the younger patients group. In particular orbital complications were frequently observed in the elder patient group (level III). Jiang and Su retrospectively compared complication rates of

171 CRS patients older than 65 years with 837 adult patients and 104 patients younger than 16 years. They found that the geriatric group experienced a disproportionately larger share of operative complications. Outcomes were similar in all three groups [1912]. A study evaluated outcome of sinus surgery in 180 patients older than 65 yrs. compared to 180 adults (15-65 yrs.), both groups with CRS. Diabetes mellitus was shown to be risk factor for complications, not so much the patients' age [1913].

Conclusion: CRS is a common condition in the elderly. Reported symptomatology before and after surgery does not differ from a younger patient population and postoperative objective signs seem to improve more in the elderly. However, higher surgical complication rates were found in 2 reports. Moreover, general anaesthesia bears higher risks and the capacity to recover from a severe surgical complication such as a CSF leak may be impaired.

6.9.3. Gender

In most studies women with CRS report higher levels of symptoms despite less extensive disease and this is likely to be due to a systematic difference in response style [1187, 1914, 1915]. In a prospective study of 514 adult patients who presented with chronic rhinosinusitis with and without nasal polyposis facial pain and headache were more prevalent among women, while nasal obstruction was more prevalent among men. This is partly explained by the fact that CRSsNP was the more common diagnosis among women, while CRSwNP was the more common diagnosis among men. There was no statistically significant difference in the improvement of the other presenting symptoms, comparing the gender [1915]. Most other studies also show comparable improvement of FESS between men and women [1909, 1910, 1915].

6.9.4. Extent of disease at baseline

Patients presenting with extensive disease suggested by C.T scan staging are at higher risk for the development of recurrences after endonasal surgery for nasal polyps [1910]. CT scan scores and polyp scores were the strongest predictors of the need for postoperative systemic medication [1909].

6.9.5. Primary versus revision surgery

The symptomatic relief that revision FESS can provide for patients with refractory chronic rhinosinusitis is similar to that following a primary FESS [1785, 1918]. However, in one study patients undergoing primary surgery were 2 times more likely to improve compared with patients undergoing revision surgery [1189].

6.9.6. Type of inflammation

The influence of the type of inflammation on treatment is contradictory.

The efficacy of macrolides appears to be less in patients with CRSwNP, severe findings on CT scans, asthma, low IgE and polyps with increased eosinophil infiltration [1708, 1713].
There is a significant positive correlation between sinus CT stage and peripheral eosinophil levels. Eighty-nine percent of the abnormal eosinophil counts (>550 cells/microL) were associated with CT scores higher than 12. Total IgE did not correlate with CT stage of disease [1919].
Patients with a total peripheral eosinophil count of 520/microl or more or mucosal eosinophilia were more likely to experience recurrence of CRS after surgery in two studies [878, 1920]. However in another study CRS patients with higher levels of eosinophils were less likely to suffer from post-operative recurrent sinonasal disease when treated post-operatively with nasal corticosteroids [27].

6.9.7. Asthma

Bronchial asthma is frequently associated with CRS with and without polyps and may have influence on sinus surgery outcomes. Prevalence of asthma is shown to be much higher in patients with CRS than in normal population. A study of 145 consecutive adult CRS patients evaluated the prevalence of asthma with CRS. The study showed 23,4% prevalence of asthma compared to the 5% in adult general population. These patients had also significantly higher prevalence of polyps (22%, p=0.004), olfactory dysfunction (6%, p=0.001) and nasal congestion (60%, p=0.037). There was no difference between CRS patients with or without asthma in the proportion of patients needing primary sinus surgery , but patients with asthma did require significantly more revision sinus surgeries (mean 2.9 vs 1.5) p=0.0003 [1921].
More severe sinus disease in CRS patients with concomitant asthma has been reported [746, 762, 1922, 1923]. Clinically, CRS patients with polyps and asthma have higher CT-scores, more severe nasal obstruction and hyposmia, and more severe asthma, while CRS patients without polyps and asthma experience more severe headache and postnasal discharge [746, 1922-1924]. The incidence of self reported rhinosinusitis in asthma patients was recently evaluated employing the data of two major asthma trials [1925]. Self reported rhinosinusitis was associated with bronchial asthma in 70% of the 2500 study participants. Asthma patients with concomitant rhinosinusitis had more asthma exacerbations, worse asthma symptoms, worse cough, and worse sleep quality. Investigations of concomitant asthma on sinus surgery outcomes in CRS patients with or without nasal polyps yielded inconsistent results [1417]. Concomitant asthma was associated with worse postoperative endoscopy findings in two retrospective analyses [1761, 1775], but had no independent influence on other outcome parameters (level IV). Consistently, symptom scores improved significantly in both asthmatics and non-asthmatics postoperatively, but asthmatics exhibited

significantly worse postoperative endoscopic. Asthma with and without aspirin intolerance was shown to be a determinant of recurrence after FESS in patients with CRSsNP and CRSwNP [878, 1521, 1923], but not in all studies [1910, 1926].

6.9.7.1. Asthma in CRSsNP

There is a strong association of asthma with CRS (adjusted OR: 3.47; 95% CI: 3.20-3.76) at all ages [1927]. Concomitant asthma is frequent in CRSsNP patients [122]. Asthma was shown to be a determinant of recurrence after FESS in patients with CRSsNP [878, 1923], but not in all studies [1926].

6.9.7.2. Asthma in CRSwNP

Asthma is more prevalent in white patients with CRSwNP than in patients with CRSsNP, however the same does not seem to hold for chinese polyps [585, 621]. Asthma with and without aspirin intolerance was shown to be a determinant of recurrence after FESS especially in patients with CRSwNP [878, 1521, 1923], but not in all studies [1910, 1926].

6.9.7.3. Effect of treatment on bronchial asthma

The question, how sinus surgery and medical CRS treatment may alter the course of bronchial asthma, was reviewed by Lund [1928] and Scadding [1929]. The authors describe the somewhat intricate base of evidence and conclude that the weight of evidence suggests a beneficial effect. Studies published thereafter support this view [1416, 1924, 1930, 1931]. In a case series study, 50 CRS patients with concomitant asthma were included [1924]. Ragab and co-workers report a prospective evaluation of a subgroup of 43 asthma patients joining a randomised trial comparing the effects of sinus surgery and medical treatment in CRS patients with and without polyps [1423]. Outcome parameters included asthma symptoms, control, forced expiratory volume in one second (FEV1), peak flow, exhaled nitric oxide, medication use and hospitalisation at 6 and 12 months from the start of the study. Overall asthma control improved significantly following both treatment modalities, but was better maintained after medical therapy, where improvement could also be demonstrated in the subgroup with nasal polyps. Medical treatment was superior to surgery with respect to a decrease in exhaled nitric oxide and increase in FEV1 in the polyp patients. Two patients noted worsening of asthma postoperatively. Treatment of chronic rhinosinusitis, medical or surgical, benefits concomitant asthma; that associated with nasal polyposis benefits more from medical therapy (level Ib). Haruna and coworkers also showed that asthma was negative factor in the treatment with macrolides [1713].

Palmer and coworkers retrospectively reviewed the charts of a subgroup of 15 CRS patients with steroid dependent asthma selected from a group of 75 consecutive CRS patients with asthma who underwent endoscopic sinus surgery [1932]. Outcome parameters included the number of days and total dose of oral prednisone and antibiotics in the year before and after sinus surgery. Fourteen of the 15 patients meeting study criteria decreased their postoperative prednisone requirement by total number of days Antibiotic use also decreased ($p < 0.045$), with an average use of antibiotic nine weeks preoperatively versus seven weeks postoperatively (Evidence level IV).

Conclusion

Apparently, various confounders not yet sufficiently defined influence the effects of surgical CRS treatment on concomitant asthma. In studies published in recent years, predominantly positive effects of surgical CRS treatment on concomitant asthma severity were reported However, the level of evidence is low [122].

6.9.8. Aspirin exacerbated disease (AERD)

The majority of CRS patients with AERD have diffuse, extensive rhinosinusitis [762]. AERD patients usually present with more severe asthma [1519]. AERD is rather consistently found to adversely affect sinus surgery outcomes [1419, 1420, 1504, 1517, 1933, 1934]. The asthmatic complaints of aspirin intolerant and aspirin tolerant patients improved significantly after ESS but CT scan improved more in the aspirin tolerant patients than in the aspirin patients [1519]. Although FESS helped both groups of patients, AERD patients had statistically significant better results compared with aspirin tolerant patients in asthma severity scores and decreased need for ICS [1518]. The olfactory recovery after FESS for nasal polyposis is significantly affected by the concomitant presence of AERD [1520]. Patients with AERD were significantly more likely to have a recurrence and undergo a second surgery following recurrence (risk-odds ratio, 2.7; 95% confidence interval, 1.5 to 3.2; $p < 0.01$) than were patients without asthma or with only asthma from the triad [1521].

Conclusion

CRS patients with AERD tend to suffer from more extensive sinus disease. They benefit from sinus surgery, but to a lesser extent than patients without AERD. They are more prone to disease recurrence and more frequently undergo revision surgery than aspirin tolerant CRS patients.

6.9.9. Allergy and atopy

In most studies, the diagnosis of allergy was based solely on the presence of a positive skin prick test and/or serum specific IgE determinations. This indicates atopy, but may not suffice to diagnose allergic rhinitis (AR), particularly persistent AR [1933]. Consistently, the reported incidence of atopy in CRS patients ranges between 50 and 80%, which is higher than in the general population. The risk-ratio of chronic sinusitis in the AR group in a large cohort was shown to be 4.5 [1935]. CRS in atopic patients

appears to be more severe [530, 1623, 1936-1940]. Atopy was equally frequently associated with CRS with and without polyps [1941]. Reports on potential negative effects of allergy on outcomes of surgery are various. There are a number of studies indicating a negative outcome of atopy [1775, 1887, 1900]. But also quit some studies did not interference with atopy In recent studies allergy did not seem to be a determinant of treatment failure [1926, 1942-1944].

6.9.10. Cystic fibrosis

In cystic fibrosis (CF), CRS with and without nasal polyps is observed [1945]. The inflammatory profile of CRS in CF patients differs from CRS in patients without CF [18, 1482, 1945]. Persistent colonisation with Pseudomonas aeruginosa is a common finding. The paranasal sinuses often harbor distinct bacterial subpopulations, and in the early colonization phases there seems to be a migration from the sinuses to the lower airways, suggesting that independent adaptation and evolution take place in the sinuses. The paranasal sinuses potentially constitute a protected niche of adapted clones of P. aeruginosa, which can intermittently seed the lungs and pave the way for subsequent chronic lung infections [1437].

In 37 patients with cystic fibrosis after lung transplantation, sinus surgery was performed and repeated sinus aspirates and broncho-alveolar lavages were obtained for microbiological examinations. Sinus surgery was successful (three or less Pseudomonas aeruginosa positive aspirates) in 54% and partially successful (4 or 5 positive aspirates) in 27% of patients [1459]. A significant correlation of bacterial growth in sinus aspirates and broncho-alveolar lavages was observed ($p < 0,0001$). Successful sinus management led to a lower incidence of tracheobronchitis and pneumonia ($p = 0,009$) and a trend toward a lower incidence ($p = 0,23$) of bronchiolitis obliterans syndrome (Evidence level IV). FESS with subsequent monthly antimicrobial antral lavages (n=32) was compared with a historic control group receiving conventional sinus surgery without postoperative lavages (n=19). The group treated with FESS and antral lavages had fewer operations per patient, and a decrease in repeated surgery at 1 year (10% vs. 47%) and 2 year follow up (22% vs 72%) (Evidence level IV). Not all studies report positive effects of sinus surgery on the lower airways [1946].

In general improvement after FESS is significant but quit often recurrences are seen [1947, 1948]. While baseline measures of disease severity are worse in the CF population, objective and QoL improvements for adult patients with comorbid CF are comparable to patients without CF [1456].

Conclusion

CF patients frequently suffer from severe CRS, in particular with diffuse polyps refractory to medical treatment. Due to a tendency to recur, repeated sinus surgery is often needed to achieve symptomatic relief. In CF patients, the paranasal sinuses may serve as a source for Pseudomonas aeruginosa induced lung infections. Consequent local antibiotic lavages help to prevent recurrent CRS and lung infection.

6.9.11. Immune dysfunction

Immune deficiency states are frequently associated with CRS include HIV-infection, bone marrow transplantation and humoral immunodeficiencies.

6.9.11.1. HIV-positive/AIDS patients

The first line treatment of sinusitis in HIV-positive patients is medical, in refractory cases targeted to the identified organisms. Surgical treatment is reserved for patients who do not respond to targeted medical treatment. Sabini and co-authors retrospectively reviewed their experience with performing endoscopic sinus surgery in 16 acquired immune deficiency (AIDS) patients [563]. At an average follow-up time of 16 months, 14 of the endoscopic sinus surgery patients reported improvement from their preoperative condition (Evidence level IV). In a retrospective case series study, 106 HIV+ patients who underwent sinus surgery between 1987 and 1998 were evaluated [1949]. Between 1987 and 1991, 36 patients were treated with minimal invasive sinus surgery just addressing the involved sinus with only 20% clinical improvement. Since 1992, the authors treated their HIV+ patients with more extensive surgery including sphenoethmoidectomy, middle meatal antrostomy and drainage of the frontal recess, which resulted in a clinical improvement rate of 75%, irrespective of the CD4 counts (Evidence level IV). In two case series, Murphy and co-workers observed the clinical outcome of 30 HIV-positive CRS patients refractory to medical treatment [1950]. Outcome parameters included olfactory tests, symptom scores, and a quality of well-being assessment. Symptom and well-being scores improved significantly following endoscopic sinus surgery, whereas olfactory thresholds did not improve significantly (Evidence level IV). Patients with AIDS may develop acute invasive fungal sinusitis. If detected early, combined surgical and antifungal treatment may be beneficial [1951, 1952].

6.9.11.2. Bone marrow transplant

Bone marrow transplantation (BMT) is a frequent cause of acquired immune deficiency. Allogeneic BMT is associated with acute and chronic CRS in approximately 40% [1953]. Sinus microbiology was investigated in 18 BMT patients who developed sinusitis evaluating 41 microbiological specimens obtained by antral puncture and nasal swabs from the middle meatus [1954]. Agents most commonly isolated were gram-negative bacteria including Pseudomonas aeruginosa and Searratia marescens. Gram-positive bacteria were isolated in 27%. Various fungi were isolated in 16% of the specimens.

Microbiological results of antral punctures and nasal swabs were consistent in 5 of 41 specimens. Kennedy and co-workers report on 29 bone marrow transplant recipients with documented invasive fungal infections of the sinuses and paranasal tissues (1.7% of 1,692 bone marrow transplants performed). All patients received medical management, such as amphotericin, rifampin, and colony-stimulating factors, in addition to surgical intervention [1955]. Surgical management ranged from minimally invasive procedures to extensive resections including medial maxillectomies. The mortality rate from the initial fungal infection was 62%. Twenty-seven percent resolved the initial infections but subsequently died of other causes. Prognosis was poor when cranial and orbital involvement and/or bony erosion occurred. Extensive surgery was not superior to endoscopic functional surgery (Evidence level IV). Sinus surgery was performed in 28 of 311 bone marrow trans-plant patients retrospectively evaluated [1956]. No fungal sinusitis was observed. An aggressive surgical approach yielded a high mortality rate whereas limited surgical approaches with intensive postoperative care proved appropriate (Evidence level IV).

6.9.11.3. Non-acquired immunodeficiencies

Patients with humoral immunodeficiencies including common variable immunodeficiency, ataxia telangiectasia, or X-linked agammaglobulinaemia are at increased risk to develop CRS [1543, 1957-1959]. Chee and co-workers selected 79 out of 316 patients with CRS with and without polyps, who suffered from severe CRS refractory to medical treatment [560]. Fifty-seven patients had undergone one or more previous sinus surgeries. Approximately 30% of the 79 included patients suffered from decreased T-cell function and approximately 20% had some form of immunoglobulin deficiency. Common variable immunodeficiency was diagnosed in 10%. Accordingly, in a high number of patients with long lasting rhinosinusitis, humoral deficiencies were identified, particularly of the IgG3-subclass [1633, 1960]. Also Carr et al. showed that patients with medically refractory CRS may have a high prevalence of lower serum IgA levels, low pre-immunization anti-pneumococcal titres and specific antibody deficiency [1533].

However, in unselected patients with sinus fungus ball, CRS with and without polyps, humoral deficiencies were not more frequent than in the general population [1961]. Recently, the relevance of isolated immunoglobulin or IgG subclass deficiencies has been challenged and vaccine response to protein and capsular polysaccharides has been suggested superior to assess humoral immune function in CRS patients [1962 , 1963 , 1964 , 1965]. Surgical outcome in patients with immunodeficiencies seems comparable to other CRS patients [1544, 1966].

Conclusion

In the small series available in HIV-positive patients, patients with bone marrow transplantation and patients with non-acquired immunodeficiencies endoscopic sinus surgery seems to be effective. In bone marrow transplantation patients with (fungal) infections extensive surgery was not superior to FESS. In non-acquired immunodeficiencies surgical outcomes are comparable to other CRS patients.

6.9.12. Fatigue

Fatigue is a common symptom in patients with CRS [75] and is associated with severity scores approximating those of facial pressure, headache, and nasal discharge. In a meta-analysis measuring the effect of FESS on fatigue, significant improvement in fatigue was noted equalling the improvement of pooled major CRS criteria [1967]. In a study with subgroup analysis of 11 independent studies measured the response of fatigue following FESS in various groups, patients with more severe fatigue showed more pronounced improvement than patients with less severe fatigue [1968]. Preoperative fatigue severity was less in patients with CRS and nasal polyposis than in patients with CRS only; however, preoperative fatigue was more severe in patients with fibromyalgia or depression.

6.9.13. Fibromyalgia

Patients with CRS and comorbid fibromyalgia showed similar improvements in QoL after FESS when compared with patients without fibromyalgia when controlling for age, gender, and disease severity [1969].

6.9.14. Biofilm

Bacterial biofilm formation was shown to be significantly associated with positive culture results, prior sinus surgeries, and nasal steroid use in the month prior to sample collection but not significantly associated with polyps, allergy, Samter's triad, sleep apnea, smoking status, age, or gender [1970].

Different biofilm species are associated with different disease phenotypes. *H. influenzae* biofilms are typically found in patients with mild disease, whereas S. aureus is associated with a more severe, surgically recalcitrant pattern [692]. Patients with biofilms have more severe disease preoperatively and persistence of postoperative symptoms, ongoing mucosal inflammation, and infections [686, 693, 1923, 1971]. Asthma and biofilm-forming bacteria were shown to be independently associated with revision sinus surgeries for chronic rhinosinusitis [1923].

6.9.15. Smoking

The effect of smoking on outcome of FESS is unclear. Most studies show no effect of smoking on FESS outcomes [770, 1972-1974]. Although one of the studies suggest that increased smoking may contribute to worse post-operative endoscopy scores [770].

Another study showed that while smoking did not influence preoperative symptoms, smokers had worse postoperative outcomes [763].

6.9.16. Occupational exposure

It is known that airway exposure to occupational agents can give rise to occupational airway disease [1975]. It was recently shown that exposure at work also appears to be a risk factor for the occurrence of CRS and for its recurrence or persistence, as evidenced by the need for revision surgery [1976].

6.9.17. Gastro-oesophageal reflux

Chambers et al [1421] showed in one hundred eighty-two patients that only gastro-oesophageal reflux disease was statistically significant as a predictor of poor symptomatic outcome. However, a number of other studies have failed to replicate this finding and it is likely that gastro-oesophageal reflux can mimic the symptoms of CRS rather that contribute to it [1788].

6.9.18. Osteitis

In a recent retrospective study the grade of osteitis was directly correlated with the number of revision surgeries, with an almost linear response. However, from the nature of the study it could not be clear if that was a cause-effect or a secondary association [1388]. A study assessing the correlation between postoperative outcome and osteitis showed similar results, adding to the evidence for a link [1778] (Evidence level IV).

6.10. Management of Paediatric Chronic Rhinosinusitis

6.10.1. Summary

CRS in children is not as well studied as the same entity in adults. Multiple factors contribute to the disease including bacteriologic and inflammatory factors. The adenoids are a prominent contributor to this entity in the paediatric age group. The mainstay of therapy is medical with surgical therapy reserved for the minority of patients who do not respond to medical treatment.

6.10.2. Medical treatment of chronic rhinosinusitis in children

6.10.2.1. antibiotics

There is no good evidence in the literature to support the use of antibiotics in CRS in children. Otten and colleagues investigated 141 children between the ages of 3 and 10 years with CRS as defined by purulent nasal drainage lasting at least 3 months, signs of purulent rhinitis on rhinoscopy, and unilateral or bilateral abnormalities of the maxillary sinus on plain films [1977]. The patients were assigned non-selectively to receive one of the following 4 treatments for 10 days: saline nose drops (placebo), xylometazoline 0.5% nose drops with amoxicillin 250 mg PO TID, drainage of the maxillary sinus under anaesthesia and irrigation via indwelling catheter for at least 5 days, and a combination of drainage and irrigation with xylometazoline and amoxicillin. They followed the patients for up to 26 weeks after treatment and show no significant differences in cure rate among the treatments based on history, physical exam or maxillary sinus films. In the total group, the cure rate was around 69%. Although this study did not show a significant difference between the treatments, it suffers from some methodological limitations including lack of randomization or blinding, and that the placebo group actually received saline drops which might have been helpful in and of themselves. Further, this study does not assess the state of the ethmoid sinuses and used plain X-rays as the objective diagnostic modality. In a later study, the same group performed a randomized, double-blind study of cefaclor (20 mg/kg/day) vs placebo in 79 healthy children between the ages of 2 and 12 years with chronic sinusitis defined essentially as in the first study [1978]. All patients had a tap and washout and were then randomized to cefaclor or placebo PO for 1 week and were followed at 6 weeks. After 6 weeks, there was no significant difference in resolution rate between the children on cefaclor (64.8%) and those on placebo (52.5%). Among the limitations of this study which could have influenced the outcome is that all children had an initial tap and washout which could have helped the whole group even before enrolment, making the antibiotic irrelevant, and plain radiographs were used to evaluate the sinuses.

Despite the lack of good evidence to support the use of antibiotics for any length of time in children with CRS, in practice, these children are often treated with the same antibiotics listed in the section on acute rhinosinusitis but typically for longer periods of time that vary between 3 and 6 weeks. Because of the lack of data to support this practice, its usefulness must be weighed against the increasing risks of inducing antimicrobial resistance. It is also difficult to ascertain whether what is actually being treated is CRS or acute exacerbations on top of pre-existing chronic disease. The exact type of antibiotics used is usually dependent on local resistance patterns which might be different in different countries. Further, it is advisable to always treat with as narrow a spectrum of antibiotics as will likely cover the bacteria that are prevalent in a specific geographic locale.

In sum, available data does not justify the use of short-term oral antibiotics for the treatment of CRS in children (Strength of recommendation: B). There might a place for longer-term antibiotics for the treatment of CRS in children (equivalent to CRS in adults) (Strength of recommendation: D).

Intravenous antibiotic therapy for CRS resistant to maximal

medical treatment has been studied as an alternative to endoscopic sinus surgery. In a retrospective analysis of 70 children aged 10 months to 15 years with CRS, Don et al found that 89% had complete resolution of symptoms after maxillary sinus irrigation and selective adenoidectomy followed by one to 4 weeks of culture-directed intravenous antibiotics [1979]. Cefuroxime IV was most frequently used followed by ampicillin-sulbactam, ticarcillin clavulanate and vancomycin. Despite the good success rate, the therapy was not without adverse effects which included superficial thrombophlebtitis (9%), dislodgment of wire during placement necessitating venotomy (1%), and antibiotic related complications such as serum sickness, pseudomembranous colitis, and drug fevers. A similar retrospective study evaluated 22 children with CRS refractory to medical therapy and with an age range between 1.25 to14.5 years [1980]. They all underwent adenoidectomy, maxillary sinus aspiration and irrigation and placement of intravenous catheters and then culture-directed IV antibiotic therapy until resolution of symptoms (mean duration of therapy was 5 weeks). All patients achieved control of symptoms at the end of IV therapy and 89% demonstrated long term amelioration of CRS symptoms (>12 months after cessation of IV therapy). The retrospective design, lack of randomization, and lack of placebo arms limit the value of the above studies. Furthermore, it is hard to assign benefit to intravenous antibiotic therapy when other interventions were utilized such as irrigation/aspiration of the sinus and adenoidectomy. Therefore available data does not justify the use of intravenous antibiotics alone for the treatment of CRS in children (Strength of recommendation: C).

6.10.2.2. Corticosteroids

There are no randomized controlled trials evaluating the effect of intranasal corticosteroids in children with CRS. However the combination of proven efficacy of intranasal corticosteroids in CRS with and without nasal polyps in adults (see chapter 6.1 and 6.5) and proven efficacy and safety of intranasal corticosteroids in allergic rhinitis in children makes intranasal corticosteroid the first line of treatment in CRS [1981, 1982, 1983]. A recent randomized, placebo-controlled, double blind trial was conducted in children with CRS with signs and symptoms of more than 3 months duration and CT abnormalities [1984]. Children were all treated with amoxicillin/clavulanate for 30 days and randomized to receive methylprednisolone or placebo PO for first 15 days of treatment (1mg/kg/day (max 40 mg) for 10 days, 0.75 mg/kg/day for 2 days, 0.5 mg/kg/day for 2 days, and 0.25 mg/kg/day for 1 day). The average age of the children was 8 years and the total CT score was between 11-12 (maximal score=24) suggesting mild-moderate disease. When comparing post treatment outcomes to baseline, there were significant improvements in all parameters (symptoms and CT scores) in both groups suggesting that antibiotics alone and antibiotics and steroids together both improved outcomes compared to baseline. Furthermore, there was a significant additional effect of oral steroids over placebo in cough, CT scan, nasal obstruction, postnasal drainage and total symptom scores. The strength of the evidence for the efficacy of antibiotics alone is unfortunately diminished by the absence of a placebo group, but the superiority of the combination of antibiotics and steroids over antibiotics alone is clearly supported by this trial.
Nasal corticosteroid treatment is a first line treatment in CRS with and without nasal polyps in children (Strength of recommendation: D).

6.10.2.3. Ancillary treatments

Nasal irrigations and decongestants have been thought to help in decreasing the frequency of rhinosinusitis episodes. Michel et al in 2005 performed a randomized, prospective, double-blind, controlled study looking at the effect of a 14-day treatment (1-2 sprays) with either isotonic saline solution or a nasal decongestant in children 2-6 years of age [1985]. Outcomes evaluated included the degree of mucosal inflammation and nasal patency. They found that both groups experienced improvement in outcomes measured with no significant differences between the groups. There were no side effects observed with the saline spray. The decongestant group used 120% more drug than prescribed, demonstrating the potential for these medications to be overused. No cases of rhinitis medicamentosa were reported.

A recent Cochrane review analysed randomized controlled trials in which saline was evaluated in comparison with either no treatment, a placebo, as an adjunct to other treatments, or against other treatments [1736]. A total of 8 trials satisfied inclusion criteria of which 3 were conducted in children. The studies included a broad range of delivery techniques, tonicity of saline used, and comparator treatments. Overall there was evidence that saline is beneficial in the treatment of the symptoms of CRS when used as the sole modality of treatment. Evidence also exists in favor of saline as a treatment adjunct and saline was not as effective as an intranasal steroid. Various forms of administration of saline were well tolerated. In a more recent trial, Wei and colleagues enrolled 40 children with CRS in a randomized, prospective, double-blind study comparing once daily irrigation with saline or saline/gentamicin for 6 weeks [1986]. There were statistically significant improvements in quality of life scores after 3 weeks and a reduction of CT scores after 6 weeks in both groups with no significant difference between the groups, suggesting that the addition of gentamycin to saline irrigations provided no additional benefit.

Clinicians have certainly tried other treatments for CRS including antihistamines and leukotriene modifiers, especially in light of

their effectiveness in treating allergic rhinitis. However no data exists about their potential efficacy and thus usefulness in the context of CRS in children. We reserve the use of these agents for children with documented allergic rhinitis.

6.10.3. Surgical treatment of chronic rhinosinusitis in children

Adenoidectomy is successful in improving CRS symptoms in 50% of operated children. Whether this is due to the fact that the symptoms were related to adenoiditis per se or to the elimination of the contribution of the adenoids to sinus disease is not clear

Surgical intervention for rhinosinusitis is usually considered for patients with CRS who have failed maximal medical therapy. This is hard to define but usually includes a course of antibiotics and intranasal and/or systemic steroids and differs widely between practitioners and practice locations. Adenoidectomy with or without antral irrigation and balloon sinus dilation, and functional endoscopic sinus surgery (FESS) are the most commonly used modalities.

6.10.3.1 Adenoidectomy with/without sinus irrigation and balloon dilation

The rationale behind removal of the adenoids in patients with CRS stems from the hypothesis that the adenoids are a nasopharyngeal bacterial reservoir (as detailed earlier) and the possibility that many of the symptoms might be related to adenoiditis proper. The benefit of adenoidectomy alone in the treatment of children with CRS was recently evaluated by a meta-analysis [1987]. The review included 9 studies that met the inclusion criteria. Mean sample size was 46 subjects with a mean age of 5.8 years (range 4.4-6.9 years). All studies showed that sinusitis symptoms or outcomes improved in half or more patients after adenoidectomy. Eight of nine studies were sufficiently similar to undergo meta-analysis and, in these, the summary estimate of the proportion of patients who significantly improved after adenoidectomy was 69.3%. Ramadan and Tiu reported on the failures of adenoidectomy over a ten year period and found that children younger than 7 years of age and those with asthma were more likely to fail after adenoidectomy and go on to require salvage FESS [1988]. Maxillary antral irrigation is frequently performed in conjunction with adenoidectomy. To evaluate the efficacy of this added intervention, Ramadan and colleagues analysed 60 children who underwent adenoidectomy for CRS (symptoms and positive scans despite prolonged medical treatment), 32 of which also had a sinus wash and culture via the middle meatus [1989]. All children received post-operative antibiotics for 2 weeks and outcomes were assessed at least 12 months postoperatively. Patients who underwent adenoidectomy alone had a 61% success rate at 12 months compared to children who underwent adenoidectomy with a sinus wash who had a higher success rate of 88%. Children with a high Lund-Mackay CT score and asthma had better success with adenoidectomy with a wash compared to adenoidectomy alone. In a similar retrospective study, Criddle and colleagues reviewed the records of 23 children who had adenoidectomy with a sinus wash for CRS (persistent symptoms in all and a positive scan in 7/23) followed by a course of post-op oral antibiotics (average duration 5.8 weeks) [1990]. If there was no improvement after the procedure

Table 6.10.1. Effect of antibiotics+steroids in CRSwNP.

Author	Intervention	Age Range	Outcome	Category of Evidence
Ozturk 2011 [1984]	Amoxicillin/Clavulanate PO x 30 days and methyl-prednisolone or placebo PO x 15 days	6-17 years	CT scan and symptom scores improved in all with superiority of the combination treatment	Ib
Adappa 2006 [1980]	Intravenous antibiotics (5 weeks)+maxillary irrigation and adenoidectomy	1-14 years	89% long term improvement in CRS symptoms (>12 months after therapy)	III
Don 2001 [1979]	Intravenous antibiotics+maxillary irrigation and adenoidectomy	10 mos-15 years	89% complete resolution of symptoms	III
Otten 1994 [1978]	Tap and washout followed by randomization to cefaclor or placebo PO for 1 week	2-12 years	No difference in resolution rate at 6 weeks	Ib(-)*
Otten 1988 [1977]	saline nose drops (placebo), xylometazoline 0.5% nose drops with amoxicillin 250 mg PO TID, drainage of the maxillary sinus under anesthesia and irrigation, and a combination of drainage and irrigation with xylometazoline and amoxicillin for 10 days	3-10 years	No difference in cure rate between groups at 6 or 26 weeks	IIa(-)**

* Ib (-): Ib study with a negative outcome.

** IIa(-): IIa study with a negative outcome.

on oral antibiotics, intravenous antibiotics were utilized in a small proportion of the children. Long-term resolution rate was reported in 78% of the 18 patients who did not need intravenous antibiotics. This data suggests that antral irrigation adds to the efficacy of adenoidectomy and also suggests that a prolonged course of IV antibiotics (as reported above) might not be necessary to obtain a good result.

Balloon sinuplasty was approved by the FDA for use in children in the United States in 2006, and a preliminary study in children has shown the procedure to be safe and feasible [1991]. In this study, the cannulation success rate was 91% and the majority of the sinuses addressed were maxillaries. The most common cause of failure of cannulation with the balloon catheter was the presence of a hypoplastic maxillary sinus. Most surgeons now use the illuminated catheter to confirm cannulation of the sinus thus avoiding fluoroscopy and its inherent risks. In a recent nonrandomized, prospective evaluation of children with CRS failing maximal medical therapy, balloon catheter sinuplasty and adenoidectomy were compared [1992]. Outcomes were assessed at 1 year after surgery and were based on SN-5 scores and the need for revision surgery. Twenty four/30 patients (80%) who underwent balloon sinuplasty showed improvement in their symptoms compared to 10/19 (52.6%) of the patients who underwent adenoidectomy ($p<0.05$). As some of the balloon patients also underwent irrigation, it is hard to discern the effect of dilation vs irrigation from this study. In sum, most of the available surgical data support adenoidectomy with sinus irrigation as a first step in the management of the child with CRS refractory to maximal medical management. Whether or not balloon maxillary sinuplasty imparts additional benefit to irrigation alone, in combination with adenoidectomy, cannot be established with available data to date (Strength of recommendation: C).

6.10.3.2. Functional Endoscopic Sinus Surgery (FESS)

A meta-analysis of FESS results in the paediatric population has shown that this surgical modality is effective in reducing symptoms with an 88% success rate and a low complication rate [1993]. Initial concerns about possible adverse effects of FESS on facial growth have been allayed by a long term follow up study by Bothwell and colleagues that showed no impact of FESS on qualitative and quantitative parameters of paediatric facial growth, evaluated up to 10 years postoperatively [1994]. Many advocate a limited approach to FESS in children consisting of removal of any obvious obstruction (such as polyps and concha bullosa), as well as anterior bulla ethmoidectomy and maxillary antrostomy. This approach typically yields significant improvements in nasal obstruction (91%), rhinorrhoea (90%), PND (90%), headache (97%), hyposmia (89%) and chronic cough (96%) [1995].

Whereas second look procedures were common after FESS to clean the cavities, the advent of absorbable packing has made it possible to avoid a second look procedure. Walner et al found comparable rates of revision sinus surgery in children with and without a second look procedure suggesting that it may not be necessary [1996]. Ramadan and colleagues observed that the use of corticosteroids during initial FESS might obviate a second look procedure [1997]. Younis in a review of available data suggested that a second look is not necessary in most children after FESS [1998].

There are few reports on the causes of failure of ESS in children. The most comprehensive describes 23 of 176 (13%) children who failed FESS and required revision [1991]. The most common findings in these patients were adhesions (57%) and maxillary sinus ostium stenosis or missed maxillary sinus ostium (52%). In 39% of the cases, disease recurred in the operated sinuses, whereas in 26% of the cases, surgery was needed because of

Table 6.10.2. Surgical Treatment of Pediatric CRS.

Author	Intervention	Age	Outcome	Category of Evidence
Hebert (1993)	Meta-analysis of 8 published FESS studies (n=832) and author's unpublished data (n=50)	11 mos-18 years	88.7% positive outcome with an average of 3.7 years of combined follow up	Ia
Brietzke (1987)	Meta-analysis of 9 adenoidectomy studies	4.4-6.9 years	69% improvement rate	Ia
Ramadan (1989)	Adenoidectomy (n=28) vs Adenoidectomy with maxillary wash (n=32)	Average= 6.3 yrs, Range= 3-13 yrs	Success rate at 12 months postop: Adenoidectomy= 61% Adenoidectomy + wash= 88%	III
Criddle (1990)	Adenoidectomy + wash and postop antibiotics (n=23)	Average= 2.3 yrs Range= 6 mos-6 yrs	78% long term improvement in patients who did not receive IV antibiotics (n=18)	III
Ramadan (1992)	Adenoidectomy (n=19) Adenoidectomy with Balloon maxillary sinuplasty + irrigation (as necessary) (n=30)	Average= 6.6 yrs Range= 2-11 yrs	80% improvement after 12 months for balloon vs 53% for adenoidectomy alone ($p<0.05$)	III

disease present in sinuses that were not originally operated. In another report, a retrospective review of children with CRS having undergone ESS yielded 39.6% who continued to have mucopurulent nasal drainage for more than 3 months after surgery [1999]. Sinonasal polyposis, history of allergic rhinitis, and male gender were significantly more frequently observed in the group that continued to have problems after ESS.

In summary, the most supported surgical approach to the child with CRS who has failed maximal medical therapy probably consists of an initial attempt at an adenoidectomy with a maxillary sinus wash plus/minus balloon dilation followed by FESS in case of recurrence of symptoms. An exception to this statement are children with cystic fibrosis, nasal polyposis, antrochoanal polyposis, or AFS where FESS to decrease disease burden is the initial favoured surgical option. Unfortunately, most of the data supporting this recommendation are not based on randomized prospective studies. It is therefore clear that prospective, randomised, controlled clinical trials should be undertaken. In these trials, severity of disease on CT scans and symptom questionnaire should ideally be matched preoperatively and the following interventions would be compared: adenoidectomy alone, adenoidectomy with a wash, adenoidectomy with a wash and balloon maxillary sinuplasty, and endoscopic sinus surgery. An additional arm that includes medical therapy might also be included.

7. Burden of Rhinosinusitis

7.1. Quality of Life measurements in the diagnosis and outcome measurement of CRS with and without NP

7.1.1. Introduction

There is now growing acceptance that patients' views are essential in the delivery of high quality care. In addition to enquiries regarding overall severity of CRS symptoms using the VAS, individual symptom severity may be recorded, either using a VAS, or using validated symptom-based questionnaires. Patient Reported Outcome Measures (PROMs) are measures of health-related quality of life (HRQOL) that are self-rated and reported directly by patient. They usually refer to a single time point or clearly defined preceding period, thus 'outcome' measure in this setting is a misnomer. The impact of chronic disease or medical care can be determined by comparing repeated measures of patient's self reported health status. As symptoms drive a patient to seek medical care, measurement of the impact of these symptoms will better reflect the efficacy of treatment from the patient's perspective than a clinician-rated outcome.

Quality of life is measured using one of a growing number of 'instruments'; typically these are questionnaires, but in some cases visual scales or grading systems can be used. These allow quantitative assessment of otherwise subjective results. The questionnaires usually require the patient to rate the impact of their disease across a number of specified 'domains' or areas of interest. Individual questions are scored according to severity or impact of disease, and then scores are combined to produce an overall score. Some PROMs have been developed for particular conditions or treatments (disease-specific) while others are designed for use in all patient groups or healthy individuals and measure the patient's perception of their general health (generic measures).

Generic PROMS allow comparison between conditions or treatments, and therefore can be used to determine the impact of different diseases on patient groups, the relative cost utility of different interventions and to inform commissioning decisions. However, they are often lack sensitivity to detect small but important changes in disease specific QOL. There are now several different rhinosinusitis-specific instruments available, differing in terms of aims of use, number of items, setting and ease of use. In addition, the choice of instrument will depend upon the aim of outcome measurement.

HRQOL is defined across two main domains; psychosocial and physical functioning, and the impact that disease has on this as rated by the patient. Therefore an instrument that measures HRQOL should include items pertaining to both domains. In addition, there are a number of validated questionnaires that include only physical functioning as defined by disease specific symptoms only, without a psychosocial domain, and some measuring cost-effectiveness. These have been included for completeness.

7.1.2. Assessment of Instruments

All instruments must have a published psychometric validation in the appropriate setting (e.g. for inclusion under ARS instruments, the instrument must be validated in a group of patients with ARS) to be considered for inclusion – several questionnaires were excluded on this basis. Further quality assessment was undertaken using the scoring system described by van Oene [(2000)] et al. in a systematic review of outcome tools undertaken in 2007. This excellent scoring system comprehensively captures aspects of instrument validity, including construction of the questionnaire, description of the items and domains, feasibility and respondent burden, size of validation study and reliability in terms of internal consistency, test-retest reliability, content, convergent and discriminant validity, responsiveness, and calculation of the minimally important difference.

The time to complete an instrument will determine it's practical applications, and the times presented were taken from the validation papers where published, and by trialling the tools directly.

Finally, the number of published studies utilising each instrument (excluding those reporting the validation of the instrument), and the number of validated translations are presented. If an instrument is to be translated, it must be done in both a forward and backward direction to ensure the original

meaning of the items is retained, and then must be revalidated to ensure it has the same psychometric properties.

7.1.3. Results

The identified outcome instruments and key properties are summarised in Table 7.1.

There are several validated tools available for use in CRS in the adult population.
The predominant differences between the tools are the number of items. There is a direct relationship between the number of items and the respondent burden, and this should be considered when selecting an instrument for use. 2 instruments (SNOT-20 and SNOT-22) including general HRQOL items rate highly in terms of psychometric quality, and have a significant volume of published studies where the tools have been used, to provide comparative data. However, the SNOT-20 lacks items pertaining to nasal obstruction and reduced sense of smell, and as they are essential for the diagnosis of CRS, we do not feel the SNOT-20 to have adequate content validity to recommend use. The CSS contains only disease specific items but is widely used in the literature.

There are fewer tools available for adult ARS, and for both paediatric CRS and ARS.

Although there are many generic HRQOL instruments, the SF-36 has been extensively used both in rhinosinusitis and other chronic diseases, and provides a wealth of normative and comparative data. The short form 36 (SF-36) is a multipurpose, 36-item survey that measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It has been widely used in many medical conditions and over 5000 publications, with normative values available for the general population (SF website). It has been used to measure both the impact of CRS on quality of life, and to assess the outcome of treatment [15, 2001].

Health related quality of life can be measured using a large number of disease-specific or global patient-rated outcome measures

Table 7.1. Recommended outcome tools based on current literature.

Adult CRS – SNOT22 or RSOM-31
Adult ARS – SNOT-16
Paediatric CRS – SN-5
Paediatric ARS – S5

7.1.4. Impact of ARS on quality of life

While the socio-economic burden of acute rhinosinusitis has been measured in terms of medical consultation, medication usage and absenteeism, there is a relative paucity in the literature regarding the impact of acute sinusitis on quality of life. As episodes are by definition short-lived, impairment in quality of life should also be transient, returning to baseline levels after recovery. In addition, due to variation in the definition used in studies, most groups described in clinical trials are a heterogeneous group of patient with a viral 'common cold' and acute bacterial sinusitis.

There is one disease-specific patient rated outcome measure validated for use in ARS. Using the SNOT-16 [2022] in a group of 166 patients, the mean scores declined steadily from 1.71 (SD 0.5 at onset of illness) to 1.13 (SD0.54) at day 3, 0.74 (SD 0.5) at day 7 and falling to 0.49 (SD0.44) by day 10. In terms of comparison with CRS, and normal patients one study reports the use of the SF-36, with significant differences between all groups ($p<0.001$), with patients with ARS having poorer HRQOL (mean score 60.8) than healthy individuals (51.8), but less reduction than those with CRS (75.5) [2025]. In terms of specific symptoms, a recent survey based study in France asked physicians to report symptom frequency and severity prospectively on patients with a diagnosis of acute maxillary sinusitis [228]. The most common presenting signs and symptoms were moderate-to-severe nasal obstruction (80.4%), pain on sinus palpitation (76.8%), facial pain (74.5%), rhinorrhoea (70.4%), and headache (63.6%). Symptoms were indicated as having a moderate to very significant effect on quality of life areas including activities of daily living (71.6% of patients), leisure (63.1%), and professional/school activities (59.2%). In a prospective randomized, double-blind, placebo-controlled trial [311], comparing the effect of antibiotics and topical steroids, the most severe symptoms were post-nasal discharge, need to blow nose, runny nose and waking up tired, using the SNOT-20 to assess symptom severity (which therefore does not capture nasal obstruction or anosmia). This study demonstrated significant improvement in health related quality of life from baseline to the end of the trial period at day 15, with mometasone producing a significantly greater improvement in the SNOT-20 mean total score than that seen with placebo ($p = 0.047$).

A number of disease-specific and global patient-rated outcome measures have been used to demonstrate significant impairment in HRQOL in both ARS and CRS

Table 7.2. Summary of outcome instruments and their key properties.

Instrument	HRQOL content	Items / Domains	Psychometric Quality score	MID	Normal	Completion time (min)	No of Studies	Validated translations	Notes
Adult Chronic Rhinosinusitis instruments									
RSOM-31 [2002]	+	31 / 7	15/18 + rating			20	5		
SNOT-16 [2004]	+	16 / 1	7/17 +rating			5	5	French [2003]	
SNOT-20 [20]	+	20 / 1	13/17 +rating			5 - 10	83	Japanese [2005], Piccirillo [1178], Chinese [2006], Portuguese [2007], German [2008]	
RSDI [240]	+	20 / 1	7/18	10.35		5	16	Turkish [2009]	
RhinoQOL [2011]	+	17 / 3	14/18			5 – 10	1	French [2010]	
SNOT-22 [2013]	+	22 / 1	13/17	8.9	7	5	20	Danish [2012], Czech [2014], Chinese [2015], Swedish [2016], Portuguese	
CSS [2018]	-	6 / 2	9/16	9.75		5	29	Norwegian [2017], Chinese [2019] duration based	
FNQ [2020]	-	12 / 1	9/17			<5	3	-	
SNAQ-11 [2021]	-	11 / 1	2/17			5	3	-	
Adult Acute Rhinosinuitis Instruments									
SNOT-16 [2022]	+	16 / 1	13 / 17			5	3	-	
MSSUI [2023]	-	5 / 1	8/17 + rating			>10	2	-	Complex web-based scoring system
Paediatric chronic rhinosinusitis									
SN-5 [1602]	+	5 / 5	8/17			<5	4	-	
Paediatric acute rhinosinusitis									
S-5 [2024]	-	5 / 1	10/18			<5	2	-	
Adult generic quality of life instrument									
SF-36 [43]		+	36 / 8	10 – 12.5		5 – 10	48*	>120 validated translations	

HRQOL content + includes general HRQOL / psychosocial functioning items in addition to disease-specific symptoms, - includes only disease specific symptoms.

Psychometric quality score as rated by van Oene et al. [2000]. Denominator varies, as some criteria are not applicable in every case.

No. of studies – published studies up to Sept 12th 2011 utilising the outcome instrument, excluding those related to its validation.

Validated translation – published translations where the outcome instrument has been revalidated in the new language.

*publications of use in rhinosinusitis only.

7.1.5. Impact of CRS on quality of life

Using the SF-36, chronic rhinosinusitis has been shown to have a negative impact on several aspects of quality of life, and has a greater impact on social functioning the chronic heart failure, angina or back pain [2001]. Published studies report scores below the normal population in 5 – 7 of the SF-36 domains [2001, 2026, 2027]. The SNOT-22 was shown to have a median value of 7 in healthy volunteers, compared to a mean pre-operative SNOT-22 score of 42.0 (95% CI = 41.2-42.7) in a cohort of 3,128 patients undergoing surgery for CRS [2028]. Several studies have shown that CRSwNP tend to report better QOL than those with CRSsNP despite worse CT and endoscopy scores [1885].

Improvement following both medical and surgical intervention has been demonstrated in CRS using PROMS

Quality of life measures may also be used to evaluate changes over time following either medical or surgical intervention. In the large cohort study above, the mean SNOT-22 score for all patients was 28.2 (standard deviation [SD] = 22.4) at 5 years after surgery [1758]. This was remarkably similar to the results observed at 3 months (25.5), 12 months (27.7), and 36 months (27.7), and represents a 14-point improvement over the baseline score (ES 0.8SD).

Chester et al. [2029] undertook a systematic review of the literature reporting symptomatic outcome following FESS. The meta-analysis of 21 of 289 identified FESS studies was conducted for each symptom separately with the standardized difference between the preoperative and postoperative severity scores as the effect size (ES). ESS symptom outcomes were reported using various symptom scoring systems and more than 18 survey instruments. A total of 2070 patients with CRS were studied a mean of 13.9 months after ESS. All symptoms demonstrated improvement compared with their respective preoperative severity scores by an overall ES of 1.19 (95% confidence interval, 0.96 to 1.41; I (2) = 81.7%) using the random-effects model. Nasal obstruction (ES, 1.73) improved the most, with facial pain (ES, 1.13) and postnasal discharge (ES, 1.19) demonstrating moderate improvements. Hyposmia (ES, 0.97) and headache (ES, 0.98) improved the least. When individual symptom scores were pooled by meta-analysis, most major CRS symptoms improved to a similar degree following surgery, with an overall effect size of 1.19 (95% confidence interval, 0.96-1.41; I (2) = 82%). Fatigue and bodily pain were more severe than general population normative values and improved following ESS by an effect size of approximately 0.5 SD, a change usually regarded as a minimally important clinical difference.

The impact on different treatment modalities is considered in more detail in each relevant section.

7.2. Direct Costs

7.2.1. Direct costs of chronic rhinosinusitis

Chronic rhinosinusitis (CRS) (with and without polyps) is a frequent pathology with a high impact on quality of life. The research concerning the socioeconomic impact of the disease is limited. Ray et al estimated, already in 1999 the total direct cost in the US at 5,78 billion dollars per year [2030].

In US the total cost of treating a patient with CRS was $2609 per year; in Europe the direct costs of a patient treated in a university hospital for severe chronic rhinosinusitis was $1861/year

In 2002, Murphy et al [2031] examined the direct costs of a patient with a diagnosis of CRS. These patients seemed to make 43% more outpatient and 25% more urgent care visits than a patient without CRS. CRS patients filed 43% more subscriptions, but had fewer hospital stays. The total cost of treating a patient with CRS was $2609 per year; this is 6% more than the average adult.

In Europe only one study was found, in the Netherlands, executed by van Agthoven et al. Here the direct costs of a patient treated in a university hospital for severe chronic rhinosinusitis was $1861/year [2032].

In addition to these findings, also mentioned in EPOS2007, a search was made through recent English literature 2007-December 2011. The studies discussed are all carried out by N. Bhattacharyya and his team. The studies are well performed and concern a big amount of data, but are limited to USA patients. There are no recent studies carried out in Europe.

In March 2009 Bhattacharyya [2033] published the assessment of the additional disease burden of nasal polyps in CRS. A series of patients were recruited from their centre. Patients were included according to the Rhinosinusitis symptom inventory (Task force on Rhinosinusitis criteria) and by findings with nasal endoscopy and on CT (Lund MacKay score). Three groups were composed: one with CRS without nasal polyps (CRSsNP), a second group with CRS with nasal polyps (CRSwNP) and a third with CRS with recurrent nasal polyps after surgery.

The groups with and without nasal polyps show a clear difference in symptom phenotype, but this did not translate into a difference in expenditures for physician's visits and medication costs between the first 2 groups. There was no statistically significant difference. However there was a difference in total medication costs for the last group with recurrent polyps after surgery with a higher cost for this group of $ 865.50 compared to the $ 569.60 for group 1 and $ 564.50 for group 2.

In July 2009 a contemporary assessment of the disease burden of sinusitis from Bhattacharyya [37] was published. Here data were extracted from the National Health interview survey over a 10-year period of 1997-2006. One year disease prevalences

show that one quarter (22.7%) of patients with CRS visited an emergency department, one third (33.6%) saw a medical specialist, more than half (55.8%) spent $500 or more per year on health care. Health care spending was significantly greater in sinusitis than that of other chronic diseases as ulcer disease, acute asthma and hay fever.

National health care costs in the US remain very high for CRS, at an estimated 8.6 billion dollar per year [2034].
Factors contributing to a high economic impact of this condition are: the high disease prevalence (10 to 14% of the population would be affected), it is a chronic condition with no universal cure, there are frequent exacerbations of symptoms prompting acute treatments in addition to the chronic ones already in place, there is a high quality of life-impact, a generally incomplete symptom control leading patients to seek additional therapies to achieve relief and it is difficult to accurately diagnose the condition without radiologic or diagnostic procedures [2035].

The highest costs were made by the group with recurrent polyps after surgery

In 2011 Bhattacharyya [2034] calculated the incremental health care utilization and expenditure for CRS in the United States. Patient data were extracted from the Medical Expenditure Panel Survey. With the incremental expenditure methodology, expenditures are measured attributable particular to CRS, there is adjusted for differences in variables that are having an impact on expenditures, like age, gender, insurance status etc. For the expenditures next components are taken into consideration: office-based health care expenditures, prescription expenditures and patients' self-expenditures for prescription medications. For utilization of health care, data show that CRS patients incurred ±3, 5 additional office visits and 5,5 additional prescription fills compared to patients without CRS. This extra utilization of healthcare evokes higher expenditures; a CRS patient would have a substantial incremental increase of total health care expenditure of $772 (±$300) consisting of $346(±$130) for office-based expenditures, $397(±$88) for prescription expenditures and $90(±$24) for self-expenditures. Bhattacharyya et al. [2035] reported the costs pre- and postoperative to Endoscopic Sinus Surgery (ESS). Data come from the Market Scan Commercial Claims and Encounters Database from 2003 to 2008. Numerous studies have shown the effectiveness of surgery in improving quality of life in CRS patients, but the effect of surgery on expenditures was not clarified. Patients were included if 2 CRS-related diagnoses were retrieved, confirmed by either CT-scan or endoscopy. Likely this might cause a selection of more severe cases. Patients with nasal polyps were excluded from this study. All sinus-related health care utilization costs were rolled up in the study (medication, operation costs, office visits, diagnostic assessment with radiology and endoscopy). Results show that in the year prior to ESS costs run op to $2,449 ($2,341-$2,556) with a clear increase in the last 6 months before surgery; the first semester accounts for $361 and the last semester for $1,965. This is due to an augmentation in office visits, diagnostic investigations and medication use. The augmentation in prescription medication is for the greatest part due to a higher antibiotic use; from $75 in the first to $225 in the second semester.

The ESS-procedure and the 45-day post procedure period count for $7,726 ($7,554 – $7,898).
In the first year following ESS, costs drop by $885 to an average of $1,564 per year. In the second year post procedure they drop an additional $446 to $1,118 per year. This decrease was mostly due to a lower amount of doctor visits, there was only a minor change in the costs of anti-inflammatory medication. Important to mention is that the costs in the 4th semester postoperative remain higher than in the first semester preoperative, possibly inflammation does not return to premorbid levels.

Health care spending was significantly greater in sinusitis than in other chronic diseases such as ulcer disease, acute asthma and hay fever

From above studies we see that the direct costs of CRS are quite high (average $772), also compared to other chronic diseases. In the year prior to surgery the disease burden augments and also causes a strong increase in costs ($2,449/patient/year).

Endoscopic sinus surgery is expensive ($7,726 for procedure and 45-day follow-up), but causes a drop of costs in the 2 years post operative (average $1,564 in year 1, average $1,118 in year 2). The important clinical difference in CRS with and without polyps only causes a difference in medication costs for the group with recurrence of polyps after surgery; probably this group has a higher disease severity.

Endoscopic sinus surgery is expensive, but causes a drop in costs for the 2 post-operative years

Above data is all from the same principal investigator, which shows that there is little interest in the economic burden of CRS. There were no recent European data available, although many important questions remain unanswered, like: What would be the personal costs and the health insurance costs in European

countries with different health care systems than in the US? Which link is there between disease severity and costs?

7.2.2. Direct costs of acute rhinosinusitis

Besides the pathology of chronic rhinosinusitis, also acute rhinosinusitis can be an economic burden. Anand estimated in 2004 that there are approximately 20 million cases of acute bacterial rhinosinusitis yearly in the United States [2036].
One in 3,000 adults would suffer from a recurrent acute rhinosinusitis [43]. This entity was in the study of Bhattacharyya defined as at least 4 claims of sinusitis in 12 months, with antibiotic prescription; this with a relative paucity of symptoms at baseline between episodes. Considering this definition, there might be an overlap with the diagnosis of CRS.
This patient group has an average of 5,6 health care visits/year, 9,4 prescriptions filled (40% antibiotic). Only 20% of patients had either a nasal endoscopy or CT scan annually. This probably means that only a small part sees an ENT-specialist for his complaints.
The total direct health care cost of recurrent acute rhinosinusitis would be an average of $1,091/year: $210 to antibiotics, $452 to other sinus-related prescriptions (relatively large cost due to leukotriene inhibitors who are not generically available), $47 to imaging and $382 to other visit costs.

Patients with recurrent acute rhinosinusitis have an average direct health care cost of $1,091/year in average (US)

A study in Taiwan showed that acute nasopharyngitis and acute upper respiratory tract infections were the 2 diseases with the highest number of outpatient department visits [2037]. The drug expenditure for acute respiratory infections accounted for 6% of total drug expenditure. Only 42,8% of drugs for these illnesses was described as suitable for patients' self-care.
Sinusitis cannot only cause direct costs on it's own, but especially as comorbidity with asthma it is known to augment disease burden. Bhattacharyya et al. studied in 2009 the additional disease burden from hay fever and sinusitis accompanying asthma [2038]. This showed that there were more emergency room visits from patients with asthma and sinusitis, than of those with only asthma or a comorbidity of hay fever. The total health care visits and the household healthcare expenditures are higher for this group of patients.

Total health care costs and the household healthcare expenditures are higher for patients with sinusitis and asthma

The above studies show that also acute sinusitis is an important pathology to consider economically. Because of the high prevalence, the risk of recurrence and the augmentation of disease burden to chronic conditions as asthma. Literature does not give an answer to the question how much one episode of acute sinusitis would cost; this can be an objective for future investigations.

7.3. Indirect Medical Costs

The studies of direct medical costs demonstrate a tremendous social economic burden of Rhinosinusitis. However, the total costs of rhinosinusitis are far greater when the indirect costs are considered. With 85% of patients with Rhinosinusitis of working age (between 18-65 years old) [485], indirect costs such as missed workdays (absenteeism) and decreased productivity at work (presenteeism) significantly add to the economic burden of disease.

Rhinosinusitis is one of the top ten most costly health conditions to US employers

Goetzel et al. [2039] attempted to quantify the indirect costs of rhinosinusitis. Their 2003 study resulted in rhinosinusitis being named one of the top ten most costly health conditions to US employers. A large multi-employer database was used to track insurance claims through employee health insurance, absentee days, and short-term disability claims. Episodes of illness were linked to missed workdays and disability claims, accurately correlating absenteeism to a given disease. In a large sample size (375,000), total healthcare payments per employee per year for sinusitis (acute and chronic) were found to be $60.17, 46% of which came from the cost of absenteeism and disability. These figures approximate the cost to employers, disregarding the cost incurred by other parties, and therefore tremendously underestimate the entire economic burden of the disease.

Indirect costs account for 40% of the total costs of rhinosinusitis

In his 2003 study, Bhattacharyya used patient-completed surveys from 322 patients to estimate the direct and indirect costs of chronic rhinosinusitis [2040]. Patients completed a survey assessing symptoms of disease, detailing medication use, and quantifying missed worked days attributable to CRS. The conclusions of the report included that the cost of treating CRS per patient totalled $1,539 per year with forty percent of these costs due to the indirect costs of missed work; the mean number of missed workdays in this sample of 322 patients was 4.8 days (95% CI, 3.4-6.1). The author of the study followed this up in

a 2009 report using data from the National Health Interview Survey between 1997 and 2006 encompassing nearly 315,000 individuals and reported that patients with sinusitis missed on average 5.7 days of work per year [37].

A major component of the indirect costs result from absenteeism and presenteeism

The cost burden of absenteeism is enormous, and yet it is only the beginning. The general health status of patients with CRS is poor relative to the normal US population [2001]. This decreased quality of life not only leads to absenteeism, but also contributes to the idea of "presenteeism" or decreased productivity when at work. Ray et al. estimated by the 1994 National Health Interview Survey, that missed worked days due to sinusitis was 12.5 million and restricted activity days was 58.7 million days [2030]. Economic loss due to presenteeism cannot be easily quantified as it varies from individual to individual, but clearly increases the cost burden of the disease.

Recently Stankiewicz et al. reported on the rates of absenteeism and presenteeism in a population of 71 patients undergoing surgical intervention for chronic rhinosinusitis. Prior to surgery, they report a 6.5% rate of absenteeism (i.e., 6.5% of work time missed) and 36.2% rate of presenteeism (reduction of on-job effectiveness). When combined the rate of absenteeism and presenteeism yielded a 38% work productivity loss in the study population, but no dollar value was placed on this figure [2041]. Supporting this, Stull et al. reported that nasal congestion alone resulted in poor sleep, increased fatigue, and daytime sleepiness contributing to decreased work productivity [2042].

Patients with rhinosinusitis miss on average 6 days of work annually due to the disease.

Although incidence rates may be similar to that reported in the U.S. direct and indirect costs would vary widely based upon medical costs, per-capita income and life expectancy. Although in the U.S., chronic rhinosinusitis is estimated to cost as much as $5.78 billion annually in the U.S.2, extrapolation of figures from other studies suggests the possibility of a substantially larger cost. Decreased quality of life in patients suffering from rhinosinusitis results in an average of 4.8 -5.7 missed workdays translating into $600 of decreased productivity annually per patient (2031), contributing to the cost burden of the disease not incorporated into the $5.78 billion. Whatever the precise cost, it is clear that socioeconomic burden of the disease is great and the disease has significant quality of life implications. As such it is therefore imperative that we continue to understand the pathophysiology of the disease and to devise cost effective strategies to provide relief to patients.

Absenteeism and presenteeism for "the Common cold" is also substantial. In a 2002 study, Bramely et al reported each cold experienced by a working adult caused an average of 8.7 lost work hours (2.8 absenteeism hours; 5.9 hours of on-the-job loss/presenteeism), and 1.2 work hours were lost because of attending to children under the age of 13 who were suffering from colds. The study concludes that the economic cost of lost productivity due to the common cold approaches $25 billion, of which $16.6 billion is attributed to on-the-job productivity loss, $8 billion is attributed to absenteeism, and $230 million is attributed to caregiver absenteeism [2043]. A more recent study in Sweden by Hellgren et al evaluated the productivity loosed due to the common cold and allergic rhinitis and estimated the economic burden in Sweden alone was €2.7 billion annually. Of the total costs, absenteeism (44%) was the dominant factor, followed by presenteeism (37%) and caregiver absenteeism (19%) [2044].

There are no data on ARS, research is urgently needed.

8. Evidence based schemes for diagnostic and treatment

8.1. Introduction

The following schemes for diagnosis and treatment are the result a critical evaluation of the available evidence. The tables give the level of evidence for studies with a positive outcome and well powered studies with negative outcoume. For example Ib (-) in this tables means a well designed (Ib) study with a negative outcome. The grade of recommendation for the available therapy is given.

Under relevance it is indicated whether the group of authors think this treatment to be of relevance in the indicated disease.
Since the preparation of the EP^{3}OS2007 document an increasing amount of evidence on the pathophysiology, diagnosis and treatment has been published.

However, in compiling the tables on the various forms of therapy, it may be that despite well powered level Ib trials, no

Table 8.1. Treatment evidence and recommendations for adults with acute rhinosinusitis.

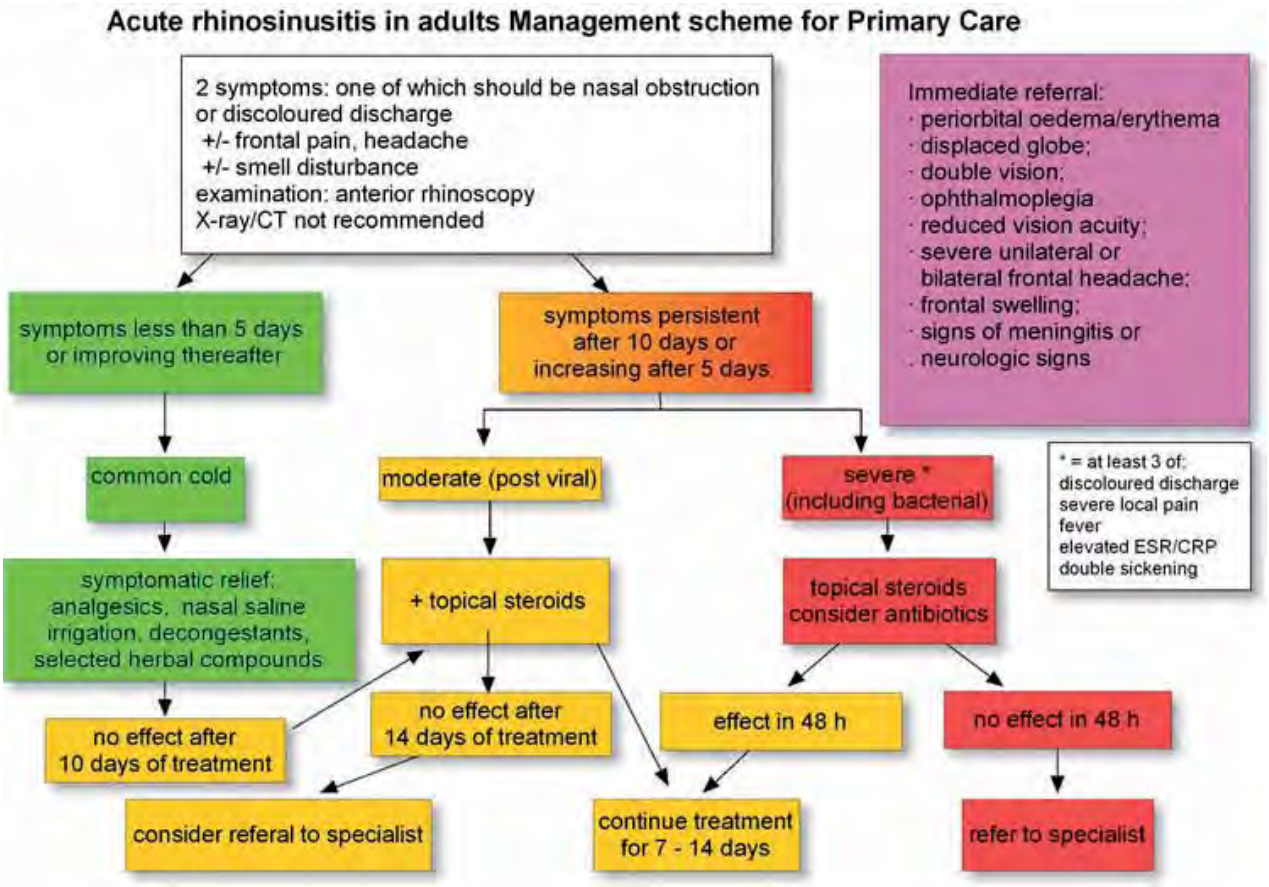
Therapy	Level	Grade of recommendation	Relevance
antibiotic	Ia	A	yes in ABRS
topical steroid	Ia	A	yes mainly in post viral ARS
addition of topical steroid to antibiotic	Ia	A	yes in ABRS
Addition of oral steroid to antibiotic	Ia	A	yes in ABRS
saline irrigation	Ia	A	yes
antihistamine analgesic-decongestion combination	Ia	A	yes in viral ARS
ipratropium bromide	Ia	A	in viral ARS
probiotics	Ia	A	to prevent viral ARS
zinc	Ia	C	no
vitamine C	Ia	C	no
echinacea	Ia	C	no
herbal medicine (pelargonium sidoides, Myrtol)	Ib	A	yes, in viral and postviral ARS
aspirin / NSAID's	Ib	A	yes, in viral and postviral ARS
acetaminophen (paracetamol)	Ib	A	yes, in viral and postviral ARS
oral antihistamine added in allergic patients	Ib (1 study)	B	no
steam inhalation	Ia(-)$^{\$}$	A(-)**	no
cromoglycate	Ib(-)*	A(-)	no
decongestion	no data for single use	D	no
mucolytics	no data	D	no

*1b (-): 1b study with negative outcome

$^{\$}$ Ia(-) Ia level of evidence that treatment is not effective.

A(-): grade A recommendation **not to use

Figure 8.1. Management scheme for primary care for adults with acute rhinosinusitis.



significant benefit has been demonstrated. Equally results may be equivocal or apparently positive results are undermined by the small number of trials conducted and/or the small number of participants in the trial(s). In these cases, after detailed discussion, the EPOS group decided in most cases, that there was no evidence at present to recommend use of the treatment in question. Alternatively for some treatments no trials have been conducted, even though the treatment is commonly used in which case a pragmatic approach has been adopted in the recommendations.

8.2. Evidence based management for adults with acute rhinosinusitis

8.2.1. Definitions

8.2.1.1. Acute rhinosinusitis in adults is defined as:

sudden onset of two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure,
± reduction or loss of smell
for <12 weeks;
with symptom free intervals if the problem is recurrent,
with validation by telephone or interview.

questions on allergic symptoms (i.e. sneezing, watery rhinorrhea, nasal itching, and itchy watery eyes) should be included. ARS can occur once or more than once in a defined time period. This is usually expressed as episodes/year but there must be complete resolution of symptoms between episodes for it to constitute genuine recurrent ARS.

8.2.1.2. Common cold/acute viral rhinosinusits is defined as duration of symptoms for less than 10 days.

8.2.1.3. Acute post-viral rhinosinusitis is defined as:

increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration.

8.2.1.4. Acute bacterial rhinosinusitis (ABRS)

Acute bacterial rhinosinusitis is suggested by the presence of at least 3 symptoms/signs of [247].

- Discoloured discharge (with unilateral predominance) and purulent secretion in cavum nasi,
- Severe local pain (with unilateral predominance)
- Fever (>38ºC)
- Elevated ESR/CRP
- 'Double sickening' (i.e. a deterioration after an initial milder phase of illness).

8.2.2. Evidence based management for adults with acute rhinosinusitis for primary care

8.2.2.1. Diagnosis

Symptom based, no need for radiology.

Not recommended: plain x-ray.

Symptoms
sudden onset of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure;
± reduction/loss of smell;

Signs (if applicable)
• nasal examination (swelling, redness, pus);
• oral examination: posterior discharge;
exclude dental infection.

8.2.2.1. Treatment

For treatment evidence and recommendations for acute rhinosinusitis see Table 8.1 Initial treatment depending on the severity of the disease (See Figure 8.1):

- Mild (viral, common cold): start with symptomatic relief (analgetics, saline irrigation, decongestants, herbal compounds);
- Moderate (postviral): additional topical steroids
- Severe (including bacterial): additional topical steroids, consider antibiotics

Table 8.2. Treatment evidence and recommendations for children with acute rhinosinusitis.

Therapy	Level	Grade of recommendation	Relevance
antibiotic	Ia	A	yes in ABRS
topical steroid	Ia	A	yes mainly in post viral ARS studies only done in children 12 years and older
addition of topical steroid to antibiotic	Ia	A	yes in ABRS
mucolytics (erdosteine)	1b (-)*	A(-)**	no
saline irrigation	IV	D	yes
oral antihistamine	IV	D	no
decongestion	IV	D	no

*1b (-): 1b study with negative outcome

A(-): grade A recommendation **not to use

8.3 Evidence based management for children with acute rhinosinusitis for primary care

8.3.1. Definitions

8.3.1.1 Acute rhinosinusitis in children

Acute rhinosinusitis in children is defined as:
sudden onset of two or more of the symptoms:

- nasal blockage/obstruction/congestion
- or discoloured nasal discharge
- or cough (daytime and night-time)

for < 12 weeks;
with symptom free intervals if the problem is recurrent; with validation by telephone or interview.

Questions on allergic symptoms (i.e. sneezing, watery rhinorrhea, nasal itching, and itchy watery eyes) should be included. ARS can occur once or more than once in a defined time period. This is usually expressed as episodes/year but there must be complete resolution of symptoms between episodes for it to constitute genuine recurrent ARS.

8.3.1.2. Common cold/ acute viral rhinosinusits is defined as: duration of symptoms for less than 10 days.

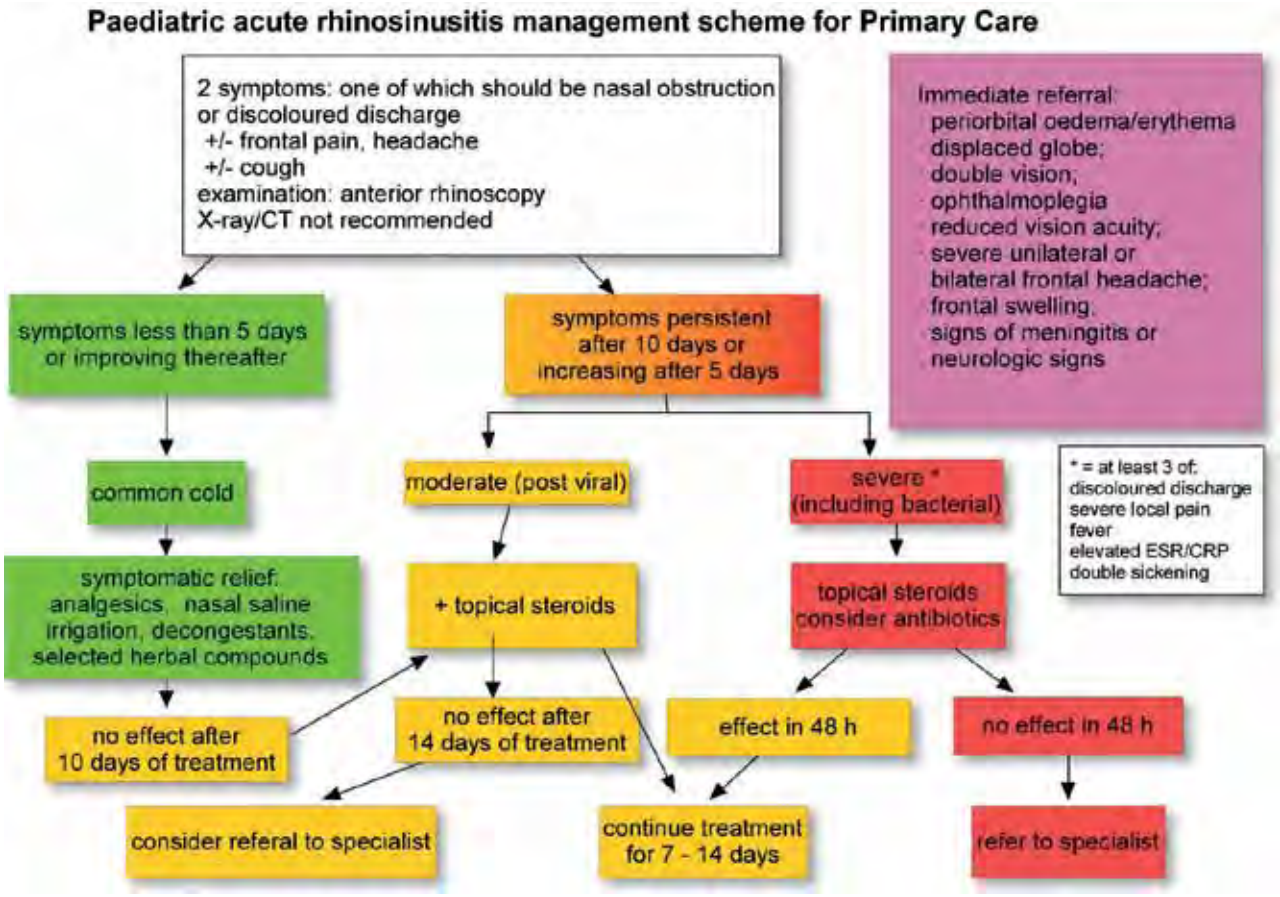
8.3.1.3. Acute post-viral rhinosinusitis is defined as: increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration.

8.3.1.4. Acute bacterial rhinosinusitis (ABRS)

Acute bacterial rhinosinusitis is suggested by the presence of at least 3 symptoms/signs of [247].

- Discoloured discharge (with unilateral predominance) and purulent secretion in cavum nasi,
- Severe local pain (with unilateral predominance)
- Fever (>38ºC)
- Elevated ESR/CRP
- 'Double sickening' (i.e. a deterioration after an initial milder phase of illness).

Figure 8.2. Management scheme for children with acute rhinosinusitis.



8.3.2. Evidence based management for children with acute rhinosinusitis in primary care

8.3.2.1. Diagnosis

Symptoms

sudden onset of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

± facial pain/pressure;

± cough

Signs (if applicable)

- nasal examination (swelling, redness, pus);
- oral examination: posterior discharge;

exclude dental infection.

Not recommended: plain x-ray.

CT-Scan is also not recommended unless additional problems such as:

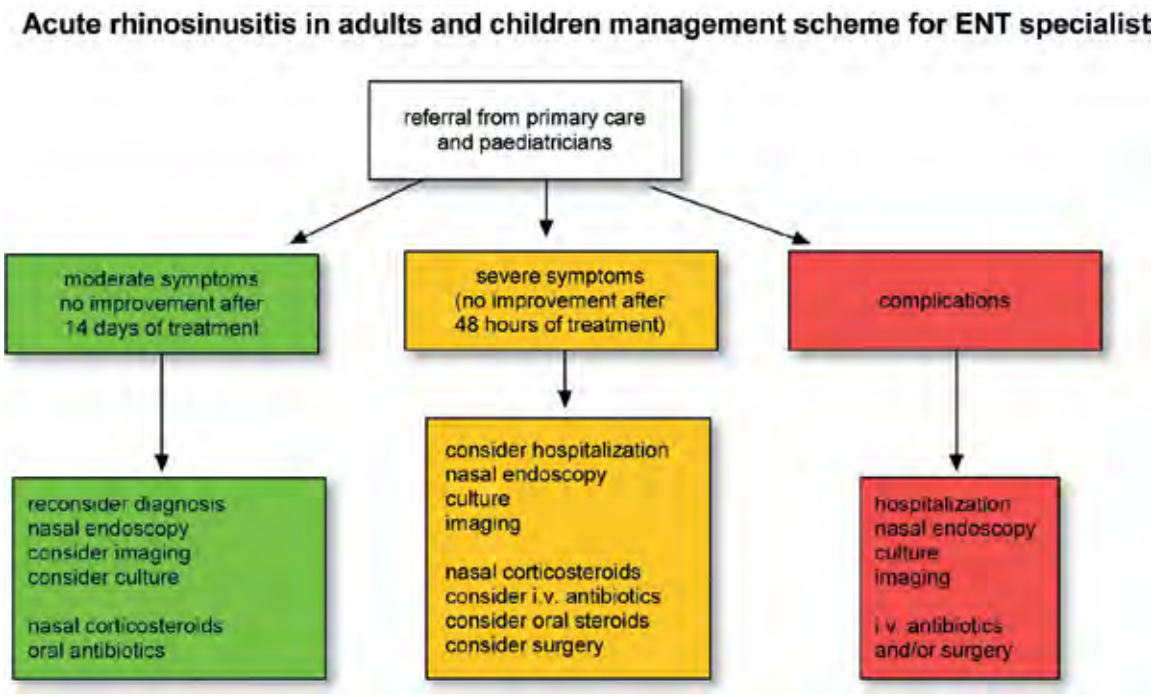
- very severe diseases,
- immunocompromised patients;
- signs of complications.

8.3.2.2. Treatment

For treatment evidence and recommendations for children with acute rhinosinusitis see Table 8.2

Initial treatment depending on the severity of the disease: see Figure 8.2.

Figure 8.3. Management scheme for ENT specialists for adults and children with acute rhinosinusitis.



8.4 Evidence based management for adults and children with acute rhinosinusitis for ENT specialists

8.4.1. Diagnosis

Symptoms

sudden onset of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

± facial pain/pressure;

± reduction/loss of smell;

Signs

- nasal examination (swelling, redness, pus);
- oral examination: posterior discharge;
- exclude dental infection.

ENT-examination including nasal endoscopy.

Not recommended: plain x-ray.

CT-Scan is also not recommended unless additional problems such as:

- very severe diseases,
- immunocompromised patients;
- signs of complications.

8.4.2. Treatment

For Treatment evidence and recommendations for acute rhinosinusitis. See Table 8.1. and Table 8.2

Initial treatment depending on the severity of the disease: See Figure 8.3.

Table 8.3. Treatment evidence and recommendations for adults with chronic rhinosinusitis without nasal polyps * [%].

Therapy	Level	Grade of recommendation	Relevance
steroid – topical	Ia	A	yes
nasal saline irrigation	Ia	A	yes
bacterial Lysates (OM-85 BV)	Ib	A	unclear
oral antibiotic therapy short term < 4 weeks	II	B	during exacerbations
oral antibiotic therapy long term ≥12 weeks**	Ib	C	yes , especially if IgE is not elevated
steroid – oral	IV	C	unclear
mucolytics	III	C	no
proton pump inhibitors	III	D	no
decongestant oral / topical	no data on single use	D	no
allergen avoidance in allergic patients	IV	D	yes
oral antihistamine added in allergic patients	no data	D	no
herbal en probiotics	no data	D	no
immunotherapy	no data	D	no
probiotics	Ib (-)	A(-)	no
antimycotics – topical	Ib (-)	A(-)	no
antimycotics - systemic	no data	A(-)	no
antibiotics – topical	Ib (-)	A(-)[$]	no

* Some of these studies also included patients with CRS with nasal polyps

[%] Acute exacerbations of CRS should be treated like acute rhinosinusitis

[#] Ib (-): Ib study with a negative outcome

[$] A(-): grade A recommendation **not** to use

** Level of evidence for macrolides in all patients with CRSsNP is Ib, and strength of recommendation C, because the two double blind placebo controlled studies are contradictory; indication exist for better efficacy in CRSsNP patients with normal IgE the recommendation A. No RCTs exist for other antibiotics.

Table 8.4 Treatment evidence and recommendations postoperative treatment for adults with chronic rhinosinusitis without nasal polyps *.

Therapy	Level	Grade of recommendation	Relevance
steroid – topical	Ia	A	yes
nasal saline irrigation	Ia	A	yes
nasal saline irrigation with xylitol	Ib	A	yes
oral antibiotic therapy short term < 4 weeks	II	B	during exacerbations
nasal saline irrigation with sodium hypochlorite	IIb	B	yes
oral antibiotic therapy long term ≥12 weeks**	Ib	C	yes , especially if IgE is not elevated
nasal saline irrigation with babyshampoo	III	C	no
steroid – oral	IV	C	unclear
antibiotics – topical	Ib (-) [#]	A(-) [$]	no

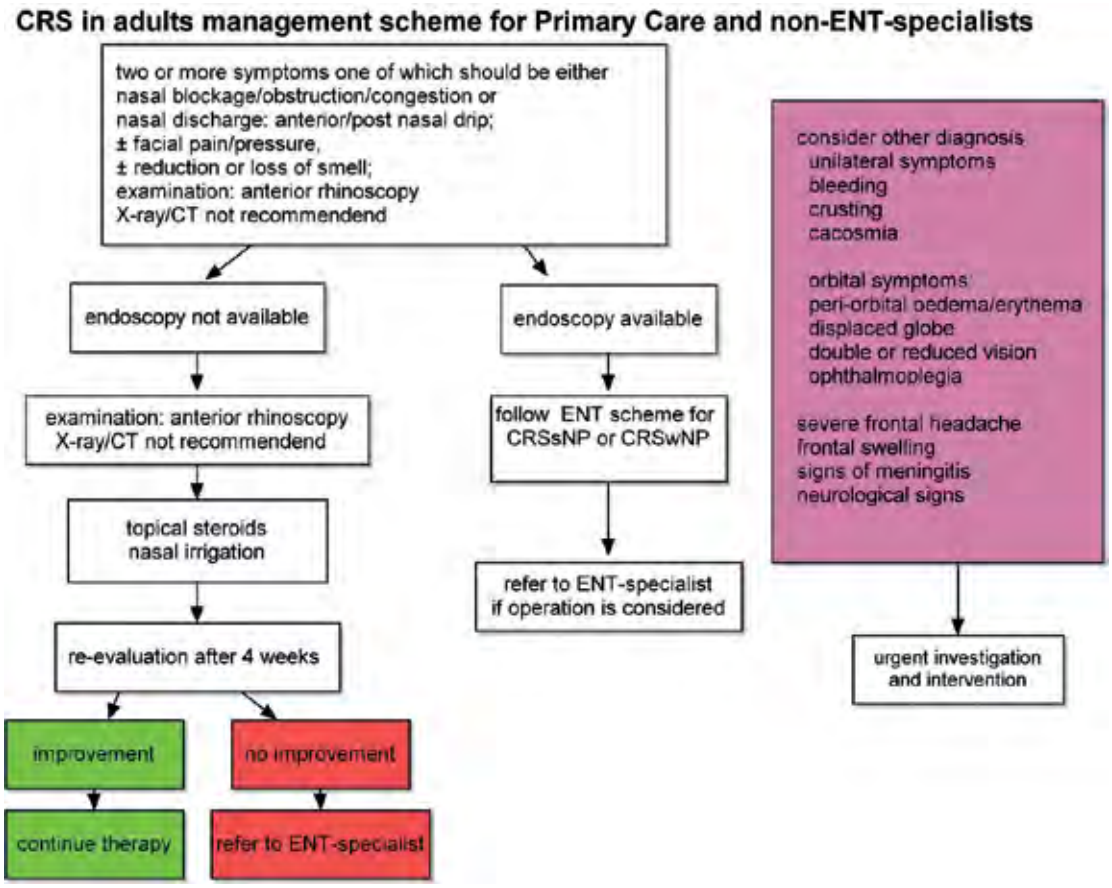
* Some of these studies also included patients with CRS with nasal polyps

[#] Ib (-): Ib study with a negative outcome

[$] A(-): grade A recommendation **not** to use

** Level of evidence for macrolides in all patients with CRSsNP is Ib, and strength of recommendation C, because the two double blind placebo controlled studies are contradictory; indication exist for better efficacy in CRSsNP patients with normal IgE the recommendation A. No RCTs exist for other antibiotics.

Figure 8.4. Management scheme for adults with CRS with or without NP for primary care and non-ENT specialists.



8.5 Evidence based management for adults with Chronic Rhinosinusitis

8.5.1. Definitions

8.5.1.1. Chronic Rhinosinusitis (with or without NP) in adults is defined as:

presence of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± Facial pain/pressure;
± reduction or loss of smell;
for ≥12 weeks;
with validation by telephone or interview.

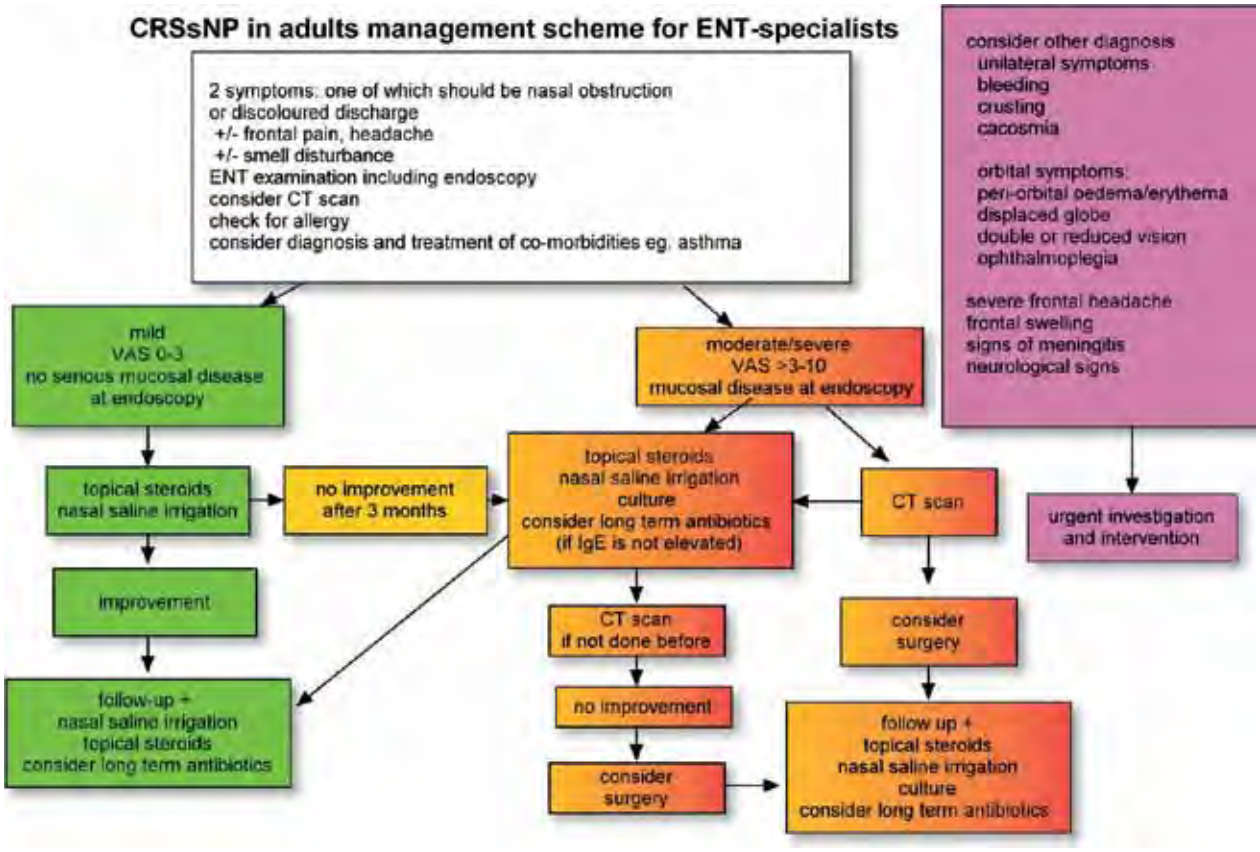
Questions on allergic symptoms (i.e. sneezing, watery rhinorrhea, nasal itching, and itchy watery eyes) should be included.

Chronic Rhinosinusitis with nasal polyps (CRSwNP): Chronic rhinosinusitis as defined above and bilateral, endoscopically visualised polyps in middle meatus.

Chronic Rhinosinusitis without nasal polyps (CRSsNP): Chronic Rhinosinusitis as defined above and no visible polyps in middle meatus, if necessary following decongestant.

This definition accepts that there is a spectrum of disease in CRS which includes polypoid change in the sinuses and/or middle meatus but excludes those with polypoid disease presenting in the nasal cavity to avoid overlap.

Figure 8.5. Management scheme for adults with CRS without NP for ENT specialists.



8.5.2. Evidence based management for adults with CRS with or without NP for primary care and non-ENT specialists

8.5.2.1. Diagnosis

Symptoms present equal or longer than 12 weeks
two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure,
± reduction or loss of smell;

Signs (if applicable)
• nasal examination
• oral examination: posterior discharge;
exclude dental infection.

Additional diagnostic information
- questions on allergy should be added and, if positive, allergy testing should be performed.

Not recommended: plain x-ray or CT-scan

8.5.2.2. Treatment

For treatment evidence and recommendations for chronic rhinosinusitis see Table 8.3 and 8.5.

Initial treatment depending on the availability of an endoscope and severity of disease: See Figure 8.4.

Acute exacerbations of CRS should be treated like acute rhinosinusitis.

8.5.3. Evidence based management for adults with CRS without NP for ENT specialists

8.5.3.1. Diagnosis

Symptoms present longer than 12 weeks
Two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure,
± reduction or loss of smell;

Signs
- ENT examination, endoscopy;
- review primary care physician's diagnosis and treatment;
- questionnaire for allergy and if positive, allergy testing if it has not already been done.

Table 8.5. Treatment evidence and recommendations for adults with chronic rhinosinusitis with nasal polyps *.

Therapy	Level	Grade of recommendation	Relevance
topical steroids	Ia	A	yes
oral steroids	Ia	A	yes
oral antibiotics short term <4 weeks	1b and 1b(-)	C%	yes, small effect
oral antibiotic long term ≥ 12 weeks	III	C	yes, especially if IgE is not elevated, small effect
capsaicin	II	C	no
proton pump inhibitors	II	C	no
aspirin desensitisation	II	C	unclear
furosemide	III	D	no
immunosuppressants	IV	D	no
nasal saline irrigation	Ib, no data in single use	D	yes for symptomatic relief
topical antibiotics	no data	D	no
anti-Il5	no data	D	unclear
phytotherapy	no data	D	no
decongestant topical / oral	no data in single use	D	no
mucolytics	no data	D	no
oral antihistamine in allergic patients	no data	D	no
antimycotics – topical	Ia (-) **	A(-)	no
antimycotics – systemic	Ib (-)#	A(-) $	no
anti leukotrienes	Ib (-)	A(-)	no
anti-IgE	Ib (-)	A(-)	no

* Some of these studies also included patients with CRS with nasal polyps

% short term antibiotics shows one positive and one negative study. Therefore recommendation C.

Ib (-): Ib study with a negative outcome

** Ia(-): Ia level of evidence that treatment is **not** effective.

$: A(-): grade A recommendation **not** to use

Table 8.6. Treatment evidence and recommendations postoperative treatment in adults with chronic rhinosinusitis with nasal polyps*.

Therapy	Level	Grade of recommendation	Relevance
topical steroids	Ia	A	yes
oral steroids	Ia	A	yes
oral antibiotics short term <4 weeks	Ib	A	yes, small effect
anti-Il-5	Ib	A	yes
oral antibiotics long term > 12 weeks	Ib	C**	yes, only when IgE is not increased
oral antihistamines in allergic patients	Ib	C	unclear
furosemide	III	D	no
nasal saline irrigation	no data	D	unclear
anti leukotrienes	Ib(-)#	A(-)$	no
anti-IgE%	Ib(-)	C	unclear

* Some of these studies also included patients with CRS with nasal polyps.

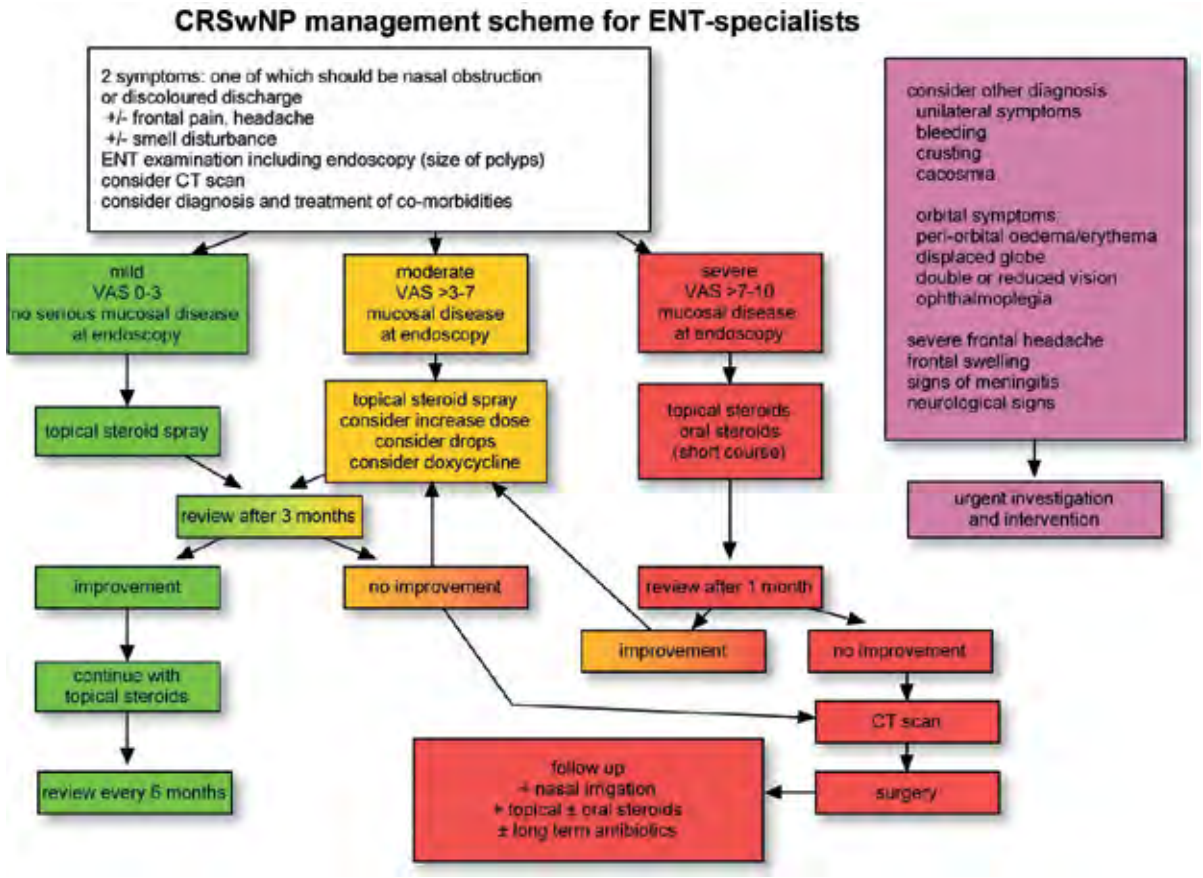
** Level of evidence for macrolides in all patients with CRSsNP is Ib, and strength of recommendation C, because the two double blind placebo controlled studies are contradictory; indication exist for better efficacy in CRSsNP patients with normal IgE the recommendation A. No RCTs exist for other antibiotics.

Ib (-): Ib study with a negative outcome.

$ A(-): grade A recommendation **not** to use

% Because positive level III evidence and positive unpublished 1b evidence recommendation is C

Figure 8.6. Management scheme for adults with CRS with NP for ENT specialists.



8.5.3.2. Treatment

For treatment evidence and recommendations for CRSsNP see Table 8.3 and 8.4.

Treatment should be based on severity of symptoms

- Decide on severity of symptomatology using VAS and endoscope. See Figure 8.5.

Acute exacerbations of CRS should be treated like acute rhinosinusitis.

8.5.4. Evidence based management for adults with CRS with NP for ENT specialists

8.5.4.1. Diagnosis

Symptoms present longer than 12 weeks

Two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

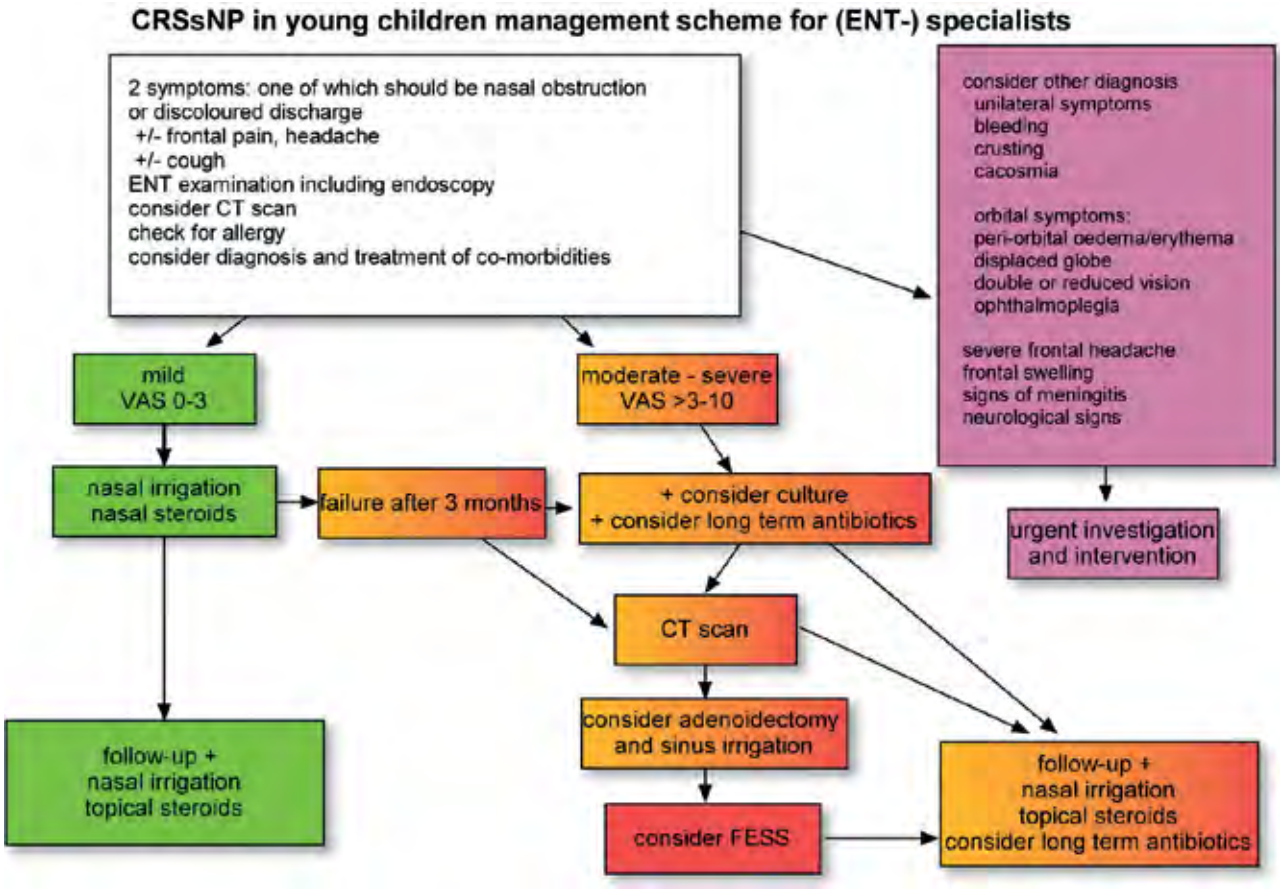
± facial pain/pressure,

± reduction or loss of smell;

Signs

- ENT examination, endoscopy;
- review primary care physician's diagnosis and treatment;
- questionnaire for allergy and if positive, allergy testing if it has not already been done.

Figure 8.7. Management scheme for young children with chronic rhinosinusitis.



8.5.4.2. Treatment

For treatment evidence and recommendations for CRSwNP see Table 8.5 and 8.6.

Treatment should be based on severity of symptoms

- Decide on severity of symptomatology using VAS and endoscope. See Figure 8.6.

8.6. Evidence based management for children with Chronic Rhinosinusitis

8.6.1. Definitions

8.6.1.1. Chronic Rhinosinusitis (with or without NP) in children is defined as:

presence of two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure;
± cough;
for ≥12 weeks;
with validation by telephone or interview.
Questions on allergic symptoms (i.e. sneezing, watery rhinorrhea, nasal itching, and itchy watery eyes) should be included.

Chronic rhinosinusitis with nasal polyps (CRSwNP): Chronic rhinosinusitis as defined above and bilateral, endoscopically visualised polyps in middle meatus.

Table 8.7. Treatment evidence and recommendations for children with chronic rhinosinusitis.

Therapy	Level	Grade of recommendation	Relevance
nasal saline irrigation	Ia	A	yes
therapy for gastro-oesophageal reflux	III	C	no
topical corticosteroid	IV	D	yes
oral antibiotic long term	no data	D	unclear
oral antibiotic short term <4 weeks	Ib(-)[#]	A(-)*	no
intravenous antibiotics	III(-)[##]	C(-) **	no

[#] Ib (-): Ib study with a negative outcome

*A(-): grade A recommendation **not** to use

[##]III(-): level III study with a negative outcome

C(-): grade C recommendation **not to use

Chronic Rhinosinusitis without nasal polyps (CRSsNP): Chronic Rhinosinusitis as defined above and no visible polyps in middle meatus, if necessary following decongestant.
This definition accepts that there is a spectrum of disease in CRS which includes polypoid change in the sinuses and/or middle meatus but excludes those with polypoid disease presenting in the nasal cavity to avoid overlap.

8.6.2. Evidence based management for children with Chronic Rhinosinusitis

8.6.2.1. Diagnosis

Symptoms present equal or longer than 12 weeks
two or more symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
± facial pain/pressure;
± cough;
Additional diagnostic information

- questions on allergy should be added and, if positive, allergy testing should be performed.

ENT examination, endoscopy if available;

Not recommended: plain x-ray or CT-scan (unless surgery is considered)

8.6.2.2. Treatment

For treatment evidence and recommendations for Chronic Rhinosinusitis in children see Table 8.7.
This management scheme is for young children. Older children (in the age that adenoids are not considered important) can be treated as adults. See Figure 8.7.

Acute exacerbations of CRS should be treated like acute rhinosinusitis.
Treatment should be based on severity of symptoms.

9. Research needs and search strategies

9.1. Introduction

The search strategies for all the (subchapters) include many pages. For that reason it was chosen to only have them online. You can find them at www.rhinologyjournal.com.

While our understanding of CRS has increased considerably, this only serves to outline areas that will require further exploration and clinical trials for validation of observations and hypotheses.

9.2. Classification and Definitions

Much of the problems which have beset our understanding of rhinosinusitis, particularly chronic forms is the difficulty of defining populations for study. Thus there remains the need for clear and widely accepted guidelines on the design of clinical trials which indicate:

- how to define the study population
- choice of outcome measurements
- choice of instruments to evaluate QoL.

It may also be advantageous to introduce some form of additional aetiological qualification to our classification systems which might be based on ICD coding.

There is also a need for the development of better objective staging systems that correlate with patient symptoms and QoL.

9.3. Acute rhinosinusitis

In acute rhinosinusitis, we need:

- To know what factors determine whether ARS patients in the community consult with a doctor, pharmacist or self-manage without professional support
- To demonstrate the prevalence of ARS in low, middle and high income countries and consider whether any predisposing factors differ dependant on income.
- To develop a validated disease-specific QoL questionnaire specific to acute rhinosinusitis.
- To establish if early use of therapies in viral URTI prevent bacterial ARS, particularly in those with recurrent ARS or at risk of complications.
- To confirm if there are combinations of symptoms and signs that predict acute bacterial rhinosinusitis in Primary and Secondary Care.
- To show if the relative frequency of different symptoms and signs in ARS predict a differential response to different therapies, such as topical steroids and antibiotics?
- To determine what constitutes a clinically important response to antibiotics in ARS eg change in purulence of nasal discharge.
- To determine biomarkers (eg CRP, procalcitonoin) that can predict acute bacterial rhinosinusitis or a clinically important response to antibiotics in ARS?
- To confirm whether topical nasal steroids can be the first-line treatment for ARS in Primary Care and consider whether there are clinically important differences between different topical nasal steroid molecules and dosing regimes
- To show whether the provision of educational and information materials for patients improve outcomes of ARS and reduce non-essential antibiotic use?
- To demonstrate whether professional education and efficient dissemination of evidence-based guidelines to clinicians improve outcomes of ARS and reduce non-essential antibiotic use?
- To show if the clinical and economic outcomes of ARS differ depending on which health professionals (e.g. rhinologists, ENT specialists, GPs, pharmacists?) manage patients.
- Large epidemiological data collection on the true incidence of complications in ARS, determining the role of Primary Care physicians in the detection and/or prevention of complications and whether complications of ARS relate to access to medical care?
- A large prospective study on the role of antibiotics in the prevention of acute complications.
- A randomised trial of drainage versus intravenous antibiotics for small abscesses in young children (orbital and intracranial)
- Large population studies characterizing co-morbidities in patients with ARS, compared to matched controls to identify significant co-morbidities or risk factors.
- Studies to establish how allergic rhinitis increases the predisposition for rhinosinusitis and specifically if it increases the likelihood of *S. pneumoniae* sinus infection.
- Assuming this is confirmed, studies to establish whether regular antihistamines and/or leukotriene receptor antagonists are effective in reducing ARS episodes in patients with allergic rhinitis.

- To determine how exposure to cigarette smoke increases the predisposition for ARS, to establish whether exposure to cigarette smoke (active or passive) augments the predisposition for ARS in patients with allergic rhinitis and to show whether smoking cessation improves the frequency of ARS compared to active smokers.
- To establish the prevalence of ARS in the Primary Ciliary Dyskinesia population, to determine whether aggressive treatment of ARS in patients with PCD prevents recurrence of ARS or development of CRS and to establish if aggressive treatment of ARS affects the progression of PCD-related bronchiectatic lung disease.

9.4. Chronic rhinosinusitis with or without NP

In chronic rhinosinusitis we need:

- To consider if the prevalence of and predisposing factors for CRSsNP and CRSwNP differs in low, middle and high income countries
- To determine the relative frequency and prognostic significance of different symptoms and signs in CRSsNP and CRSwNP in Primary Care.
- To refine severity staging and its impact on QoL, using both
. subjective and objective measures
- For endotyping and phenotyping, to define the minimal criteria for measuring sinus inflammation. eg sampling procedures and expression of data should be unified (ng of cytokine per ml, mg of tissue or protein content) so that a meta-analysis may be done.
- To refine the inclusion criteria of non-ENT control groups.
- To consider response to standard treatments for endotyping.
- A long-term study on the natural history of osteitis.
- A randomised trial comparing different treatment options for patients with CRS with significant osteitis.
- A trial to show if the purulence of nasal discharge is truly an indicator of bacterial infection and can be used as a clinically important response to antibiotics in CRS?
- To establish what, if any, childhood events increase chances of developing CRSwNP.
- To establish how smoking increases the risk of CRS and whether the risk is reduced by smoking cessation.
- To show if recognition of and appropriate treatment of allergic rhinitis reduce the incidence of CRSsNP and CRSwNP?
- To investigate the impact of psychological problems such as depression, stress exposure and anxiety on subjective severity scores and to consider the impact of neurological co-morbidities like chronic fatigue, post-traumatic stress disorder, neurological hyposmia, and measures of other neural-based disorders that play a role in non-allergic rhinitis, which may have an impact on rhinosinusitis scores.
- To consider neural aspects of facial pain, headache, smell disorders and hypersecretion.
- To consider the role of gastro-oesophageal reflux.

With respect to inflammatory mechanisms in CRSwNP and CRSsNP, we should consider if it is possible to:

- Develop a classification of CRS of phenotypes/endotypes based on "hypothesis-free" cluster analyses.
- Understand the regulation of TGF-ß and related molecules in remodeling processes.
- Understand the T regulatory cell deficit and the role of T effector cells in nasal polyp disease.
- Understand the role of dendritic cells in CRS.
- Understand the links between inflammation and remodeling.
- Understand the impact of the microbiome on inflammation
- Understand epigenetic regulation of upper airway disease.
- Understand the pathogenesis of 'allergic' fungal rhinosinusitis and AERD.
- Understand the link between CRSwNP and lower airway disease.

Nasal epithelial remodelling is a part of this natural defence mechanism, including migration, proliferation, and differentiation of epithelial cells, as well as the interactions between epithelial cells and stromal cells. To date, it is not possible to distinguish between a cause and an effect with regard to epithelium remodelling, nor are there clear roles for the many factors involved in nasal infectious and inflammatory diseases, due to a lack of intrinsic information about nasal epithelial cell responses. Most reported data are derived from lower airway studies or animal models. Therefore, research based on human nasal epithelial stem/progenitor cells can offer new light on pathophysiology of nasal airway disease from a different, more specific perspective. It will also allow molecular studies of human nasal epithelial cell interactions, differentiation, and repair, as well as responses to both environmental agents and to potential anti-inflammatory treatments.

- Further research is needed on the impact of bacterial, fungal or other microbial colonization/infection, with clear definition of such impact and we need some standardized methodology for research. For example should measures of minimal undetectable colonization, like PCR, or molecular cultivating techniques or hardly detectable immune response to colonizer be taken into account and if so, when?
- If infection is characterized by invasion, as well as by immune response to the micro-organism, we need to

define how this invasion is established at both a local and systemic level.

- Nearly all of the currently conducted human research is performed in patients who already have established disease or controls who do not. While this is useful in identifying unique contributors to the pathophysiology of CRS and subsequent treatments, it does not identify the actual cause of the disease. Currently available animal models are either allergic models or genetically manipulated animals that artificially generate an inflammatory response and again, do not answer the cause of the disease. There is thus a need for innovative experimental models in CRS.
- We should also focus on the differences between CRSwNP in western patients and elsewhere in the world. We need to identify key cytokines which mediate Th2 skewing across the epithelial barrier: TSLP vs. IL-25 vs. IL-33 vs.? The second key issue is the identity of the key effector cell(s): mast cells vs. esoinophils vs. neutrophils vs. ?
- There are variations in local anatomic immune response that are not related to airflow and environmental exposures. Research is needed into variations in immune response of the ethmoid/middle meatus for example, as this is different from the mucosal response of the septum or inferior turbinate.
- In the assessment of rhinosinusitis symptoms and examination in chronic rhinosinusitis, we need better tools for the diagnosis and differential diagnosis of facial pain.
- We need to understand the environmental factors that alter gene expression which may predispose to CRS. This may allow us to begin recognizing disease-causing agents versus disease-modifiers or exacerbating agents and in turn may allow us to alter behavior or implement therapies that can counteract any genetic predispositions and reverse/moderate epigenetic pre-disposition.

9.5. CRSwNP and CRSsNP in relation to the lower airways

To better understand the relationship of the upper and lower airways, we need:

- To conduct research on the basic physiology of the nose, including humidification and heat exchange and its effect on pulmonary function.
- To establish whether treatment of CRS affects outcomes of co-morbid lower airways disease (eg asthma, COPD).
- To undertake further RCTs studying the effects of surgery and medical treatment on the lower airways (lung function/QoL/symptoms) in CRSwNP and concomittant asthma.

9.6. Paediatric Chronic Rhinosinusitis

There is an urgent need to:

- Develop tools/tests in the context of clinical trials to differentiate the role of chronic adenoiditis from that of chronic rhinosinusitis in children with chronic nasal complaints.
- Establish the relevance of CT abnormalities in children with chronic nasal symptoms.
- Investigate immune mechanisms by better evaluating tissues obtained at the time of surgery for CRS through well organized, multi-centre collaborations.
- Undertake a multicentre randomized, placebo controlled, double- blind study evaluating the effect of oral antibiotics in paediatric CRS.
- Elucidate best surgical interventions by designing and executing prospective, randomized, multi-centre, controlled clinical trials. Severity of disease on CT scans and symptom questionnaire should ideally be matched pre-operatively and the following interventions could be compared: adenoidectomy alone, adenoidectomy with a wash-out, adenoidectomy with a wash-out and balloon maxillary sinuplasty, and endoscopic sinus surgery. An additional arm that includes medical therapy should also be included.

9.7. Management of CRSwNP and CRSsNP

We need to:

- Improve professional education and efficient dissemination of evidence-based guidelines to optimise outcomes and reduce referral rates to secondary care.
- Develop therapeutic approaches based on endotypes of disease such as IL-5 and SE-IgE positive polyps.
- Demonstrate whether the relative frequency of different symptoms and signs in CRSwNP and CRSsNP predict a differential response to different therapies, such as topical steroids and antibiotics.
- Conduct multicentre trials on endoscopic versus open management of complications of CRS, both intracranial and orbital.
- Conduct a large prospective placebo controlled study of long-term antibiotic treatment in a well-defined CRS population, exploring effects on the patient's quality of life, immune system, microbiota of the airway as well as the health economic impact.
- Seek better local therapies for immunomodulation.
- Conduct an RCT on oral steroids versus surgery on the long term outcomes of CRSwNP.
- Conduct an RCT studying the effects of oral corticosteroids on olfactory function in CRSwNP.
- Conduct multicentre RCTs on surgery versus no treatment for patients with CRSwNP to establish the natural course of disease.

- Conduct RCTs on minimal versus more extensive endoscopic sinus surgery.
- Investigate the effect of early surgical intervention on CRSwNP to see if it alters the course of the disease.

References

1. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl. 2007(20):1-136.
2. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clinic proceedings Mayo Clinic. 2011 May;86(5):427-43.
3. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. The Journal of allergy and clinical immunology. 2004 Dec;114(6 Suppl):155-212.
4. Fokkens W, Lund V, Bachert C, Clement P, Helllings P, Holmstrom M, et al. EAACI position paper on rhinosinusitis and nasal polyps executive summary. Allergy. 2005 May;60(5):583-601.
5. Fokkens W, Lund V, Mullol J. EP3OS 2007: European position paper on rhinosinusitis and nasal polyps 2007. A summary for otorhinolaryngologists. Rhinology. 2007 Jun;45(2):97-101.
6. Desrosiers M, Evans GA, Keith PK, Wright ED, Kaplan A, Bouchard J, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2011 May;40 Suppl 2:S99-193.
7. Fokkens W, Lund V, Bachert C, Clement P, Helllings P, Holmstrom M, et al. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl. 2005(18):1-87.
8. Wang DY, Wardani RS, Singh K, Thanaviratananich S, Vicente G, Xu G, et al. A survey on the management of acute rhinosinusitis among Asian physicians. Rhinology. 2011 Sep;49(3):264-71.
9. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009 May;64(5):669-77..
10. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing clinical guidelines. West J Med. 1999 Jun;170(6):348-51.
11. Tomassen P, Newson RB, Hoffmans R, Lotvall J, Cardell LO, Gunnbjornsdottir M, et al. Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis--a GA(2) LEN study. Allergy. 2011 Apr;66(4):556-61.
12. Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislimovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. Allergy. 2011 Sep;66(9):1216-23.
13. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. Allergy. 2012 Jan;67(1):91-8.
14. Van Crombruggen K, Van Bruaene N, Holtappels G, Bachert C. Chronic sinusitis and rhinitis: Clinical terminology Chronic Rhinosinusitis further supported. Rhinology. 2010 Mar 2;48(1):54-8.
15. Ragab SM, Lund VJ, Scadding G, Saleh HA, Khalifa MA. Impact of chronic rhinosinusitis therapy on quality of life; A prospective randomized controlled trial. Rhinology. 2010;48(3):305-11.
16. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. The Laryngoscope. 2004;114(5):923-30.
17. Cho SH, Hong SJ, Han B, Lee SH, Suh L, Norton J, et al. Age-related differences in the pathogenesis of chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2012 Jan 9.
18. Ebbens FA, Toppila-Salmi SK, Renkonen JA, Renkonen RL, Mullol J, van Drunen CM, et al. Endothelial L-selectin ligand expression in nasal polyps. Allergy. 2010 Jan;65(1):95-102.
19. van Drunen CM, Reinartz SM, Wigman J, Fokkens W. Inflammation in Chronic Rhinosinusitis and Nasal Polyposis. Immunology and allergy clinics of North America. 2009;29.
20. DeMarcantonio MA, Han JK. Nasal polyps: pathogenesis and treatment implications. Otolaryngologic clinics of North America. 2011 Jun;44(3):685-95, ix.
21. Zhang XH, Lu X, Long XB, You XJ, Gao QX, Cui YH, et al. Chronic rhinosinusitis with and without nasal polyps is associated with decreased expression of glucocorticoid-induced leucine zipper. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2009 May;39(5):647-54.
22. Zhang N, Van Zele T, Perez-Novo C, Van Bruaene N, Holtappels G, DeRuyck N, et al. Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. The Journal of allergy and clinical immunology. 2008 Nov;122(5):961-8.
23. Tan BK, Li QZ, Suh L, Kato A, Conley DB, Chandra RK, et al. Evidence for intranasal antinuclear autoantibodies in patients with chronic rhinosinusitis with nasal polyps. The Journal of allergy and clinical immunology. 2011 Oct 12.
24. Keswani A, Chustz RT, Suh L, Carter R, Peters AT, Tan BK, et al. Differential expression of interleukin-32 in chronic rhinosinusitis with and without nasal polyps. Allergy. 2012

Jan;67(1):25-32.

25. Kern RC, Conley DB, Walsh W, Chandra R, Kato A, Tripathi-Peters A, et al. Perspectives on the etiology of chronic rhinosinusitis: an immune barrier hypothesis. American journal of rhinology. 2008 Nov-Dec;22(6):549-59.
26. Tomassen P, Van Zele T, Zhang N, Perez-Novo C, Van Bruaene N, Gevaert P, et al. Pathophysiology of chronic rhinosinusitis. Proceedings of the American Thoracic Society. 2011 Mar;8(1):115-20.
27. Ebbens FA, Toppila-Salmi S, de Groot EJ, Renkonen J, Renkonen R, van Drunen CM, et al. Predictors of post-operative response to treatment: a double blind placebo controlled study in chronic rhinosinusitis patients. Rhinology. 2011 Oct;49(4):413-9.
28. Chan Y, Kuhn FA. An update on the classifications, diagnosis, and treatment of rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2009 Jun;17(3):204-8.
29. Marple BF, Brunton S, Ferguson BJ. Acute bacterial rhinosinusitis: A review of U.S. treatment guidelines. Otolaryngology - Head & Neck Surgery. [Review]. 2006;135(3):341-8.
30. Bachert C, Hormann K, Mosges R, Rasp G, Riechelmann H, Muller R, et al. An update on the diagnosis and treatment of sinusitis and nasal polyposis. Allergy. 2003 Mar;58(3):176-91.
31. Revai K, Dobbs LA, Nair S, Patel JA, Grady JJ, Chonmaitree T. Incidence of acute otitis media and sinusitis complicating upper respiratory tract infection: the effect of age. Pediatrics. 2007 Jun;119(6):e1408-12.
32. Uijen JH, Bindels PJ, Schellevis FG, van der Wouden JC. ENT problems in Dutch children: trends in incidence rates, antibiotic prescribing and referrals 2002-2008. Scand J Prim Health Care. 2011 Jun;29(2):75-9.
33. Neumark T, Brudin L, Engstrom S, Molstad S. Trends in number of consultations and antibiotic prescriptions for respiratory tract infections between 1999 and 2005 in primary healthcare in Kalmar County, Southern Sweden. Scand J Prim Health Care. 2009;27(1):18-24.
34. Oskarsson JP, Halldorsson S. [An evaluation of diagnosis and treatment of acute sinusitis at three health care centers]. Laeknabladid. 2010 Sep;96(9):531-5.
35. van Gageldonk-Lafeber AB, Heijnen ML, Bartelds AI, Peters MF, van der Plas SM, Wilbrink B. A case-control study of acute respiratory tract infection in general practice patients in The Netherlands. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005 Aug 15;41(4):490-7.
36. Cherry DK, Woodwell DA, Rechtsteiner EA. National Ambulatory Medical Care Survey: 2005 summary. Adv Data. 2007 Jun 29(387):1-39.
37. Bhattacharyya N. Contemporary assessment of the disease burden of sinusitis. The economic burden and symptom manifestations of chronic rhinosinusitis. Am J Rhinol Allergy. 2009;23(4):392-5.
38. Kaliner MA, Osguthorpe JD, Fireman P, Anon J, Georgitis J, Davis ML, et al. Sinusitis: bench to bedside. Current findings, future directions [published erratum appears in Otolaryngol Head Neck Surg 1997 Sep;117(3 Pt 1):187]. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1997;116(6 Pt 2):S1-20.
39. Bhutta MF, Al-Shaikh S, Latif M, Lee R, Uraiby J. Nasal polyps do not contain olfactory structures. Rhinology. 2011 Jun;49(2):185-9.
40. Louie JK, Hacker JK, Gonzales R, Mark J, Maselli JH, Yagi S, et al. Characterization of viral agents causing acute respiratory infection in a San Francisco University Medical Center Clinic during the influenza season. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005 Sep 15;41(6):822-8.
41. Varonen H, Rautakorpi UM, Huikko S, Honkanen PO, Klaukka T, Laippala P, et al. Management of acute maxillary sinusitis in Finnish primary care. Results from the nationwide MIKSTRA study. Scand J Prim Health Care. 2004 Jun;22(2):122-7.
42. Rautakorpi UM, Klaukka T, Honkanen P, Makela M, Nikkarinen T, Palva E, et al. Antibiotic use by indication: a basis for active antibiotic policy in the community. Scand J Infect Dis. 2001;33(12):920-6.
43. Bhattacharyya N, Grebner J, Martinson NG. Recurrent Acute Rhinosinusitis: Epidemiology and Health Care Cost Burden. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Oct 25.
44. Iseh KR, Makusidi M. Rhinosinusitis: a retrospective analysis of clinical pattern and outcome in north western Nigeria. Ann Afr Med. 2010 Jan-Mar;9(1):20-6.
45. Ogunleye AO, Nwargu OG, Lasisi AO, Ijaduola GT. Trends of sinusitis in Ibadan, Nigeria. West Afr J Med. 1999 Oct-Dec;18(4):298-302.
46. Treebupachatsakul P, Tiengrim S, Thamlikitkul V. Upper respiratory tract infection in Thai adults: prevalence and prediction of bacterial causes, and effectiveness of using clinical practice guidelines. J Med Assoc Thai. 2006 Aug;89(8):1178-86.
47. Suonpaa J, Antila J. Increase of acute frontal sinusitis in southwestern Finland. Scand J Infect Dis. 1990;22(5):563-8.
48. Bhattacharyya N. Air quality influences the prevalence of hay fever and sinusitis. The Laryngoscope. 2009;119(3):429-33. .
49. Tosca MA, Cosentino C, Pallestrini E, Riccio AM, Milanese M, Canonica GW, et al. Medical treatment reverses cytokine pattern in allergic and nonallergic chronic rhinosinusitis in asthmatic children. Pediatr Allergy Immunol. 2003 Jun;14(3):238-41.
50. van Gageldonk-Lafeber AB, van der Sande MA, Heijnen ML, Peeters MF, Bartelds AI, Wilbrink B. Risk factors for acute respiratory tract infections in general practitioner patients in The Netherlands: a case-control study. BMC infectious diseases. 2007;7:35.
51. Koskinen OM, Husman TM, Meklin TM,

Nevalainen AI. The relationship between moisture or mould observations in houses and the state of health of their occupants. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1999 Dec;14(6):1363-7.

52. Babar-Craig H, Gupta Y, Lund VJ. British Rhinological Society audit of the role of antibiotics in complications of acute rhinosinusitis: a national prospective audit. Rhinology. 2010 Sep;48(3):344-7.
53. Rank MA, Wollan P, Kita H, Yawn BP. Acute exacerbations of chronic rhinosinusitis occur in a distinct seasonal pattern. The Journal of allergy and clinical immunology. 2010 May 29.
54. Eccles R. An explanation for the seasonality of acute upper respiratory tract viral infections. Acta Otolaryngol. 2002 Mar;122(2):183-91.
55. Rudmik L, Muzychuk A, Oddone Paolucci E, Mechor B. Chinook wind barosinusitis: an anatomic evaluation. American journal of rhinology & allergy. 2009 Nov-Dec;23(6):e14-6.
56. Trevino RJ. Air pollution and its effect on the upper respiratory tract and on allergic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1996 Feb;114(2):239-41.
57. Zuskin E, Mustajbegovic J, Schachter EN, Kern J, Deckovic-Vukres V, Pucarin-Cvetkovic J, et al. Respiratory findings in pharmaceutical workers. Am J Ind Med. 2004 Nov;46(5):472-9.
58. Jaakkola MS, Jaakkola JJ. Office equipment and supplies: a modern occupational health concern? Am J Epidemiol. 1999 Dec 1;150(11):1223-8.
59. Duclos P, Sanderson LM, Lipsett M. The 1987 forest fire disaster in California: assessment of emergency room visits. Arch Environ Health. 1990 Jan-Feb;45(1):53-8.
60. Alkire BC, Bhattacharyya N. An assessment of sinonasal anatomic variants potentially associated with recurrent acute rhinosinusitis. The Laryngoscope. 2010 Mar;120(3):631-4.
61. Bomeli SR, Branstetter BFt, Ferguson BJ. Frequency of a dental source for acute maxillary sinusitis. The Laryngoscope. 2009 Mar;119(3):580-4.
62. Mathew AL, Pai KM, Sholapurkar AA. Maxillary sinus findings in the elderly: a panoramic radiographic study. J Contemp Dent Pract. 2009;10(6):E041-8.
63. Eyigor H, Basak S. [Evaluation of predisposing factors and bacteriologic agents in pediatric rhinosinusitis]. Kulak Burun Bogaz Ihtis Derg. 2005;15(3-4):49-55.
64. Savolainen S. Allergy in patients with acute maxillary sinusitis. Allergy. 1989 Feb;44(2):116-22.
65. Ciprandi G, Buscaglia S, Pesce G, Villaggio B, Bagnasco M, Canonica GW. Allergic subjects express intercellular adhesion molecule--1 (ICAM-1 or CD54) on epithelial cells of conjunctiva after allergen challenge. The Journal of allergy and clinical immunology. 1993 Mar;91(3):783-92.
66. Ciprandi G, Tosca MA, Fasce L. Allergic children have more numerous and severe respiratory infections than non-allergic children. Pediatr Allergy Immunol. 2006 Aug;17(5):389-91.
67. Melvin TA, Lane AP, Nguyen MT, Lin SY. Allergic rhinitis patients with recurrent acute sinusitis have increased sinonasal epithelial cell TLR9 expression. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 May;142(5):659-64.
68. An YF, Wang WH, Zhao CQ, Xue JM, Zhao HL. [Preliminary investigation into the allergic rhinitis complicated with acute bacterial sinusitis in mice]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2007 Feb;42(2):138-42.
69. Naclerio R, Blair C, Yu X, Won YS, Gabr U, Baroody FM. Allergic rhinitis augments the response to a bacterial sinus infection in mice: A review of an animal model. American journal of rhinology. 2006 Sep-Oct;20(5):524-33.
70. Blair C, Nelson M, Thompson K, Boonlayangoor S, Haney L, Gabr U, et al. Allergic inflammation enhances bacterial sinusitis in mice. The Journal of allergy and clinical immunology. 2001 Sep;108(3):424-9.
71. Mbarek C, Akrout A, Khamassi K, Ben Gamra O, Hariga I, Ben Amor M, et al. [Recurrent upper respiratory tract infections in children and allergy. A cross-sectional study of 100 cases]. Tunis Med. 2008 Apr;86(4):358-61.
72. Ulanovski D, Barenboim E, Raveh E, Grossman A, Azaria B, Shpitzer T. Sinusitis in pilots of different aircraft types: is allergic rhinitis a predisposing factor? American journal of rhinology. 2008 Mar-Apr;22(2):122-4.
73. Ruoppi P, Seppa J, Nuutinen J. Acute frontal sinusitis: etiological factors and treatment outcome. Acta Otolaryngol. 1993 Mar;113(2):201-5.
74. Schatz M, Zeiger RS, Chen W, Yang SJ, Corrao MA, Quinn VP. The burden of rhinitis in a managed care organization. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2008 Sep;101(3):240-7.
75. Eccles R. Mechanisms of the symptoms of rhinosinusitis. Rhinology. 2011 Jun;49(2):131-8.
76. Lin SW, Wang YH, Lee MY, Ku MS, Sun HL, Lu KH, et al. Clinical spectrum of acute rhinosinusitis among atopic and nonatopic children in Taiwan. Int J Pediatr Otorhinolaryngol. 2012 Jan;76(1):70-5.
77. Benoliel R, Biron A, Quek SY, Nahlieli O, Eliav E. Trigeminal neurosensory changes following acute and chronic paranasal sinusitis. Quintessence Int. 2006 Jun;37(6):437-43.
78. Vlastos I, Athanasopoulos I, Mastronikolis NS, Panogeorgou T, Margaritis V, Naxakis S, et al. Impaired mucociliary clearance in allergic rhinitis patients is related to a predisposition to rhinosinusitis. Ear, nose, & throat journal. 2009 Apr;88(4):E17-9.
79. Pant H, Ferguson BJ, Macardle PJ. The role of allergy in rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2009 Jun;17(3):232-8.
80. Alho OP. Nasal airflow, mucociliary

clearance, and sinus functioning during viral colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. American journal of rhinology. 2004 Nov-Dec;18(6):349-55.

81. Kirtsreesakul V, Blair C, Yu X, Thompson K, Naclerio RM. Desloratadine partially inhibits the augmented bacterial responses in the sinuses of allergic and infected mice. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2004 Oct;34(10):1649-54.
82. Ciprandi G, Ricca V, Tosca M, Landi M, Passalacqua G, Canonica GW. Continuous antihistamine treatment controls allergic inflammation and reduces respiratory morbidity in children with mite allergy. Allergy. 1999 Apr;54(4):358-65.
83. Braun JJ, Alabert JP, Michel FB, Quiniou M, Rat C, Cougnard J, et al. Adjunct effect of loratadine in the treatment of acute sinusitis in patients with allergic rhinitis. Allergy. 1997 Jun;52(6):650-5.
84. Tamashiro E, Xiong G, Anselmo-Lima WT, Kreindler JL, Palmer JN, Cohen NA. Cigarette smoke exposure impairs respiratory epithelial ciliogenesis. American journal of rhinology & allergy. 2009 Mar-Apr;23(2):117-22.
85. De S, Leong SC, Fenton JE, Carter SD, Clarke RW, Jones AS. The effect of passive smoking on the levels of matrix metalloproteinase 9 in nasal secretions of children. American journal of rhinology & allergy. 2011 Jul-Aug;25(4):226-30.
86. Bush A, Chodhari R, Collins N, Copeland F, Hall P, Harcourt J, et al. Primary ciliary dyskinesia: current state of the art. Arch Dis Child. 2007 Dec;92(12):1136-40.
87. Holzmann D, Felix H. Neonatal respiratory distress syndrome--a sign of primary ciliary dyskinesia? European journal of pediatrics. 2000 Nov;159(11):857-60.
88. Ferkol T, Leigh M. Primary ciliary dyskinesia and newborn respiratory distress. Semin Perinatol. 2006 Dec;30(6):335-40.
89. Hossain T, Kappelman MD, Perez-Atayde AR, Young GJ, Huttner KM, Christou H. Primary ciliary dyskinesia as a cause of neonatal respiratory distress: implications for the neonatologist. J Perinatol. 2003 Dec;23(8):684-7.
90. Torgersen J. Transposition of viscera, bronchiectasis and nasal polyps; a genetical analysis and a contribution to the problem of constitution. Acta radiol. 1947 Feb 28;28(1):17-24.
91. Afzelius BA, Stenram U. Prevalence and genetics of immotile-cilia syndrome and left-handedness. Int J Dev Biol. 2006;50(6):571-3.
92. Katsuhara K, Kawamoto S, Wakabayashi T, Belsky JL. Situs inversus totalis and Kartagener's syndrome in a Japanese population. Chest. 1972 Jan;61(1):56-61.
93. Verra F, Escudier E, Bignon J, Pinchon MC, Boucherat M, Bernaudin JF, et al. Inherited factors in diffuse bronchiectasis in the adult: a prospective study. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1991 Sep;4(8):937-44.
94. Barbato A, Frischer T, Kuehni CE, Snijders D, Azevedo I, Baktai G, et al. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2009 Dec;34(6):1264-76.
95. Pedersen M, Mygind N. Rhinitis, sinusitis and otitis media in Kartagener's syndrome (primary ciliary dyskinesia). Clinical otolaryngology and allied sciences. 1982 Dec;7(6):373-80.
96. Clinical practice guideline: management of sinusitis. Pediatrics. 2001 Sep;108(3):798-808.
97. Mygind N, Pedersen M. Nose-, sinus- and ear-symptoms in 27 patients with primary ciliary dyskinesia. Eur J Respir Dis Suppl. 1983;127:96-101.
98. Bonham GS, Wilson RW. Children's health in families with cigarette smokers. Am J Public Health. 1981 Mar;71(3):290-3.
99. Zuskin E, Mustajbegovic J, Schachter EN, Kern J, Vadjic V, Strok N, et al. Respiratory findings in mail carriers. Int Arch Occup Environ Health. 2000 Mar;73(2):136-43.
100. Lin SY, Reh DD, Clipp S, Irani L, Navas-Acien A. Allergic rhinitis and secondhand tobacco smoke: a population-based study. American journal of rhinology & allergy. 2011 Mar-Apr;25(2):e66-71.
101. Brook I. Effects of exposure to smoking on the microbial flora of children and their parents. Int J Pediatr Otorhinolaryngol. 2010 May;74(5):447-50.
102. Brook I, Gober AE. Effect of smoking cessation on the microbial flora. Archives of otolaryngology--head & neck surgery. 2007 Feb;133(2):135-8.
103. Davis KS, Casey SE, Mulligan JK, Mulligan RM, Schlosser RJ, Atkinson C. Murine complement deficiency ameliorates acute cigarette smoke-induced nasal damage. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 Jul;143(1):152-8.
104. Pacheco-Galvan A, Hart SP, Morice AH. Relationship between gastro-oesophageal reflux and airway diseases: the airway reflux paradigm. Arch Bronconeumol. 2011 Apr;47(4):195-203.
105. Flook EP, Kumar BN. Is there evidence to link acid reflux with chronic sinusitis or any nasal symptoms? A review of the evidence. Rhinology. 2011 Mar;49(1):11-6.
106. Adams TB, Wharton CM, Quilter L, Hirsch T. The association between mental health and acute infectious illness among a national sample of 18- to 24-year-old college students. J Am Coll Health. 2008 May-Jun;56(6):657-63.
107. Principi N, Esposito S. New insights into pediatric rhinosinusitis. Pediatr Allergy Immunol. 2007 Nov;18 Suppl 18:7-9.
108. Brook I, Gober AE. Frequency of recovery of pathogens from the nasopharynx of children with acute maxillary sinusitis before and after the introduction of vaccination with the 7-valent pneumococcal vaccine. Int J Pediatr Otorhinolaryngol. 2007 Apr;71(4):575-9.
109. Benninger MS. Acute bacterial rhinosinusitis and otitis media: changes in pathogenicity following widespread use of pneumococcal conjugate vaccine. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.

2008 Mar;138(3):274-8.

110. Reinert RR. The antimicrobial resistance profile of Streptococcus pneumoniae. Clin Microbiol Infect. 2009 Apr;15 Suppl 3:7-11.
111. Rybak MJ. Increased bacterial resistance: PROTEKT US--an update. The Annals of pharmacotherapy. 2004 Sep;38(9 Suppl):S8-S13.
112. Sahm DF, Benninger MS, Evangelista AT, Yee YC, Thornsberry C, Brown NP. Antimicrobial resistance trends among sinus isolates of Streptococcus pneumoniae in the United States (2001-2005). Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 Mar;136(3):385-9.
113. Loughlin J, Poulios N, Napalkov P, Wegmuller Y, Monto AS. A study of influenza and influenza-related complications among children in a large US health insurance plan database. Pharmacoeconomics. 2003;21(4):273-83.
114. Heikkinen T, Jarvinen A. The common cold. Lancet. 2003 Jan 4;361(9351):51-9.
115. Payne SC, Benninger MS. Staphylococcus aureus is a major pathogen in acute bacterial rhinosinusitis: a meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2007 Nov 15;45(10):e121-7.
116. Anonymous. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngology - Head & Neck Surgery. [Review]. 2004;130(1 SUPPL.):1-45.
117. Brook I. Bacteriology of acute and chronic frontal sinusitis. Archives of otolaryngology--head & neck surgery. 2002 May;128(5):583-5.
118. Mims C, Dockrell HM, Goering RV, Roitt I, Wakelin D, Zuckerman M. Medical Microbiology. Third edition ed: Elsevier Mosby; 2004.
119. van Cauwenberge P, Ingels K. Effects of viral and bacterial infection on nasal and sinus mucosa. Acta Otolaryngol. 1996 Mar;116(2):316-21.
120. Papi A, Johnston SL. Rhinovirus infection induces expression of its own receptor intercellular adhesion molecule 1 (ICAM-1) via increased NF-kappaB-mediated transcription. J Biol Chem. 1999 Apr 2;274(14):9707-20.
121. Bianco A, Whiteman SC, Sethi SK, Allen JT, Knight RA, Spiteri MA. Expression of intercellular adhesion molecule-1 (ICAM-1) in nasal epithelial cells of atopic subjects: a mechanism for increased rhinovirus infection? Clin Exp Immunol. 2000 Aug;121(2):339-45.
122. Hellings. Rhinosinusitis and the lower airways. Immunology and allergy clinics of North America. 2009;29(4):733-40.
123. Greve JM, Davis G, Meyer AM, Forte CP, Yost SC, Marlor CW, et al. The major human rhinovirus receptor is ICAM-1. Cell. 1989 Mar 10;56(5):839-47.
124. van Kempen M. An update on the pathophysiology of rhinovirus upper respiratory tract infections. Rhinology. 1999;37(3):97-103.
125. Bianco A, Sethi SK, Allen JT, Knight RA, Spiteri MA. Th2 cytokines exert a dominant influence on epithelial cell expression of the major group human rhinovirus receptor, ICAM-1. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1998 Sep;12(3):619-26.
126. Lund. Therapeutic targets in rhinosinusitis: infection or inflammation? Medscape J Med. 2008;10(4):105.
127. Masood A, Moumoulidis I, Panesar J. Acute rhinosinusitis in adults: an update on current management. Postgrad Med J. 2007 Jun;83(980):402-8.
128. Gnoy. A potential role for nasal obstruction in development of acute sinusitis: an infection study in rabbits. American journal of rhinology. 1998;12(6):399-404.
129. Leung RS, Katial R. The diagnosis and management of acute and chronic sinusitis. Prim Care. 2008 Mar;35(1):11-24, v-vi.
130. Skoner DP. Complications of allergic rhinitis. The Journal of allergy and clinical immunology. 2000 Jun;105(6 Pt 2):S605-9.
131. Gwaltney JM, Jr., Hendley JO, Phillips CD, Bass CR, Mygind N, Winther B. Nose blowing propels nasal fluid into the paranasal sinuses. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000 Feb;30(2):387-91.
132. Wang JH, Kwon HJ, Jang YJ. Rhinovirus enhances various bacterial adhesions to nasal epithelial cells simultaneously. The Laryngoscope. 2009 Jul;119(7):1406-11.
133. Passariello C, Schippa S, Conti C, Russo P, Poggiali F, Garaci E, et al. Rhinoviruses promote internalisation of Staphylococcus aureus into non-fully permissive cultured pneumocytes. Microbes Infect. 2006 Mar;8(3):758-66.
134. Blair C. Role of type 1 T helper cells in the resolution of acute Streptococcus pneumoniae sinusitis: a mouse model. J Infect Dis. 2005;192(7):1237-44.
135. Sabroe I, Read RC, Whyte MK, Dockrell DH, Vogel SN, Dower SK. Toll-like receptors in health and disease: complex questions remain. J Immunol. 2003 Aug 15;171(4):1630-5.
136. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. Nat Immunol. 2001 Aug;2(8):675-80.
137. Schnare M, Barton GM, Holt AC, Takeda K, Akira S, Medzhitov R. Toll-like receptors control activation of adaptive immune responses. Nat Immunol. 2001 Oct;2(10):947-50.
138. Sabroe I, Parker LC, Wilson AG, Whyte MK, Dower SK. Toll-like receptors: their role in allergy and non-allergic inflammatory disease. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2002 Jul;32(7):984-9.
139. Vandermeer J, Sha Q, Lane AP, Schleimer RP. Innate immunity of the sinonasal cavity: expression of messenger RNA for complement cascade components and toll-like receptors. Archives of otolaryngology--head & neck surgery. 2004 Dec;130(12):1374-80.
140. Fransson M, Adner M, Erjefalt J, Jansson L, Uddman R, Cardell LO. Up-regulation of Toll-like receptors 2, 3 and 4 in allergic rhinitis. Respir Res. 2005;6:100.

141. Kunzelmann K, Sun J, Meanger J, King NJ, Cook DI. Inhibition of airway Na+ transport by respiratory syncytial virus. J Virol. 2007 Apr;81(8):3714-20.
142. Kunzelmann K, Beesley AH, King NJ, Karupiah G, Young JA, Cook DI. Influenza virus inhibits amiloride-sensitive Na+ channels in respiratory epithelia. Proc Natl Acad Sci U S A. 2000 Aug 29;97(18):10282-7.
143. Kunzelmann K, Konig J, Sun J, Markovich D, King NJ, Karupiah G, et al. Acute effects of parainfluenza virus on epithelial electrolyte transport. J Biol Chem. 2004 Nov 19;279(47):48760-6.
144. Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, et al. A Toll-like receptor recognizes bacterial DNA. Nature. 2000 Dec 7;408(6813):740-5.
145. Klinman DM. Immunotherapeutic uses of CpG oligodeoxynucleotides. Nat Rev Immunol. 2004 Apr;4(4):249-58.
146. Heeg K, Dalpke A, Peter M, Zimmermann S. Structural requirements for uptake and recognition of CpG oligonucleotides. Int J Med Microbiol. 2008 Jan;298(1-2):33-8.
147. Wagner H. Interactions between bacterial CpG-DNA and TLR9 bridge innate and adaptive immunity. Curr Opin Microbiol. 2002 Feb;5(1):62-9.
148. Mansson A, Bachar O, Adner M, Cardell LO. Nasal CpG oligodeoxynucleotide administration induces a local inflammatory response in nonallergic individuals. Allergy. 2009 Sep;64(9):1292-300.
149. 149.Nagai Y, Akashi S, Nagafuku M, Ogata M, Iwakura Y, Akira S, et al. Essential role of MD-2 in LPS responsiveness and TLR4 distribution. Nat Immunol. 2002 Jul;3(7):667-72.
150. Shimazu R, Akashi S, Ogata H, Nagai Y, Fukudome K, Miyake K, et al. MD-2, a molecule that confers lipopolysaccharide responsiveness on Toll-like receptor 4. J Exp Med. 1999 Jun 7;189(11):1777-82.
151. Chow JC, Young DW, Golenbock DT, Christ WJ, Gusovsky F. Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction. J Biol Chem. 1999 Apr 16;274(16):10689-92.
152. Takeda K, Kaisho T, Akira S. Toll-like receptors. Annu Rev Immunol. 2003;21:335-76.
153. Heine H, Lien E. Toll-like receptors and their function in innate and adaptive immunity. Int Arch Allergy Immunol. 2003 Mar;130(3):180-92.
154. Hertz CJ, Kiertscher SM, Godowski PJ, Bouis DA, Norgard MV, Roth MD, et al. Microbial lipopeptides stimulate dendritic cell maturation via Toll-like receptor 2. J Immunol. 2001 Feb 15;166(4):2444-50.
155. Michelsen KS, Aicher A, Mohaupt M, Hartung T, Dimmeler S, Kirschning CJ, et al. The role of toll-like receptors (TLRs) in bacteria-induced maturation of murine dendritic cells (DCS). Peptidoglycan and lipoteichoic acid are inducers of DC maturation and require TLR2. J Biol Chem. 2001 Jul 13;276(28):25680-6.
156. van Rossum AM, Lysenko ES, Weiser JN. Host and bacterial factors contributing to the clearance of colonization by Streptococcus pneumoniae in a murine model. Infect Immun. 2005 Nov;73(11):7718-26.
157. Schwandner R, Dziarski R, Wesche H, Rothe M, Kirschning CJ. Peptidoglycan- and lipoteichoic acid-induced cell activation is mediated by toll-like receptor 2. J Biol Chem. 1999 Jun 18;274(25):17406-9.
158. Malley R, Henneke P, Morse SC, Cieslewicz MJ, Lipsitch M, Thompson CM, et al. Recognition of pneumolysin by Toll-like receptor 4 confers resistance to pneumococcal infection. Proc Natl Acad Sci U S A. 2003 Feb 18;100(4):1966-71.
159. Claeys S, de Belder T, Holtappels G, Gevaert P, Verhasselt B, van Cauwenberge P, et al. Human beta-defensins and toll-like receptors in the upper airway. Allergy. 2003 Aug;58(8):748-53.
160. Igarashi Y, Skoner DP, Doyle WJ, White MV, Fireman P, Kaliner MA. Analysis of nasal secretions during experimental rhinovirus upper respiratory infections. The Journal of allergy and clinical immunology. 1993 Nov;92(5):722-31.
161. Naclerio RM, Proud D, Lichtenstein LM, Kagey-Sobotka A, Hendley JO, Sorrentino J, et al. Kinins are generated during experimental rhinovirus colds. J Infect Dis. 1988 Jan;157(1):133-42.
162. Shibayama Y, Skoner D, Suehiro S, Konishi JE, Fireman P, Kaplan AP. Bradykinin levels during experimental nasal infection with rhinovirus and attenuated influenza virus. Immunopharmacology. 1996 Jun;33(1-3):311-3.
163. Proud D, Gwaltney JM, Jr., Hendley JO, Dinarello CA, Gillis S, Schleimer RP. Increased levels of interleukin-1 are detected in nasal secretions of volunteers during experimental rhinovirus colds. J Infect Dis. 1994 May;169(5):1007-13.
164. Tamaoki J, Kobayashi K, Sakai N, Chiyotani A, Kanemura T, Takizawa T. Effect of bradykinin on airway ciliary motility and its modulation by neutral endopeptidase. Am Rev Respir Dis. 1989 Aug;140(2):430-5.
165. Proud D. Kinins in the pathogenesis of human airway diseases. Braz J Med Biol Res. 1994 Aug;27(8):2021-31.
166. Dear JW, Ghali S, Foreman JC. Attenuation of human nasal airway responses to bradykinin and histamine by inhibitors of nitric oxide synthase. Br J Pharmacol. 1996 Jul;118(5):1177-82.
167. 167.Maeda H, Akaike T, Wu J, Noguchi Y, Sakata Y. Bradykinin and nitric oxide in infectious disease and cancer. Immunopharmacology. 1996 Jun;33(1-3):222-30.
168. Djupesland PG. Nitric oxide in the nasal airway: a new dimension in otorhinolaryngology. Am J Otolaryngol. 2001;22(1):19-32.
169. Sahin G. Nitric oxide: a promising methodological approach in airway diseases. Int Arch Allergy Immunol 2011;156(4):352-61.
170. Lundberg JO. Airborne nitric oxide: inflammatory marker and aerocrine messenger in man. Acta Physiol Scand Suppl. 1996;633:1-27.
171. Barnes PJ, Belvisi MG. Nitric oxide and lung disease. Thorax. 1993 Oct;48(10):1034-43.
172. Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. American journal of respiratory and critical care medicine. 2001 Jun;163(7):1693-722.

173. Croen KD. Evidence for antiviral effect of nitric oxide. Inhibition of herpes simplex virus type 1 replication. J Clin Invest. 1993 Jun;91(6):2446-52.
174. Mancinelli RL, McKay CP. Effects of nitric oxide and nitrogen dioxide on bacterial growth. Appl Environ Microbiol. 1983 Jul;46(1):198-202.
175. Guven M, Aladag I, Eyibilen A, Filiz NO, Ozyurt H, Yelken K. Experimentally induced acute sinusitis and efficacy of vitamin A. Acta Otolaryngol. 2007 Aug;127(8):855-60.
176. Carraro S. Exhaled nitric oxide in children with asthma and sinusitis. Pediatr Allergy Immunol. 2007;18(suppl):28-30.
177. Baraldi E, Azzolin NM, Biban P, Zacchello F. Effect of antibiotic therapy on nasal nitric oxide concentration in children with acute sinusitis. American journal of respiratory and critical care medicine. 1997 May;155(5):1680-3.
178. Marriott HM, Ali F, Read RC, Mitchell TJ, Whyte MK, Dockrell DH. Nitric oxide levels regulate macrophage commitment to apoptosis or necrosis during pneumococcal infection. FASEB J. 2004 Jul;18(10):1126-8.
179. Bertrand C, Geppetti P. Tachykinin and kinin receptor antagonists: therapeutic perspectives in allergic airway disease. Trends Pharmacol Sci. 1996 Jul;17(7):255-9.
180. Van Cauwenberge PB, Vermeiren JS, van Kempen MJ. Viral rhinitis and asthma. Curr Opin Allergy Clin Immunol. 2001 Feb;1(1):21-5.
181. Gabr U, Won YS, Boonlayangoor S, Thompson K, Baroody FM, Naclerio RM. C57Bl/6 and BALB/c mice have similar neutrophil response to acute Streptococcus pneumoniae sinus infections. Archives of otolaryngology--head & neck surgery. 2001 Aug;127(8):985-90.
182. O'Doherty U, Peng M, Gezelter S, Swiggard WJ, Betjes M, Bhardwaj N, et al. Human blood contains two subsets of dendritic cells, one immunologically mature and the other immature. Immunology. 1994 Jul;82(3):487-93.
183. Hartmann E, Graefe H, Hopert A, Pries R, Rothenfusser S, Poeck H, et al. Analysis of plasmacytoid and myeloid dendritic cells in nasal epithelium. Clin Vaccine Immunol. 2006 Nov;13(11):1278-86.
184. Hamilos DL. Antigen presenting cells. Immunol Res. 1989;8(2):98-117.
185. Chen ZM, Mao JH, Du LZ, Tang YM. Association of cytokine responses with disease severity in infants with respiratory syncytial virus infection. Acta Paediatr. 2002;91(9):914-22.
186. Garofalo RP, Hintz KH, Hill V, Ogra PL, Welliver RC, Sr. Production of interferon gamma in respiratory syncytial virus infection of humans is not associated with interleukins 12 and 18. J Med Virol. 2004 Jun;73(2):289-94.
187. Kaiser L, Fritz RS, Straus SE, Gubareva L, Hayden FG. Symptom pathogenesis during acute influenza: interleukin-6 and other cytokine responses. J Med Virol. 2001 Jul;64(3):262-8.
188. Oh JW, Lee HB, Park IK, Kang JO. Interleukin-6, interleukin-8, interleukin-11, and interferon-gamma levels in nasopharyngeal aspirates from wheezing children with respiratory syncytial virus or influenza A virus infection. Pediatr Allergy Immunol. 2002 Oct;13(5):350-6.
189. Borish L, Rosenwasser LJ. Update on cytokines. The Journal of allergy and clinical immunology. 1996 Mar;97(3):719-33; quiz 34.
190. Heinecke L, Proud D, Sanders S, Schleimer RP, Kim J. Induction of B7-H1 and B7-DC expression on airway epithelial cells by the Toll-like receptor 3 agonist double-stranded RNA and human rhinovirus infection: In vivo and in vitro studies. The Journal of allergy and clinical immunology. 2008 May;121(5):1155-60.
191. Kim J, Myers AC, Chen L, Pardoll DM, Truong-Tran QA, Lane AP, et al. Constitutive and inducible expression of b7 family of ligands by human airway epithelial cells. Am J Respir Cell Mol Biol. 2005 Sep;33(3):280-9.
192. Kurosawa S, Myers AC, Chen L, Wang S, Ni J, Plitt JR, et al. Expression of the costimulatory molecule B7-H2 (inducible costimulator ligand) by human airway epithelial cells. Am J Respir Cell Mol Biol. 2003 May;28(5):563-73.
193. Kemp K, Bruunsgaard H, Skinhoj P, Klarlund Pedersen B. Pneumococcal infections in humans are associated with increased apoptosis and trafficking of type 1 cytokine-producing T cells. Infect Immun. 2002 Sep;70(9):5019-25.
194. Malley R, Trzcinski K, Srivastava A, Thompson CM, Anderson PW, Lipsitch M. CD4+ T cells mediate antibody-independent acquired immunity to pneumococcal colonization. Proc Natl Acad Sci U S A. 2005 Mar 29;102(13):4848-53.
195. McCool TL, Weiser JN. Limited role of antibody in clearance of Streptococcus pneumoniae in a murine model of colonization. Infect Immun. 2004 Oct;72(10):5807-13.
196. Gern JE, Martin MS, Anklam KA, Shen K, Roberg KA, Carlson-Dakes KT, et al. Relationships among specific viral pathogens, virus-induced interleukin-8, and respiratory symptoms in infancy. Pediatr Allergy Immunol. 2002 Dec;13(6):386-93.
197. Hornsleth A, Loland L, Larsen LB. Cytokines and chemokines in respiratory secretion and severity of disease in infants with respiratory syncytial virus (RSV) infection. J Clin Virol. 2001 May;21(2):163-70.
198. Noah TL, Becker S. Chemokines in nasal secretions of normal adults experimentally infected with respiratory syncytial virus. Clin Immunol. 2000 Oct;97(1):43-9.
199. Sheeran P, Jafri H, Carubelli C, Saavedra J, Johnson C, Krisher K, et al. Elevated cytokine concentrations in the nasopharyngeal and tracheal secretions of children with respiratory syncytial virus disease. Pediatr Infect Dis J. 1999 Feb;18(2):115-22.
200. 200.Bussolino F, Breviario F, Tetta C, Aglietta M, Mantovani A, Dejana E. Interleukin 1 stimulates platelet-activating factor production in cultured human endothelial cells. J Clin Invest. 1986 Jun;77(6):2027-33.

201. Becker S, Koren HS, Henke DC. Interleukin-8 expression in normal nasal epithelium and its modulation by infection with respiratory syncytial virus and cytokines tumor necrosis factor, interleukin-1, and interleukin-6. Am J Respir Cell Mol Biol. 1993 Jan;8(1):20-7.
202. Strieter RM, Kunkel SL, Showell HJ, Remick DG, Phan SH, Ward PA, et al. Endothelial cell gene expression of a neutrophil chemotactic factor by TNF-alpha, LPS, and IL-1 beta. Science (New York, NY). 1989 Mar 17;243(4897):1467-9.
203. van Benten I. Reduced nasal IL-10 and enhanced TNFalpha responses during rhinovirus and RSV-induced upper respiratory tract infection in atopic and non-atopic infants. J Med Virol. 2005;75(2):348-57.
204. Gern JE. Rhinovirus respiratory infections and asthma. Am J Med. 2002;112(6a):19S-27S.
205. Gern JE, Vrtis R, Grindle KA, Swenson C, Busse WW. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. American journal of respiratory and critical care medicine. 2000 Dec;162(6):2226-31.
206. Linden M, Greiff L, Andersson M, Svensson C, Akerlund A, Bende M, et al. Nasal cytokines in common cold and allergic rhinitis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1995 Feb;25(2):166-72.
207. Riechelmann H, Deutschle T, Rozsasi A, Keck T, Polzehl D, Burner H. Nasal biomarker profiles in acute and chronic rhinosinusitis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2005 Sep;35(9):1186-91.
208. Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol. 2003 Feb;3(2):133-46.
209. Yamamoto N, Kawakami K, Kinjo Y, Miyagi K, Kinjo T, Uezu K, et al. Essential role for the p40 subunit of interleukin-12 in neutrophil-mediated early host defense against pulmonary infection with Streptococcus pneumoniae: involvement of interferon-gamma. Microbes Infect. 2004 Nov;6(14):1241-9.
210. Happel KI, Zheng M, Young E, Quinton LJ, Lockhart E, Ramsay AJ, et al. Cutting edge: roles of Toll-like receptor 4 and IL-23 in IL-17 expression in response to Klebsiella pneumoniae infection. J Immunol. 2003 May 1;170(9):4432-6.
211. Avila PC. Effects of allergic inflammation of the nasal mucosa on the severity of rhinovirus 16 cold. The Journal of allergy and clinical immunology. 2000;105(5):923-32.
212. Skoner DP, Whiteside TL, Wilson JW, Doyle WJ, Herberman RB, Fireman P. Effect of rhinovirus 39 infection on cellular immune parameters in allergic and nonallergic subjects. The Journal of allergy and clinical immunology. 1993 Nov;92(5):732-43.
213. Skoner DP, Doyle WJ, Tanner EP, Kiss J, Fireman P. Effect of rhinovirus 39 (RV-39) infection on immune and inflammatory parameters in allergic and non-allergic subjects. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1995 Jun;25(6):561-7.
214. Alho OP, Karttunen R, Karttunen TJ. Nasal mucosa in natural colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. Clin Exp Immunol. 2004 Aug;137(2):366-72.
215. Alho OP, Karttunen TJ, Karttunen R, Tuokko H, Koskela M, Suramo I, et al. Subjects with allergic rhinitis show signs of more severely impaired paranasal sinus functioning during viral colds than nonallergic subjects. Allergy. 2003 Aug;58(8):767-71.
216. Alho. Nasal airflow, mucociliary clearance, and sinus functioning during viral colds: effects of allergic rhinitis and susceptibility to recurrent sinusitis. American journal of rhinology. 2004;18(6):349-55.
217. Klemens C, Rasp G, Jund F, Hilgert E, Devens C, Pfrogner E, et al. Mediators and cytokines in allergic and viral-triggered rhinitis. Allergy and asthma proceedings : the official journal of regional and state allergy societies. 2007 Jul-Aug;28(4):434-41.
218. Khoury P. Effect of montelukast on bacterial sinusitis in allergic mice. Ann Allergy Asthma Immunol 2006;sep(97(3)):329-35.
219. Perloff JR, Palmer JN. Evidence of bacterial biofilms in a rabbit model of sinusitis. American journal of rhinology. 2005 Jan-Feb;19(1):1-6.
220. Yu X, Sperling A, Blair C, Thompson K, Naclerio R. Antigen stimulation of TH2 cells augments acute bacterial sinusitis in mice. The Journal of allergy and clinical immunology. 2004 Aug;114(2):328-34.
221. Ramadan HH, Meek RB, Dawson GS, Spirou GA, Cuff CF, Berrebi AS. Histologic and immunologic observations of viral-induced rhinosinusitis in the mouse. American journal of rhinology. 2002 Jan-Feb;16(1):61-7.
222. Rudack C, Stoll W, Bachert C. Cytokines in nasal polyposis, acute and chronic sinusitis. American journal of rhinology. 1998 Nov-Dec;12(6):383-8.
223. Thomas M, Yawn BP, Price D, Lund V, Mullol J, Fokkens W. EPOS Primary Care Guidelines: European Position Paper on the Primary Care Diagnosis and Management of Rhinosinusitis and Nasal Polyps 2007 - a summary. Prim Care Respir J. 2008 Jun;17(2):79-89.
224. Steurer J, Held U, Bachmann LM, Holzmann D, Ott P, Miettinen OS. Clinical diagnosis of acute bacterial rhinosinusitis, typical of experts. J Eval Clin Pract. 2009 Aug;15(4):614-9.
225. Ashworth M, Charlton J, Ballard K, Latinovic R, Gulliford M. Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995-2000. Br J Gen Pract. 2005 Aug;55(517):603-8.
226. Hansen JG. Management of acute rhinosinusitis in Danish general practice: a survey. Clin Epidemiol. 2011;3:213-6.
227. Desrosiers M, Evans GA, Keith PK, Wright ED, Kaplan A, Bouchard J, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. Allergy Asthma Clin

Immunol. 2011;7(1):2.

228. Klossek JM, Mesbah K. Presentation and treatment of acute maxillary sinusitis in general practice: a French observational study. Rhinology. 2011 Mar;49(1):84-9.
229. Hoffmans R, Schermer T, van Weel C, Fokkens W. Management of rhinosinusitis in Dutch general practice. Prim Care Respir J. 2011 Mar;20(1):64-70.
230. McQuillan L, Crane LA, Kempe A. Diagnosis and management of acute sinusitis by pediatricians. Pediatrics. 2009 Feb;123(2):e193-8.
231. Piatt JH, Jr. Intracranial suppuration complicating sinusitis among children: an epidemiological and clinical study. J Neurosurg Pediatr. 2011 Jun;7(6):567-74.
232. Hansen FS, Hoffmans R, Georgalas C, Fokkens WJ. Complications of acute rhinosinusitis in The Netherlands. Fam Pract. 2011 Sep 5.
233. Kristo A, Uhari M. Timing of rhinosinusitis complications in children. Pediatr Infect Dis J. 2009 Sep;28(9):769-71.
234. Hicks CW, Weber JG, Reid JR, Moodley M. Identifying and managing intracranial complications of sinusitis in children: a retrospective series. Pediatr Infect Dis J. 2011 Mar;30(3):222-6.
235. Dykewicz MS. 7. Rhinitis and sinusitis. The Journal of allergy and clinical immunology. 2003 Feb;111(2 Suppl):S520-9.
236. Berg O, Carenfelt C. Analysis of symptoms and clinical signs in the maxillary sinus empyema. Acta Otolaryngol. 1988 Mar-Apr;105(3-4):343-9.
237. Williams JW, Jr., Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis. Making the diagnosis by history and physical examination. Ann Intern Med. 1992 Nov 1;117(9):705-10.
238. Spector S. Parameters for the diagnosis and management of sinusitis The Journal of allergy and clinical immunology. 1998;dec(102):107-44.
239. Damm M, Quante G, Jungehuelsing M, Stennert E. Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. The Laryngoscope. 2002 Feb;112(2):310-5.
240. Benninger MS, Senior BA. The development of the Rhinosinusitis Disability Index. Archives of otolaryngology--head & neck surgery. 1997 Nov;123(11):1175-9.
241. Metson RB, Gliklich RE. Clinical outcomes in patients with chronic sinusitis. The Laryngoscope. 2000 Mar;110(3 Pt 3):24-8.
242. Lacroix JS, Ricchetti A, Lew D, Delhumeau C, Morabia A, Stalder H, et al. Symptoms and clinical and radiological signs predicting the presence of pathogenic bacteria in acute rhinosinusitis. Acta Otolaryngol. 2002 Mar;122(2):192-6.
243. Amoore JE, Ollman BG. Practical test kits for quantitatively evaluating the sense of smell. Rhinology. 1983 Mar;21(1):49-54.
244. Cain WS. Testing olfaction in a clinical setting. Ear, nose, & throat journal. 1989 Apr;68(4):316, 22-8.
245. Cardesin A, Alobid I, Benitez P, Sierra E, de Haro J, Bernal-Sprekelsen M, et al. Barcelona Smell Test - 24 (BAST-24): validation and smell characteristics in the healthy Spanish population. Rhinology. 2006 Mar;44(1):83-9.
246. Hansen JG, Hojbjerg T, Rosborg J. Symptoms and signs in culture-proven acute maxillary sinusitis in a general practice population. Apmis. 2009 Oct;117(10):724-9.
247. Lindbaek M, Hjortdahl P, Johnsen UL. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. Fam Med. 1996 Mar;28(3):183-8.
248. Benninger MS, Payne SC, Ferguson BJ, Hadley JA, Ahmad N. Endoscopically directed middle meatal cultures versus maxillary sinus taps in acute bacterial maxillary rhinosinusitis: a meta-analysis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2006 Jan;134(1):3-9.
249. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Ann Fam Med. 2010 Mar-Apr;8(2):124-33.
250. Hirshoren N, Hirschenbein A, Eliashar R. Risk stratification of severe acute rhinosinusitis unresponsive to oral antibiotics. Acta Otolaryngol. 2010 Sep;130(9):1065-9.
251. 251.Hansen JG, Lund E. The association between paranasal computerized tomography scans and symptoms and signs in a general practice population with acute maxillary sinusitis. Apmis. 2011 Jan;119(1):44-8.
252. Hansen JG, Schmidt H, Rosborg J, Lund E. Predicting acute maxillary sinusitis in a general practice population. BMJ (Clinical research ed). 1995 Jul 22;311(6999):233-6.
253. Aabenhus R, Jensen JU. Procalcitonin-guided antibiotic treatment of respiratory tract infections in a primary care setting: are we there yet? Prim Care Respir J. 2011 Dec;20(4):360-7.
254. Korczowski B, Malek U, Kowalczyk JR, Rybak A, Zinkiewicz A, Chmielewska A. [Two diagnostic assays for serum procalcitonin measurement in clinical practice]. Przegl Lek. 2003;60(5):345-8.
255. Gruffydd-Jones K, Ward S, Stonham C, Macfarlane TV, Thomas M. The use of exhaled nitric oxide monitoring in primary care asthma clinics: a pilot study. Prim Care Respir J. 2007 Dec;16(6):349-56.
256. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. Physiol Behav. 1984 Mar;32(3):489-502.
257. Lanz MJ, Prendes S, Peyrou N, Toledo G, Ferrer CM. Nasal nitric oxide as a noninvasive marker in the antibiotic treatment of acute bacterial sinusitis. The Journal of allergy and clinical immunology. 2008 Feb;121(2):530-1.
258. Gwaltney. Rhinovirus infection of the normal human airway. American journal of respiratory and critical care medicine. 1995;152(s36):9.
259. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision.

The Journal of allergy and clinical immunology. 2010 Sep;126(3):466-76.

260. Kasapoglu F, Coskun H, Ozmen OA, Akalin H, Ener B. Acute invasive fungal rhinosinusitis: evaluation of 26 patients treated with endonasal or open surgical procedures. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 Nov;143(5):614-20.
261. Suslu AE, Ogretmenoglu O, Suslu N, Yucel OT, Onerci TM. Acute invasive fungal rhinosinusitis: our experience with 19 patients. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2009 Jan;266(1):77-82.
262. Marshall AH, Jones NS, Robertson IJ. CSF rhinorrhoea: the place of endoscopic sinus surgery. Br J Neurosurg. 2001 Feb;15(1):8-12.
263. Klossek JM, Dubreuil L, Richet H, Richet B, Sedallian A, Beutter P. Bacteriology of the adult middle meatus. J Laryngol Otol. 1996 Sep;110(9):847-9.
264. Gold SM, Tami TA. Role of middle meatus aspiration culture in the diagnosis of chronic sinusitis. The Laryngoscope. 1997 Dec;107(12 Pt 1):1586-9.
265. Vogan JC, Bolger WE, Keyes AS. Endoscopically guided sinonasal cultures: a direct comparison with maxillary sinus aspirate cultures. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2000 Mar;122(3):370-3.
266. Casiano RR, Cohn S, Villasuso E, 3rd, Brown M, Memari F, Barquist E, et al. Comparison of antral tap with endoscopically directed nasal culture. The Laryngoscope. 2001 Aug;111(8):1333-7.
267. Joniau S, Vlaminck S, Van Landuyt H, Kuhweide R, Dick C. Microbiology of sinus puncture versus middle meatal aspiration in acute bacterial maxillary sinusitis. American journal of rhinology. 2005;19(2):135-40.
268. Berger G, Berger RL. The contribution of flexible endoscopy for diagnosis of acute bacterial rhinosinusitis. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2011 Feb;268(2):235-40.
269. Marseglia GL, Castellazzi AM, Licari A, Marseglia A, Leone M, Pagella F, et al. Inflammation of paranasal sinuses: the clinical pattern is age-dependent. Pediatr Allergy Immunol. 2007 Nov;18 Suppl 18:10-2.
270. Marseglia GL, Pagella F, Klersy C, Barberi S, Licari A, Ciprandi G. The 10-day mark is a good way to diagnose not only acute rhinosinusitis but also adenoiditis, as confirmed by endoscopy. Int J Pediatr Otorhinolaryngol. 2007 Apr;71(4):581-3.
271. Talbot GH, Kennedy DW, Scheld WM, Granito K. Rigid nasal endoscopy versus sinus puncture and aspiration for microbiologic documentation of acute bacterial maxillary sinusitis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2001 Nov 15;33(10):1668-75.
272. Kazkayasi M, Karadeniz Y, Arikan OK. Anatomic variations of the sphenoid sinus on computed tomography. Rhinology. 2005;43(2):109-14.
273. Erdem G, Erdem T, Miman MC, Ozturan O. A radiological anatomic study of the cribriform plate compared with constant structures. Rhinology. 2004 Dec;42(4):225-9.
274. Arikan OK, Unal B, Kazkayasi M, Koc C. The analysis of anterior skull base from two different perspectives: coronal and reconstructed sagittal computed tomography. Rhinology. 2005 Jun;43(2):115-20.
275. Badia L, Lund VJ, Wei W, Ho WK. Ethnic variation in sinonasal anatomy on CT-scanning. Rhinology. 2005 Sep;43(3):210-4.
276. Baumann I, Blumenstock G. Impact of gender on general health-related quality of life in patients with chronic sinusitis. American journal of rhinology. 2005;19(3):282-7.
277. Lloyd GA. CT of the paranasal sinuses: study of a control series in relation to endoscopic sinus surgery. J Laryngol Otol. 1990 Jun;104(6):477-81.
278. Wittkopf ML, Beddow PA, Russell PT, Duncavage JA, Becker SS. Revisiting the interpretation of positive sinus CT findings: a radiological and symptom-based review. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009 Mar;140(3):306-11.
279. Triulzi F, Zirpoli S. Imaging techniques in the diagnosis and management of rhinosinusitis in children. Pediatr Allergy Immunol. 2007 Nov;18 Suppl 18:46-9.
280. Jonas I, Mann W. [Misleading x-ray diagnosis due to maxillary sinus asymmetries (author's transl)]. Laryngol Rhinol Otol (Stuttg). 1976 Nov;55(11):905-13.
281. McAlister WH, Lusk R, Muntz HR. Comparison of plain radiographs and coronal CT scans in infants and children with recurrent sinusitis. AJR Am J Roentgenol. 1989 Dec;153(6):1259-64.
282. Iinuma T, Hirota Y, Kase Y. Radio-opacity of the paranasal sinuses. Conventional views and CT. Rhinology. 1994 Sep;32(3):134-6.
283. Landman MD. Ultrasound screening for sinus disease. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1986 Feb;94(2):157-64.
284. Otten FW, Grote JJ. The diagnostic value of transillumination for maxillary sinusitis in children. Int J Pediatr Otorhinolaryngol. 1989 Sep;18(1):9-11.
285. Varonen H, Savolainen S, Kunnamo I, Heikkinen R, Revonta M. Acute rhinosinusitis in primary care: a comparison of symptoms, signs, ultrasound, and radiography. Rhinology. 2003 Mar;41(1):37-43.
286. Vento SI, Ertama LO, Hytonen ML, Malmberg CH. A-mode ultrasound in the diagnosis of chronic polypous sinusitis. Acta Otolaryngol. 1999;119(8):916-20.
287. Laine K, Maatta T, Varonen H, Makela M.

Diagnosing acute maxillary sinusitis in primary care: a comparison of ultrasound, clinical examination and radiography. Rhinology. 1998 Mar;36(1):2-6.

288. Padua FG, Bezerra TF, Voegels RL, Bento RF. The efficacy of functional endoscopic sinus surgery in the evolution of fever of unknown origin in ICU patients. Acta Otolaryngol. 2011 Feb;131(2):166-72.
289. Jardim Vieira FM, Nunes da Silva R, Stefanini R, Filho LB, de Paula Santos R, Stamm A, et al. Safety of sphenoid aspiration for diagnosis and treatment of intensive care unit rhinosinusitis. American journal of rhinology & allergy. 2010 Sep-Oct;24(5):389-91.
290. Chakrabarti A, Denning DW, Ferguson BJ, Ponikau J, Buzina W, Kita H, et al. Fungal rhinosinusitis: a categorization and definitional schema addressing current controversies. The Laryngoscope. 2009 Sep;119(9):1809-18.
291. Poetker DM, Litvack JR, Mace JC, Smith TL. Recurrent acute rhinosinusitis: presentation and outcomes of sinus surgery. American journal of rhinology. 2008 May-Jun;22(3):329-33.
292. Costa Carvalho BT, Nagao AT, Arslanian C, Carneiro Sampaio MMS, Naspitz CK, Sorensen RU, et al. Immunological evaluation of allergic respiratory children with recurrent sinusitis. Pediatric Allergy & Immunology. 2005;16(6):534-8.
293. Hickner JM, Bartlett JG, Besser RE, Gonzales R, Hoffman JR, MA S. Principles of appropriate antibiotic use for acute rhinosinusitis in adults: background. Ann Intern Med. 2001;134(6):498-505.
294. van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, . PM. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet. 1997;349(9053):683-7.
295. Young J, De Sutter A, Merenstein D, van Essen GA, Kaiser L, Varonen H, et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. Lancet. 2008;371(9616):908-14.
296. Anon JB, Jacobs MR, Poole MD, Ambrose PG, Benninger MS, Hadley JA, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2004 130(1 Suppl):1-45.
297. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, Varonen H, Rautakorpi UM, Williams JW Jr, et al. Antibiotics for acute maxillary sinusitis. Cochrane database of systematic reviews (Online). 2008;16(2):CD000243.
298. Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaiou DK. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. Br J Clin Pharmacol. 2009 Feb;67(2):161-71.
299. Williams JW Jr, Aguilar C, Cornell J, Chiquette ED, Makela M, Holleman DR, et al. Antibiotics for acute maxillary sinusitis. Cochrane database of systematic reviews (Online). 2003(2):CD000243.
300. Cars O, Mölstad S, Melander A. Variation in antibiotic use in the European Union. Lancet. 2001;357(9271):1851-3.
301. Wise R, Hart T, Cars O, Streulens M, Helmuth R, Huovinen P, et al. Antimicrobial resistance. Is a major threat to public health. BMJ (Clinical research ed). 1998;317(7159):609-10.
302. Felmingham D, Reinert RR, Hirakata Y, Rodloff A. Increasing prevalence of antimicrobial resistance among isolates of Streptococcus pneumoniae from the PROTEKT surveillance study, and compatative in vitro activity of the ketolide, telithromycin. The Journal of antimicrobial chemotherapy. 2002;50(Suppl S1):25-37.
303. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005;365(9459):579-87.
304. Nayak AS. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2002;89(3):271-8.
305. Dolor R, Witsell DL, Hellkamp AS, Simel DL. Treatment of rhinosinusitis with or without intranasal steroids. 105th Annual Meeting of the American Academy of Otolaryngology - Head and Neck Surgery Foundation (AAO-HNS) , Denver, Colorado, 9-12 September, 2001 Otolaryngology - Head and Neck Surgery. 2001;125(2):P102.
306. Meltzer EO, Charous BL, Busse WW, Zinreich SJ, Lorber RR, Danzig MR. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. The Nasonex Sinusitis Group. The Journal of allergy and clinical immunology. 2000 Oct;106(4):630-7.
307. Barlan IB, Erkan E, Bakir M, Berrak S, Basaran MM. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 1997 Jun;78(6):598-601.
308. 308.Meltzer E. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. The Journal of allergy and clinical immunology. 2005;30(2):103-12.
309. 309.Qvarnberg Y, Kantola O, Salo J, Toivanen M, Valtonen H, Vuori E. Influence of topical steroid treatment on maxillary sinusitis. Rhinology. 1992 Jun;30(2):103-12.
310. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. The Journal of allergy and clinical immunology. 2005 Dec;116(6):1289-95.
311. Bachert C, Meltzer EO. Effect of mometasone furoate nasal spray on quality of life of patients with acute rhinosinusitis. Rhinology. 2007 Sep;45(3):190-6.
312. Williamson IG, Rumsby K, Benge S, Moore M, Smith PW, Cross M, et al. Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: a randomized controlled trial. JAMA. 2007 Dec

5;298(21):2487-96.

313. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. Cochrane database of systematic reviews (Online). 2009(4):CD005149.
314. Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del Mar CB, Perera R, et al. Systemic corticosteroids for acute sinusitis. Cochrane database of systematic reviews (Online). 2011;12:CD008115.
315. Gehanno P, Beauvillain C, Bobin S, Chobaut JC, Desaulty A, Dubreuil C, et al. Short therapy with amoxicillin-clavulanate and corticosteroids in acute sinusitis: results of a multicentre study in adults. Scand J Infect Dis. 2000;32(6):679-84.
316. Klossek JM, Desmonts-Gohler C, Deslandes B, Coriat F, Bordure P, Dubreuil C, et al. Treatment of functional signs of acute maxillary rhinosinusitis in adults: Efficacy and tolerance of administration of oral prednisone for 3 days. [French]. Presse Medicale. 2004;33(5):303-9.
317. Puhakka T, Makela MJ, Malmstrom K, Uhari M, Savolainen J, Terho EO, et al. The common cold: effects of intranasal fluticasone propionate treatment. The Journal of allergy and clinical immunology. 1998 Jun;101(6 Pt 1):726-31.
318. Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its Impact on Asthma. The Journal of allergy and clinical immunology. 2001;108(5 Suppl):S147-334.
319. 319.Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A ea. Allergic rhinitis and its Impact on Asthma (ARIA) 2008 Update. Allergy 2008;63(Suppl 86):1-160.
320. Stringer SP, Mancuso AA, Avino AJ. Effect of a topical vasoconstrictor on computed tomography of paranasal sinus disease. The Laryngoscope. 1993;103(1 Pt 1):6-9.
321. Benammar-Englmaier M, Hallermeier JK, Englmaier B. Alphamimetic effects on nasal mucosa in magnetic resonance tomography. Digitale Bilddiagn. 1990;10(2):46-50.
322. Westerveld GJ, Voss HP, van der Hee RM, de Haan-Koelewijn GJ, den Hartog GJ, Scheeren RA, et al. Inhibition of nitric oxide synthase by nasal decongestants. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2000;16(3):437-44.
323. 323.Westerveld GJ, Scheeren RA, Dekker I, Griffioen DH, Voss HP, Bast A. Anti-oxidant actions of oxymethazoline and xylomethazoline. Eur J Pharmacol. 1995;291(1):27-31.
324. Inanli S, Ozturk O, Korkmaz M, Tutkun A, Batman C. The effects of topical agents of fluticasone propionate, oxymetazoline, and 3% and 0.9% sodium chloride solutions on mucociliary clearance in the therapy of acute bacterial rhinosinusitis in vivo. The Laryngoscope. 2002;112(2)):320-5.
325. Wiklund L, Stierna P, Berglund R, Westrin KM, Tonnesson M. The efficacy of oxymetazoline administered with a nasal bellows container and combined with oral phenoxymethyl-penicillin in the treatment of acute maxillary sinusitis. Acta Otolaryngol Suppl. 1994;515:57-64.
326. McCormick DP, John SD, Swischuk LE, Uchida T. A doubleblind, placebo-controlled trial of decongestant-antihistamine for the treatment of sinusitis in children. Clin Pediatr (Phila). 1996;35(9):457-60.
327. Pneumatikos I, Konstantonis D, Dragoumanis C, Danielides V, Bouros D. Preventing nosocomial sinusitis in the ICU: Reply to van Zanten et al. [12]. Intensive Care Medicine. [Letter]. 2006;32(9):1452-3.
328. Shaikh N, Wald ER, Pi M. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. Cochrane database of systematic reviews (Online). 2010(12):CD007909.
329. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. The Laryngoscope. 1997;107(4):500-3.
330. Adam P, Stiffman M, Blake RL J. A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis. Arch Fam Med. 1998;7(1):39-43.
331. Axelsson A, Grebelius N, Jensen C, Melin O, Singer F. Treatment of acute maxillary sinusitis. IV. Ampicillin, cephradine and erythromycinestolate with and without irrigation. Acta Otolaryngol. 1975;79(5-6):466-72.
332. Kassel JC, King D, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. Cochrane database of systematic reviews (Online). 2010;17(3):CD006821.
333. Hildenbrand T, Weber R, Heubach C, Mösges R. Nasal douching in acute rhinosinusitis (Article in German). Laryngorhinootologie. 2011;90(6):346-51.
334. Tarantino V, Stura M MG, Leproux GB, Cremonesi G. Advantages of treatment with bromhexine in acute sinus inflammation in children. Randomized double-blind study versus placebo. Minerva Pediatr. 1988;40(11):649-52.
335. Unuvar E, Tamay Z, Yildiz I, Toprak S, Kilic A, Aydin S, et al. Effectiveness of erdosteine, a second generation mucolytic agent, in children with acute rhinosinusitis: a randomized, placebo controlled, double-blinded clinical study. Acta Paediatr. 2010 Apr;99(4):585-9.
336. Timmer A, Gunther J, Rucker G, Motschall E, Antes G, Kern WV. Pelargonium sidoides extract for acute respiratory tract infections. Cochrane database of systematic reviews (Online). 2008(3):CD006323.
337. Bachert C, Schapowal A, Funk P, Kieser M. Treatment of acute rhinosinusitis with the preparation from Pelargonium sidoides EPs 7630: a randomized, double-blind, placebo-controlled trial. Rhinology. 2009 Mar;47(1):51-8.
338. Lizogub VG, Riley DS, Heger M. Efficacy of a pelargonium sidoides preparation in patients with the common cold: a randomized, double blind, placebo-controlled clinical trial. Explore (NY). 2007 Nov-Dec;3(6):573-84.
339. Federspil P, Wulkow R, Zimmermann T. [Effects of standardized Myrtol in therapy of acute sinusitis--results of a double-blind, randomized multicenter study compared with placebo]. Laryngorhinootologie. 1997 Jan;76(1):23-7.

340. Stuck BA, Bachert C, Federspil P, Hosemann W, Klimek L, Mösges R, et al. Rhinosinusitis guidelines of the German Society for Otorhinolaryngology, Head and Neck Surgery. HNO. 2007 55(10):758-60.

341. Benninger MS, Manz R. The impact of vaccination on rhinosinusitis and otitis media. Current allergy and asthma reports. 2010 Nov;10(6):411-8.

342. Rychkova OA, Kazakevich NV, Sennikova NP, Semeniuk EN. [Assessment of effectiveness of immunization against Hib-infection]. Zh Mikrobiol Epidemiol Immunobiol. 2010 May-Jun(3):48-52.

343. Bachert C, Chuchalin AG, Eisebitt R, Netayzhenko VZ, Voelker M. Aspirin compared with acetaminophen in the treatment of fever and other symptoms of upper respiratory tract infection in adults: a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, single-dose, 6-hour dose-ranging study. Clin Ther. 2005 Jul;27(7):993-1003.

344. Sederberg-Olsen JF, Sederberg-Olsen AE. Intranasal sodium cromoglycate in post-catarrhal hyperreactive rhinosinusitis: a double-blind placebo controlled trial. Rhinology. 1989 Dec;27(4):251-5.

345. Falagas ME, Giannopoulou KP, Vardakas KZ, Dimopoulos G, Karageorgopoulos DE. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. Lancet Infect Dis. 2008 Sep;8(9):543-52.

346. Burton MJ, Kuppersmith RB, RM R. Extracts from The Cochrane Library: Antibiotics for acute maxillary sinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2008;139(4):486-9.

347. Rosenfeld RM, Singer M, Jones S. Systematic review of antimicrobial therapy in patients with acute rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 Sep;137(3 Suppl):S32-45.

348. Arroll B. Antibiotics for upper respiratory tract infections: an overview of Cochrane reviews. Respiratory medicine. 2005 Mar;99(3):255-61.

349. Stalman W, van Essen GA, van der Graaf Y, de Melker RA. The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? A placebo-controlled double-blind randomized doxycycline trial. Br J Gen Pract. 1997 Dec;47(425):794-9.

350. Hadley JA, Mosges R, Desrosiers M, Haverstock D, van Veenhuyzen D, Herman-Gnjidic Z. Moxifloxacin five-day therapy versus placebo in acute bacterial rhinosinusitis. The Laryngoscope. 2010 May;120(5):1057-62.

351. Wald ER, Nash D, Eickhoff J. Effectiveness of amoxicillin/clavulanate potassium in the treatment of acute bacterial sinusitis in children. Pediatrics. 2009 Jul;124(1):9-15.

352. Kristo A, Uhari M, Luotonen J, Ilkko E, Koivunen P, Alho OP. Cefuroxime axetil versus placebo for children with acute respiratory infection and imaging evidence of sinusitis: a randomized, controlled trial. Acta Paediatr. 2005 Sep;94(9):1208-13.

353. Bucher HC, Tschudi P, Young J, Periat P, Welge-Lussen A, Zust H, et al. Effect of amoxicillin-clavulanate in clinically diagnosed acute, rhinosinusitis: A placebo-controlled, double-blind, randomized trial in general practice. Archives of Internal Medicine. 2003;163(15):1793-8.

354. Varonen H, Kunnamo I, Savolainen S, Makela M, Revonta M, Ruotsalainen J, et al. Treatment of acute rhinosinusitis diagnosed by clinical criteria or ultrasound in primary care. A placebo-controlled randomised trial. Scand J Prim Health Care. 2003 Jun;21(2):121-6.

355. Hansen JG, Schmidt H, Grinsted P. [Penicillin treatment of acute maxillary sinusitis in adults. A randomized, double-blind, placebo-controlled trial from general practice]. Ugeskr Laeger. 2000 Oct 2;162(40):5351-3.

356. Lindbaek M, Hjortdahl P, Johnsen UL. Randomised, double blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults. BMJ (Clinical research ed). 1996 Aug 10;313(7053):325-9.

357. Wald ER, Chiponis D, Ledesma-Medina J. Comparative effectiveness of amoxicillin and amoxicillin-clavulanate potassium in acute paranasal sinus infections in children: a double-blind, placebo-controlled trial. Pediatrics. 1986 Jun;77(6):795-800.

358. Marple BF, Roberts CS, de Caprariis PJ, Reisman A. Onset of symptom resolution in adults with acute bacterial rhinosinusitis treated with a single dose of azithromycin extended release compared with 10 days of levofloxacin: a retrospective analysis of a randomized, double-blind, double-dummy trial. Clin Ther. 2007 Dec;29(12):2690-8.

359. Upchurch J, Rosemore M, Tosiello R, Kowalsky S, Echols R. Randomized double-blind study comparing 7- and 10-day regimens of faropenem medoxomil with a 10-day cefuroxime axetil regimen for treatment of acute bacterial sinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2006 Oct;135(4):511-7.

360. Tellier G, Brunton SA, Nusrat R. Telithromycin for the treatment of acute bacterial maxillary sinusitis: a review of a new antibacterial agent. South Med J. 2005 Sep;98(9):863-8.

361. Murray JJ, Emparanza P, Lesinskas E, Tawadrous M, Breen JD. Efficacy and safety of a novel, single-dose azithromycin microsphere formulation versus 10 days of levofloxacin for the treatment of acute bacterial sinusitis in adults. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2005 Aug;133(2):194-200.

362. Henry DC, Kapral D, Busman TA, Paris MM. Cefdinir versus levofloxacin in patients with acute rhinosinusitis of presumed bacterial etiology: a multicenter, randomized, double-blind study. Clin Ther.

2004 Dec;26(12):2026-33.

363. Gehanno P, Berche P, Hercot O, D'Arras L, Cabrillac-Rives S, Derobert E, et al. Efficiency of a four-day course of pristinamycin compared to a five-day course of cefuroxime axetil for acute bacterial maxillary sinusitis in adult outpatients. [French]. Medecine et Maladies Infectieuses. 2004;34(7):293-302.
364. Ferguson BJ, Guzzetta RV, Spector SL, Hadley JA. Efficacy and safety of oral telithromycin once daily for 5 days versus moxifloxacin once daily for 10 days in the treatment of acute bacterial rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2004 Sep;131(3):207-14.
365. Buchanan PP, Stephens TA, Leroy B. A comparison of the efficacy of telithromycin versus cefuroxime axetil in the treatment of acute bacterial maxillary sinusitis. American journal of rhinology. 2003 Nov-Dec;17(6):369-77.
366. Luterman M, Tellier G, Lasko B, Leroy B. Efficacy and tolerability of telithromycin for 5 or 10 days vs amoxicillin/clavulanic acid for 10 days in acute maxillary sinusitis. Ear, nose, & throat journal. 2003 Aug;82(8):576-80, 82-4, 86 passim.
367. Henry DC, Riffer E, Sokol WN, Chaudry NI, Swanson RN. Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis. Antimicrob Agents Chemother. 2003 Sep;47(9):2770-4.
368. Siegert R, Berg O, Gehanno P, Leiberman A, Martinkenas JL, Nikolaidis P, et al. Comparison of the efficacy and safety of faropenem daloxate and cefuroxime axetil for the treatment of acute bacterial maxillary sinusitis in adults. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2003 Apr;260(4):186-94.
369. Klossek JM, Siegert R, Nikolaidis P, Arvis P, Leberre MA. Comparison of the efficacy and safety of moxifloxacin and trovafloxacin for the treatment of acute, bacterial maxillary sinusitis in adults. J Laryngol Otol. 2003 Jan;117(1):43-51.
370. Siegert R, Gehanno P, Nikolaidis P, Bagger-Sjoback D, Ibanez JM, Hampel B, et al. A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults. The Sinusitis Study Group. Respiratory medicine. 2000 Apr;94(4):337-44.
371. Burke T, Villanueva C, Mariano H, Jr., Huck W, Orchard D, Haverstock D, et al. Comparison of moxifloxacin and cefuroxime axetil in the treatment of acute maxillary sinusitis. Sinusitis Infection Study Group. Clin Ther. 1999 Oct;21(10):1664-77.
372. Lasko B, Lau CY, Saint-Pierre C, Reddington JL, Martel A, Anstey RJ. Efficacy and safety of oral levofloxacin compared with clarithromycin in the treatment of acute sinusitis in adults: a multicentre, double-blind, randomized study. The Canadian Sinusitis Study Group. J Int Med Res. 1998 Dec;26(6):281-91.
373. Henry DC, Sydnor A, Jr., Settipane GA, Allen J, Burroughs S, Cobb MM, et al. Comparison of cefuroxime axetil and amoxicillin/clavulanate in the treatment of acute bacterial sinusitis. Clin Ther. 1999 Jul;21(7):1158-70.
374. Clifford K, Huck W, Shan M, Tosiello R, Echols RM, Heyd A. Double-blind comparative trial of ciprofloxacin versus clarithromycin in the treatment of acute bacterial sinusitis. Sinusitis Infection Study Group. The Annals of otology, rhinology, and laryngology. 1999 Apr;108(4):360-7.
375. Henry DC. Comparison of sparfloxacin and clarithromycin in the treatment of acute bacterial maxillary sinusitis. Sparfloxacin Multicenter AMS Study Group. Clin Ther 1999;21(2):340-52.
376. Hayle R, Lingaas E, Hoivik HO, Odegard T. Efficacy and safety of azithromycin versus phenoxymethylpenicillin in the treatment of acute maxillary sinusitis. Eur J Clin Microbiol Infect Dis. 1996 Nov;15(11):849-53.
377. Gehanno P, Berche P. Sparfloxacin versus cefuroxime axetil in the treatment of acute purulent sinusitis. Sinusitis Study Group. The Journal of antimicrobial chemotherapy. 1996 May;37 Suppl A:105-14.
378. von Sydow C, Savolainen S, Soderqvist A. Treatment of acute maxillary sinusitis--comparing cefpodoxime proxetil with amoxicillin. Scand J Infect Dis. 1995;27(3):229-34.
379. Kohler W, Schenk P. [Cephalosporin treatment of maxillary sinusitis]. Laryngorhinootologie. 1995 Jun;74(6):355-60.
380. Loracarbef versus doxycycline in the treatment of acute bacterial maxillary sinusitis. Scandinavian Study Group. The Journal of antimicrobial chemotherapy. 1993 Jun;31(6):949-61.
381. Husfeldt P, Egede F, Nielsen PB. Antibiotic treatment of sinusitis in general practice. A double-blind study comparing ofloxacin and erythromycin. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 1993;250 Suppl 1:S23-5.
382. Scheld WM, Sydnor A, Jr., Farr B, Gratz JC, Gwaltney JM, Jr. Comparison of cyclacillin and amoxicillin for therapy for acute maxillary sinusitis. Antimicrob Agents Chemother. 1986 Sep;30(3):350-3.
383. Poole M, Anon J, Paglia M, Xiang J, Khashab M, Kahn J. A trial of high-dose, short-course levofloxacin for the treatment of acute bacterial sinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2006 Jan;134(1):10-7.
384. Gehanno P, Loncle-Provot V, Le Kerneau J. Efficacy of cefotiam hexetil in acute maxillary sinusitis, with a short five day vs ten day treatment. [French]. Medecine et Maladies Infectieuses. 2004;34(10):455-9.
385. Ferguson BJ, Anon J, Poole MD, Hendrick K, Gilson M, Seltzer EG. Short treatment

durations for acute bacterial rhinosinusitis: Five days of gemifloxacin versus 7 days of gemifloxacin. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002 Jul;127(1):1-6.

386. Roos K, Brunswig-Pitschner C, Kostrica R, Pietola M, Leroy B, Rangaraju M, et al. Efficacy and tolerability of once-daily therapy with telithromycin for 5 or 10 days for the treatment of acute maxillary sinusitis. Chemotherapy. 2002 May;48(2):100-8.
387. Murray JJ, Solomon E, McCluskey D, Zhang J, Palmer R, Notario G. Phase III, randomized, double-blind study of clarithromycin extended-release and immediate-release formulations in the treatment of adult patients with acute maxillary sinusitis. Clin Ther. 2000 Dec;22(12):1421-32.
388. Seggev JS, Enrique RR, Brandon ML, Larsen LS, Van Tuyl RA, Rowinski CA. A combination of amoxicillin and clavulanate every 12 hours vs every 8 hours for treatment of acute bacterial maxillary sinusitis. Archives of otolaryngology--head & neck surgery. 1998 Aug;124(8):921-5.
389. Zeckel ML, Johns D, Jr., Masica DN, Farlow D. Twice-daily dosing of loracarbef 200 mg versus 400 mg in the treatment of patients with acute maxillary sinusitis. Clin Ther. 1995 Mar-Apr;17(2):214-30.
390. Sorri M, Peltomaki E, Jokinen K. Bacampicillin in acute maxillary sinusitis: concentration in sinus secretion and clinical effect. A randomized, double-blind study of two dosage regimens. Scand J Infect Dis. 1981;13(4):277-80.
391. Ratau NP, Snyman JR, Swanepoel C. Short-course, low-dose oral betamethasone as an adjunct in the treatment of acute infective sinusitis: A comparative study with placebo. Clinical Drug Investigation. 2004;24(10):577-82.
392. Pfaar O, Mullol J, Anders C, Hormann K, Klimek L. Cyclamen europaeum nasal spray, a novel phytotherapeutic product for the management of acute rhinosinusitis: a randomized double-blind, placebo-controlled trial. Rhinology. 2012 Mar;50(1):37-44.
393. Tesche S, Metternich F, Sonnemann U, Engelke JC, Dethlefsen U. The value of herbal medicines in the treatment of acute non-purulent rhinosinusitis. Results of a double-blind, randomised, controlled trial. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2008 Nov;265(11):1355-9.
394. Zabolotnyi DI, Kneis KC, Richardson A, Rettenberger R, Heger M, Kaszkin-Bettag M, et al. Efficacy of a complex homeopathic medication (Sinfrontal) in patients with acute maxillary sinusitis: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial. Explore (NY). 2007 Mar-Apr;3(2):98-109.
395. Friese KH, Zabalotnyi DI. [Homeopathy in acute rhinosinusitis: a double-blind, placebo controlled study shows the efficiency and tolerability of a homeopathic combination remedy]. HNO. 2007 Apr;55(4):271-7.
396. Kehrl W, Sonnemann U, Dethlefsen U. Therapy for acute nonpurulent rhinosinusitis with cineole: results of a double-blind, randomized, placebo-controlled trial. The Laryngoscope. 2004 Apr;114(4):738-42.
397. Gabrielian ES, Shukarian AK, Goukasova GI, Chandanian GL, Panossian AG, Wikman G, et al. A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis. Phytomedicine. 2002 Oct;9(7):589-97.
398. Mirza S, Lobo CJ, Counter P, Farrington WT. Lacrimal gland abscess: an unusual complication of rhinosinusitis. ORL J Otorhinolaryngol Relat Spec. 2001 Nov-Dec;63(6):379-81.
399. Patel N, Khalil HM, Amirfeyz R, Kaddour HS. Lacrimal gland abscess complicating acute sinusitis. Int J Pediatr Otorhinolaryngol. 2003 Aug;67(8):917-9.
400. Kuo WT, Lee TJ, Chen YL, Huang CC. Nasal septal perforation caused by invasive fungal sinusitis. Chang Gung Med J. 2002 Nov;25(11):769-73.
401. Gouws P. Visual-field loss caused by sinusitis: a case report. Ear, nose, & throat journal. 2003 Jan;82(1):42-5.
402. 402.Gungor A, Adusumilli V, Corey JP. Fungal sinusitis: progression of disease in immunosuppression--a case report. Ear, nose, & throat journal. 1998 Mar;77(3):207-10, 15.
403. Chandler JR, Langenbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. The Laryngoscope. 1970 Sep;80(9):1414-28.
404. Giannoni CM, Stewart MG, Alford EL. Intracranial complications of sinusitis. The Laryngoscope. 1997 Jul;107(7):863-7.
405. Maniglia AJ, Goodwin WJ, Arnold JE, Ganz E. Intracranial abscesses secondary to nasal, sinus, and orbital infections in adults and children. Archives of otolaryngology--head & neck surgery. 1989 Dec;115(12):1424-9.
406. Botting AM, McIntosh D, Mahadevan M. Paediatric pre- and post-septal peri-orbital infections are different diseases. A retrospective review of 262 cases. Int J Pediatr Otorhinolaryngol. 2008 Mar;72(3):377-83.
407. Oxford LE, McClay J. Complications of acute sinusitis in children. Otolaryngology - Head & Neck Surgery. 2005;133(1):32-7.
408. Younis RT, Lazar RH, Anand VK. Intracranial complications of sinusitis: a 15-year review of 39 cases. Ear, nose, & throat journal. 2002 Sep;81(9):636-8, 40-2, 44.
409. Ogunleye AO, Nwaorgu OG, Lasisi AO. Complications of sinusitis in Ibadan, Nigeria. West Afr J Med. 2001 Apr-Jun;20(2):98-101.
410. Eufinger H, Machtens E. Purulent pansinusitis, orbital cellulitis and rhinogenic intracranial complications. J Craniomaxillofac Surg. 2001 Apr;29(2):111-7.
411. Mortimore S, Wormald PJ. The Groote Schuur hospital classification of the orbital complications of sinusitis. J Laryngol Otol.

1997 Aug;111(8):719-23.

412. Bayonne E, Kania R, Tran P, Huy B, Herman P. Intracranial complications of rhinosinusitis. A review, typical imaging data and algorithm of management. Rhinology. 2009 Mar;47(1):59-65.
413. Clayman GL, Adams GL, Paugh DR, Koopmann CF, Jr. Intracranial complications of paranasal sinusitis: a combined institutional review. The Laryngoscope. 1991 Mar;101(3):234-9.
414. Stoll D, Klossek JM, Barbaza MO. [Prospective study of 43 severe complications of acute rhinosinusitis]. Rev Laryngol Otol Rhinol (Bord). 2006;127(4):195-201.
415. Huang SF, Lee TJ, Lee YS, Chen CC, Chin SC, Wang NC. Acute rhinosinusitis-related orbital infection in pediatric patients: a retrospective analysis. The Annals of otology, rhinology, and laryngology. 2011 Mar;120(3):185-90.
416. Rumelt S, Rubin PA. Potential sources for orbital cellulitis. Int Ophthalmol Clin. 1996 Summer;36(3):207-21.
417. Mekhitarian Neto L, Pignatari S, Mitsuda S, Fava AS, Stamm A. Acute sinusitis in children: a retrospective study of orbital complications. Brazilian journal of otorhinolaryngology. 2007 Jan-Feb;73(1):75-9.
418. Eustis HS, Mafee MF, Walton C, Mondonca J. MR imaging and CT of orbital infections and complications in acute rhinosinusitis. Radiol Clin North Am. 1998 Nov;36(6):1165-83, xi.
419. Gordts F, Herzeel R. Orbital involvement in sinus pathology: often without ocular pain. Bull Soc Belge Ophtalmol. 2002(285):9-14.
420. Velasco e Cruz AA, Demarco RC, Valera FC, dos Santos AC, Anselmo-Lima WT, Marquezini RM. Orbital complications of acute rhinosinusitis: a new classification. Brazilian journal of otorhinolaryngology. 2007 Sep-Oct;73(5):684-8.
421. Voegels RL, Pinna Fde R. Sinusitis orbitary complications classification: simple and practical answers. Brazilian journal of otorhinolaryngology. 2007 Sep-Oct;73(5):578.
422. Sobol SE, Marchand J, Tewfik TL, Manoukian JJ, Schloss MD. Orbital complications of sinusitis in children. J Otolaryngol. 2002 Jun;31(3):131-6.
423. Wald ER. Sinusitis in children. The New England journal of medicine. 1992 Jan 30;326(5):319-23.
424. Osborn MK, Steinberg JP. Subdural empyema and other suppurative complications of paranasal sinusitis. Lancet Infect Dis. 2007 Jan;7(1):62-7.
425. Josephson JS, Rosenberg SI. Sinusitis. Clin Symp. 1994;46(2):1-32.
426. Lessner A, Stern GA. Preseptal and orbital cellulitis. Infect Dis Clin North Am. 1992 Dec;6(4):933-52.
427. Georgakopoulos CD, Eliopoulou MI, Stasinos S, Exarchou A, Pharmakakis N, Varvarigou A. Periorbital and orbital cellulitis: a 10-year review of hospitalized children. Eur J Ophthalmol. 2010 Nov-Dec;20(6):1066-72.
428. Chaudhry IA, Shamsi FA, Elzaridi E, Al-Rashed W, Al-Amri A, Arat YO. Inpatient preseptal cellulitis: experience from a tertiary eye care centre. Br J Ophthalmol. 2008 Oct;92(10):1337-41.
429. Gonzalez MO, Durairaj VD. Understanding pediatric bacterial preseptal and orbital cellulitis. Middle East Afr J Ophthalmol. 2010 Apr;17(2):134-7.
430. Babar TF, Zaman M, Khan MN, Khan MD. Risk factors of preseptal and orbital cellulitis. J Coll Physicians Surg Pak. 2009 Jan;19(1):39-42.
431. Dunham ME. New light on sinusitis. Contemp Pediatr. 1994 Oct;11(10):102-6, 8, 10 passim.
432. Ho CF, Huang YC, Wang CJ, Chiu CH, Lin TY. Clinical analysis of computed tomography-staged orbital cellulitis in children. J Microbiol Immunol Infect. 2007 Dec;40(6):518-24.
433. Gungor A, Corey JP. Pediatric sinusitis: a literature review with emphasis on the role of allergy. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1997 Jan;116(1):4-15.
434. Bergin DJ, Wright JE. Orbital cellulitis. Br J Ophthalmol. 1986 Mar;70(3):174-8.
435. Hoxworth JM, Glastonbury CM. Orbital and intracranial complications of acute sinusitis. Neuroimaging Clin N Am. 2010 Nov;20(4):511-26.
436. Eviatar E, Gavriel H, Pitaro K, Vaiman M, Goldman M, Kessler A. Conservative treatment in rhinosinusitis orbital complications in children aged 2 years and younger. Rhinology. 2008 Dec;46(4):334-7.
437. Todman MS, Enzer YR. Medical management versus surgical intervention of pediatric orbital cellulitis: the importance of subperiosteal abscess volume as a new criterion. Ophthal Plast Reconstr Surg. 2011 Jul-Aug;27(4):255-9.
438. Gavriel H, Yeheskeli E, Aviram E, Yehoshua L, Eviatar E. Dimension of subperiosteal orbital abscess as an indication for surgical management in children. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Nov;145(5):823-7.
439. Coenraad S, Buwalda J. Surgical or medical management of subperiosteal orbital abscess in children: a critical appraisal of the literature. Rhinology. 2009 Mar;47(1):18-23.
440. Jones NS, Walker JL, Bassi S, Jones T, Punt J. The intracranial complications of rhinosinusitis: can they be prevented? The Laryngoscope. 2002 Jan;112(1):59-63.
441. Oxford LE, McClay J. Medical and surgical management of subperiosteal orbital abscess secondary to acute sinusitis in children. Int J Pediatr Otorhinolaryngol. 2006 Nov;70(11):1853-61.
442. Wenig BL, Goldstein MN, Abramson AL. Frontal sinusitis and its intracranial complications. Int J Pediatr Otorhinolaryngol. 1983 Jul;5(3):285-302.
443. Siedek V, Kremer A, Betz CS, Tschiesner U, Berghaus A, Leunig A. Management of orbital complications due to rhinosinusitis. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck

Surgery. 2010 Dec;267(12):1881-6.

444. Albu S, Tomescu E, Bassam S, Merca Z. Intracranial complications of sinusitis. Acta Otorhinolaryngol Belg. 2001;55(4):265-72.
445. Gallagher RM, Gross CW, Phillips CD. Suppurative intracranial complications of sinusitis. The Laryngoscope. 1998 Nov;108(11 Pt 1):1635-42.
446. Daya S, To SS. A 'silent' intracranial complication of frontal sinusitis. J Laryngol Otol. 1990 Aug;104(8):645-7.
447. DelGaudio JM, Evans SH, Sobol SE, Parikh SL. Intracranial complications of sinusitis: what is the role of endoscopic sinus surgery in the acute setting. Am J Otolaryngol. 2010 Jan-Feb;31(1):25-8.
448. Germiller JA, Monin DL, Sparano AM, Tom LW. Intracranial complications of sinusitis in children and adolescents and their outcomes. Archives of otolaryngology--head & neck surgery. 2006 Sep;132(9):969-76.
449. Quraishi H, Zevallos JP. Subdural empyema as a complication of sinusitis in the pediatric population. International Journal of Pediatric Otorhinolaryngology. 2006;70(9):1581-6.
450. Eweiss A, Mukonoweshuro W, Khalil HS. Cavernous sinus thrombosis secondary to contralateral sphenoid sinusitis: a diagnostic challenge. J Laryngol Otol. 2010 Aug;124(8):928-30.
451. Kombogiorgas D, Seth R, Athwal R, Modha J, Singh J. Suppurative intracranial complications of sinusitis in adolescence. Single institute experience and review of literature. Br J Neurosurg. 2007 Dec;21(6):603-9.
452. Hakim HE, Malik AC, Aronyk K, Ledi E, Bhargava R. The prevalence of intracranial complications in pediatric frontal sinusitis. Int J Pediatr Otorhinolaryngol. 2006 Aug;70(8):1383-7.
453. Berenholz L, Kessler A, Shlomkovitz N, Sarfati S, Segal S. Superior ophthalmic vein thrombosis: complication of ethmoidal rhinosinusitis. Archives of otolaryngology--head & neck surgery. 1998 Jan;124(1):95-7.
454. Broberg T, Murr A, Fischbein N. Devastating complications of acute pediatric bacterial sinusitis. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1999 Apr;120(4):575-9.
455. Bhatia K, Jones NS. Septic cavernous sinus thrombosis secondary to sinusitis: are anticoagulants indicated? A review of the literature. J Laryngol Otol. 2002 Sep;116(9):667-76.
456. Lang EE, Curran AJ, Patil N, Walsh RM, Rawluk D, Walsh MA. Intracranial complications of acute frontal sinusitis. Clinical otolaryngology and allied sciences. 2001 Dec;26(6):452-7.
457. Park HW, Lee BJ, Chung YS. Orbital subperiosteal hematoma associated with sinus infection. Rhinology. 2010 Mar;48(1):117-22.
458. Gradoni P, Fois P. Nasal septal abscess complicating isolated acute sphenoiditis: case report and literature review. B-Ent. 2010;6(4):303-5.
459. Pang KP, Sethi DS. Nasal septal abscess: an unusual complication of acute spheno-ethmoiditis. J Laryngol Otol. 2002 Jul;116(7):543-5.
460. Siberry GK, Costarangos C, Cohen BA. Destruction of the nasal septum by aspergillus infection after autologous bone marrow transplantation. The New England journal of medicine. 1997 Jul 24;337(4):275-6.
461. Wu VF, Smith TL, Poetker DM. Sinocutaneous fistula secondary to chronic frontal rhinosinusitis: case series and literature review. The Annals of otology, rhinology, and laryngology. 2008 Oct;117(10):759-63.
462. Laurens MB, Becker RM, Johnson JK, Wolf JS, Kotloff KL. MRSA with progression from otitis media and sphenoid sinusitis to clival osteomyelitis, pachymeningitis and abducens nerve palsy in an immunocompetent 10-year-old patient. Int J Pediatr Otorhinolaryngol. 2008 Jul;72(7):945-51.
463. Righini CA, Bing F, Bessou P, Boubagra K, Reyt E. An acute ischemic stroke secondary to sphenoid sinusitis. Ear, nose, & throat journal. 2009 Nov;88(11):E23-8.
464. Rimal D, Hashmi SM, Prinsley PR. An unusual presentation of sphenoid sinusitis with septicaemia in a healthy young adult. Emerg Med J. 2006 Jun;23(6):e36.
465. Spaeth J, Krugelstein U, Schlondorff G. The paranasal sinuses in CT-imaging: development from birth to age 25. Int J Pediatr Otorhinolaryngol. 1997 Feb 14;39(1):25-40.
466. Park IH, Song JS, Choi H, Kim TH, Hoon S, Lee SH, et al. Volumetric study in the development of paranasal sinuses by CT imaging in Asian: a pilot study. Int J Pediatr Otorhinolaryngol. 2010 Dec;74(12):1347-50.
467. Kristo A, Uhari M, Luotonen J, Koivunen P, Ilkko E, Tapiainen T, et al. Paranasal sinus findings in children during respiratory infection evaluated with magnetic resonance imaging. Pediatrics. 2003 May;111(5 Pt 1):e586-9.
468. Wald ER. Beginning antibiotics for acute rhinosinusitis and choosing the right treatment. Clinical Reviews in Allergy & Immunology. [Review]. 2006;30(3):143-51.
469. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. Pediatrics. 1991 Feb;87(2):129-33.
470. Monto AS, Ullman BM. Acute respiratory illness in an American community. The Tecumseh study. JAMA. 1974 Jan 14;227(2):164-9.
471. Fox JP, Hall CE, Cooney MK, Luce RE, Kronmal RA. The Seattle virus watch. II. Objectives, study population and its observation, data processing and summary of illnesses. Am J Epidemiol. 1972 Oct;96(4):270-85.
472. Stahlberg MR. [Effect of the type of day care on the occurence of acute respiratory tract infections among young children]. Duodecim. 1981;97(17):1394-403.
473. Vogler RC, Ii FJ, Pilgram TK. Age-specific size of the normal adenoid pad on magnetic resonance imaging. Clinical otolaryngology and allied sciences. 2000 Oct;25(5):392-5.
474. Wald ER, Milmoe GJ, Bowen A, Ledesma-Medina J, Salamon N, Bluestone CD. Acute

maxillary sinusitis in children. The New England journal of medicine. 1981 Mar 26;304(13):749-54.

475. Shapiro DJ, Gonzales R, Cabana MD, Hersh AL. National trends in visit rates and antibiotic prescribing for children with acute sinusitis. Pediatrics. 2011 Jan;127(1):28-34.
476. Huang WH, Fang SY. High prevalence of antibiotic resistance in isolates from the middle meatus of children and adults with acute rhinosinusitis. American journal of rhinology. 2004;18(6):387-91.
477. Brook I. Bacteriology of acute and chronic ethmoid sinusitis. Journal of Clinical Microbiology. 2005;43(7):3479-80.
478. Brook I. Microbiology of acute and chronic maxillary sinusitis associated with an odontogenic origin. The Laryngoscope. 2005;115(5):823-5.
479. Clement PA, Bluestone CD, Gordts F, Lusk RP, Otten FW, Goossens H, et al. Management of rhinosinusitis in children. Int J Pediatr Otorhinolaryngol. 1999 Oct 5;49 Suppl 1:S95-100.
480. Tatli MM, San I, Karaoglanoglu M. Paranasal sinus computed tomographic findings of children with chronic cough. Int J Pediatr Otorhinolaryngol. 2001 Sep 28;60(3):213-7.
481. Poachanukoon O, Kitcharoensakkul M. Efficacy of cefditoren pivoxil and amoxicillin/clavulanate in the treatment of pediatric patients with acute bacterial rhinosinusitis in Thailand: a randomized, investigator-blinded, controlled trial. Clin Ther. 2008 Oct;30(10):1870-9.
482. Meltzer EO, Orgel HA, Backhaus JW, Busse WW, Druce HM, Metzger WJ, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. The Journal of allergy and clinical immunology. 1993 Dec;92(6):812-23.
483. Bousquet J, Bachert C, Canonica GW, Casale TB, Cruz AA, Lockey RJ, et al. Unmet needs in severe chronic upper airway disease (SCUAD). The Journal of allergy and clinical immunology. 2009 Sep;124(3):428-33.
484. Collins JG, Blackwell DL, Tonthat L, Shashy RG, Moore EJ, Weaver A, et al. Prevalence of selected chronic conditions: United States, 1990-1992 Summary health statistics for the U.S. population: National Health Interview Survey, 1997 Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota The role of nasal endoscopy in outpatient management. Vital Health Stat 10. 1997;130(194):1-89.
485. Blackwell DL, Collins JG, Coles R. Summary health statistics for U.S. adults: National Health Interview Survey, 1997. Vital Health Stat 10. 2002 May(205):1-109.
486. Shashy RG, Moore EJ, Weaver A. Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota. Archives of otolaryngology--head & neck surgery. 2004 Mar;130(3):320-3.
487. Hughes RG, Jones NS. The role of nasal endoscopy in outpatient management. Clinical otolaryngology and allied sciences. 1998 Jun;23(3):224-6.
488. Bhattacharyya N. Clinical and symptom criteria for the accurate diagnosis of chronic rhinosinusitis. The Laryngoscope. 2006 Jul;116(7 Pt 2 Suppl 110):1-22.
489. Bonfils P, Nores JM, Halimi P, Avan P, Le Bihan C, Landais P. Correlation between nasosinusal symptoms and topographic diagnosis in chronic rhinosinusitis. Annals of Otology, Rhinology & Laryngology. 2005;114(1 I):74-83.
490. Chen Y, Dales R, Lin M. The epidemiology of chronic rhinosinusitis in Canadians. The Laryngoscope. 2003 Jul;113(7):1199-205.
491. Greisner WA, 3rd, Settipane GA. Hereditary factor for nasal polyps. Allergy and asthma proceedings : the official journal of regional and state allergy societies. 1996 Sep-Oct;17(5):283-6.
492. Gordts F, Clement PA, Buisseret T. Prevalence of sinusitis signs in a non-ENT population. ORL J Otorhinolaryngol Relat Spec. 1996 Nov-Dec;58(6):315-9.
493. Ahsan SF, Jumans S, Nunez DA. Chronic rhinosinusitis: a comparative study of disease occurrence in North of Scotland and Southern Caribbean otolaryngology outpatient clinics over a two month period. Scott Med J. 2004 Nov;49(4):130-3.
494. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde population-based study. The Annals of otology, rhinology, and laryngology. 2003 Jul;112(7):625-9.
495. el Hasnaoui A, Jankowski R, Serrano E, Pribil C, Neukirch F, Klossek JM. Evaluation of a diagnostic questionnaire for nasal polyposis: an observational, cross-sectional study. Rhinology. 2004 Mar;42(1):1-7.
496. Klossek JM, Neukirch F, Pribil C, Jankowski R, Serrano E, Chanal I, et al. Prevalence of nasal polyposis in France: A cross-sectional, case-control study. Allergy. 2005;60(2):233-7.
497. Johansson L, Bramerson A, Holmberg K, Melen I, Akerlund A, Bende M. Clinical relevance of nasal polyps in individuals recruited from a general population-based study. Acta Otolaryngol. 2004 Jan;124(1):77-81.
498. Min YG, Jung HW, Kim HS, Park SK, Yoo KY. Prevalence and risk factors of chronic sinusitis in Korea: results of a nationwide survey. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 1996;253(7):435-9.
499. Hedman J, Kaprio J, Poussa T, Nieminen MM. Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. Int J Epidemiol. 1999 Aug;28(4):717-22.
500. Larsen PL, Tos M. Origin of nasal polyps. The Laryngoscope. 1991 Mar;101(3):305-12.
501. Larsen PL, Tos M. Site of origin of nasal polyps. Transcranially removed naso-ethmoidal blocks as a screening method for nasal polyps in autopsy material. Rhinology. 1995 Dec;33(4):185-8.
502. Larsen P. Anatomic site of origin of nasal polyps: endoscopic nasal and paranasal sinus surgery as a screening method for nasal polyps in autopsy material. American journal of rhinology.

1996(10):211-6.

503. Drake-Lee. Nasal polyps. In: Mygind N, Naclerio RM, editor. Allergic and non-allergic rhinitis. Copenhagen: Munksgaard. 1993.
504. Larsen K, Tos M. The estimated incidence of symptomatic nasal polyps. Acta Otolaryngol. 2002 Mar;122(2):179-82.
505. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. The Journal of allergy and clinical immunology. 1977 Jan;59(1):17-21.
506. Larsen K. The clinical relationship of nasal polyps to asthma. Settipane G LV, Bernstein JM, Tos M, editor. Rhode Island: Oceanside Publications; 1997.
507. Larsen K, Tos M. A long-term follow-up study of nasal polyp patients after simple polypectomies. European Archives of Oto-Rhino-Laryngology. 1997;254:S85-S8.
508. Rugina M, Serrano E, Klossek JM, Crampette L, Stoll D, Bebear JP, et al. Epidemiological and clinical aspects of nasal polyposis in France; the ORLI group experience. Rhinology. 2002 Jun;40(2):75-9.
509. Collins MM, Pang YT, Loughran S, Wilson JA. Environmental risk factors and gender in nasal polyposis. Clinical otolaryngology and allied sciences. 2002 Oct;27(5):314-7.
510. Drake-Lee AB, Lowe D, Swanston A, Grace A. Clinical profile and recurrence of nasal polyps. J Laryngol Otol. 1984 Aug;98(8):783-93.
511. Moloney JR. Nasal polyps, nasal polypectomy, asthma, and aspirin sensitivity. Their association in 445 cases of nasal polyps. J Laryngol Otol. 1977 Oct;91(10):837-46.
512. Larsen K, Tos M. Clinical course of patients with primary nasal polyps. Acta Otolaryngol. 1994 Sep;114(5):556-9.
513. Settipane GA. Epidemiology of nasal polyps. Settipane G LV, Bernstein JM, Tos M, editor. Rhode Island: Oceanside Publications; 1997.
514. Hosemann W, Gode U, Wagner W. Epidemiology, pathophysiology of nasal polyposis, and spectrum of endonasal sinus surgery. Am J Otolaryngol. 1994 Mar-Apr;15(2):85-98.
515. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2000 Sep;16(3):432-6.
516. Al-Rawi MM, Edelstein DR, Erlandson RA. Changes in nasal epithelium in patients with severe chronic sinusitis: a clinicopathologic and electron microscopic study. The Laryngoscope. 1998 Dec;108(12):1816-23.
517. Hadfield PJ, Rowe-Jones JM, Mackay IS. The prevalence of nasal polyps in adults with cystic fibrosis. Clinical otolaryngology and allied sciences. 2000 Feb;25(1):19-22.
518. Kaliner M. Treatment of sinusitis in the next millennium. Allergy and asthma proceedings : the official journal of regional and state allergy societies. 1998 Jul-Aug;19(4):181-4.
519. Krause HF. Allergy and chronic rhinosinusitis. Otolaryngology - Head & Neck Surgery. 2003;128(1):14-6.
520. Jones NS, Carney AS, Davis A. The prevalence of allergic rhinosinusitis: a review. J Laryngol Otol. 1998 Nov;112(11):1019-30.
521. Bailey B. The impact of pollution on the upper alimentary and respiratory tracts. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1992(106):736-40.
522. Stammberger H. Functional endoscopic sinus surgery. Philadelphia: B.C. Decker; 1991.
523. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. [Review]. 1997 Sep;117(3 Pt 2):S1-7.
524. Hamilos DL, Leung DY, Wood R, Cunningham L, Bean DK, Yasruel Z, et al. Evidence for distinct cytokine expression in allergic versus nonallergic chronic sinusitis. The Journal of allergy and clinical immunology. 1995 Oct;96(4):537-44.
525. Slavin RG. Sinusitis in adults and its relation to allergic rhinitis, asthma, and nasal polyps. The Journal of allergy and clinical immunology. 1988 Nov;82(5 Pt 2):950-6.
526. Hamilos DL, Leung DY, Wood R, Meyers A, Stephens JK, Barkans J, et al. Chronic hyperplastic sinusitis: association of tissue eosinophilia with mRNA expression of granulocyte-macrophage colony-stimulating factor and interleukin-3. The Journal of allergy and clinical immunology. 1993 Jul;92(1 Pt 1):39-48.
527. Rachelefsky GS, Goldberg M, Katz RM, Boris G, Gyepes MT, Shapiro MJ, et al. Sinus disease in children with respiratory allergy. The Journal of allergy and clinical immunology. 1978 May;61(5):310-4.
528. Shapiro GG. Role of allergy in sinusitis. Pediatr Infect Dis. 1985 Nov-Dec;4(6 Suppl):S55-9.
529. Benninger MS. Rhinitis, sinusitis and their relationships to allergies. American journal of rhinology. 1992;6:37-43.
530. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2000 Dec;123(6):687-91.
531. Grove R. Chronic hyperplastic sinusitis in allergic patients: a bacteriologic study of 200 operative cases. The Journal of allergy and clinical immunology. 1990(11):271-6.
532. Karlsson G, Holmberg K. Does allergic rhinitis predispose to sinusitis? Acta Otolaryngol Suppl. 1994;515:26-8; discussion 9.
533. Lane AP, Pine HS, Pillsbury HC, 3rd. Allergy testing and immunotherapy in an academic otolaryngology practice: a 20-year review. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2001 Jan;124(1):9-15.
534. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? Ann Allergy. 1971 Dec;29(12):631-4.
535. Bunnag C, Pacharee P, Vipulakom P, Siriyananda C. A study of allergic factor in nasal polyp patients. Ann Allergy. 1983

Feb;50(2):126-32.

536. Kern R. Allergy: a constant factor in the etiology of so-called mucous nasal polyps. J Allergy. 1993;4:483.
537. Blumstein GI, Tuft L. Allergy treatment in recurrent nasal polyposis: its importance and value. Am J Med Sci. 1957 Sep;234(3):269-80.
538. English G. Nasal polyposis. E G, editor. Philadelphia: Harper and Row; 1985.
539. Drake-Lee AB. Histamine and its release from nasal polyps: preliminary communication. J R Soc Med. 1984 Feb;77(2):120-4.
540. Pepys J, Duveen GW. Negative skin tests in allergic rhinitis and nasal polyposis. Int Arch Allergy Appl Immunol. 1951;2(2):147-60.
541. Liu CM, Shun CT, Hsu MM. Lymphocyte subsets and antigen-specific IgE antibody in nasal polyps. Ann Allergy. 1994 Jan;72(1):19-24.
542. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. The Journal of allergy and clinical immunology. 2001 Apr;107(4):607-14.
543. Collins MM, Loughran S, Davidson P, Wilson JA. Nasal polyposis: prevalence of positive food and inhalant skin tests. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2006 Nov;135(5):680-3.
544. Pang YT, Eskici O, Wilson JA. Nasal polyposis: role of subclinical delayed food hypersensitivity. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2000 Feb;122(2):298-301.
545. Salvin RG, Cannon RE, Friedman WH, Palitang E, Sundaram M. Sinusitis and bronchial asthma. The Journal of allergy and clinical immunology. 1980 Sep;66(3):250-7.
546. Schwartz HJ, Thompson JS, Sher TH, Ross RJ. Occult sinus abnormalities in the asthmatic patient. Arch Intern Med. 1987 Dec;147(12):2194-6.
547. Serrano E, Neukirch F, Pribil C, Jankowski R, Klossek JM, Chanal I, et al. Nasal polyposis in France: Impact on sleep and quality of life. Journal of Laryngology & Otology. 2005;119(7):543-9.
548. Downing E. Bronchial reactivity in patients with nasal polyposis before and after polypectomy. The Journal of allergy and clinical immunology. 1982;69(2):102.
549. Alobid I, Cardelus S, Benitez P, Guilemany JM, Roca-Ferrer J, Picado C, et al. Persistent asthma has an accumulative impact on the loss of smell in patients with nasal polyposis. Rhinology. 2011 Dec 1;49(5):519-24.
550. Sun Y, Zhou B, Wang C, Huang Qian, Zhang Qi, Han Ye-hua et al. Clinical and histopathologic features of Biofilm-associated chronic rhinosinusitis with nasal polyps in Chinese patients. Chinese Medical Journal 2012;125, 6:1104-1109.
551. Chafee FH. Aspirin intolerance. I. Frequency in an allergic population. Allergy Clin Immunol. 1974(53):193-9.
552. Weber RW, Hoffman M, Raine DA, Jr., Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. The Journal of allergy and clinical immunology. 1979 Jul;64(1):32-7.
553. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. The Journal of allergy and clinical immunology. 1977 Nov;60(5):276-84.
554. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. The Journal of allergy and clinical immunology. 1979 Dec;64(6 Pt 1):500-6.
555. Ogino S. Aspirin-induced asthma and nasal polyps. Acta Otolaryngol Suppl. 1986(430):21-7.
556. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. The Journal of allergy and clinical immunology. 1999 Jul;104(1):5-13.
557. May A, Wagner D, Langenbeck U, Weber A. [Family study of patients with aspirin intolerance and rhinosinusitis]. HNO. 2000 Sep;48(9):650-4.
558. Moloney JR, Oliver RT. HLA antigens, nasal polyps and asthma. Clinical otolaryngology and allied sciences. 1980 Jun;5(3):183-9.
559. Zhang N, Gevaert P, van Zele T, Perez-Novo C, Patou J, Holtappels G, et al. An update on the impact of Staphylococcus aureus enterotoxins in chronic sinusitis with nasal polyposis. Rhinology. 2005 Sep;43(3):162-8.
560. Chee L, Graham SM, Carothers DG, Ballas ZK. Immune dysfunction in refractory sinusitis in a tertiary care setting. The Laryngoscope. 2001 Feb;111(2):233-5.
561. Porter JP, Patel AA, Dewey CM, Stewart MG. Prevalence of sinonasal symptoms in patients with HIV infection. American journal of rhinology. 1999 May-Jun;13(3):203-8.
562. Garcia-Rodriguez JF, Corominas M, Fernandez-Viladrich P, Monfort JL, Dicenta M. Rhinosinusitis and atopy in patients infected with HIV. The Laryngoscope. 1999 Jun;109(6):939-44.
563. Sabini P, Josephson GD, Reisacher WR, Pincus R. The role of endoscopic sinus surgery in patients with acquired immune deficiency syndrome. Am J Otolaryngol. 1998 Nov-Dec;19(6):351-6.
564. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science (New York, NY). 1989 Sep 8;245(4922):1066-73.
565. Ellegard EK. The etiology and management of pregnancy rhinitis. Am J Respir Med. 2003;2(6):469-75.
566. Sobol SE, Frenkiel S, Nachtigal D, Wiener D, Teblum C. Clinical manifestations of sinonasal pathology during pregnancy. J Otolaryngol. 2001 Feb;30(1):24-8.
567. Sorri M, Hartikainen-Sorri AL, Karja J. Rhinitis during pregnancy. Rhinology. 1980 Jun;18(2):83-6.
568. Zinreich SJ, Mattox DE, Kennedy DW, Chisholm HL, Diffley DM, Rosenbaum AE.

Concha bullosa: CT evaluation. J Comput Assist Tomogr. 1988 Sep-Oct;12(5):778-84.

569. Caughey RJ, Jameson MJ, Gross CW, Han JK. Anatomic risk factors for sinus disease: fact or fiction? American journal of rhinology. 2005 Jul-Aug;19(4):334-9.
570. Jones NS. CT of the paranasal sinuses: a review of the correlation with clinical, surgical and histopathological findings. Clinical otolaryngology and allied sciences. 2002 Feb;27(1):11-7.
571. Bolger WE, Butzin CA, Parsons DS. Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery. The Laryngoscope. 1991 Jan;101(1 Pt 1):56-64.
572. Nouraei SA, Elisay AR, Dimarco A, Abdi R, Majidi H, Madani SA, et al. Variations in paranasal sinus anatomy: implications for the pathophysiology of chronic rhinosinusitis and safety of endoscopic sinus surgery. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2009 Feb;38(1):32-7.
573. Holbrook EH, Brown CL, Lyden ER, Leopold DA. Lack of significant correlation between rhinosinusitis symptoms and specific regions of sinus computer tomography scans. American journal of rhinology. 2005;19(4):382-7.
574. Wagenmann M, Naclerio RM. Complications of sinusitis. The Journal of allergy and clinical immunology. 1992 Sep;90(3 Pt 2):552-4.
575. Jones NS, Strobl A, Holland I. A study of the CT findings in 100 patients with rhinosinusitis and 100 controls. Clinical otolaryngology and allied sciences. 1997 Feb;22(1):47-51.
576. Willner A, Choi SS, Vezina LG, Lazar RH. Intranasal anatomic variations in pediatric sinusitis. American journal of rhinology. 1997 Sep-Oct;11(5):355-60.
577. 577.Yasan H, Dogru H, Baykal B, Douner F, Tuz M. What is the relationship between chronic sinus disease and isolated nasal septal deviation? Otolaryngology - Head & Neck Surgery. 2005;133(2):190-3.
578. Calhoun KH, Waggenspack GA, Simpson CB, Hokanson JA, Bailey BJ. CT evaluation of the paranasal sinuses in symptomatic and asymptomatic populations. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1991 Apr;104(4):480-3.
579. Kayalioglu G, Oyar O, Govsa F. Nasal cavity and paranasal sinus bony variations: a computed tomographic study. Rhinology. 2000 Sep;38(3):108-13.
580. Perez P, Sabate J, Carmona A, Catalina-Herrera CJ, Jimenez-Castellanos J. Anatomical variations in the human paranasal sinus region studied by CT. J Anat. 2000 Aug;197 (Pt 2):221-7.
581. Hoskison E, Daniel M, Rowson JE, Jones NS. Evidence of an increase in the incidence of odontogenic sinusitis over the last decade in the UK. J Laryngol Otol. 2012 Jan;126(1):43-6.
582. Cohen M, Kofonow J, Nayak JV, Palmer JN, Chiu AG, Leid JG, et al. Biofilms in chronic rhinosinusitis: a review. American journal of rhinology & allergy. 2009 May-Jun;23(3):255-60.
583. Genoway KA, Philpott CM, Javer AR. Pathogen yield and antimicrobial resistance patterns of chronic rhinosinusitis patients presenting to a tertiary rhinology centre. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2011 Jun 1;40(3):232-7.
584. Bhattacharyya N, Kepnes LJ. Assessment of trends in antimicrobial resistance in chronic rhinosinusitis. The Annals of otology, rhinology, and laryngology. 2008 Jun;117(6):448-52.
585. Bachert C, Zhang N, Holtappels G, De Lobel L, van Cauwenberge P, Liu S, et al. Presence of IL-5 protein and IgE antibodies to staphylococcal enterotoxins in nasal polyps is associated with comorbid asthma. The Journal of allergy and clinical immunology. 2010 Nov;126(5):962-8, 8 e1-6.
586. Kim J, Hanley JA. The role of woodstoves in the etiology of nasal polyposis. Archives of otolaryngology--head & neck surgery. 2002 Jun;128(6):682-6.
587. Raynal M, Peynegre R, Beautru R, Coste A. [Sinus mucoceles and surgery in iatrogenic diseases]. Ann Otolaryngol Chir Cervicofac. 1999 May;116(2):85-91.
588. Gutman M, Houser S. Iatrogenic maxillary sinus recirculation and beyond. Ear, nose, & throat journal. 2003 Jan;82(1):61-3.
589. Morinaka S, Ichimiya M, Nakamura H. Detection of Helicobacter pylori in nasal and maxillary sinus specimens from patients with chronic sinusitis. The Laryngoscope. 2003 Sep;113(9):1557-63.
590. Ozdek A, Cirak MY, Samim E, Bayiz U, Safak MA, Turet S. A possible role of Helicobacter pylori in chronic rhinosinusitis: A preliminary report. The Laryngoscope. 2003;113(4):679-82.
591. Telmesani LM, Al-Shawarby M. Osteitis in chronic rhinosinusitis with nasal polyps: a comparative study between primary and recurrent cases. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2010 May;267(5):721-4.
592. Ponikau JU, Sherris DA, Kern EB, Homburger HA, Frigas E, Gaffey TA, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clinic proceedings Mayo Clinic. 1999 Sep;74(9):877-84.
593. Sasama J, Sherris DA, Shin SH, Kephart GM, Kern EB, Ponikau JU. New paradigm for the roles of fungi and eosinophils in chronic rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2005 Feb;13(1):2-8.
594. Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: Inflammation. The Journal of allergy and clinical immunology. 2011.
595. Roca-Ferrer J, Garcia-Garcia FJ, Pereda J, Perez-Gonzalez M, Pujols L, Alobid I, et al. Reduced expression of COXs and production of prostaglandin E(2) in patients with nasal polyps with or without aspirin-intolerant asthma. The Journal of allergy and clinical immunology. 2011 Jul;128(1):66-72 e1.

596. Bachert C, Zhang N, Patou J, van Zele T, Gevaert P. Role of staphylococcal superantigens in upper airway disease. Curr Opin Allergy Clin Immunol. 2008 Feb;8(1):34-8.

597. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2009 Jul;124(1):37-42.

598. Peters AT, Kato A, Zhang N, Conley DB, Suh L, Tancowny B, et al. Evidence for altered activity of the IL-6 pathway in chronic rhinosinusitis with nasal polyps. The Journal of allergy and clinical immunology. 2010 Feb;125(2):397-403 e10.

599. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. The New England journal of medicine. 2007 Oct 18;357(16):1608-19.

600. Kato A, Peters A, Suh L, Carter R, Harris KE, Chandra R, et al. Evidence of a role for B cell-activating factor of the TNF family in the pathogenesis of chronic rhinosinusitis with nasal polyps. The Journal of allergy and clinical immunology. 2008 Jun;121(6):1385-92, 92 e1-2.

601. Hammad H, Lambrecht BN. Dendritic cells and airway epithelial cells at the interface between innate and adaptive immune responses. Allergy. 2011 May;66(5):579-87.

602. Patadia M, Dixon J, Conley D, Chandra R, Peters A, Suh LA, et al. Evaluation of the presence of B-cell attractant chemokines in chronic rhinosinusitis. American journal of rhinology & allergy. 2009 Sep 28.

603. Foreman A, Holtappels G, Psaltis AJ, Jervis-Bardy J, Field J, Wormald PJ, et al. Adaptive immune responses in Staphylococcus aureus biofilm-associated chronic rhinosinusitis. Allergy. 2011 Aug 11;66(11):1449-56.

604. Ohlrich EJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease. Aust Dent J. 2009 Sep;54 Suppl 1:S2-10.

605. Perez-Novo CA, Waeytens A, Claeys C, Cauwenberge PV, Bachert C. Staphylococcus aureus enterotoxin B regulates prostaglandin E2 synthesis, growth, and migration in nasal tissue fibroblasts. J Infect Dis. 2008 Apr 1;197(7):1036-43.

606. Okano M, Fujikura T, Haruna T, Kariya S, Makihara S, Higaki T, et al. Prostaglandin E2 suppresses staphylococcal enterotoxin-induced eosinophilia-associated cellular responses dominantly through an E-prostanoid 2-mediated pathway in nasal polyps. The Journal of allergy and clinical immunology. 2009;123(4):868-71.

607. Corriveau MN, Zhang N, Holtappels G, Van Roy N, Bachert C. Detection of Staphylococcus aureus in nasal tissue with peptide nucleic acid-fluorescence in situ hybridization. American journal of rhinology & allergy. 2009 Sep-Oct;23(5):461-5.

608. Sachse F, Becker K, von Eiff C, Metze D, Rudack C. Staphylococcus aureus invades the epithelium in nasal polyposis and induces IL-6 in nasal epithelial cells in vitro. Allergy. 2010 Nov;65(11):1430-7.

609. Krysko O, Holtappels G, Zhang N, Kubica M, Deswarte K, Derycke L, et al. Alternatively activated macrophages and impaired phagocytosis of S. aureus in chronic rhinosinusitis. Allergy. 2011 Mar;66(3):396-403.

610. Poposki JA, Uzzaman A, Nagarkar DR, Chustz RT, Peters AT, Suh LA, et al. Increased expression of the chemokine CCL23 in eosinophilic chronic rhinosinusitis with nasal polyps. The Journal of allergy and clinical immunology. 2011 Jul;128(1):73-81 e4.

611. Ooi EH, Psaltis AJ, Witterick IJ, Wormald PJ. Innate immunity. Otolaryngologic clinics of North America. 2010 Jun;43(3):473-87, vii.

612. Cimmino M, Cavaliere M, Nardone M, Plantulli A, Orefice A, Esposito V, et al. Clinical characteristics and genotype analysis of patients with cystic fibrosis and nasal polyposis. Clinical otolaryngology and allied sciences. 2003 Apr;28(2):125-32.

613. Hull J, Thomson AH. Contribution of genetic factors other than CFTR to disease severity in cystic fibrosis. Thorax. 1998 Dec;53(12):1018-21.

614. Tewfik MA, Bosse Y, Al-Shemari H, Desrosiers M. Genetics of chronic rhinosinusitis: a primer. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2010 Feb 1;39(1):62-8.

615. Meyers DA. Genetics of asthma and allergy: what have we learned? The Journal of allergy and clinical immunology. 2010 Sep;126(3):439-46; quiz 47-8.

616. Vercelli D. Genetics, epigenetics, and the environment: switching, buffering, releasing. The Journal of allergy and clinical immunology. 2004 Mar;113(3):381-6; quiz 7.

617. Vuillermin PJ, Ponsonby AL, Saffery R, Tang ML, Ellis JA, Sly P, et al. Microbial exposure, interferon gamma gene demethylation in naive T-cells, and the risk of allergic disease. Allergy. 2009 Mar;64(3):348-53.

618. Martino DJ, Prescott SL. Silent mysteries: epigenetic paradigms could hold the key to conquering the epidemic of allergy and immune disease. Allergy. 2010 Jan;65(1):7-15.

619. Ho SM. Environmental epigenetics of asthma: an update. The Journal of allergy and clinical immunology. 2010 Sep;126(3):453-65.

620. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy. 2006 Nov;61(11):1280-9.

621. Bachert C, Claeys SE, Tomassen P, van Zele T, Zhang N. Rhinosinusitis and asthma: a link for asthma severity. Current allergy and asthma reports. 2010 May;10(3):194-201.

622. Van Bruaene N, Bachert C. Tissue remodeling in chronic rhinosinusitis. Curr Opin Allergy Clin Immunol. 2011 Feb;11(1):8-11.

623. Ba L, Zhang N, Meng J, Zhang J, Lin P, Zhou P, et al. The association between bacterial colonization and inflammatory pattern in Chinese chronic rhinosinusitis

patients with nasal polymps. Allergy . 2011.

624. Littman DR, Pamer EG. Role of the commensal microbiota in normal and pathogenic host immune responses. Cell Host Microbe. 2011 Oct 4;10(4):311-23.
625. Leung R, Conley D, Kern R, Chandra R. OMC Obstruction is Not Associated with Adjacent Sinus Disease in Chronic Rhinosinusitis with Polyps. AJRA. 2011:In Press.
626. Payne SC, Borish L, Steinke JW. Genetics and phenotyping in chronic sinusitis. The Journal of allergy and clinical immunology. 2011 Jun 23.
627. Payne SC, Early SB, Huyett P, Han JK, Borish L, Steinke JW. Evidence for distinct histological profile of nasal polyps: with and without eosinophilia. The Laryngoscope. 2011;121(10):2262-7.
628. Bachert C, Van Bruaene N, Toskala E, Zhang N, Olze H, Scadding G, et al. Important research questions in allergy and related diseases: 3-chronic rhinosinusitis and nasal polyposis - a GALEN study. Allergy. 2009 Apr;64(4):520-33.
629. Feazel LM, Frank DN, Ramakrishnan V. Update on bacterial detection methods in chronic rhinosinusitis: implications for clinicians and research scientists. International forum of allergy & rhinology. 2011:1-9.
630. Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, et al. Disordered microbial communities in asthmatic airways. PLoS One. 2010;5(1):e8578.
631. Cho KS, Kim CS, Lee HS, Seo SK, Park HY, Roh HJ. Role of interferon-gamma-producing t cells in the pathogenesis of chronic rhinosinusitis with nasal polyps associated with staphylococcal superantigen. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2010 Oct;39(5):600-5.
632. Lemon KP, Klepac-Ceraj V, Schiffer HK, Brodie EL, Lynch SV, Kolter R. Comparative analyses of the bacterial microbiota of the human nostril and oropharynx. MBio. 2010;1(3).
633. Frank DN, Feazel LM, Bessesen MT, Price CS, Janoff EN, Pace NR. The human nasal microbiota and Staphylococcus aureus carriage. PLoS One. 2010;5(5):e10598.
634. Abou-Hamad W, Matar N, Elias M, Nasr M, Sarkis-Karam D, Hokayem N, et al. Bacterial flora in normal adult maxillary sinuses. American journal of rhinology & allergy. 2009 May-Jun;23(3):261-3.
635. Benninger M, Brook I, Bernstein JM, Casey JR, Roos K, Marple B, et al. Bacterial interference in upper respiratory tract infections: a systematic review. American journal of rhinology & allergy. 2011 Mar-Apr;25(2):82-8.
636. Herbst T, Sichelstiel A, Schar C, Yadava K, Burki K, Cahenzli J, et al. Dysregulation of allergic airway inflammation in the absence of microbial colonization. American journal of respiratory and critical care medicine. 2011 Jul 15;184(2):198-205.
637. Belkaid Y, Tarbell K. Regulatory T cells in the control of host-microorganism interactions (*). Annu Rev Immunol. 2009;27:551-89.
638. Cernadas M. It Takes a Microbiome: Commensals, Immune Regulation, and Allergy. American journal of respiratory and critical care medicine. 2011;184:149-58.
639. Araujo E, Palombini BC, Cantarelli V, Pereira A, Mariante A. Microbiology of middle meatus in chronic rhinosinusitis. American journal of rhinology. 2003 Jan-Feb;17(1):9-15.
640. Doyle PW, Woodham JD. Evaluation of the microbiology of chronic ethmoid sinusitis. J Clin Microbiol. 1991 Nov;29(11):2396-400.
641. Hoyt WH. Bacterial patterns found in surgery patients wtih chronic sinusitis. J Am Osteopath Assoc. 1992;92(205).
642. Hsu J, Lanza DC, Kennedy DW. Antimicrobial resistance in bacterial chronic sinusitis. American journal of rhinology. 1998 Jul-Aug;12(4):243-8.
643. Jiang RS, Lin JF, Hsu CY. Correlations between bacteriology of the middle meatus and ethmoid sinus in chronic sinusitis. J Laryngol Otol. 2002;116:443-6.
644. Kim HJ, Lee K, Yoo JB, Song JW, Yoon JH. Bacteriological findings and antimicrobial susceptibility in chronic sinusitis with nasal polyp. Acta Otolaryngol. 2006 May;126(5):489-97.
645. Finegold SM, Flynn MJ, Rose FV, Jousimies-Somer H, Jakielaszek C, McTeague M, et al. Bacteriologic findings associated with chronic bacterial maxillary sinusitis in adults. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2002 Aug 15;35(4):428-33.
646. Brook I. Microbiology of sinusitis. Proceedings of the American Thoracic Society. 2011 Mar;8(1):90-100.
647. Mantovani K, Bisanha AA, Demarco RC, Tamashiro E, Martinez R, Anselmo-Lima WT. Maxillary sinuses microbiology from patients with chronic rhinosinusitis. Brazilian journal of otorhinolaryngology. 2010 Sep-Oct;76(5):548-51.
648. Niederfuhr A, Kirsche H, Deutschle T, Poppert S, Riechelmann H, Wellinghausen N. Staphylococcus aureus in nasal lavage and biopsy of patients with chronic rhinosinusitis. Allergy. 2008 Oct;63(10):1359-67.
649. Niederfuhr A, Kirsche H, Riechelmann H, Wellinghausen N. The bacteriology of chronic rhinosinusitis with and without nasal polyps. Archives of otolaryngology--head & neck surgery. 2009 Feb;135(2):131-6.
650. Bhattacharyya N. Bacterial infection in chronic rhinosinusitis: A controlled paired analysis. American journal of rhinology. 2005;19(6):544-8.
651. Bhattacharyya N, Gopal HV, Lee KH. Bacterial Infection after Endoscopic Sinus Surgery: A Controlled Prospective Study. The Laryngoscope. 2004;114(4):765-7.
652. Shiomori T, Yoshida S, Miyamoto H, Makishima K. Relationship of nasal carriage of Staphylococcus aureus to pathogenesis of perennial allergic rhinitis. The Journal of allergy and clinical immunology. 2000 Mar;105(3):449-54.
653. Clement S, Vaudaux P, Francois P, Schrenzel J, Huggler E, Kampf S, et al. Evidence of an intracellular reservoir

in the nasal mucosa of patients with recurrent Staphylococcus aureus rhinosinusitis. Journal of Infectious Diseases. 2005;192(6):1023-8.

654. Plouin-Gaudon I, Clement S, Huggler E, Chaponnier C, Francois P, Lew D, et al. Intracellular residency is frequently associated with recurrent Staphylococcus aureus rhinosinusitis. Rhinology. 2006;44:249-54.
655. Stephenson MF, Mfuna L, Dowd SE, Wolcott RD, Barbeau J, Poisson M, et al. Molecular characterization of the polymicrobial flora in chronic rhinosinusitis. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2010 Apr;39(2):182-7.
656. Proctor LM. The human microbiome project in 2011 and beyond. Cell Host Microbe. 2011 Oct 4;10(4):287-91.
657. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. Science (New York, NY). 2009 Dec 18;326(5960):1694-7.
658. Robinson CJ, Bohannan BJ, Young VB. From structure to function: the ecology of host-associated microbial communities. Microbiol Mol Biol Rev. 2010 Sep;74(3):453-76.
659. Qiao F, Xie Y, Yin WJ, Kang MJ, Guo XJ, Chen HJ. Nasal colonization by opportunistic pathogens among health care workers: a survey. Chin J Nosocomiol. 2008;18:1371-3.
660. Larson DA, Han JK. Microbiology of sinusitis: does allergy or endoscopic sinus surgery affect the microbiologic flora? Current opinion in otolaryngology & head and neck surgery. 2011 Jun;19(3):199-203.
661. Van Zele T, Gevaert P, Watelet JB, Claeys G, Holtappels G, Claeys C, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. The Journal of allergy and clinical immunology. 2004 Oct;114(4):981-3.
662. Bernstein J, Ballow M, Schlievert PM. A Superantigen hypothesis for the pathogenesis of chronic hyperplastic sinusitis with massive nasal polyposis. Am J Rhinol. 2003;17:321-6.
663. Conley DB, Tripathi A, Seiberling KA, Schleimer RP, Suh LA, Harris K, et al. Superantigens and chronic rhinosinusitis: skewing of T-cell receptor V beta-distributions in polyp-derived CD4+ and CD8+ T cells. American journal of rhinology. 2006 Sep-Oct;20(5):534-9.
664. Conley DB, Tripathi A, Seiberling KA, Suh LA, Harris KE, Paniagua MC, et al. Superantigens and chronic rhinosinusitis II: analysis of T-cell receptor V beta domains in nasal polyps. American journal of rhinology. 2006 Jul-Aug;20(4):451-5.
665. Tripathi A, Conley DB, Grammer LC, Ditto AM, Lowery MM, Seiberling KA, et al. Immunoglobulin E to staphylococcal and streptococcal toxins in patients with chronic sinusitis/nasal polyposis. The Laryngoscope. 2004;114(10 I):1822-6.
666. Wang M, Shi P, Yue Z, Chen B, Zhang H, Zhang D, et al. Superantigens and the expression of T-cell receptor repertoire in chronic rhinosinusitis with nasal polyps. Acta Otolaryngol. 2008 Aug;128(8):901-8.
667. Seiberling KA, Conley DB, Tripathi A, Grammer LC, Shuh L, Haines IG, et al. Superantigens and chronic rhinosinusitis: Detection of staphylococcal exotoxins in nasal polyps. The Laryngoscope. 2005;115(9):1580-5.
668. Patou J, Gevaert P, Van Zele T, Holtappels G, van Cauwenberge P, Bachert C. Staphylococcus aureus enterotoxin B, protein A, and lipoteichoic acid stimulations in nasal polyps. The Journal of allergy and clinical immunology. 2008 Jan;121(1):110-5.
669. Perez Novo CA, Jedrzejczak-Czechowicz M, Lewandowska-Polak A, Claeys C, Holtappels G, Van Cauwenberge P, et al. T cell inflammatory response, Foxp3 and TNFRS18-L regulation of peripheral blood mononuclear cells from patients with nasal polyps-asthma after staphylococcal superantigen stimulation. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2010 Sep;40(9):1323-32.
670. Langier S, Landsberg R, Sade K, Kivity S. Anti-IL-5 immunomodulates the effect of Staphylococcus aureus enterotoxin on T cell response in nasal polyps. Rhinology. 2011;49(5):570-6.
671. Huvenne W, Callebaut I, Reekmans K, Hens G, Bobic S, Jorissen M, et al. Staphylococcus aureus enterotoxin B augments granulocyte migration and survival via airway epithelial cell activation. Allergy. 2010 Aug;65(8):1013-20.
672. Wang JH, Kwon HJ, Jang YJ. Staphylococcus aureus increases cytokine and matrix metalloproteinase expression in nasal mucosae of patients with chronic rhinosinusitis and nasal polyps. American journal of rhinology & allergy. 2010 Nov-Dec;24(6):422-7.
673. Wang M, Shi P, Chen B, Shi G, Li H, Wang H. Superantigen-Induced Glucocorticoid Insensitivity in the Recurrence of Chronic Rhinosinusitis with Nasal Polyps. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Jul 4.
674. Van Zele T, Vaneechoutte M, Holtappels G, Gevaert P, van Cauwenberge P, Bachert C. Detection of enterotoxin DNA in Staphylococcus aureus strains obtained from the middle meatus in controls and nasal polyp patients. American journal of rhinology. 2008 May-Jun;22(3):223-7.
675. Falkow S. Molecular Koch's postulates applied to bacterial pathogenicity--a personal recollection 15 years later. Nat Rev Microbiol. 2004 Jan;2(1):67-72.
676. Inglis TJ. Principia aetiologica: taking causality beyond Koch's postulates. J Med Microbiol. 2007 Nov;56(Pt 11):1419-22.
677. Suh JD, Cohen NA, Palmer JN. Biofilms in chronic rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2010 Feb;18(1):27-31.
678. Suh JD, Ramakrishnan V, Palmer JN. Biofilms. Otolaryngologic clinics of North America. 2010 Jun;43(3):521-30, viii.
679. Lewis K. Persister cells, dormancy and infectious disease. Nat Rev Microbiol. 2007 Jan;5(1):48-56.

680. Palmer JN. Bacterial biofilms: Do they play a role in chronic sinusitis? Otolaryngologic clinics of North America. [Review]. 2005;38(6):1193-201.
681. Perloff JR, Palmer JN. Evidence of bacterial biofilms on frontal recess stents in patients with chronic rhinosinusitis. American journal of rhinology. 2004;18(6):377-80.
682. Ferguson BJ, Stolz DB. Demonstration of biofilm in human bacterial chronic rhinosinusitis. American journal of rhinology. 2005 Sep-Oct;19(5):452-7.
683. Ramadan HH, Sanclement JA, Thomas JG. Chronic rhinosinusitis and biofilms. Otolaryngology - Head & Neck Surgery. [Review]. 2005;132(3):414-7.
684. Sanderson AR, Leid JG, Hunsaker D. Bacterial biofilms on the sinus mucosa of human subjects with chronic rhinosinusitis. The Laryngoscope. 2006;116(7):1121-6.
685. Sanclement JA, Webster P, Thomas J, Ramadan HH. Bacterial biofilms in surgical specimens of patients with chronic rhinosinusitis. The Laryngoscope. 2005;115(4):578-82.
686. Psaltis AJ, Weitzel EK, Ha KR, Wormald PJ. The effect of bacterial biofilms on post-sinus surgical outcomes. American journal of rhinology. 2008 Jan-Feb;22(1):1-6.
687. Prince AA, Steiger JD, Khalid AN, Dogrhamji L, Reger C, Eau Claire S, et al. Prevalence of biofilm-forming bacteria in chronic rhinosinusitis. American journal of rhinology. 2008 May-Jun;22(3):239-45.
688. Mladina R, Poje G, Vukovic K, Ristic M, Music S. Biofilm in nasal polyps. Rhinology. 2008 Dec;46(4):302-7.
689. Foreman A, Psaltis AJ, Tan LW, Wormald PJ. Characterization of bacterial and fungal biofilms in chronic rhinosinusitis. American journal of rhinology & allergy. 2009 Nov-Dec;23(6):556-61.
690. Zernotti ME, Angel Villegas N, Roques Revol M, Baena-Cagnani CE, Arce Miranda JE, Paredes ME, et al. Evidence of bacterial biofilms in nasal polyposis. J Investig Allergol Clin Immunol. 2010;20(5):380-5.
691. Bendouah Z, Barbeau J, Hamad WA, Desrosiers M. Biofilm formation by Staphylococcus aureus and Pseudomonas aeruginosa is associated with an unfavorable evolution after surgery for chronic sinusitis and nasal polyposis. Otolaryngology - Head & Neck Surgery. 2006;134(6):991-6.
692. Foreman A, Wormald PJ. Different biofilms, different disease? A clinical outcomes study. The Laryngoscope. 2010 Aug;120(8):1701-6.
693. Singhal D, Foreman A, Bardy JJ, Wormald PJ. Staphylococcus aureus biofilms: Nemesis of endoscopic sinus surgery. The Laryngoscope. 2011 Jul;121(7):1578-83.
694. Hekiert AM, Kofonow JM, Doghramji L, Kennedy DW, Chiu AG, Palmer JN, et al. Biofilms correlate with TH1 inflammation in the sinonasal tissue of patients with chronic rhinosinusitis. Otolaryngology - Head and Neck Surgery. 2009;141:448-53.
695. Wood AJ, Fraser J, Swift S, Amirapu S, Douglas R. Are biofilms associated with an inflammatory response in chronic rhinosinusitis? International forum of allergy & rhinology. 2011:1-5.
696. Foreman A, Jervis-Bardy J, Wormald PJ. Do Biofilms Contribute to the Initiation and Recalcitrance of Chronic Rhinosinusitis? The Laryngoscope. 2011(121):1085-91.
697. Ebbens F, Georgalas C, Fokkens W. Fungas as the cause of chronic rhinosinusitis: the case remains unproven. Otolaryngology - Head and Neck Surgery. 2009;17:43-9.
698. Ebbens FA, Georgalas C, Fokkens WJ. The mold conundrum in chronic hyperplastic sinusitis. Current allergy and asthma reports. 2009 Mar;9(2):114-20.
699. Braun H, Buzina W, Freudenschuss K, Beham A, Stammberger H. 'Eosinophilic fungal rhinosinusitis': a common disorder in Europe? The Laryngoscope. 2003 Feb;113(2):264-9.
700. Davis LJ, Kita H. Pathogenesis of chronic rhinosinusitis: role of airborne fungi and bacteria. Immunology and allergy clinics of North America. 2004 Feb;24(1):59-73.
701. Ponikau J, Sherris DA, Kephart GM, Kern EB, Congdon D, Adolphson CR, et al. Striking deposition of toxic eosinophil major basic protein in mucus: Implications from chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2005;116(2):362-9.
702. Shin SH, Ponikau JU, Sherris DA, Congdon D, Frigas E, Homburger HA, et al. Chronic rhinosinusitis: An enhanced immune response to ubiquitous airborne fungi. Journal of Allergy & Clinical Immunology. 2004;114(6):1369-75.
703. Wei JL, Kita H, Sherris DA, Kern EB, Weaver A, Ponikau JU. The chemotactic behavior of eosinophils in patients with chronic rhinosinusitis. The Laryngoscope. 2003;113(2):303-6.
704. Inoue Y, Matsuwaki Y, Shin SH, Ponikau JU, Kita H. Nonpathogenic, environmental fungi induce activation and degranulation of human eosinophils. J Immunol. 2005 Oct 15;175(8):5439-47.
705. Romani L. Immunity to fungal infections. Nat Rev Immunol. 2011 Apr;11(4):275-88.
706. Douglas R, Bruhn M, Tan LW, Ooi E, Psaltis A, Wormald PJ. Response of peripheral blood lymphocytes to fungal extracts and staphylococcal superantigen B in chronic rhinosinusitis. The Laryngoscope. 2007 Mar;117(3):411-4.
707. Orlandi RR, Marple BF, Georgelas A, Durtschi D, Barr L. Immunologic response to fungus is not universally associated with rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009 Dec;141(6):750-6 e1-2.
708. Ponikau JU, Sherris DA, Kita H, Kern EB. Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2002 Dec;110(6):862-6.
709. Ponikau JU, Sherris DA, Weaver A, Kita H. Treatment of chronic rhinosinusitis with intranasal amphotericin B: a randomized, placebo-controlled, double-blind pilot trial. The Journal of allergy and clinical immunology. 2005 Jan;115(1):125-31.
710. Weschta M, Rimek D, Formanek M, Polzehl D, Podbielski A, Riechelmann H. Topical antifungal treatment of chronic rhinosinusitis with nasal polyps: a randomized, double-blind clinical trial. The Journal of allergy and clinical

immunology. 2004 Jun;113(6):1122-8.

711. Liang KL, Su MC, Shiao JY, Tseng HC, Hsin CH, Lin JF, et al. Amphotericin B irrigation for the treatment of chronic rhinosinusitis without nasal polyps: a randomized, placebo-controlled, double-blind study. American journal of rhinology. 2008 Jan-Feb;22(1):52-8.
712. Ebbens FA, Scadding GK, Badia L, Hellings PW, Jorissen M, Mullol J, et al. Amphotericin B nasal lavages: not a solution for patients with chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2006 Nov;118(5):1149-56.
713. Ebbens FA, Georgalas C, Luiten S, van Drunen CM, Badia L, Scadding GK, et al. The effect of topical amphotericin B on inflammatory markers in patients with chronic rhinosinusitis: a multicenter randomized controlled study. The Laryngoscope. 2009 Feb;119(2):401-8.
714. Isaacs S, Fakhri S, Luong A, Citardi MJ. A meta-analysis of topical amphotericin B for the treatment of chronic rhinosinusitis. International forum of allergy & rhinology. 2011;1(4):250-4.
715. Orlandi RR, Marple BF. Fungus and chronic rhinosinusitis: weighing the evidence. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 Nov;143(5):611-3.
716. Orlandi RR, Marple BF. The role of fungus in chronic rhinosinusitis. Otolaryngologic clinics of North America. 2010 Jun;43(3):531-7, viii.
717. Shin SH, Lee SH, Jeong HS, Kita H. The effect of nasal polyp epithelial cells on eosinophil activation. The Laryngoscope. 2003 Aug;113(8):1374-7.
718. Shin SH, Lee YH, Jeon CH. Protease-dependent activation of nasal polyp epithelial cells by airborne fungi leads to migration of eosinophils and neutrophils. Acta Otolaryngol. 2006 Dec;126(12):1286-94.
719. Ebbens FA, Fokkens WJ. The mold conundrum in chronic rhinosinusitis: where do we stand today? Current allergy and asthma reports. 2008 Apr;8(2):93-101.
720. Rudack C, Steinhoff M, Mooren F, Buddenkotte J, Becker K, von Eiff C, et al. PAR-2 activation regulates IL-8 and GRO-alpha synthesis by NF-kappaB, but not RANTES, IL-6, eotaxin or TARC expression in nasal epithelium. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2007 Jul;37(7):1009-22.
721. Bent JP, 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1994 Nov;111(5):580-8.
722. Ryan MW. Allergic fungal rhinosinusitis. Otolaryngologic clinics of North America. 2011 Jun;44(3):697-710, ix-x.
723. Hutcheson PS, Schubert MS, Slavin RG. Districtions between allergic fungal rhinosinusitis and chronic rhinosinusitis. American Journal of Rhinology and Allergy. 2010;24(6):405-8.
724. Luong A, Davis LS, Marple BF. Peripheral blood mononuclear cells from allergic fungal rhinosinusitis adults express a Th2 cytokine response to fungal antigens. American journal of rhinology & allergy. 2009 May-Jun;23(3):281-7.
725. Collins M, Nair S, Smith W, Kette F, Gillis D, Wormald PJ. Role of local immunoglobulin E production in the pathophysiology of noninvasive fungal sinusitis. The Laryngoscope. 2004;114(7):1242-6.
726. Ahn CN, Wise SK, Lathers DM, Mulligan RM, Harvey RJ, Schlosser RJ. Local production of antigen-specific IgE in different anatomic subsites of allergic fungal rhinosinusitis patients. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009 Jul;141(1):97-103.
727. Carney AS, Tan LW, Adams D, Varelias A, Ooi EH, Wormald PJ. Th2 immunological inflammation in allergic fungal sinusitis, nonallergic eosinophilic fungal sinusitis, and chronic rhinosinusitis. American journal of rhinology. 2006;20(2):145-9.
728. Pant H, Kette FE, Smith WB, Macardle PJ, Wormald PJ. Eosinophilic mucus chronic rhinosinusitis: Clinical subgroups or a homogeneous pathogenic entity? The Laryngoscope. 2006;116(7):1241-7.
729. Pant H, Beroukas D, Kette FE, Smith WB, Wormald PJ, Macardle PJ. Nasal polyp cell populations and fungal-specific peripheral blood lymphocyte proliferation in allergic fungal sinusitis. American journal of rhinology & allergy. 2009 Sep-Oct;23(5):453-60.
730. Orlandi RR, Thibeault SL, Ferguson BJ. Microarray analysis of allergic fungal sinusitis and eosinophilic mucin rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 May;136(5):707-13.
731. Pant H, Schembri MA, Wormald PJ, Macardle PJ. IgE-mediated fungal allergy in allergic fungal sinusitis. The Laryngoscope. 2009 Jun;119(6):1046-52.
732. Lee CG, Da Silva CA, Dela Cruz CS, Ahangari F, Ma B, Kang MJ, et al. Role of chitin and chitinase/chitinase-like proteins in inflammation, tissue remodeling, and injury. Annu Rev Physiol. 2011 Mar 17;73:479-501.
733. Reese TA, Liang HE, Tager AM, Luster AD, Van Rooijen N, Voehringer D, et al. Chitin induces accumulation in tissue of innate immune cells associated with allergy. Nature. 2007 May 3;447(7140):92-6.
734. Zhu Z, Zheng T, Homer RJ, Kim YK, Chen NY, Cohn L, et al. Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. Science (New York, NY). 2004 Jun 11;304(5677):1678-82.
735. Ramanathan Jr M, Lee WK, Lane AP. Increased expression of acidic mammalian chitinase in chronic rhinosinusitis with nasal polyps. American journal of rhinology. 2006;20(3):330-5.
736. Park SK, Cho HW, Heo KW, Hur DY, Lee HK. Role of acidic mammalian chitinase and chitotriosidase in nasal polyps. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009 Oct;141(4):462-6.
737. Park SK, Heo KW, Hur DY, Yang YI.

Chitinolytic activity in nasal polyps. American journal of rhinology & allergy. 2011 Jan-Feb;25(1):12-4.

738. Gu Z, Cao Z, Jin M. Expression and role of acidic mammalian chitinase and eotaxin-3 in chronic rhinosinusitis with nasal polyps. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2011 Feb;40(1):64-9.
739. Lalaker A, Nkrumah L, Lee WK, Ramanathan M, Lane AP. Chitin stimulates expression of acidic mammalian chitinase and eotaxin-3 by human sinonasal epithelial cells in vitro. American journal of rhinology & allergy. 2009 Jan-Feb;23(1):8-14.
740. Tan BK, Zirkle W, Chandra RK, Lin D, Conley DB, Peters AT, et al. Atopic profile of patients failing medical therapy for chronic rhinosinusitis. International forum of allergy & rhinology. 2011;1(2):88-94.
741. Baroody FM, Mucha SM, Detineo M, Naclerio RM. Nasal challenge with allergen leads to maxillary sinus inflammation. The Journal of allergy and clinical immunology. 2008 May;121(5):1126-32 e7.
742. Naclerio RM, deTineo ML, Baroody FM. Ragweed allergic rhinitis and the paranasal sinuses. A computed tomographic study. Archives of otolaryngology--head & neck surgery. 1997 Feb;123(2):193-6.
743. Liu F, Zhang J, Liu Y, Zhang N, Holtappels G, Lin P, et al. Inflammatory profiles in nasal mucosa of patients with persistent vs intermittent allergic rhinitis. Allergy. 2010 Sep;65(9):1149-57.
744. Keith PK, Conway M, Evans S, Wong DA, Jordana G, Pengelly D, et al. Nasal polyps: effects of seasonal allergen exposure. The Journal of allergy and clinical immunology. 1994 Mar;93(3):567-74.
745. Robinson S, Douglas R, Wormald P-J. The relationship between atopy and chronic rhinosinusitis. American journal of rhinology. 2006;20(6):625-8.
746. Pearlman AN, Chandra RK, Chang D, Conley DB, Tripathi-Peters A, Grammer LC, et al. Relationships between severity of chronic rhinosinusitis and nasal polyposis, asthma, and atopy. American journal of rhinology & allergy. 2009 Mar-Apr;23(2):145-8.
747. Zhang N, Holtappels G, Gevaert P, Patou J, Dhaliwal B, Gould H, et al. Mucosal tissue polyclonal IgE is functional in response to allergen and SEB. Allergy. 2011 Jan;66(1):141-8.
748. Kohlmeier JE, Woodland DL. Immunity to respiratory viruses. Annu Rev Immunol. 2009;27:61-82.
749. Gwaltney JM, Phillis CD, Miller RD, Riker DK. Computed tomographic study of the common cold. The New England journal of medicine. 1994;330(25-30.).
750. Wood AJ, Antoszewska H, Fraser J, Douglas RG. Is chronic rhinosinusitis caused by persistent respiratory virus infection? International forum of allergy & rhinology. 2011;1(2):95-100.
751. Jang YJ, Kwon HJ, Park HW, Lee BJ. Detection of rhinovirus in turbinate epithelial cells of chronic sinusitis. American journal of rhinology. 2006 Nov-Dec;20(6):634-6.
752. Sigurs N. Epidemiologic and clinical evidence of a respiratory syncytial virus-reactive airway disease link. American journal of respiratory and critical care medicine. 2001 Mar;163(3 Pt 2):S2-6.
753. Sly PD, Kusel M, Holt PG. Do early-life viral infections cause asthma? The Journal of allergy and clinical immunology. 2010 ;125(6):1202-5.
754. Sykes A, Johnston SL. Etiology of asthma exacerbations. The Journal of allergy and clinical immunology. 2008 Oct;122(4):685-8.
755. Rosenthal LA, Avila PC, Heymann PW, Martin RJ, Miller EK, Papadopoulos NG, et al. Viral respiratory tract infections and asthma: the course ahead. The Journal of allergy and clinical immunology. 2010 Jun;125(6):1212-7.
756. Holt PG, Strickland DH. Interactions between innate and adaptive immunity in asthma pathogenesis: New perspectives from studies on acute exacerbations. 125. 2010:963-72.
757. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. The Journal of allergy and clinical immunology. 2010 Jun;125(6):1178-87; quiz 88-9.
758. Yamin M, Holbrook EH, Gray ST, Harold R, Busaba N, Sridhar A, et al. Cigarette smoke combined with Toll-like receptor 3 signaling triggers exaggerated epithelial regulated upon activation, normal T-cell expressed and secreted/CCL5 expression in chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2008 Dec;122(6):1145-53 e3.
759. Pedersen M, Sakakura Y, Winther B, Brofeldt S, Mygind N. Nasal mucociliary transport, number of ciliated cells, and beating pattern in naturally acquired common colds. Eur J Respir Dis Suppl. 1983;128 (Pt 1):355-65.
760. Lieu JE, Feinstein AR. Confirmations and surprises in the association of tobacco use with sinusitis. Archives of otolaryngology--head & neck surgery. 2000 Aug;126(8):940-6.
761. Houser SM, Keen KJ. The role of allergy and smoking in chronic rhinosinusitis and polyposis. The Laryngoscope. 2008 Sep;118(9):1521-7.
762. Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. The Laryngoscope. 1992 Dec;102(12 Pt 2 Suppl 57):1-18.
763. Krzeski A, Galewicz A, Chmielewski R, Kisiel M. Influence of cigarette smoking on endoscopic sinus surgery long-term outcomes. Rhinology. 2011;49:1-6.
764. Cohen NA, Zhang S, Sharp DB, Tamashiro E, Chen B, Sorscher EJ, et al. Cigarette smoke condensate inhibits transepithelial chloride transport and ciliary beat frequency. The Laryngoscope. 2009 Nov;119(11):2269-74.
765. Goldstein-Daruech N, Cope EK, Zhao KQ, Vukovic K, Kofonow JM, Doghramji L, et al. Tobacco smoke mediated induction of sinonasal microbial biofilms. PLoS One. 2011;6(1):e15700.
766. Misso NL, Thompson PJ. Oxidative stress and antioxidant deficiencies in asthma: potential modification by diet. Redox Rep. 2005;10(5):247-55.
767. Comhair SA, Bhathena PR, Farver C,

Thunnissen FB, Erzurum SC. Extracellular glutathione peroxidase induction in asthmatic lungs: evidence for redox regulation of expression in human airway epithelial cells. FASEB J. 2001 Jan;15(1):70-8.

768. Xiao C, Puddicombe SM, Field S, Haywood J, Broughton-Head V, Puxeddu I, et al. Defective epithelial barrier function in asthma. The Journal of allergy and clinical immunology. 2011 Jul 11.

769. Huvenne W, Perez-Novo CA, Derycke L, De Ruyck N, Krysko O, Maes T, et al. Different regulation of cigarette smoke induced inflammation in upper versus lower airways. Respir Res. 2010;11:100.

770. Rudmik L, Mace JC, Smith TL. Smoking and Endoscopic Sinus Surgery: Does smoking volume contribute to clinical outcome? International forum of allergy & rhinology. 2011 May;1(2):145-52.

771. Chandra RK, Lin D, Tan B, Tudor RS, Conley DB, Peters AT, et al. Chronic rhinosinusitis in the setting of other chronic inflammatory diseases. Am J Otolaryngol. 2011 Sep 9;32(5):388-91.

772. Johansson ME, Larsson JM, Hansson GC. The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host-microbial interactions. Proc Natl Acad Sci U S A. 2011 Mar 15;108 Suppl 1:4659-65.

773. Antunes MB, Gudis DA, Cohen NA. Epithelium, cilia, and mucus: their importance in chronic rhinosinusitis. Immunology and allergy clinics of North America. 2009 Nov;29(4):631-43.

774. Cutting GR. Modifier genetics: cystic fibrosis. Annu Rev Genomics Hum Genet. 2005;6:237-60.

775. Chen B, Antunes MB, Claire SE, Palmer JN, Chiu AG, Kennedy DW, et al. Reversal of chronic rhinosinusitis-associated sinonasal ciliary dysfunction. American journal of rhinology. 2007 May-Jun;21(3):346-53.

776. Saito D, Innes A, Pletcher S. Rheologic properties of sinonasal mucus in patients with chronic sinusitis. American journal of rhinology & allergy. 2010;24(1):1-5.

777. Virgin F, Zhang S, Schuster D, Azbell C, Fortenberry J, Sorscher EJ, et al. The bioflavonoid compound, sinupret, stimulates transepithelial chloride transport in vitro and in vivo. The Laryngoscope. 2010 May;120(5):1051-6.

778. Azbell C, Zhang S, Skinner D, Fortenberry J, Sorscher EJ, Woodworth BA. Hesperidin stimulates cystic fibrosis transmembrane conductance regulator-mediated chloride secretion and ciliary beat frequency in sinonasal epithelium. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 Sep;143(3):397-404.

779. Zhang S, Smith N, Schuster D, Azbell C, Sorscher EJ, Rowe SM, et al. Quercertin increases cystic fibrosis transmembrane conductance regulator-mediated chloride transport and ciliary beat frequency: Therapeutic implications for chronic rhinosinusitis. American Journal of Rhinology and Allergy. 2011;25(5):307-12.

780. Zuckerman JD, Lee WY, DelGaudio JM, Moore CE, Nava P, Nusrat A, et al. Pathophysiology of nasal polyposis: the role of desmosomal junctions. American journal of rhinology. 2008 Nov-Dec;22(6):589-97.

781. Rogers G, Beste, K.E. H, Parkos CA, Nusrat A, DelGaudio JM, et al. Epithelial tight junction alterations in nasal polyposis. International forum of allergy & rhinology. 2011;1(1):50-4.

782. Richer SL, Truong-Tran AQ, Conley DB, Carter R, Vermylen D, Grammer LC, et al. Epithelial genes in chronic rhinosinusitis with and without nasal polyps. American journal of rhinology. 2008 May-Jun;22(3):228-34.

783. Descargues P, Deraison C, Bonnart C, Kreft M, Kishibe M, Ishida-Yamamoto A, et al. Spink5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. Nat Genet. 2005 Jan;37(1):56-65.

784. Dejima K, Randell SH, Stutts MJ, Senior BA, Boucher RC. Potential role of abnormal ion transport in the pathogenesis of chronic sinusitis. Archives of otolaryngology--head & neck surgery. 2006 Dec;132(12):1352-62.

785. Bernstein JM, Yankaskas JR. Increased ion transport in cultured nasal polyp epithelial cells. Archives of otolaryngology--head & neck surgery. 1994 Sep;120(9):993-6.

786. Bernstein JM, Gorfien J, Noble B, Yankaskas JR. Nasal polyposis: immunohistochemistry and bioelectrical findings (a hypothesis for the development of nasal polyps). The Journal of allergy and clinical immunology. 1997 Feb;99(2):165-75.

787. Schleimer RP, Kato A, Kern R, Kuperman D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. The Journal of allergy and clinical immunology. 2007 Dec;120(6):1279-84.

788. Schleimer RP, Lane AP, Kim J. Innate and acquired immunity and epithelial cell function in chronic rhinosinusitis. Clin Allergy Immunol. 2007;20:51-78.

789. Sha Q, Truong-Tran AQ, Plitt JR, Beck LA, Schleimer RP. Activation of airway epithelial cells by toll-like receptor agonists. Am J Respir Cell Mol Biol. 2004 Sep;31(3):358-64.

790. Lane AP, Truong-Tran QA, Myers A, Bickel C, Schleimer RP. Serum amyloid A, properdin, complement 3, and toll-like receptors are expressed locally in human sinonasal tissue. American journal of rhinology. 2006;20(1):117-23.

791. Lane AP, Truong-Tran QA, Schleimer RP. Altered expression of genes associated with innate immunity and inflammation in recalcitrant rhinosinusitis with polyps. American journal of rhinology. 2006;20(2):138-44.

792. Bianchi ME, Manfredi AA. Immunology. Dangers in and out. Science (New York, NY). 2009 Mar 27;323(5922):1683-4.

793. Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. Nat Immunol. 2004 Oct;5(10):987-95.

794. Vroling AB, Fokkens WJ, van Drunen CM. How epithelial cells detect danger: aiding the immune response. Allergy. 2008 Sep;63(9):1110-23.

795. Kato A, Schleimer RP. Beyond inflammation: airway epithelial cells are at the interface of innate and adaptive

immunity. Curr Opin Immunol. 2007 Dec;19(6):711-20.

796. Dong Z, Yang Z, Wang C. Expression of TLR2 and TLR4 messenger RNA in the epithelial cells of the nasal airway. American journal of rhinology. 2005 May-Jun;19(3):236-9.
797. Claeys S, Van Hoecke H, Holtappels G, Gevaert P, De Belder T, Verhasselt B, et al. Nasal polyps in patients with and without cystic fibrosis: A differentiation by innate markers and inflammatory mediators. Clinical & Experimental Allergy. 2005;35(4):467-72.
798. Ramanathan M, Jr., Lee WK, Dubin MG, Lin S, Spannhake EW, Lane AP. Sinonasal epithelial cell expression of toll-like receptor 9 is decreased in chronic rhinosinusitis with polyps. American journal of rhinology. 2007 Jan-Feb;21(1):110-6.
799. Bogefors J, Rydberg C, Uddman R, Fransson M, Mansson A, Benson M, et al. Nod1, Nod2 and Nalp3 receptors, new potential targets in treatment of allergic rhinitis? Allergy. 2010 Oct;65(10):1222-6.
800. Mansson A, Bogefors J, Cervin A, Uddman R, Cardell LO. NOD-like receptors in the human upper airways: a potential role in nasal polyposis. Allergy. 2011 May;66(5):621-8.
801. Ossovskaya VS, Bunnett NW. Protease-activated receptors: contribution to physiology and disease. Physiol Rev. 2004 Apr;84(2):579-621.
802. Hershenson MB. Proteases and Protease-activated receptors signalling: at the crossroads of acquired and innate immunity. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2007 Jul;37(7):963-6.
803. Rudack C, Sachse F, Albert N, Becker K, von Eiff C. Immunomodulation of nasal epithelial cells by Staphylococcus aureus-derived serine proteases. J Immunol. 2009 Dec 1;183(11):7592-601.
804. Briot A, Deraison C, Lacroix M, Bonnart C, Robin A, Besson C, et al. Kallikrein 5 induces atopic dermatitis-like lesions through PAR2-mediated thymic stromal lymphopoietin expression in Netherton syndrome. J Exp Med. 2009 May 11;206(5):1135-47.
805. Avila PC, Schleimer RP. Airway Epithelium. In: Kay AB, Kaplan AP, Bousquet J, Holt PG, editors. Allergy and allergic diseases. 2nd ed. Chichester, West Sussex, UK ; Hoboken, NJ: Wiley-Blackwell; 2008.
806. Laudien M, Dressel S, Harder J, Glaser R. Differential expression pattern of antimicrobial peptides in nasal mucosa and secretion. Rhinology. 2011 Mar;49(1):107-11.
807. Kim ST, Cha HE, Kim DY, Han GC, Chung YS, Lee YJ, et al. Antimicrobial peptide LL-37 is upregulated in chronic nasal inflammatory disease. Acta Otolaryngol. 2003 Jan;123(1):81-5.
808. Lee HM, Kang HJ, Woo JS, Chae SW, Lee SH, Hwang SJ. Upregulation of surfactant protein A in chronic rhinosinusitis. The Laryngoscope. 2006 Feb;116(2):328-30.
809. Van Zele T, Coppieters F, Gevaert P, Holtappels G, Van Cauwenberge P, Bachert C. Local complement activation in nasal polyposis. The Laryngoscope. 2009 Sep;119(9):1753-8.
810. Schlosser RJ, Mulligan RM, Casey SE, Varela JC, Harvey RJ, Atkinson C. Alterations in gene expression of complement components in chronic rhinosinusitis. American journal of rhinology & allergy. 2010 Jan-Feb;24(1):21-5.
811. Lee JT, Jansen M, Yilma AN, Nguyen A, Desharnais R, Porter E. Antimicrobial lipids: novel innate defense molecules are elevated in sinus secretions of patients with chronic rhinosinusitis. American journal of rhinology & allergy. 2010 Mar-Apr;24(2):99-104.
812. Psaltis AJ, Bruhn MA, Ooi EH, Tan LW, Wormald PJ. Nasal mucosa expression of lactoferrin in patients with chronic rhinosinusitis. The Laryngoscope. 2007 Nov;117(11):2030-5.
813. Tieu DD, Peters AT, Carter RG, Suh L, Conley DB, Chandra R, et al. Evidence for diminished levels of epithelial psoriasin and calprotectin in chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2010 Mar;125(3):667-75.
814. Meyer JE, Harder J, Sipos B, Maune S, Kloppel G, Bartels J, et al. Psoriasin (S100A7) is a principal antimicrobial peptide of the human tongue. Mucosal Immunol. 2008 May;1(3):239-43.
815. Seshadri S, Lin D, Kato A, Carter R, Suh L, Peters A, et al. Reduced Expression of Antimicrobial PLUNC Proteins in Nasal Polyp Tissue. The Journal of allergy and clinical immunology. 2009;125(2):AB61.
816. Ramanathan M, Jr., Lee WK, Spannhake EW, Lane AP. Th2 cytokines associated with chronic rhinosinusitis with polyps down-regulate the antimicrobial immune function of human sinonasal epithelial cells. American journal of rhinology. 2008 Mar-Apr;22(2):115-21.
817. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. Immunity. 2004 Aug;21(2):241-54.
818. Wolk K, Witte E, Wallace E, Docke WD, Kunz S, Asadullah K, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. Eur J Immunol. 2006 May;36(5):1309-23.
819. Pickert G, Neufert C, Leppkes M, Zheng Y, Wittkopf N, Warntjen M, et al. STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. J Exp Med. 2009 Jul 6;206(7):1465-72.
820. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, et al. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med. 2008 Mar;14(3):275-81.
821. Hulse K, Norton J, Harris K, Conley D, Chandra R, Kern R, et al. Epithelial STAT3 activation is associated with expression of the antimicrobial peptide S100A7. J Immunol 2010 184(14).
822. Aujla SJ, Kolls JK. IL-22: a critical mediator in mucosal host defense. J Mol Med. 2009 May;87(5):451-4.
823. Ramanathan M, Jr., Spannhake EW, Lane AP. Chronic rhinosinusitis with nasal polyps is associated with decreased expression of mucosal interleukin 22 receptor. The Laryngoscope. 2007

Oct;117(10):1839-43.

824. Kowalski ML, Lewandowska-Polak A, Wozniak J, Ptasinska A, Jankowski A, Wagrowska-Danilewicz M, et al. Association of stem cell factor expression in nasal polyp epithelial cells with aspirin sensitivity and asthma. Allergy. 2005;60(5):631-7.
825. Nishi Y, Takeno S, Ishino T, Hirakawa K. Glucocorticoids suppress NF-kappaB activation induced by LPS and PGN in paranasal sinus epithelial cells. Rhinology. 2009 Dec;47(4):413-8.
826. Lu X, Zhang XH, Wang H, Long XB, You XJ, Gao QX, et al. Expression of osteopontin in chronic rhinosinusitis with and without nasal polyps. Allergy. 2009 Jan;64(1):104-11.
827. Hammad H, Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. Nat Rev Immunol. 2008 Mar;8(3):193-204.
828. Watanabe K, Shirasaki H, Kanaizumi E, Himi T. Effects of glucocorticoids on infiltrating cells and epithelial cells of nasal polyps. The Annals of otology, rhinology, and laryngology. 2004 Jun;113(6):465-73.
829. Schaefer D, Meyer JE, Pods R, Pethe W, Hedderich J, Schmidt C, et al. Endothelial and epithelial expression of eotaxin-2 (CCL24) in nasal polyps. International Archives of Allergy & Immunology. 2006;140(3):205-14.
830. Basinski TM, Holzmann D, Eiwegger T, Zimmermann M, Klunker S, Meyer N, et al. Dual nature of T cell-epithelium interaction in chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2009 Jul;124(1):74-80 e1-8.
831. Damm M, Quante G, Rosenbohm J, Rieckmann R. Proinflammatory effects of Staphylococcus aureus exotoxin B on nasal epithelial cells. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2006 Feb;134(2):245-9.
832. Peterson S, Poposki JA, Nagarkar DR, Chustz RT, Peters AT, Suh LA, et al. Increased expression of CC chemokine ligand 18 in patients with chronic rhinosinusitis with nasal polyps. The Journal of allergy and clinical immunology. 2011 Sep 22.
833. Mulligan JK, Mulligan RM, Atkinson C, Schlosser RJ. Human sinonasal epithelial cells direct dendritic function and T-cell T helper 1/T helper 2 skewing following Aspergillus exposure. International forum of allergy & rhinology. 2011;1(4):268-74.
834. Bulek K, Swaidani S, Aronica M, Li X. Epithelium: the interplay between innate and Th2 immunity. Immunol Cell Biol. 2010 Mar-Apr;88(3):257-68.
835. Allakhverdi Z, Comeau MR, Smith DE, Toy D, Endam LM, Desrosiers M, et al. CD34+ hemopoietic progenitor cells are potent effectors of allergic inflammation. The Journal of allergy and clinical immunology. 2009 Feb;123(2):472-8.
836. Nonaka M, Fukumoto A, Ogihara N, Sakanushi A, Pawankar R, Yagi T. Synergistic induction of thymic stromal lymphopoietin by tumor necrosis factor alpha and Th2 cytokine in nasal polyp fibroblasts. American journal of rhinology & allergy. 2010 Jan-Feb;24(1):e14-8.
837. Liu T, Li TL, Zhao F, Xie C, Liu AM, Chen X, et al. Role of thymic stromal lymphopoietin in the pathogenesis of nasal polyposis. Am J Med Sci. 2011 Jan;341(1):40-7.
838. Kimura S, Pawankar R, Mori S, Nonaka M, Masuno S, Yagi T, et al. Increased expression and role of thymic stromal lymphopoietin in nasal polyposis. Allergy Asthma Immunol Res. 2011 Jul;3(3):186-93.
839. Reh DD, Wang Y, Ramanathan M, Jr., Lane AP. Treatment-recalcitrant chronic rhinosinusitis with polyps is associated with altered epithelial cell expression of interleukin-33. American journal of rhinology & allergy. 2010 Mar-Apr;24(2):105-9.
840. Buysschaert ID, Grulois V, Eloy P, Jorissen M, Rombaux P, Bertrand B, et al. Genetic evidence for a role of IL33 in nasal polyposis. Allergy. 2010 May;65(5):616-22.
841. Mullol J, Roca-Ferrer J, Alobid I, Pujols L, Valero A, Xaubet A, et al. Effect of desloratadine on epithelial cell granulocyte-macrophage colony-stimulating factor secretion and eosinophil survival. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2006 Jan;36(1):52-8.
842. Sachse F, Becker K, Basel TJ, Weiss D, Rudack C. IKK-2 inhibitor TPCA-1 represses nasal epithelial inflammation in vitro. Rhinology. 2011 Jun;49(2):168-73.
843. Schleimer RP. Glucocorticoids suppress inflammation but spare innate immune responses in airway epithelium. Proceedings of the American Thoracic Society. 2004;1(3):222-30.
844. Bobic S, van Drunen CM, Callebaut I, Hox V, Jorissen M, Fokkens WJ, et al. Dexamethasone-induced apoptosis of freshly isolated human nasal epithelial cells concomitant with abrogation of IL-8 production. Rhinology. 2010 Dec;48(4):401-7.
845. Li N, Hao M, Phalen RF, Hinds WC, Nel AE. Particulate air pollutants and asthma. A paradigm for the role of oxidative stress in PM-induced adverse health effects. Clin Immunol. 2003 Dec;109(3):250-65.
846. Lundberg JO, Farkas-Szallasi T, Weitzberg E, Rinder J, Lidholm J, Anggaard A, et al. High nitric oxide production in human paranasal sinuses. Nat Med. 1995 Apr;1(4):370-3.
847. Lindberg S, Cervin A, Runer T. Low levels of nasal nitric oxide (NO) correlate to impaired mucociliary function in the upper airways. Acta Otolaryngol. 1997 Sep;117(5):728-34.
848. Lindberg S, Cervin A, Runer T. Nitric oxide (NO) production in the upper airways is decreased in chronic sinusitis. Acta Otolaryngol. 1997 Jan;117(1):113-7.
849. Colantonio D, Brouillette L, Parikh A, Scadding GK. Paradoxical low nasal nitric oxide in nasal polyposis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2002 May;32(5):698-701.
850. Ragab SM, Lund VJ, Saleh HA, Scadding G. Nasal nitric oxide in objective evaluation of chronic rhinosinusitis therapy. Allergy. 2006 Jun;61(6):717-24.

851. Phillips PS, Sacks R, Marcells GN, Cohen NA, Harvey RJ. Nasal nitric oxide and sinonasal disease: a systematic review of published evidence. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Feb;144(2):159-69.

852. Cannady SB, Batra PS, Leahy R, Citardi MJ, Janocha A, Ricci K, et al. Signal transduction and oxidative processes in sinonasal polyposis. The Journal of allergy and clinical immunology. 2007 Dec;120(6):1346-53.

853. Cardell LO. The paranasal sinuses and a unique role in airway nitric oxide production? American journal of respiratory and critical care medicine. 2002 Jul 15;166(2):131-2.

854. Jardeleza c, Foreman A, Baker L, Paramasivan S, Field J, Tan LW, et al. The effects of nitric oxide on Staphylococcus aureus biofilm growth and its implications in chronic rhinosinusitis. International forum of allergy & rhinology. 2011:1-7.

855. Kirihene R, Rees G, Wormald PJ. The influence of the size of the maxillary sinus ostium on the nasal and sinus nitric oxide levels. American journal of rhinology. 2002;16:261-4.

856. Haas N, Hamann K, Grabbe J, Niehus J, Kunkel G, Kolde G, et al. Demonstration of the high-affinity IgE receptor (Fc epsilon RI) on Langerhans' cells of diseased nasal mucosa. Allergy. 1997 Apr;52(4):436-9.

857. Reinartz SM, van Tongeren J, van Egmond D, de Groot EJJ. Dendritic cells in nasal mucosa of subjects with different allergic sensitizations. Journal of Allergy and Clinical Immunology. 2011:1-3.

858. Rampey AM, Lathers DM, Woodworth BA, Schlosser RJ. Immunolocalization of dendritic cells and pattern recognition receptors in chronic rhinosinusitis. American journal of rhinology. 2007 Jan-Feb;21(1):117-21.

859. Kirsche H, Niederfuhr A, Deutschle T, Fuchs C, Riechelmann H. Ratio of myeloid and plasmacytoid dendritic cells and TH2 skew in CRS with nasal polyps. Allergy. 2010 Jan;65(1):24-31.

860. Ayers CM, Schlosser RJ, O'Connel BP, Atkinson C, Mulligan RM, Casey SE, et al. Increased presence of dendritic cells and dendritic cell chemokines in the sinus mucosa of chronic rhinosinusitis with nasal polyps and allergic fungal rhinosinusitis. International forum of allergy & rhinology. 2011;1(4):296-302.

861. Martinez FO, Helming L, Gordon S. Alternative activation of macrophages: an immunologic functional perspective. Annu Rev Immunol. 2009;27:451-83.

862. Sobol SE, Christodoulopoulos P, Manoukian JJ, Hauber HP, Frenkiel S, Desrosiers M, et al. Cytokine profile of chronic sinusitis in patients with cystic fibrosis. Archives of otolaryngology--head & neck surgery. 2002 Nov;128(11):1295-8.

863. Claeys S, Be Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, et al. Macrophage mannose receptor in chronic sinus disease. Allergy. 2004;59(6):606-12.

864. Lee JJ, Jacobsen EA, McGarry MP, Schleimer RP, Lee NA. Eosinophils in health and disease: the LIAR hypothesis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2010 Apr;40(4):563-75.

865. 865.Harlin SL, Ansel DG, Lane SR, Myers J, Kephart GM, Gleich GJ. A clinical and pathologic study of chronic sinusitis: the role of the eosinophil. The Journal of allergy and clinical immunology. 1988 May;81(5 Pt 1):867-75.

866. Jankowski R, Bouchoua F, Coffinet L, Vignaud JM. Clinical factors influencing the eosinophil infiltration of nasal polyps. Rhinology. 2002 Dec;40(4):173-8.

867. Bhattacharyya N, Vyas DK, Fechner FP, Gliklich RE, Metson R. Tissue eosinophilia in chronic sinusitis: quantification techniques. Archives of otolaryngology--head & neck surgery. 2001 Sep;127(9):1102-5.

868. Szucs E, Ravandi S, Goossens A, Beel M, Clement PA. Eosinophilia in the ethmoid mucosa and its relationship to the severity of inflammation in chronic rhinosinusitis. American journal of rhinology. 2002 May-Jun;16(3):131-4.

869. Bachert C, Gevaert P, Howarth P, Holtappels G, van Cauwenberge P, Johansson SG. IgE to Staphylococcus aureus enterotoxins in serum is related to severity of asthma. The Journal of allergy and clinical immunology. 2003 May;111(5):1131-2.

870. Soler Z, Sauer D, Mace J, Smith T. Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. Otolaryngology - Head and Neck Surgery. 2009(141):454-61.

871. Oppenheimer EH, Rosenstein BJ. Differential pathology of nasal polyps in cystic fibrosis and atopy. Lab Invest. 1979 Apr;40(4):445-9.

872. Jankowski R, Bene MC, Moneret-Vautrin AD, Haas F, Faure G, Simon C, et al. Immunohistological characteristics of nasal polyps. A comparison with healthy mucosa and chronic sinusitis. Rhinol Suppl. 1989;8:51-8.

873. Rudack C, Sachse F, Alberty J. Chronic rhinosinusitis - Need for further classification? Inflammation Research. 2004;53(3):111-7.

874. Polzehl D, Moeller P, Riechelmann H, Perner S. Distinct features of chronic rhinosinusitis with and without nasal polyps. Allergy. 2006 Nov;61(11):1275-9.

875. Zhang N, Holtappels G, Claeys C, Huang G, van Cauwenberge P, Bachert C. Pattern of inflammation and impact of Staphylococcus aureus enterotoxins in nasal polyps from southern China. American journal of rhinology. 2006 Jul-Aug;20(4):445-50.

876. Kim JW, Hong SL, Kim YK, Lee CH, Min YG, Rhee CS. Histological and immunological features of non-eosinophilic nasal polyps. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 Dec;137(6):925-30.

877. Cao PP, Li HB, Wang BF, Wang SB, You XJ, Cui YH, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. The Journal of allergy and clinical immunology. 2009 Jun 19.

878. Matsuwaki Y, Ookushi T, Asaka D, Mori E, Nakajima T, Yoshida T, et al. Chronic rhinosinusitis: risk factors for the recurrence of chronic rhinosinusitis based on 5-year follow-up after endoscopic sinus surgery. Int Arch Allergy Immunol. 2008;146 Suppl 1:77-81.

879. Soler ZM, Sauer D, Mace J, Smith TL. Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 Jan;142(1):64-71.

880. Schleimer R, Kato A, Kern RC. "Eosinophils in CRS". Eosinophils in Health and Disease2011

881. Combadiere C, Ahuja SK, Tiffany HL, Murphy PM. Cloning and functional expression of CC CKR5, a human monocyte CC chemokine receptor selective for MIP-1(alpha), MIP-1(beta), and RANTES. J Leukoc Biol. 1996 Jul;60(1):147-52.

882. Daugherty BL, Siciliano SJ, DeMartino JA, Malkowitz L, Sirotina A, Springer MS. Cloning, expression, and characterization of the human eosinophil eotaxin receptor. J Exp Med. 1996 May 1;183(5):2349-54.

883. Beck LA, Stellato C, Beall LD, Schall TJ, Leopold D, Bickel CA, et al. Detection of the chemokine RANTES and endothelial adhesion molecules in nasal polyps. The Journal of allergy and clinical immunology. 1996 Oct;98(4):766-80.

884. Allen JS, Eisma R, LaFreniere D, Leonard G, Kreutzer D. Characterization of the eosinophil chemokine RANTES in nasal polyps. The Annals of otology, rhinology, and laryngology. 1998 May;107(5 Pt 1):416-20.

885. Meyer JE, Bartels J, Gorogh T, Sticherling M, Rudack C, Ross DA, et al. The role of RANTES in nasal polyposis. American journal of rhinology. 2005;19(1):15-20.

886. Bartels J, Maune S, Meyer JE, Kulke R, Schluter C, Rowert J, et al. Increased eotaxin-mRNA expression in non-atopic and atopic nasal polyps: comparison to RANTES and MCP-3 expression. Rhinology. 1997 Dec;35(4):171-4.

887. Jahnsen FL, Haye R, Gran E, Brandtzaeg P, Johansen FE. Glucocorticosteroids inhibit mRNA expression for eotaxin, eotaxin-2, and monocyte-chemotactic protein-4 in human airway inflammation with eosinophilia. J Immunol. 1999 Aug 1;163(3):1545-51.

888. Shin SH, Park JY, Jeon CH, Choi JK, Lee SH. Quantitative analysis of eotaxin and RANTES messenger RNA in nasal polyps: association of tissue and nasal eosinophils. The Laryngoscope. 2000 Aug;110(8):1353-7.

889. Molinaro RJ, Bernstein JM, Koury ST. Localization and quantitation of eotaxin mRNA in human nasal polyps. Immunol Invest. 2003 Aug;32(3):143-54.

890. Olze H, Forster U, Zuberbier T, Morawietz L, Luger EO. Eosinophilic nasal polyps are a rich source of eotaxin, eotaxin-2 and eotaxin-3. Rhinology. 2006;44(2):145-50.

891. Yao T, Kojima Y, Koyanagi A, Yokoi H, Saito T, Kawano K, et al. Eotaxin-1, -2, and -3 immunoreactivity and protein concentration in the nasal polyps of eosinophilic chronic rhinosinusitis patients. The Laryngoscope. 2009 Jun;119(6):1053-9.

892. Matsukura S, Stellato C, Plitt JR, Bickel C, Miura K, Georas SN, et al. Activation of eotaxin gene transcription by NF-kappa B and STAT6 in human airway epithelial cells. J Immunol. 1999 Dec 15;163(12):6876-83.

893. Kuperman DA, Schleimer RP. Interleukin-4, interleukin-13, signal transducer and activator of transcription factor 6, and allergic asthma. Curr Mol Med. 2008 Aug;8(5):384-92.

894. Ying S, Meng Q, Taborda-Barata L, Corrigan CJ, Barkans J, Assoufi B, et al. Human eosinophils express messenger RNA encoding RANTES and store and release biologically active RANTES protein. Eur J Immunol. 1996;26:70-6.

895. Denburg JA, Otsuka H, Ohnisi M, Ruhno J, Bienenstock J, Dolovich J. Contribution of basophil/mast cell and eosinophil growth and differentiation to the allergic tissue inflammatory response. Int Arch Allergy Appl Immunol. 1987;82(3-4):321-6.

896. Ohnishi M, Ruhno J, Bienenstock J, Milner R, Dolovich J, Denburg JA. Human nasal polyp epithelial basophil/mast cell and eosinophil colony-stimulating activity. The effect is T-cell-dependent. Am Rev Respir Dis. 1988 Sep;138(3):560-4.

897. Park HS, Jung KS, Shute J, Roberts K, Holgate ST, Djukanovic R. Allergen-induced release of GM-CSF and IL-8 in vitro by nasal polyp tissue from atopic subjects prolongs eosinophil survival. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1997 Jul;10(7):1476-82.

898. Gauldie J, Cox G, Jordana M, Ohno I, Kirpalani H. Growth and colony-stimulating factors mediate eosinophil fibroblast interactions in chronic airway inflammation. Ann N Y Acad Sci. 1994 May 28;725:83-90.

899. Xaubet A, Mullol J, Lopez E, Roca-Ferrer J, Rozman M, Carrion T, et al. Comparison of the role of nasal polyp and normal nasal mucosal epithelial cells on in vitro eosinophil survival. Mediation by GM-CSF and inhibition by dexamethasone. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. [Comparative Study In Vitro Research Support, Non-U.S. Gov't]. 1994 Apr;24(4):307-17.

900. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. The Journal of allergy and clinical immunology. 1997;99:837-42.

901. Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. J Immunol. 1997 Apr 15;158(8):3902-8.

902. Hamilos DL, Leung DY, Huston DP, Kamil A, Wood R, Hamid Q. GM-CSF, IL-5 and RANTES immunoreactivity and mRNA expression in chronic hyperplastic sinusitis with nasal polyposis (NP). Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1998 Sep;28(9):1145-52.

903. Lamblin C, Bolard F, Gosset P, Tsicopoulos A, Perez T, Darras J, et al. Bronchial interleukin-5 and eotaxin expression in nasal polyposis. Relationship with (a)symptomatic bronchial hyperresponsiveness. American journal of respiratory and critical care medicine. 2001 Apr;163(5):1226-32.
904. Bachert C, Wagenmann M, Rudack C, Hopken K, Hillebrandt M, Wang D, et al. The role of cytokines in infectious sinusitis and nasal polyposis. Allergy. 1998 Jan;53(1):2-13.
905. Wagenmann M, Helmig P. Increased production of type-2 and type-1 cytokines in nasal polyps. The Journal of allergy and clinical immunology. 2000;105:S210.
906. Beck LA, Schall TJ, Beall LD, Leopold D, Bickel C, Baroody F, et al. Detection of the chemokine RANTES and activation of vascular endothelium in nasal polyps. The Journal of allergy and clinical immunology. 1994;93:A234.
907. Jahnsen FL, Haraldsen G, Aanesen JP, Haye R, Brandtzaeg P. Eosinophil infiltration is related to increased expression of vascular cell adhesion molecule-1 in nasal polyps. Am J Respir Cell Mol Biol. 1995 Jun;12(6):624-32.
908. Hamilos DL, Leung DY, Wood R, Bean DK, Song YL, Schotman E, et al. Eosinophil infiltration in nonallergic chronic hyperplastic sinusitis with nasal polyposis (CHS/NP) is associated with endothelial VCAM-1 upregulation and expression of TNF-alpha. Am J Respir Cell Mol Biol. 1996 Oct;15(4):443-50.
909. Corsi MM, Pagani D, Dogliotti G, Perona F, Sambataro G, Pignataro L. Protein biochip array of adhesion molecule expression in peripheral blood of patients with nasal polyposis. Int J Biol Markers. 2008;23:115-20.
910. Eweiss A, Dogheim Y, Hassab M, Tayel H, Hammad Z. VCAM-1 and eosinophilia in diffuse sino-nasal polyps. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2009 Mar;266(3):377-83.
911. Symon FA, Walsh GM, Watson SR, Wardlaw AJ. Eosinophil adhesion to nasal polyp endothelium is P-selectin-dependent. J Exp Med. 1994 Jul 1;180(1):371-6.
912. Toppila-Salmi SK, Myller JP, Torkkeli TVM, Muhonen JV, Renkonen JA, Rautiainen ME, et al. Endothelial L-selectin ligands in sinus mucosa during chronic maxillary rhinosinusitis. American Journal of Respiratory & Critical Care Medicine. 2005;171(12):1350-7.
913. Tan BK, Schleimer RP, Kern RC. Perspectives on the etiology of chronic rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2010 Feb;18(1):21-6.
914. Perez-Novo CA, Claeys C, Van Zele T, Holtapples G, Van Cauwenberge P, Bachert C. Eicosanoid metabolism and eosinophilic inflammation in nasal polyp patients with immune response to Staphylococcus aureus enterotoxins. American journal of rhinology. 2006 Jul-Aug;20(4):456-60.
915. Perez-Novo CA, Claeys C, Van Cauwenberge P, Bachert C. Expression of eicosanoid receptors subtypes and eosinophilic inflammation: implication on chronic rhinosinusitis. Respir Res. 2006;7:75.
916. Bernardes JF, Shan J, Tewfik M, Hamid Q, Frenkiel S, Eidelman DH. Protein nitration in chronic sinusitis and nasal polyposis: Role of eosinophils. Otolaryngology - Head & Neck Surgery. 2004;131(5):696-703.
917. Bachert C, Gevaert P, Holtappels G, Cuvelier C, van Cauwenberge P. Nasal polyposis: from cytokines to growth. American journal of rhinology. 2000 Sep-Oct;14(5):279-90.
918. Abu-Ghazaleh RI, Fujisawa T, Mestecky J, Kyle RA, Gleich GJ. IgA-induced eosinophil degranulation. J Immunol. 1989 Apr 1;142(7):2393-400.
919. Pleass RJ, Lang ML, Kerr MA, Woof JM. IgA is a more potent inducer of NADPH oxidase activation and degranulation in blood eosinophils than IgE. Mol Immunol. 2007 Feb;44(6):1401-8.
920. Bartemes KR, Cooper KM, Drain KL, Kita H. Secretory IgA induces antigen-independent eosinophil survival and cytokine production without inducing effector functions. The Journal of allergy and clinical immunology. 2005 Oct;116(4):827-35.
921. Van Zele T, Gevaert P, Holtappels G, van Cauwenberge P, Bachert C. Local immunoglobulin production in nasal polyposis is modulated by superantigens. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2007 Dec;37(12):1840-7.
922. Laitinen LA, Laitinen L. Structural and cellular changes in asthma. Eur Respir Rev. 1994;4:348-51.
923. Flood-Page P, Menzies-Gow A, Phipps S, Ying S, Wangoo A, Ludwig MS, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. J Clin Invest. 2003 Oct;112(7):1029-36.
924. Ohno I, Nitta Y, Yamauchi K, Hoshi H, Honma M, Woolley K, et al. Eosinophils as a potential source of platelet-derived growth factor B-chain (PDGF-B) in nasal polyposis and bronchial asthma. Am J Respir Cell Mol Biol. 1995 Dec;13(6):639-47.
925. Ohno I, Nitta Y, Yamauchi K, Hoshi H, Honma M, Woolley K, et al. Transforming growth factor beta 1 (TGF beta 1) gene expression by eosinophils in asthmatic airway inflammation. Am J Respir Cell Mol Biol. 1996;15:404-9.
926. Elovic A, Wong DT, Weller PF, Matossian K, Galli SJ. Expression of transforming growth factors-alpha and beta 1 messenger RNA and product by eosinophils in nasal polyps. The Journal of allergy and clinical immunology. 1994;93:864-9.
927. Schleimer RP, Bochner BS. The effects of glucocorticoids on human eosinophils. The Journal of allergy and clinical immunology. 1994;94:1202-13.
928. Van Zele T, Gevaert P, Holtappels G,

Beule A, Wormald PJ, Mayr S, et al. Oral steroids and doxycycline: two different approaches to treat nasal polyps. The Journal of allergy and clinical immunology. 2010;125(5):1069-76.e4.

929. Gevaert P, Bachert C, Holtappels G, Novo CP, Van der Heyden J, Fransen L, et al. Enhanced soluable interleukin-5 receptor alpha expression in nasal polyposis. Allergy. 2003;58:371-9.
930. Gevaert P, Hellman C, Lundblad L, Lundahl J, Holtappels G, van Cauwenberge P, et al. Differential expression of the interleukin 5 receptor alpha isoforms in blood and tissue eosinophils of nasal polyp patients. Allergy. 2009 May;64(5):725-32.
931. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. The Journal of allergy and clinical immunology. 2006 Nov;118(5):1133-41.
932. Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. The Journal of allergy and clinical immunology. 2011 Sep 27.
933. Allen JS, Eisma R, Leonard G, Lafreniere D, Kreutzer D. Interleukin-8 expression in human nasal polyps. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1997 Nov;117(5):535-41.
934. Chen YS, Arab SF, Westhofen M, Lorenzen J. Expression of interleukin-5, interleukin-8, and interleukin-10 mRNA in the osteomeatal complex in nasal polyposis. American journal of rhinology. 2005;19(2):117-23.
935. Ural A, Tezer MS, Yucel A, Atilla H, Ileri F. Interleukin-4, interleukin-8 and E-selectin levels in intranasal polyposis patients with and without allergy: a comparative study. J Int Med Res. 2006 Sep-Oct;34(5):520-4.
936. Huvenne W, van Bruaene N, Zhang N, van Zele T, Patou J, Gevaert P, et al. Chronic rhinosinusitis with and without nasal polyps: what is the difference? Current allergy and asthma reports. 2009 May;9(3):213-20.
937. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol. 2011;11(8):519-31.
938. Weathington NM, van Houwelingen AH, Noerager BD, Jackson PL, Kraneveld AD, Galin FS, et al. A novel peptide CXCR ligand derived from extracellular matrix degradation during airway inflammation. Nat Med. 2006 Mar;12(3):317-23.
939. Snelgrove RJ, Jackson PL, Hardison MT, Noerager BD, Kinloch A, Gaggar A, et al. A critical role for LTA4H in limiting chronic pulmonary neutrophilic inflammation. Science (New York, NY). 2010 Oct 1;330(6000):90-4.
940. Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. The Journal of allergy and clinical immunology. 2010 Feb;125(2 Suppl 2):S73-80.
941. Balzar S, Strand M, Rhodes D, Wenzel SE. IgE expression pattern in lung: relation to systemic IgE and asthma phenotypes. The Journal of allergy and clinical immunology. 2007 Apr;119(4):855-62.
942. Pawankar R, Lee KH, Nonaka M, Takizawa R. Role of mast cells and basophils in chronic rhinosinusitis. Clin Allergy Immunol. 2007;20:93-101.
943. Xue L, Gyles SL, Wettey FR, Gazi L, Townsend E, Hunter MG, et al. Prostaglandin D2 causes preferential induction of proinflammatory Th2 cytokine production through an action on chemoattractant receptor-like molecule expressed on Th2 cells. J Immunol. 2005 Nov 15;175(10):6531-6.
944. Kramer MF, Burow G, Pfrogner E, Rasp G. In vitro diagnosis of chronic nasal inflammation. Clinical & Experimental Allergy. [Conference Paper]. 2004;34(7):1086-92.
945. Ruhno J, Howie K, Anderson M, Andersson B, Vanzieleghem M, Hitch D, et al. The increased number of epithelial mast cells in nasal polyps and adjacent turbinates is not allergy-dependent. Allergy. 1990 Jul;45(5):370-4.
946. Otsuka H, Ohkubo K, Seki H, Ohnishi M, Fujikura T. Mast cell quantitation in nasal polyps, sinus mucosa and nasal turbinate mucosa. J Laryngol Otol. 1993 May;107(5):418-22.
947. Drake-Lee AB, Chevreton E, Lowe D. The effects of different fixations on the distribution and numbers of mast cells in patients with nasal polyps. J Laryngol Otol. 1988 Dec;102(12):1099-101.
948. Kitapci F, Muluk NB, Atasoy P, Koc C. Role of mast and goblet cells in the pathogenesis of nasal polyps. Journal of Otolaryngology. 2006;35(2):122-32.
949. Patou J, Holtappels G, Affleck K, Gevaert P, Perez-Novo C, Van Cauwenberge P, et al. Enhanced release of IgE-dependent early phase mediators from nasal polyp tissue. J Inflamm (Lond). 2009;6:11.
950. Patou J, Holtappels G, Affleck K, van Cauwenberge P, Bachert C. Syk-kinase inhibition prevents mast cell activation in nasal polyps. Rhinology. 2011 Mar;49(1):100-6.
951. Cerutti A, Chen K, Chorny A. Immunoglobulin responses at the mucosal interface. Annu Rev Immunol. 2011 Apr 23;29:273-93.
952. Chen K, Cerutti A. New insights into the enigma of immunoglobulin D. Immunological Reviews. 2010;237:160-79.
953. Chen K, Xu W, Wilson M, He B, Miller NW, Bengten E, et al. Immunoglobulin D enhances immune surveillance by activating antimicrobial, proinflammatory and B cell-stimulating programs in basophils. Nat Immunol. 2009 Aug;10(8):889-98.
954. Karasuyama H, Mukai K, Tsujimura Y, Obata K. Newly discovered roles for basophils: a neglected minority gains new respect. Nat Rev Immunol. 2009 Jan;9(1):9-13.
955. Mechtcheriakova D, Sobanov Y, Holtappels G, Bajna E, Svoboda M, Jaritz M, et al. Activation-Induced Cytidine Deaminase (AID)-Associated Multigene Signature to Assess Impact of AID in Etiology of Diseases with Inflammatory Component. PLoS ONE. 2011;6(10):1-12.
956. Morinaka S, Nakamura H. Inflammatory

cells in nasal mucosa and nasal polyps Auris Nasus Larynx. 2000;27:59-64.

957. Sabirov A, Hamilton RG, Jacobs JB, Hillman DE, Lebowitz RA, Watts JD. Role of local immunoglobulin E specific for Alternaria alternata in the pathogenesis of nasal polyposis. The Laryngoscope. 2008 Jan;118(1):4-9.
958. Smurthwaite L, Walker SN, Wilson DR, Birch DS, Merrett TG, Durham SR, et al. Persistent IgE synthesis in the nasal mucosa of hay fever patients. Eur J Immunol. 2001 Dec;31(12):3422-31.
959. Smurthwaite L, Durham SR. Local IgE synthesis in allergic rhinitis and asthma. Current allergy and asthma reports. 2002 May;2(3):231-8.
960. Gevaert P, Holtappels G, Johansson SGO, Cuvelier C, Van Cauwenberge P, Bachert C. Organization of secondary lymphoid tissue and local IgE formation to Staphylococcus aureus enterotoxins in nasal polyp tissue. Allergy. 2005;60(1):71-9.
961. Zhang Y, Endam LM, Filali-Mouhim A, Bosse Y, Castano R, Desrosiers M. Polymorphisms in the nitric oxide synthase 1 gene are associated with severe chronic rhinosinusitis. American journal of rhinology & allergy. 2011 Mar-Apr;25(2):e49-54.
962. Verbruggen K, Van Cauwenberge P, Bachert C. Anti-IgE for the treatment of allergic rhinitis--and eventually nasal polyps? Int Arch Allergy Immunol. 2009;148(2):87-98.
963. Pinto JM, Mehta N, DiTineo M, Wang J, Baroody FM, Naclerio RM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. Rhinology. 2010 Sep;48(3):318-24.
964. Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, et al. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J Exp Med. 1999 Dec 6;190(11):1697-710.
965. Mygind N, Dahl R, Bachert C. Nasal polyposis, eosinophil dominated inflammation, and allergy. Thorax. 2000 Oct;55 Suppl 2:S79-83.
966. Sokol CL, Chu NQ, Yu S, Nish SA, Laufer TM, Medzhitov R. Basophils function as antigen-presenting cells for an allergen-induced T helper type 2 response. Nat Immunol. 2009 Jul;10(7):713-20.
967. Miller SA, Weinmann AS. Common themes emerge in the transcriptional control of T helper and developmental cell fate decisions regulated by the T-box, GATA and ROR families. Immunology. 2009 Mar;126(3):306-15.
968. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol. 2010 Mar;28:445-89.
969. Miller LS, Cho JS. Immunity against Staphylococcus aureus cutaneous infections. Nat Rev Immunol. 2011 Aug;11(8):505-18.
970. Spits H, Di Santo JP. The expanding family of innate lymphoid cells: regulators and effectors of immunity and tissue remodeling. Nat Immunol. 2011 Jan;12(1):21-7.
971. Neill DR, Wong SH, Bellosi A, Flynn RJ, Daly M, Langford TK, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. Nature. 2010 Apr 29;464(7293):1367-70.
972. Saenz SA, Siracusa MC, Perrigoue JG, Spencer SP, Urban JF, Jr., Tocker JE, et al. IL25 elicits a multipotent progenitor cell population that promotes T(H)2 cytokine responses. Nature. 2010 Apr 29;464(7293):1362-6.
973. Mjoesberg J, Trifari S, Crellin NK, Peters CP, van Drunen CM, Piet B, et al. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CRTH2 and CD161. Nature Immunology. 2011:1-8.
974. Allakhverdi Z, Delespesse G. Hematopoietic progenitor cells are innate Th2 cytokine-producing cells. Allergy. 2012 Jan;67(1):4-9.
975. Prussin C, Yin Y, Upadhyaya B. T(H)2 heterogeneity: Does function follow form? The Journal of allergy and clinical immunology. 2010 Dec;126(6):1094-8.
976. Wan YY. Multi-tasking of helper T cells. Immunology. 2010 Jun;130(2):166-71.
977. Paul WE, Zhu J. How are TH2-type immune responses initiated and amplified? Immunology 2010;10:225-35.
978. Paul WE. What determines Th2 differentiation, in vitro and in vivo? Immunology and Cell Biology. 2010;88:236-9.
979. Commins SP, Borish L, Steinke JW. Immunologic messenger molecules: cytokines, interferons, and chemokines. The Journal of allergy and clinical immunology. 2010 Feb;125(2 Suppl 2):S53-72.
980. Mucida D, Salek-Ardakani S. Regulation of TH17 cells in the mucosal surfaces. The Journal of allergy and clinical immunology. 2009 May;123(5):997-1003.
981. Dubin PJ, Kolls JK. IL-17 in Cystic Fibrosis: More Than Just Th17 Cells. American journal of respiratory and critical care medicine. 2011;184:155-6.
982. Sanchez-Segura A, Brieva JA, Rodriguez C. T lymphocytes that infiltrate nasal polyps have a specialized phenotype and produce a mixed TH1/TH2 pattern of cytokines. The Journal of allergy and clinical immunology. 1998;102(6):953-60.
983. Robinson DS. The role of the T cell in asthma. The Journal of allergy and clinical immunology. 2010 Dec;126(6):1081-91; quiz 92-3.
984. Van Bruaene N, Perez-Novo CA, Basinski TM, Van Zele T, Holtappels G, De Ruyck N, et al. T-cell regulation in chronic paranasal sinus disease. The Journal of allergy and clinical immunology. 2008 Jun;121(6):1435-41, 41 e1-3.
985. Kim TH, Lee JY, Lee HM, Lee SH, Cho WS, Ju YH, et al. Remodelling of nasal mucosa in mild and severe persistent allergic rhinitis with special reference to the distribution of collagen, proteoglycans, and lymphatic vessels. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2010 Dec;40(12):1742-54.
986. Jiang XD, Li GY, Li L, Dong Z, Zhu DD. The characterization of IL-17A expression in patients with chronic rhinosinusitis with nasal polyps. American Journal of Rhinology and Allergy. 2011;25(5):171-5.
987. Shen Y, Tang XY, Yang YC, Ke X, Kou W, Pan CK, et al. Impaired balance of Th17/Treg

in patients with nasal polyposis. Scand J Immunol. 2011 Aug;74(2):176-85.

988. Li CW, Shi L, Zhang KK, Li TY, Lin ZB, Lim MK, et al. Role of p63/p73 in epithelial remodeling and their response to steroid treatmentin nasal polyposis. The Journal of allergy and clinical immunology. 2011;127(3):765-72.
989. Fan Y, Xia W, Liu W, Chen R, Li X, Xu R, et al. Increased nasal IL-5 levels act as a predisposing factor of asthma in southern China. The Journal of allergy and clinical immunology. 2011 May;127(5):1312-3; author reply 3-4.
990. Li X, Meng J, Qiao X, Liu Y, Liu F, Zhang N, et al. Expression of TGF, matrix metalloproteinases, and tissue inhibitors in Chinese chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2010 May;125(5):1061-8.
991. Winther B, Innes DJ, Jr., Mills SE, Mygind N, Zito D, Hayden FG. Lymphocyte subsets in normal airway mucosa of the human nose. Archives of otolaryngology--head & neck surgery. 1987 Jan;113(1):59-62.
992. Hao J, Pang YT, Wang DY. Diffuse mucosal inflammation in nasal polyps and adjacent middle turbinate. Otolaryngology - Head & Neck Surgery. 2006;134(2):267-75.
993. Al-Muhsen S, Johnson JR, Hamid Q. Remodeling in asthma. The Journal of allergy and clinical immunology. 2011;128(3):451-62.
994. Rehl RM, Balla AA, Cabay RJ, Hearp ML, Pytynia KB, Joe SA. Mucosal remodeling in chronic rhinosinusitis. American journal of rhinology. 2007;21(6):651-7.
995. Holgate ST. Has the time come to rethink the pathogenesis of asthma? Allergy and Clinical Immunology. 2010;10:48-53.
996. Saitoh T, Kusunoki T, Yao T, Kawano K, Kojima Y, Miyahara K, et al. Relationship between epithelial damage or basement membrane thickness and eosinophilic infiltration in nasal polyps with chronic rhinosinusitis. Rhinology. 2009;47:275-9.
997. Kouzaki H, Seno S, Fukui J, Owaki S, Shimizu T. Role of platelet-derived growth factor in airway remodeling in rhinosinusitis. American journal of rhinology & allergy. 2009 May-Jun;23(3):273-80.
998. Berger G, Kattan A, Bernheim J, Ophir D. Polypoid mucosa with eosinophilia and glandular hyperplasia in chronic sinusitis: a histopathological and immunohistochemical study. The Laryngoscope. 2002 Apr;112(4):738-45.
999. Halwani R, Al-Muhsen S, Al-Jahdali H, Hamid Q. Role of TGT-Beta in airway remodeling in Asthma Am J Respir Cell Mol Biol. 2011;44(127-33.).
1000. Van Bruaene N, Derycke L, Perez-Novo CA, Gevaert P, Holtappels G, De Ruyck N, et al. TGF-β signaling and collagen deposition in chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2009;124(2):253-9.
1001. Van Bruaene N, Perez-Novo C, Van Crombruggen K, Deruyck N, Holtappels G, Van Cauwenberge P, et al. Inflammation and remodelling patterns in early stage chronic rhinosinusitis. Clinical & Experimental Allergy. 2011:1-8.
1002. Araujo BB, Dolhnikoff M, Silva LF, Elliot J, Lindeman JH, Ferreira DS, et al. Extracellular matrix components and regulators in the airway smooth muscle in asthma. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2008 Jul;32(1):61-9.
1003. Lechapt-Zalcman E, Coste A, d'Ortho MP, Frisdal E, Harf A, Lafuma C, et al. Increased expression of matrix metalloproteinase-9 in nasal polyps. J Pathol. 2001 Feb;193(2):233-41.
1004. Watelet JB, Bachert C, Claeys C, Van Cauwenberge P. Matrix metalloproteinases MMP-7, MMP-9 and their tissue inhibitor TIMP-1: expression in chronic sinusitis vs nasal polyposis. Allergy. 2004 Jan;59(1):54-60.
1005. Can IH, Ceylan K, Caydere M, Samim EE, Ustun H, Karasoy DS. The expression of MMP-2, MMP-7, MMP-9, and TIMP-1 in chronic rhinosinusitis and nasal polyposis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2008 Aug;139(2):211-5.
1006. Hwang KS, Park IH, Choi H, Lee SH, Lee HM. Increased expression of angiogenin in nasal polyps. American journal of rhinology & allergy. 2011 Jan-Feb;25(1):e23-6.
1007. Wittekindt C, Hess A, Bloch W, Sultanie S, Michel O. Immunohistochemical expression of VEGF and VEGF receptors in nasal polyps as compared to normal turbinate mucosa. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2002 Jul;259(6):294-8.
1008. Hu KH, Lee FP, Cheng YJ, Huang HM. Vascular endothelial growth factor and children featuring nasal polyps. Int J Pediatr Otorhinolaryngol. 2007 Jan;71(1):23-8.
1009. Lee HS, Myers A, Kim J. Vascular endothelial growth factor drives autocrine epithelial cell proliferation and survival in chronic rhinosinusitis with nasal polyposis. American journal of respiratory and critical care medicine. 2009 Dec 1;180(11):1056-67.
1010. Gosepath J, Brieger J, Mann WJ. New immunohistologic findings on the differential role of cyclooxygenase 1 and cyclooxygenase 2 in nasal polyposis. American journal of rhinology. 2005;19(2):111-6.
1011. Matsune S, Kono M, Sun D, Ushikai M, Kurono Y. Hypoxia in paranasal sinuses of patients with chronic sinusitis with or without the complication of nasal allergy. Acta Otolaryngol. 2003 May;123(4):519-23.
1012. Sun D, Matsune S, Ohori J, Fukuiwa T, Ushikai M, Kurono Y. TNF-alpha and endotoxin increase hypoxia-induced VEGF production by cultured human nasal fibroblasts in synergistic fashion. Auris Nasus Larynx. 2005 Sep;32(3):243-9.
1013. Matsune S, Sun D, Ohori J, Nishimoto K, Fukuiwa T, Ushikai M, et al. Inhibition of vascular endothelial growth factor by macrolides in cultured fibroblasts from nasal polyps. The Laryngoscope. 2005 Nov;115(11):1953-6.
1014. Chien CY, Tai CF, Ho KY, Kuo WR,

Chai CY, Hsu YC, et al. Expression of hypoxia-inducible factor 1alpha in the nasal polyps by real-time RT-PCR and immunohistochemistry. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2008 Aug;139(2):206-10.

1015. Steinke JW, Woodard CR, Borish L. Role of hypoxia in inflammatory upper airway disease. Curr Opin Allergy Clin Immunol. 2008 Feb;8(1):16-20.
1016. Shun CT, Lin SK, Hong CY, Huang HM, Liu CM. Hypoxia induces cysteine-rich 61, vascular endothelial growth factor, and interleukin-8 expressions in human nasal polyp fibroblasts: An implication of neutrophils in the pathogenesis of nasal polyposis. American journal of rhinology & allergy. 2011 Jan-Feb;25(1):15-8.
1017. Payne SC, Han JK, Huyett P, Negri J, Kropf EZ, Borish L, et al. Microarray analysis of distinct gene transcription profiles in non-eosinophilic chronic sinusitis with nasal polyps. American journal of rhinology. 2008 Nov-Dec;22(6):568-81.
1018. Ahmed SK, Williams JL, Drake-Lee A, Egginton S. No significant role for angiogenesis in nasal polyposis. American journal of rhinology. 2008;22:24-8.
1019. Hudlicka O, Brown M, Egginton S. Angiogenesis in skeletal and cardiac muscle. Physiol Rev. 1992 Apr;72(2):369-417.
1020. Shimizu S, Gabazza EC, Ogawa T, Tojima I, Hoshi E, Kouzaki H, et al. Role of thrombin in chronic rhinosinusitis-associated tissue remodeling. American journal of rhinology & allergy. 2011 Jan-Feb;25(1):7-11.
1021. Sejima T, Holtappels G, Bachert C. The expression of fibrinolytic components in chronic paranasal sinus disease. American journal of rhinology & allergy. 2011 Jan-Feb;25(1):1-6.
1022. Lee JT, Kennedy DW, Palmer JN, Feldman M, Chiu AG. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. American journal of rhinology. 2006 May-Jun;20(3):278-82.
1023. Kennedy DW, Senior BA, Gannon FH, Montone KT, Hwang P, Lanza DC. Histology and histomorphometry of ethmoid bone in chronic rhinosinusitis. The Laryngoscope. 1998 Apr;108(4 Pt 1):502-7.
1024. Perloff JR, Gannon FH, Bolger WE, Montone KT, Orlandi R, Kennedy DW. Bone involvement in sinusitis: an apparent pathway for the spread of disease. The Laryngoscope. 2000 Dec;110(12):2095-9.
1025. Hamilton DW. Functional role of periostin in development and wound repair: implications for connective tissue disease. J Cell Commun Signal. 2008 Jun;2(1-2):9-17.
1026. Choi ST, Kim JH, Kang EJ, Lee SW, Park MC, Park YB, et al. Osteopontin might be invovled in bone remodelling rather than in inflammation in ankylosing spondylitis. Rheumatology. 2008;47:1775-9.
1027. Samitas K, Zervas E, Vittorakis S, Semitekolou M, Alissafi T, Bossios A, et al. Osteopontin expression and relation to disease severity in human asthma. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2011 Feb;37(2):331-41.
1028. Daines S, Wang Y, Orlandi R. Periostin and osteopontin are overexpressed in chronically inflamed sinuses. International forum of allergy & rhinology. 2011;1(2):101-5.
1029. Stankovic KM, Goldsztein H, Reh DD, Platt MP, Metson R. Gene expression profiling of nasal polyps associated with chronic sinusitis and aspirin-sensitive asthma. The Laryngoscope. 2008 May;118(5):881-9.
1030. Videler WJ, Georgalas C, Menger DJ, Freling NJ, van Drunen CM, Fokkens WJ. Osteitic bone in recalcitrant chronic rhinosinusitis. Rhinology. 2011 Jun;49(2):139-47.
1031. Martinez-Anton A, Roca-Ferrer J, Mullol J. Mucin gene expression in rhinitis syndromes. Current Allergy & Asthma Reports. [Review]. 2006;6(3):189-97.
1032. Martinez-Anton A, de Bolos C, Garrido M, Roca-Ferrer J, Barranco C, Alobid I, et al. Mucin genes have different expression patterns in healthy and diseased upper airway mucosa. Clinical & Experimental Allergy. 2006;36:448-57.
1033. Kanoh S, Tanabe T, Rubin BK. IL-13-induced MUC5AC production and goblet cell differentiation is steroid resistant in human airway cells. Clinical & Experimental Allergy. 2011:1-10.
1034. Malekzadeh S, McGuire JF. The new histologic classification of chronic rhinosinusitis. Current Allergy & Asthma Reports. [Review]. 2003;3(3):221-6.
1035. Ding GQ, Zheng CQ. The expression of MUC5AC and MUC5B mucin genes in the mucosa of chronic rhinosinusitis and nasal polyposis. American journal of rhinology. 2007 May-Jun;21(3):359-66.
1036. Kim DH, Chu HS, Lee JY, Hwang SJ, Lee SH, Lee HM. Up-regulation of MUC5AC and MUC5B mucin genes in chronic rhinosinusitis. Archives of Otolaryngology -- Head & Neck Surgery. 2004;130(6):747-52.
1037. Harvey RJ, Wallwork BD, Lund VJ. Anti-inflammatory effects of macrolides: applications in chronic rhinosinusitis. Immunology and allergy clinics of North America. 2009 Nov;29(4):689-703.
1038. Ali MS, Pearson JP. Upper airway mucin gene expression: a review. The Laryngoscope. 2007 May;117(5):932-8.
1039. Ali M. Nasosinus mucin expression in normal and inflammatory conditions. Allergy and Clinical Immunology. 2009;9:10-5.
1040. Ali M. Mucin Expression in Nasal Polyps. In: Oenerci TM, Ferguson BJ, editors. Nasal Polyposis. Berlin: Springer Verlag; 2010. p. 65-73.
1041. Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. Science (New York, NY). 2001 Nov 30;294(5548):1871-5.
1042. Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. Pharmacol Rev. 2004 Sep;56(3):387-437.
1043. Steinke JW, Bradley D, Arango P, Crouse CD, Frierson H, Kountakis SE, et al. Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal

polyposis: importance to eosinophilia and asthma. The Journal of allergy and clinical immunology. 2003 Feb;111(2):342-9.

1044. Hirata H, Arima M, Fukushima Y, Honda K, Sugiyama K, Tokuhisa T, et al. Over-expression of the LTC4 synthase gene in mice reproduces human aspirin-induced asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2011 Aug;41(8):1133-42.
1045. Sampson AP. Leukotriene C4 synthase: the engine of aspirin intolerance? Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2011 Aug;41(8):1050-3.
1046. Perez-Novo CA, Watelet JB, Claeys C, Van Cauwenberge P, Bachert C. Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis. The Journal of allergy and clinical immunology. 2005 Jun;115(6):1189-96.
1047. Ebbens FA, Maldonado M, de Groot EJ, Alobid I, van Drunen CM, Picado C, et al. Topical glucocorticoids downregulate COX-1 positive cells in nasal polyps. Allergy. 2009 Jan;64(1):96-103.
1048. Gervais FG, Cruz RP, Chateauneuf A, Gale S, Sawyer N, Nantel F, et al. Selective modulation of chemokinesis, degranulation, and apoptosis in eosinophils through the PGD2 receptors CRTH2 and DP. The Journal of allergy and clinical immunology. 2001 Dec;108(6):982-8.
1049. Schratl P, Royer JF, Kostenis E, Ulven T, Sturm EM, Waldhoer M, et al. The role of the prostaglandin D2 receptor, DP, in eosinophil trafficking. J Immunol. 2007 Oct 1;179(7):4792-9.
1050. Nantel F, Fong C, Lamontagne S, Wright DH, Giaid A, Desrosiers M, et al. Expression of prostaglandin D synthase and the prostaglandin D2 receptors DP and CRTH2 in human nasal mucosa. Prostaglandins Other Lipid Mediat. 2004 Jan;73(1-2):87-101.
1051. Perez-Novo CA, Holtappels G, Vinall SL, Xue L, Zhang N, Bachert C, et al. CRTH2 mediates the activation of human Th2 cells in response to PGD(2) released from IgE/anti-IgE treated nasal polyp tissue. Allergy. 2010 Mar;65(3):304-10.
1052. Okano M, Fujiwara T, Yamamoto M, Sugata Y, Matsumoto R, Fukushima K, et al. Role of prostaglandin D2 and E2 terminal synthases in chronic rhinosinusitis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2006 Aug;36(8):1028-38.
1053. Yamamoto M, Okano M, Fujiwara T, Kariya S, Higaki T, Nagatsuka H, et al. Expression and Characterization of PGD2 Receptors in Chronic Rhinosinusitis: Modulation of DP and CRTH2 by PGD2. International Archives of Allergy and Immunology. 2009;148:127-36.
1054. Fortner CN, Breyer RM, Paul RJ. EP2 receptors mediate airway relaxation to substance P, ATP, and PGE2. Am J Physiol Lung Cell Mol Physiol. 2001 Aug;281(2):L469-74.
1055. Picado C, Fernandez-Morata JC, Juan M, Roca-Ferrer J, Fuentes M, Xaubet A, et al. Cyclooxygenase-2 mRNA is downexpressed in nasal polyps from aspirin-sensitive asthmatics. American journal of respiratory and critical care medicine. 1999 Jul;160(1):291-6.
1056. Mullol J, Fernandez-Morata JC, Roca-Ferrer J, Pujols L, Xaubet A, Benitez P, et al. Cyclooxygenase 1 and cyclooxygenase 2 expression is abnormally regulated in human nasal polyps. The Journal of allergy and clinical immunology. 2002 May;109(5):824-30.
1057. Fritz SB, Terrell JE, Conner ER, Kukowska-Latallo JF, Baker JR. Nasal mucosal gene expression in patients with allergic rhinitis with and without nasal polyps. The Journal of allergy and clinical immunology. 2003 Dec;112(6):1057-63.
1058. Benson M, Carlsson L, Adner M, Jernas M, Rudemo M, Sjogren A, et al. Gene profiling reveals increased expression of uteroglobin and other anti-inflammatory genes in glucocorticoid-treated nasal polyps. The Journal of allergy and clinical immunology. 2004 Jun;113(6):1137-43.
1059. Liu Z, Kim J, Sypek JP, Wang IM, Horton H, Oppenheim FG, et al. Gene expression profiles in human nasal polyp tissues studied by means of DNA microarray. Journal of Allergy & Clinical Immunology. 2004;114(4):783-90.
1060. Sidhu SS, Yuan S, Innes AL, Kerr S, Woodruff PG, Hou L, et al. Roles of epithelial cell-derived periostin in TGF-beta activation, collagen production, and collagen gel elasticity in asthma. Proc Natl Acad Sci U S A. 2010 Aug 10;107(32):14170-5.
1061. Rho HS, Lee SH, Lee HM, Jung HH, Choi J, Park MK, et al. Overexpression of hepatocyte growth factor and its receptor c-Met in nasal polyps. Archives of otolaryngology--head & neck surgery. 2006 Sep;132(9):985-9.
1062. Castano R, Bosse Y, Endam LM, Filali-Mouhim A, Desrosiers M. c-MET pathway involvement in chronic rhinosinusitis: a genetic association analysis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 May;142(5):665-71 e1-2.
1063. Reh DD, Ramanathan M, Jr., Sultan B, Wang Y, May L, Lane AP. The role of hepatocyte growth factor/c-Met in chronic rhinosinusitis with nasal polyps. American journal of rhinology & allergy. 2010 Jul-Aug;24(4):266-70.
1064. Anand VK, Kacker A, Orjuela AF, Huang C, Manarey C, Xiang J. Inflammatory pathway gene expression in chronic rhinosinusitis. American journal of rhinology. 2006 Jul-Aug;20(4):471-6.
1065. Wang X, Dong Z, Zhu DD, Guan B. Expression profile of immune-associated genes in nasal polyps. Annals of Otology, Rhinology & Laryngology. 2006;115(6):450-6.
1066. Lee J, Kang H, Woo J, Chae S, Lee S, Hwang S. Up-regulation of chemokine ligand 20 in chronic rhinosinusitis. Archives of otolaryngology--head & neck surgery. 2006;132(5):537-41.
1067. Figueiredo CR, Santos RP, Silva ID, Weckx LL. Microarray cDNA to identify inflammatory genes in nasal polyposis. American journal of rhinology. 2007 Mar-Apr;21(2):231-5.

1068. Bolger WE, Joshi AS, Spear S, Nelson M, Govindaraj K. Gene expression analysis in sinonasal polyposis before and after oral corticosteroids: a preliminary investigation. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 Jul;137(1):27-33.

1069. Wu J, Bing L, Jin H, Jingping F. Gene expression profiles of nasal polyps associated with allergic rhinitis. Am J Otolaryngol. 2009 Jan-Feb;30(1):24-32.

1070. Rostkowska-Nadolska B, Kapral M, Fraczek M, Kowalczyk M, Gawron W, Mazurek U. A microarray study of gene expression profiles in nasal polyps. Auris Nasus Larynx. 2011 Feb;38(1):58-64.

1071. Lund V. Quantification for staging sinusitis. The staging and Therapy Group. The Annals of otology, rhinology, and laryngology. 1995(167):17-21.

1072. Ferguson BJ, Narita M, Yu VL, Wagener MM, Gwaltney JM, Jr. Prospective observational study of chronic rhinosinusitis: environmental triggers and antibiotic implications. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012 Jan;54(1):62-8.

1073. Stankiewicz JA, Chow JM. Nasal endoscopy and the definition and diagnosis of chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002 Jun;126(6):623-7.

1074. Bhattacharyya N, Lee LN. Evaluating the diagnosis of chronic rhinosinusitis based on clinical guidelines and endoscopy. Otolaryngol Head Neck Surg. 2010;143(1):147-51.

1075. Ling FT, Kountakis SE. Important clinical symptoms in patients undergoing functional endoscopic sinus surgery for chronic rhinosinusitis. The Laryngoscope. 2007 Jun;117(6):1090-3.

1076. West B, Jones NS. Endoscopy-negative, computed tomography-negative facial pain in a nasal clinic. The Laryngoscope. 2001 Apr;111(4 Pt 1):581-6.

1077. Aaseth K, Grande RB, Kvaerner K, Lundqvist C, Russell MB. Chronic rhinosinusitis gives a ninefold increased risk of chronic headache. The Akershus study of chronic headache. Cephalalgia : an international journal of headache. 2010 Feb;30(2):152-60.

1078. Schubert CR, Cruickshanks KJ, Klein BE, Klein R, Nondahl DM. Olfactory impairment in older adults: five-year incidence and risk factors. The Laryngoscope. 2011 Apr;121(4):873-8.

1079. Litvack JR, Fong K, Mace J, James KE, Smith TL. Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. The Laryngoscope. 2008 Dec;118(12):2225-30.

1080. Craig TJ, Ferguson BJ, Krouse JH. Sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyposis. Am J Otolaryngol. 2008 May-Jun;29(3):209-17.

1081. Rombaux P, Liistro G, Hamoir M, Bertrand B, Aubert G, Verses T, et al. Nasal obstruction and its impact on sleep-related breathing disorders. Rhinology. 2005 Dec;43(4):242-50.

1082. Storms W, Yawn B, Fromer L. Therapeutic options for reducing sleep impairment in allergic rhinitis, rhinosinusitis, and nasal polyposis. Current medical research and opinion. 2007;23(9):2135-46.

1083. Lim M, Lew-Gor S, Darby Y, Brookes N, Scadding G, Lund VJ. The relationship between subjective assessment instruments in chronic rhinosinusitis. Rhinology. 2007 Jun;45(2):144-7.

1084. Ryan WR, Ramachandra T, Hwang PH. Correlations between symptoms, nasal endoscopy, and in-office computed tomography in post-surgical chronic rhinosinusitis patients. The Laryngoscope. 2011 Mar;121(3):674-8.

1085. Lildholdt T, Rundcrantz H, Bende M, Larsen K. Glucocorticoid treatment for nasal polyps. The use of topical budesonide powder, intramuscular betamethasone, and surgical treatment. Archives of otolaryngology--head & neck surgery. 1997;123(6):595-600.

1086. Ragab A, Clement P, Vincken W. Correlation between the cytology of the nasal middle meatus and BAL in chronic rhinosinusitis. Rhinology. 2005 Mar;43(1):11-7.

1087. Ozcan M, Unal A, Aksaray S, Yalcin F, Akdeniz T. Correlation of middle meatus and ethmoid sinus microbiology in patients with chronic sinusitis. Rhinology. 2002;40(1):24-7.

1088. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. The New England journal of medicine. 2007 Nov 29;357(22):2277-84.

1089. Brenner DJ. Should we be concerned about the rapid increase in CT usage? Reviews on environmental health. 2010 Jan-Mar;25(1):63-8.

1090. Schell B, Bauer RW, Lehnert T, Kerl JM, Hambek M, May A, et al. Low-dose computed tomography of the paranasal sinus and facial skull using a high-pitch dual-source system--first clinical results. European radiology. 2011 Jan;21(1):107-12.

1091. Hodez C, Griffaton-Taillandier C, Bensimon I. Cone-beam imaging: applications in ENT. European annals of otorhinolaryngology, head and neck diseases. 2011 Apr;128(2):65-78.

1092. Bachert K. Evaluation of effective patient dose in paranasal sinus imaging:comparison of cone beam CT, digital tomosynthesis and multislice CT. World Congress on medical Physics and Biomedical Engineering. 2009(25):458-60.

1093. Lin HW, Bhattacharyya N, Brenner DJ, Schell B, Bauer RW, Lehnert T, et al. Diagnostic and staging accuracy of magnetic resonance imaging for the assessment of sinonasal disease. Should we be concerned about the rapid increase in CT usage? Low-dose computed tomography of the paranasal sinus and facial skull using a high-pitch dual-source system--first clinical results. Cone-beam imaging: applications in ENT. Am J Rhinol Allergy. 2009;23(1):36-9.

1094. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology. 1993;31(4):183-4.

1095. Metson R, Gliklich RE, Stankiewicz JA, Kennedy DW, Duncavage JA,

Hoffman SR, et al. Comparison of sinus computed tomography staging systems. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1997;117(4):372-9.

1096. Oluwole M, Russell N, Tan L, Gardiner Q, White P. A comparison of computerized tomographic staging systems in chronic sinusitis. Clin Otolaryngol. 1996;21(1):91-5.
1097. Andersen I, Camner P, Jensen PL, Philipson K, Proctor DF. Nasal clearance in monozygotic twins. Am Rev Respir Dis. 1974;110(3):301-5.
1098. Puchelle E, Aug F, Pham QT, Bertrand A. Comparison of three methods for measuring nasal mucociliary clearance in man. Acta Otolaryngol. 1981 Mar-Apr;91(3-4):297-303.
1099. Passali D, Bellussi L, Bianchini Ciampoli M, De Seta E. Experiences in the determination of nasal mucociliary transport time. Acta Otolaryngol. 1984 Mar-Apr;97(3-4):319-23.
1100. Passali D, Ferri R, Becchini G, Passali GC, Bellussi L. Alterations of nasal mucociliary transport in patients with hypertrophy of the inferior turbinates, deviations of the nasal septum and chronic sinusitis. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 1999;256(7):335-7.
1101. Rutland J, Dewar A, Cox T, Cole P. Nasal brushing for the study of ciliary ultrastructure. J Clin Pathol. 1982;35(3):357-9.
1102. Rautiainen M, Matsune S, Shima S, Sakamoto K, Hanamure Y, Ohyama M. Ciliary beat of cultured human respiratory cells studied with differential interference microscope and high speed video system. Acta Otolaryngol. 1992 Sep;112(5):845-51.
1103. Lund VJ, Scadding GK. Objective assessment of endoscopic sinus surgery in the management of chronic rhinosinusitis: an update. J Laryngol Otol. 1994;108(9):749-53.
1104. Abdel-Hak B, Gunkel A, Kanonier G, Schrott-Fischer A, Ulmer H, Thumfart WI. Ciliary beat frequency, olfaction and endoscopic sinus surgery. ORL J Otorhinolaryngol Relat Spec. 1998;60(4):202-5.
1105. Jorissen M, Van der Schueren B, Van den Berghe H, Cassiman JJ. Contribution of in vitro culture methods for respiratory epithelial cells to the study of the physiology of the respiratory tract. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1991 Feb;4(2):210-7.
1106. Afzelius BA. A human syndrome caused by immotile cilia. Science (New York, NY). 1976 Jul 23;193(4250):317-9.
1107. Delclaux C, Malinvaud D, Chevalier-Bidaud B, Callens E, Mahut B, Bonfils P. Nitric oxide evaluation in upper and lower respiratory tracts in nasal polyposis. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2008 Jul;38(7):1140-7.
1108. Holmstrom M, Scadding GK, Lund VJ, Darby YC. Assessment of nasal obstruction. A comparison between rhinomanometry and nasal inspiratory peak flow. Rhinology. 1990;28(3):191-6.
1109. Lund VJ, Flood J, Sykes AP, Richards DH. Effect of fluticasone in severe polyposis. Archives of Otolaryngology - Head and Neck Surgery. 1998;124(5):513-8.
1110. Hox V, Bobic S, Callebaux I, Jorissen M, Hellings PW. Nasal obstruction and smell impairment in nasal polyp disease: correlation between objective and subjective parameters. Rhinology. 2010 Dec;48(4):426-32.
1111. Ottaviano G, Scadding GK, Coles S, Lund VJ. Peak nasal inspiratory flow; normal range in adult population. Rhinology. 2006 Mar;44(1):32-5.
1112. da Cunha Ibiapina C, Ribeiro de Andrade C, Moreira Camargos PA, Goncalves Alvim C, Augusto Cruz A. Reference values for peak nasal inspiratory flow in children and adolescents in Brazil. Rhinology. 2011 Aug;49(3):304-8.
1113. Spronsen v. Peak nasal inspiratory flow in health children. Rhinol Suppl. 2012;in press.
1114. Ottaviano G, Lund VJ, Coles S, Staffieri A, Scadding GK. Does peak nasal inspiratory flow relate to peak expiratory flow? Rhinology. 2008 Sep;46(3):200-3.
1115. Timperley D, Srubisky A, Stow N, Marcells GN, Harvey RJ. Minimal clinically important differences in nasal peak inspiratory flow. Rhinology. 2011 Mar;49(1):37-40.
1116. Thulesius HL, Cervin A, Jessen M. Can we always trust rhinomanometry? Rhinology. 2011 Mar;49(1):46-52.
1117. Clement PA, Gordts F. Consensus report on acoustic rhinometry and rhinomanometry. Rhinology. 2005 Sep;43(3):169-79.
1118. Straszek SP, Schlunssen V, Sigsgaard T, Pedersen OF. Reference values for acoustic rhinometry in decongested school children and adults: the most sensitive measurement for change in nasal patency. Rhinology. 2007 Mar;45(1):36-9.
1119. Haavisto LE, Vahlberg TJ, Sipila JI. A follow-up study with acoustic rhinometry in children using nasal insulin. Rhinology. 2010 Mar;48(1):95-9.
1120. Haavisto LE, Vahlberg TJ, Sipila JI. Reference values for acoustic rhinometry in children at baseline and after decongestion. Rhinology. 2011 Jun;49(2):243-7.
1121. Lund VJ, Holmstrom M, Scadding GK. Functional endoscopic sinus surgery in the management of chronic rhinosinusitis. An objective assessment. J Laryngol Otol. 1991;105(10):832-5.
1122. Numminen J, Dastidar P, Heinonen T, Karhuketo T, Rautiainen M. Reliability of acoustic rhinometry. Respiratory medicine. 2003;97(4):421-7.
1123. Munoz-Cano R, Salvador R, Valero A, Berenguer J, Alobid I, Bartra J, et al. Accuracy of acoustic rhinometry versus computed tomography in the evaluation of nasal cavity in patients with nasal polyposis. Rhinology. 2010 Jun;48(2):224-7.
1124. Juto JE, Lundberg C. An optical method for determining changes in mucosal

congestion in the nose in man. Acta Otolaryngol. 1982;94(1-2):149-56.

1125. Ellegard E. Practical aspects on rhinostereometry. Rhinology. 2002 Sep;40(3):115-7.
1126. Lane AP, Turner J, May L, Reed R. A genetic model of chronic rhinosinusitis-associated olfactory inflammation reveals reversible functional impairment and dramatic neuroepithelial reorganization. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2010 Feb 10;30(6):2324-9.
1127. Amoore JE. Odor standards in squeeze bottlekits for matching quality and intensity. Wat Sci Tech. 1992;25:1-9.
1128. Rowe-Jones JM, Mackay IS. A prospective study of olfaction following endoscopic sinus surgery with adjuvant medical treatment. Clin Otolaryngol. 1997;22(4):377-81.
1129. Delank KW, Stoll W. Olfactory function after functional endoscopic sinus surgery for chronic sinusitis. Rhinology. 1998;36(1):15-9.
1130. Simmen D. Screeningtest des Geruchssinnes mit Riechdisketten. Laryngorhinootologie. 1998;77:1-6.
1131. Briner HR, Simmen D, Jones N. Impaired sense of smell in patients with nasal surgery. Clinical otolaryngology and allied sciences. 2003 Oct;28(5):417-9.
1132. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin' sticks": screening of olfactory performance. Rhinology. 1996;34(4):222-6.
1133. Welge-Lussen A, Gudziol V, Wolfensberger M, Hummel T. Olfactory testing in clinical settings - is there additional benefit from unilateral testing? Rhinology. 2010 Jun;48(2):156-9.
1134. Thomas-Danguin T, Rouby C, Sicard G, Vigouroux M, Farget V, Johanson A, et al. Development of the ETOC: a European test of olfactory capabilities. Rhinology. 2003 Sep;41(3):142-51.
1135. Wang Y, Zhuang L. [Endoscopic sinus surgery, clinical observation with 40 cases]. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2002;16(8):418-9.
1136. Ji X, Liang C, Wu X, Xie J. [Evaluation on hemorrhage factors secondary to endoscopic sinus surgery with multiple stepwise regression analysis]. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2002;16(8):404-6.
1137. Gaby AR. Intravenous nutrient therapy: the "Myers' cocktail". Altern Med Rev. 2002;7(5):389-403.
1138. Adachi M, Furuta S, Suzuki S, Maeda Tl. [Bacterial examination of sinusitis using antral puncture and irrigation]. Nippon Jibiinkoka Gakkai Kaiho. 2002;105(9):925-30.
1139. Shamsiev DF, Mirazizov KD. [Endoscopic maxillary sinusotomy]. Vestn Otorinolaringol. 2002(4):39-40.
1140. Vladimirova EB. [The course of repair processes in the maxillary sinuses after radical surgery]. Vestn Otorinolaringol. 2002(4):11-4.
1141. Djordjevic V, Milovanovic J, Janosevic L. [Treatment of otitis and sinusitis with antibiotics]. Srp Arh Celok Lek. 2002;130(Suppl 1):59-61.
1142. Dragojlovic J, Milosevic B, Sasic M. [Endocranial bacterial infections originating in the otorhinolaryngologic area]. Srp Arh Celok Lek. 2002;130(Suppl 1):16-21.
1143. Ladich ER, Lewin-Smith MR, Specht CS, Moroz AL, Kalasinsky VF, Mullick FG. A histopathological study of head and neck specimens from a cohort of Persian Gulf War military veterans. Mil Med. 2002;167(10):864-7.
1144. Jaber R. Respiratory and allergic diseases: from upper respiratory tract infections to asthma. Prim Care. 2002 Jun;29(2):231-61.
1145. Balbisi EAl. Cefditoren, a new aminothiazolyl cephalosporin. Pharmacotherapy. 2002;22(10):1278-93.
1146. File TM, Jr., Jacobs MR, Poole MD, Wynne B. Outcome of treatment of respiratory tract infections due to Streptococcus pneumoniae, including drug-resistant strains, with pharmacokinetically enhanced amoxycillin/clavulanate. Int J Antimicrob Agents. 2002;20(4):235-47.
1147. Ehnhage A, Kolbeck KG, Juto JE, Dahlen B, Stjarne P. Evaluation of nasal mucosal swelling and microcirculation throughout nasal and bronchial provocation tests with lysine-aspirin in asthmatics with nasal polyposis. Rhinology. 2010 Jun;48(2):216-23.
1148. Cambau E. [C-reactive protein: general review and role in the study of infections]. Pathol Biol (Paris). 1988 Dec;36(10):1232-6.
1149. Ahlers AA, Schonheyder HC. [C-reactive protein in patients with infection]. Ugeskr Laeger. 1990 Dec 31;153(1):13-6.
1150. Bjerrum L, Gahrn-Hansen B, Munck AP. C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis. British Journal of General Practice. 2004;54(506):659-62.
1151. Scadding G. Diagnostic tools in Rhinology EAACI position Paper. Clin Transl Allergy. 2011(12):1-39.
1152. Stull DE, Krouse J, Meltzer EO, Roberts L, Kim S, Frank L, et al. Development and validation of the Congestion Quantifier seven-item test (CQ7): a screening tool for nasal congestion. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2007 Nov-Dec;10(6):457-65.
1153. Fairley JW, Durham LH, Ell SR. Correlation of subjective sensation of nasal patency with nasal inspiratory peak flow rate. Clinical otolaryngology and allied sciences. 1993 Feb;18(1):19-22.
1154. Sipila J, Suonpaa J, Laippala P. Sensation of nasal obstruction compared to rhinomanometric results in patients referred for septoplasty. Rhinology. 1994;32(3):141-4.
1155. Simola M, Malmberg H. Sensation of nasal airflow compared with nasal airway resistance in patients with rhinitis. Clin Otolaryngol. 1997;22(3):260-2.
1156. Hirschberg A, Rezek O. Correlation between objective and subjective assessments of nasal patency. ORL J Otorhinolaryngol Relat Spec. 1998;60(4):206-11.
1157. Nathan RA, Eccles R, Howarth PH, Steinsvag SK, Togias A. Objective monitoring of nasal patency and nasal physiology in rhinitis. The Journal of allergy and clinical immunology. 2005 Mar;115(3 Suppl 1):S442-59.

1158. Numminen J, Ahtinen M, Huhtala H, Rautiainen M. Comparison of rhinometric measurements methods in intranasal pathology. Rhinology. 2003;41(2):65-8.
1159. Jones AS, Willatt DJ, Durham LM. Nasal airflow: resistance and sensation. J Laryngol Otol. 1989;103(10):909-11.
1160. Eccles R, Jones AS. The effect of menthol on nasal resistance to air flow. J Laryngol Otol. 1983 Aug;97(8):705-9.
1161. Roithmann R, Cole P, Chapnik J, Barreto SM, Szalai JP, Zamel N. Acoustic rhinometry, rhinomanometry, and the sensation of nasal patency: a correlative study. J Otolaryngol. 1994 Dec;23(6):454-8.
1162. Panagou P, Loukides S, Tsipra S, Syrigou K, Anastasakis C, Kalogeropoulos N. Evaluation of nasal patency: comparison of patient and clinician assessments with rhinomanometry. Acta Otolaryngol. 1998 Nov;118(6):847-51.
1163. Szucs E, Clement PA. Acoustic rhinometry and rhinomanometry in the evaluation of nasal patency of patients with nasal septal deviation. American journal of rhinology. 1998;12(5):345-52.
1164. Eccles R, Jawad MS, Jawad SS, Angello JT, Druce HM. Efficacy and safety of single and multiple doses of pseudoephedrine in the treatment of nasal congestion associated with common cold. American journal of rhinology. 2005 Jan-Feb;19(1):25-31.
1165. Larsson C, Millqvist E, Bende M. Relationship between subjective nasal stuffiness and nasal patency measured by acoustic rhinometry. American journal of rhinology. 2001 Nov-Dec;15(6):403-5.
1166. Ostberg B, Winther B, Borum P, Mygind N. Common cold and high-dose ipratropium bromide: use of anticholinergic medication as an indicator of reflex-mediated hypersecretion. Rhinology. 1997 Jun;35(2):58-62.
1167. Malmberg H, Grahne B, Holopainen E, Binder E. Ipratropium (Atrovent) in the treatment of vasomotor rhinitis of elderly patients. Clin Otolaryngol. 1983 Aug;8(4):273-6.
1168. Simola M. Allergic and non-allergic rhinitis: a long term clinical follow up study. Helsinki University. 2001.
1169. Benitez P, Alobid I, de Haro J, Berenguer J, Bernal-Sprekelsen M, Pujols L, et al. A short course of oral prednisone followed by intranasal budesonide is an effective treatment of severe nasal polyps. The Laryngoscope. 2006 May;116(5):770-5.
1170. Pade J, Hummel T. Olfactory function following nasal surgery. The Laryngoscope. 2008 Jul;118(7):1260-4.
1171. Minovi A, Hummel T, Ural A, Draf W, Bockmuhl U. Predictors of the outcome of nasal surgery in terms of olfactory function. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2008 Jan;265(1):57-61.
1172. Olsson P, Ehnhage A, Nordin S, Stjarne P. Quality of life is improved by endoscopic surgery and fluticasone in nasal polyposis with asthma. Rhinology. 2010 sep;48(3):325-30.
1173. Williams JW, Jr., Roberts L, Jr., Distell B, Simel DL. Diagnosing sinusitis by X-ray: is a single Waters view adequate? J Gen Intern Med. 1992 Sep-Oct;7(5):481-5.
1174. Jones NS, Cooney TR. Facial pain and sinonasal surgery. Rhinology. 2003 Dec;41(4):193-200.
1175. Agius AM. Chronic sinusitis in Malta--correlation between symptoms and CT scan. Rhinology. 2010 Mar;48(1):59-64.
1176. Agius AM. Long-term follow-up of patients with facial pain in chronic rhinosinusitis--correlation with nasal endoscopy and CT. Rhinology. 2010 Mar;48(1):65-70.
1177. Mudgil SP, Wise SW, Hopper KD, Kasales CJ, Mauger D, Fornadley JA. Correlation between presumed sinusitis-induced pain and paranasal sinus computed tomographic findings. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2002 Feb;88(2):223-6.
1178. Piccirillo JF, Merritt MG, Jr., Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002 Jan;126(1):41-7.
1179. Bhattacharyya T, Piccirillo J, Wippold FJ, 2nd. Relationship between patient-based descriptions of sinusitis and paranasal sinus computed tomographic findings. Archives of otolaryngology--head & neck surgery. 1997 Nov;123(11):1189-92.
1180. Wabnitz DAM, Nair S, Wormald PJ. Correlation between preoperative symptom scores, quality-of-life questionnaires, and staging with computed tomography in patients with chronic rhinosinusitis. American journal of rhinology. 2005;19(1):91-6.
1181. Stewart MG, Sicard MW, Piccirillo JF, Diaz-Marchan PJ. Severity staging in chronic sinusitis: are CT scan findings related to patient symptoms? American journal of rhinology. 1999 May-Jun;13(3):161-7.
1182. Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 Oct;137(4):555-61.
1183. Andre RF, Vuyk HD, Ahmed A, Graamans K, Nolst Trenite GJ. Correlation between subjective and objective evaluation of the nasal airway. A systematic review of the highest level of evidence. Clin Otolaryngol. 2009 Dec;34(6):518-25.
1184. Girman CJ, Jacobsen SJ, Guess HA, Oesterling JE, Chute CG, Panser LA, et al. Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. J Urol. 1995 May;153(5):1510-5.
1185. Alonso J, Anto JM, Gonzalez M, Fiz JA, Izquierdo J, Morera J. Measurement of general health status of non-oxygen-dependent chronic obstructive pulmonary disease patients. Med Care. 1992 May;30(5 Suppl):MS125-35.
1186. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life.

A conceptual model of patient outcomes. JAMA. 1995 Jan 4;273(1):59-65.

1187. Baumann I, Blumenstock G, Zalaman IM, Praetorius M, Klingmann C, Sittel C, et al. Impact of gender, age, and comorbidities on quality of life in patients with chronic rhinosinusitis. Rhinology. 2007 Dec;45(4):268-72.
1188. Brandsted R, Sindwani R. Impact of depression on disease-specific symptoms and quality of life in patients with chronic rhinosinusitis. American journal of rhinology. 2007 Jan-Feb;21(1):50-4.
1189. Smith TL, Litvack JR, Hwang PH, Loehrl TA, Mace JC, Fong KJ, et al. Determinants of outcomes of sinus surgery: a multi-institutional prospective cohort study. Otolaryngol Head Neck Surg. 2010;142(1):55-63.
1190. Stewart M. Sinus pain: is it real? Current Opinions in Otorhinolaryngology & Head and Neck Surgery. 2002(10):29-32.
1191. Clifton NJ, Jones NS. Prevalence of facial pain in 108 consecutive patients with paranasal mucopurulent discharge at endoscopy. J Laryngol Otol. 2007 Apr;121(4):345-8.
1192. Fahy C, Jones NS. Nasal polyposis and facial pain. Clinical otolaryngology and allied sciences. 2001 Dec;26(6):510-3.
1193. Tarabichi M. Characteristics of sinus-related pain. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2000 Jun;122(6):842-7.
1194. The International Classification of Headache Disorders: 2nd edition. Cephalalgia : an international journal of headache. 2004;24 Suppl 1:9-160.
1195. Shields G, Seikaly H, LeBoeuf M, Guinto F, LeBoeuf H, Pincus T, et al. Correlation between facial pain or headache and computed tomography in rhinosinusitis in Canadian and U.S. subjects. The Laryngoscope. 2003;113(6):943-5.
1196. Cady RK, Schreiber CP. Sinus problems as a cause of headache refractoriness and migraine chronification. Current pain and headache reports. 2009 Aug;13(4):319-25.
1197. Howe L, Jones NS. Guidelines for the management of periorbital cellulitis/abscess. Clinical otolaryngology and allied sciences. 2004 Dec;29(6):725-8.
1198. Mehle ME, Kremer PS. Sinus CT scan findings in "sinus headache" migraineurs. Headache. 2008 Jan;48(1):67-71.
1199. Marshall AH, Jones NS. The utility of radiologic studies in the diagnosis and management of rhinosinusitis. Current Infectious Disease Reports. [Review]. 2003;5(3):199-204.
1200. Jeffrey Modell Foundation. National Primary Immunodeficiency Centre. Available from: http://www.jmfworld.org http://www.jmfworld.org.
1201. Cooney TR, Huissoon AP, Powell RJ, Jones NS. Investigation for immunodeficiency in patients with recurrent ENT infections. Clinical otolaryngology and allied sciences. 2001 Jun;26(3):184-8.
1202. Gwaltney JM, Jr. Acute community-acquired sinusitis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 1996 Dec;23(6):1209-23; quiz 24-5.
1203. Berg O, Carenfelt C, Kronvall G. Bacteriology of maxillary sinusitis in relation to character of inflammation and prior treatment. Scand J Infect Dis. 1988;20(5):511-6.
1204. Ruoff G. Upper respiratory tract infections in family practice. Pediatr Infect Dis J. 1998 Aug;17(8 Suppl):S73-8.
1205. Benninger MS. Adult chronic rhinosinusitis: Definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngology - Head & Neck Surgery. [Review]. 2003;129(3 SUPPL.):S1-S32.
1206. Brook I. Microbiology and management of sinusitis. J Otolaryngol. 1996 Aug;25(4):249-56.
1207. Terris MH, Davidson TM. Review of published results for endoscopic sinus surgery. Ear, nose, & throat journal. 1994 Aug;73(8):574-80.
1208. Levine HL. Functional endoscopic sinus surgery: evaluation, surgery, and follow-up of 250 patients. The Laryngoscope. 1990 Jan;100(1):79-84.
1209. Khalid AN, Quraishi SA, Kennedy DW. Long-term quality of life measures after functional endoscopic sinus surgery. American journal of rhinology. 2004;18(3):131-6.
1210. Kennedy DW, Zinreich SJ, Shaalan H, Kuhn F, Naclerio R, Loch E. Endoscopic middle meatal antrostomy: theory, technique, and patency. The Laryngoscope. 1987 Aug;97(8 Pt 3 Suppl 43):1-9.
1211. Hosemann W, Wigand ME, Fehle R, Sebastian J, Diepgen DL. [Results of endonasal ethmoid bone operations in diffuse hyperplastic chronic paranasal sinusitis]. Hno. 1988 Feb;36(2):54-9.
1212. Schaefer SD, Manning S, Close LG. Endoscopic paranasal sinus surgery: indications and considerations. The Laryngoscope. 1989 Jan;99(1):1-5.
1213. Stammberger H, Posawetz W. Functional endoscopic sinus surgery. Concept, indications and results of the Messerklinger technique. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 1990;247(2):63-76.
1214. Wigand ME, Hosemann WG. Results of endoscopic surgery of the paranasal sinuses and anterior skull base. J Otolaryngol. 1991 Dec;20(6):385-90.
1215. Schaitkin B, May M, Shapiro A, Fucci M, Mester SJ. Endoscopic sinus surgery: 4-year follow-up on the first 100 patients. The Laryngoscope. 1993 Oct;103(10):1117-20.
1216. Vleming M, Middelweerd MJ, de Vries N. [Good results of endoscopic paranasal sinus surgery for chronic or recurrent sinusitis and for nasal polyps]. Ned Tijdschr Geneeskd. 1993 Jul 17;137(29):1453-6.
1217. Danielsen A, Olofsson J. Endoscopic endonasal sinus surgery. A long-term follow-up study. Acta Otolaryngol. 1996 Jul;116(4):611-9.
1218. Jakobsen J, Svendstrup F. Functional endoscopic sinus surgery in chronic sinusitis--a series of 237 consecutively operated patients. Acta Otolaryngol Suppl. 2000;543:158-61.
1219. Mehanna H, Mills J, Kelly B, McGarry GW. Benefit from endoscopic sinus surgery.

Clinical otolaryngology and allied sciences. 2002 Dec;27(6):464-71.

1220. Obermann M, Yoon MS, Dommes P, Kuznetsova J, Maschke M, Weimar C, et al. Prevalence of trigeminal autonomic symptoms in migraine: a population-based study. Cephalalgia : an international journal of headache. 2007 Jun;27(6):504-9.
1221. Daudia AT, Jones NS. Facial migraine in a rhinological setting. Clinical otolaryngology and allied sciences. 2002 Dec;27(6):521-5.
1222. Barbanti P, Fabbrini G, Pesare M, Vanacore N, Cerbo R. Unilateral cranial autonomic symptoms in migraine. Cephalalgia : an international journal of headache. 2002 May;22(4):256-9.
1223. Kari E, DelGaudio JM. Treatment of sinus headache as migraine: the diagnostic utility of triptans. The Laryngoscope. 2008 Dec;118(12):2235-9.
1224. Jones NS. Classification and diagnosis of facial pain. Hosp Med. 2001 Oct;62(10):598-606.
1225. Obermann M, Mueller D, Yoon MS, Pageler L, Diener H, Katsarava Z. Migraine with isolated facial pain: a diagnostic challenge. Cephalalgia : an international journal of headache. 2007 Nov;27(11):1278-82.
1226. Yoon MS, Mueller D, Hansen N, Poitz F, Slomke M, Dommes P, et al. Prevalence of facial pain in migraine: a population-based study. Cephalalgia : an international journal of headache. 2010 Jan;30(1):92-6.
1227. Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life-span study. Cephalalgia : an international journal of headache. 2010 Sep;30(9):1065-72.
1228. Griggs RC, Nutt JG. Episodic ataxias as channelopathies. Ann Neurol. 1995 Mar;37(3):285-7.
1229. Ophoff RA, Terwindt GM, Vergouwe MN, van Eijk R, Oefner PJ, Hoffman SM, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell. 1996 Nov 1;87(3):543-52.
1230. Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, et al. Brain stem activation in spontaneous human migraine attacks. Nat Med. 1995 Jul;1(7):658-60.
1231. May A, Goadsby PJ. Cluster headache: imaging and other developments. Curr Opin Neurol. 1998 Jun;11(3):199-203.
1232. May A, Goadsby PJ. Hypothalamic involvement and activation in cluster headache. Current pain and headache reports. 2001 Feb;5(1):60-6.
1233. Edvinsson L, Goadsby PJ. Neuropeptides in the cerebral circulation: relevance to headache. Cephalalgia : an international journal of headache. 1995;15(4):272-6.
1234. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol. 1993 Jan;33(1):48-56.
1235. Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. Ann Neurol. 1988 Feb;23(2):193-6.
1236. Goadsby PJ. Neuroimaging in headache. Microsc Res Tech. 2001 May 1;53(3):179-87.
1237. Olesen J. Clinical and pathophysiological observations in migraine and tension-type headache explained by integration of vascular, supraspinal and myofascial inputs. Pain. 1991 Aug;46(2):125-32.
1238. Burstein R, Jakubowski M, Garcia-Nicas E, Kainz V, Bajwa Z, Hargreaves R, et al. Thalamic sensitization transforms localized pain into widespread allodynia. Ann Neurol. 2010 Jul;68(1):81-91.
1239. Silberstein SD, Goadsby PJ, Lipton RB. Management of migraine: an algorithmic approach. Neurology. 2000;55(9 Suppl 2):S46-52.
1240. Goadsby PJ. Mechanisms and management of headache. J R Coll Physicians Lond. 1999 May-Jun;33(3):228-34.
1241. Goadsby PJ, Olesen J. Diagnosis and management of migraine. BMJ (Clinical research ed). 1996 May 18;312(7041):1279-83.
1242. Lanteri-Minet M, Mick G, Allaf B. Early dosing and efficacy of triptans in acute migraine treatment: The TEMPO study. Cephalalgia : an international journal of headache. 2012 Jan 10.
1243. Gray RN, Goslin RE, McCrory DC, Eberlein K, Tulsky J, Hasselblad V. Drug Treatments for the Prevention of Migraine Headache. Rockville MD1999.
1244. Afshari D, Rafizadeh S, Rezaei M. A comparative study of the effects of low-dose topiramate versus sodium valproate in migraine prophylaxis. The International journal of neuroscience. 2012 Feb;122(2):60-8.
1245. Goadsby PJ. Cluster headache: new perspectives. Cephalalgia : an international journal of headache. 1999 Dec;19 Suppl 25:39-41.
1246. Ashkenazi A, Schwedt T. Cluster headache--acute and prophylactic therapy. Headache. 2011 Feb;51(2):272-86.
1247. Saunte C. Chronic paroxysmal hemicrania: salivation, tearing and nasal secretion. Cephalalgia : an international journal of headache. 1984 Mar;4(1):25-32.
1248. Saunte C, Russell D, Sjaastad O. Chronic paroxysmal hemicrania. IX. On the mechanism of attack-related sweating. Cephalalgia : an international journal of headache. 1983 Sep;3(3):191-9.
1249. Antonaci F, Sjaastad O. Chronic paroxysmal hemicrania (CPH): a review of the clinical manifestations. Headache. 1989 Nov;29(10):648-56.
1250. Kudrow DB, Kudrow L. Successful aspirin prophylaxis in a child with chronic paroxysmal hemicrania. Headache. 1989 May;29(5):280-1.
1251. Cittadini E, Matharu MS, Goadsby PJ. Paroxysmal hemicrania: a prospective clinical study of 31 cases. Brain : a journal of neurology. 2008 Apr;131(Pt 4):1142-55.
1252. Newman LC, Lipton RB, Solomon S. Episodic paroxysmal hemicrania: 3 new cases and a review of the literature. Headache. 1993 Apr;33(4):195-7.
1253. Warner JS, Wamil AW, McLean MJ. Acetazolamide for the treatment of chronic paroxysmal hemicrania. Headache. 1994 Nov-Dec;34(10):597-9.
1254. Fuad F, Jones NS. Paroxysmal hemicrania

and cluster headache: two discrete entities or is there an overlap? Clinical otolaryngology and allied sciences. 2002 Dec;27(6):472-9.

1255. Pareja J, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua. Interval between indomethacin administration and response. Headache. 1996 Jan;36(1):20-3.
1256. Antonaci F, Pareja JA, Caminero AB, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua. Parenteral indomethacin: the 'indotest'. Headache. 1998 Feb;38(2):122-8.
1257. Sjaastad O, Stovner LJ, Stolt-Nielsen A, Antonaci F, Fredriksen TA. CPH and hemicrania continua: requirements of high indomethacin dosages--an ominous sign? Headache. 1995 Jun;35(6):363-7.
1258. Shabbir N, McAbee G. Adolescent chronic paroxysmal hemicrania responsive to verapamil monotherapy. Headache. 1994 Apr;34(4):209-10.
1259. Evers S, Husstedt IW. Alternatives in drug treatment of chronic paroxysmal hemicrania. Headache. 1996 Jul-Aug;36(7):429-32.
1260. Hannerz J, Jogestrand T. Intracranial hypertension and sumatriptan efficacy in a case of chronic paroxysmal hemicrania which became bilateral. (The mechanism of indomethacin in CPH). Headache. 1993 Jun;33(6):320-3.
1261. Sjaastad O, Spierings EL. "Hemicrania continua": another headache absolutely responsive to indomethacin. Cephalalgia : an international journal of headache. 1984 Mar;4(1):65-70.
1262. Cittadini E, Goadsby PJ. Update on hemicrania continua. Current pain and headache reports. 2011 Feb;15(1):51-6.
1263. Goadsby PJ. Short-lasting primary headaches: focus on trigeminal automatic cephalgias and indomethacin-sensitive headaches. Curr Opin Neurol. 1999 Jun;12(3):273-7.
1264. Shigeno S, Fritschka E, Shigeno T, Brock M. Effects of indomethacin on rCBF during and after focal cerebral ischemia in the cat. Stroke. 1985 Mar-Apr;16(2):235-40.
1265. Reichman HR, Farrell CL, Del Maestro RF. Effects of steroids and nonsteroid anti-inflammatory agents on vascular permeability in a rat glioma model. J Neurosurg. 1986 Aug;65(2):233-7.
1266. Sicuteri F, Michelacci S, Anselmi B. TERMINATION OF MIGRAINE HEADACHE BY A NEW ANTI-INFLAMMATORY VASOCONSTRICTOR AGENT. Clin Pharmacol Ther. 1965 May-Jun;6:336-44.
1267. Schmidt-Wilcke T, Hierlmeier S, Leinisch E. Altered regional brain morphology in patients with chronic facial pain. Headache. 2010 Sep;50(8):1278-85.
1268. Aggarwal VR, Macfarlane GJ, Farragher TM, McBeth J. Risk factors for onset of chronic oro-facial pain--results of the North Cheshire oro-facial pain prospective population study. Pain. 2010 May;149(2):354-9.
1269. Gatchel RJ, Okifuji A. Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. J Pain. 2006 Nov;7(11):779-93.
1270. Eccleston C, Palermo TM, Williams AC, Lewandowski A, Morley S. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane database of systematic reviews (Online). 2009(2):CD003968.
1271. Tepper SJ. New thoughts on sinus headache. Allergy and asthma proceedings : the official journal of regional and state allergy societies. 2004 Mar-Apr;25(2):95-6.
1272. Eross E, Dodick D, Eross M. The Sinus, Allergy and Migraine Study (SAMS). Headache. 2007 Feb;47(2):213-24.
1273. Guerrero AL, Rojo E, Herrero S, Neri MJ, Bautista L, Penas ML, et al. Characteristics of the first 1000 headaches in an outpatient headache clinic registry. Headache. 2011 Feb;51(2):226-31.
1274. Cady RK, Schreiber CP. Sinus headache: a clinical conundrum. Otolaryngologic clinics of North America. 2004 Apr;37(2):267-88.
1275. Schreiber CP, Hutchinson S, Webster CJ, Ames M, Richardson MS, Powers C. Prevalence of migraine in patients with a history of self-reported or physician-diagnosed 'sinus' headache. Archives of Internal Medicine. 2004;164(16):1769-72.
1276. Levine HL, Setzen M, Cady RK, Dodick DW, Schreiber CP, Eross EJ, et al. An otolaryngology, neurology, allergy, and primary care consensus on diagnosis and treatment of sinus headache. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2006 Mar;134(3):516-23.
1277. Spierings EL. Acute, subacute, and chronic headache. Otolaryngologic clinics of North America. 2003 Dec;36(6):1095-107, vi.
1278. Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population--a prevalence study. J Clin Epidemiol. 1991;44(11):1147-57.
1279. Bendtsen L. Central sensitization in tension-type headache--possible pathophysiological mechanisms. Cephalalgia : an international journal of headache. 2000 Jun;20(5):486-508.
1280. Jensen R, Olesen J. Tension-type headache: an update on mechanisms and treatment. Curr Opin Neurol. 2000 Jun;13(3):285-9.
1281. Bendtsen L, Jensen R, Olesen J. A non-selective (amitriptyline), but not a selective (citalopram), serotonin reuptake inhibitor is effective in the prophylactic treatment of chronic tension-type headache. J Neurol Neurosurg Psychiatry. 1996 Sep;61(3):285-90.
1282. Tomkins GE, Jackson JL, O'Malley PG, Balden E, Santoro JE. Treatment of chronic headache with antidepressants: a meta-analysis. Am J Med. 2001 Jul;111(1):54-63.
1283. Jones NS. Midfacial segment pain: implications for rhinitis and sinusitis. Current allergy and asthma reports. 2004 May;4(3):187-92.
1284. Khan OA, Majumdar S, Jones NS. Facial pain following sinonasal surgery or facial trauma. Clinical otolaryngology and allied sciences. 2002 Jun;27(3):171-4.
1285. Babar-Craig H, Kayhanian H, De Silva DJ, Rose GE, Lund VJ. Spontaneous silent

sinus syndrome (imploding antrum syndrome): case series of 16 patients. Rhinology. 2011 Aug;49(3):315-7.

1286. Cook PR, Nishioka GJ, Davis WE, McKinsey JP. Functional endoscopic sinus surgery in patients with normal computed tomography scans. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1994 Jun;110(6):505-9.
1287. Parsons DS, Batra PS. Functional endoscopic sinus surgical outcomes for contact point headaches. The Laryngoscope. 1998 May;108(5):696-702.
1288. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008 Apr 29;70(18):1630-5.
1289. Acquadro MA, Salman SD, Joseph MP. Analysis of pain and endoscopic sinus surgery for sinusitis. The Annals of otology, rhinology, and laryngology. 1997 Apr;106(4):305-9.
1290. Low WK. Complications of the Caldwell-Luc operation and how to avoid them. Aust N Z J Surg. 1995 Aug;65(8):582-4.
1291. Romer HC. Medical management of facial pain. Hosp Med. 2001 Oct;62(10):607-10.
1292. Solberg WK, Graff-Radford SB. Orodental considerations in facial pain. Semin Neurol. 1988 Dec;8(4):318-23.
1293. Mc AG, Mueller GC, Wolff HG. Experimental studies on headache: pain originating in nasal and paranasal structures. N Y State J Med. 1950 May 1;50(9):1113-6.
1294. Gerbe RW, Fry TL, Fischer ND. Headache of nasal spur origin: an easily diagnosed and surgically correctable cause of facial pain. Headache. 1984 Nov;24(6):329-30.
1295. Abu-Bakra M, Jones NS. Does stimulation of nasal mucosa cause referred pain to the face? Clinical otolaryngology and allied sciences. 2001 Oct;26(5):430-2.
1296. Abu-Bakra M, Jones NS. Prevalence of nasal mucosal contact points in patients with facial pain compared with patients without facial pain. J Laryngol Otol. 2001 Aug;115(8):629-32.
1297. Stammberger H, Wolf G. Headaches and sinus disease: the endoscopic approach. Ann Otol Rhinol Laryngol Suppl. 1988 Sep-Oct;134:3-23.
1298. Hennekens. Epidemiology in medicine. SL EM, editor. Boston: Little Brown and Company; 1987.
1299. Blaugrund SM. Nasal obstruction. The nasal septum and concha bullosa. Otolaryngologic clinics of North America. 1989 Apr;22(2):291-306.
1300. Morgenstein KM, Krieger MK. Experiences in middle turbinectomy. The Laryngoscope. 1980 Oct;90(10 Pt 1):1596-603.
1301. Goldsmith A. Middle turbinate headache syndrome. American journal of rhinology. 1993;7(1):17-23.
1302. Clerico DM. Pneumatized superior turbinate as a cause of referred migraine headache. The Laryngoscope. 1996 Jul;106(7):874-9.
1303. Basic N, Basic V, Jukic T, Basic M, Jelic M, Hat J. Computed tomographic imaging to determine the frequency of anatomical variations in pneumatization of the ethmoid bone. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 1999;256(2):69-71.
1304. Medina J, Tom LW, Marsh RR, Bilaniuk LT. Development of the paranasal sinuses in children with sinus disease. American journal of rhinology. 1999 Jan-Feb;13(1):23-6.
1305. Sonkens JW, Harnsberger HR, Blanch GM, Babbel RW, Hunt S. The impact of screening sinus CT on the planning of functional endoscopic sinus surgery. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1991 Dec;105(6):802-13.
1306. Arslan H, Aydinlioglu A, Bozkurt M, Egeli E. Anatomic variations of the paranasal sinuses: CT examination for endoscopic sinus surgery. Auris Nasus Larynx. 1999 Jan;26(1):39-48.
1307. Danese M, Duvoisin B, Agrifoglio A, Cherpillod J, Krayenbuhl M. [Influence of naso-sinusal anatomic variants on recurrent, persistent or chronic sinusitis. X-ray computed tomographic evaluation in 112 patients]. J Radiol. 1997 Sep;78(9):651-7.
1308. Lloyd GA, Lund VJ, Scadding GK. CT of the paranasal sinuses and functional endoscopic surgery: a critical analysis of 100 symptomatic patients. J Laryngol Otol. 1991 Mar;105(3):181-5.
1309. Clark S. The incidence of concha bullosa and its relationship to chronic sinonasal disease. American journal of rhinology. 1989(3):11-2.
1310. Tonai A, Baba S. Anatomic variations of the bone in sinonasal CT. Acta Otolaryngol Suppl. 1996;525:9-13.
1311. Homer JJ, Sheard CE, Jones NS. Cognitive dissonance, the placebo effect and the evaluation of surgical results. Clinical otolaryngology and allied sciences. 2000 Jun;25(3):195-9.
1312. Sessle BJ. Acute and chronic craniofacial pain: brainstem mechanisms of nociceptive transmission and neuroplasticity, and their clinical correlates. Crit Rev Oral Biol Med. 2000;11(1):57-91.
1313. Behin F, Behin B, Bigal ME, Lipton RB. Surgical treatment of patients with refractory migraine headaches and intranasal contact points. Cephalalgia : an international journal of headache. 2005 Jun;25(6):439-43.
1314. Larsen A, Piepgras D, Chyatte D, Rizzolo D. Trigeminal neuralgia: diagnosis and medical and surgical management. JAAPA : official journal of the American Academy of Physician Assistants. 2011 Jul;24(7):20-5.
1315. Wang QP, Bai M. Topiramate versus carbamazepine for the treatment of classical trigeminal neuralgia: a meta-analysis. CNS drugs. 2011 Oct 1;25(10):847-57.
1316. Edelsberg JS, Lord C, Oster G. Systematic review and meta-analysis of efficacy, safety, and tolerability data from randomized controlled trials of drugs

used to treat postherpetic neuralgia. The Annals of pharmacotherapy. 2011 Dec;45(12):1483-90.

1317. Guler N, Durmus E, Tuncer S. Long-term follow-up of patients with atypical facial pain treated with amitriptyline. The New York state dental journal. 2005 Jun-Jul;71(4):38-42.
1318. Ishida S, Kimura H. [Therapy for atypical facial pain]. Nihon rinsho Japanese journal of clinical medicine. 2009 Sep;67(9):1803-9.
1319. Grant SF, Hakonarson H. Microarray technology and applications in the arena of genome-wide association. Clin Chem. 2008 Jul;54(7):1116-24.
1320. Alexiou A, Sourtzi P, Dimakopoulou K, Manolis E, Velonakis E. Nasal polyps: heredity, allergies, and environmental and occupational exposure. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2011 Feb;40(1):58-63.
1321. Mfuna-Endam L, Zhang Y, Desrosiers MY. Genetics of rhinosinusitis. Current allergy and asthma reports. 2011 Jun;11(3):236-46.
1322. Lockey RF, Rucknagel DL, Vanselow NA. Familial occurrence of asthma, nasal polyps and aspirin intolerance. Ann Intern Med. 1973 Jan;78(1):57-63.
1323. Settipane G. Benefit/risk ratio of aspirin. NES Allergy Proceedings. 1981(2):96-102.
1324. Drake-Lee A. Nasal polyps in identical twins. J Laryngol Otol. 1992 Dec;106(12):1084-5.
1325. Bosse Y, Bacot F, Montpetit A, Rung J, Qu HQ, Engert JC, et al. Identification of susceptibility genes for complex diseases using pooling-based genome-wide association scans. Hum Genet. 2009 Apr;125(3):305-18.
1326. Pearson JV, Huentelman MJ, Halperin RF, Tembe WD, Melquist S, Homer N, et al. Identification of the genetic basis for complex disorders by use of pooling-based genomewide single-nucleotide-polymorphism association studies. Am J Hum Genet. 2007 Jan;80(1):126-39.
1327. Karjalainen J, Joki-Erkkila VP, Hulkkonen J, Pessi T, Nieminen MM, Aromaa A, et al. The IL1A genotype is associated with nasal polyposis in asthmatic adults. Allergy. 2003 May;58(5):393-6.
1328. Mfuna Endam L, Cormier C, Bosse Y, Filali-Mouhim A, Desrosiers M. Association of IL1A, IL1B, and TNF gene polymorphisms with chronic rhinosinusitis with and without nasal polyposis: A replication study. Archives of otolaryngology--head & neck surgery. 2010 Feb;136(2):187-92.
1329. Bernstein JM, Anon JB, Rontal M, Conroy J, Wang C, Sucheston L. Genetic polymorphisms in chronic hyperplastic sinusitis with nasal polyposis. The Laryngoscope. 2009 Jul;119(7):1258-64.
1330. Erbek SS, Yurtcu E, Erbek S, Atac FB, Sahin FI, Cakmak O. Proinflammatory cytokine single nucleotide polymorphisms in nasal polyposis. Archives of otolaryngology--head & neck surgery. 2007 Jul;133(7):705-9.
1331. Endam LM, Bosse Y, Filali-Mouhim A, Cormier C, Boisvert P, Boulet LP, et al. Polymorphisms in the interleukin-22 receptor alpha-1 gene are associated with severe chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009 May;140(5):741-7.
1332. Kilty SJ, Desrosiers MY. Chronic sinusitis and alpha1-antitrypsin deficiency: potential role for protease in rhinosinusitis? Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2008 Dec;37(6):E179-82.
1333. Tewfik MA, Bosse Y, Lemire M, Hudson TJ, Vallee-Smejda S, Al-Shemari H, et al. Polymorphisms in interleukin-1 receptor-associated kinase 4 are associated with total serum IgE. Allergy. 2009 May;64(5):746-53.
1334. Castano R, Bosse Y, Endam LM, Desrosiers M. Evidence of association of interleukin-1 receptor-like 1 gene polymorphisms with chronic rhinosinusitis. American journal of rhinology & allergy. 2009 Jul-Aug;23(4):377-84.
1335. Park CS, Cho JH, Park YJ. Toll-like receptor 2 gene polymorphisms in a Korean population: association with chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Jan;144(1):96-100.
1336. Yea SS, Yang YI, Park SK, Jang WH, Lee SS, Seog DH, et al. Interleukin-4 C-590T polymorphism is associated with protection against nasal polyps in a Korean population. American journal of rhinology. 2006 Sep-Oct;20(5):550-3.
1337. Pinto JM, Hayes MG, Schneider D, Naclerio RM, Ober C. A genomewide screen for chronic rhinosinusitis genes identifies a locus on chromosome 7q. The Laryngoscope. 2008 Nov;118(11):2067-72.
1338. Luxenberger W, Posch U, Berghold A, Hofmann T, Lang-Loidolt D. HLA patterns in patients with nasal polyposis. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2000;257(3):137-9.
1339. Molnar-Gabor E, Endreffy E, Rozsasi A. HLA-DRB1, -DQA1, and -DQB1 genotypes in patients with nasal polyposis. The Laryngoscope. 2000 Mar;110(3 Pt 1):422-5.
1340. Fajardo-Dolci G, Solorio-Abreu J, Romero-Alvarez JC, Zavaleta-Villa B, Cerezo-Camacho O, Jimenez-Lucio R, et al. DQA1 and DQB1 association and nasal polyposis. Otolaryngology - Head & Neck Surgery. 2006;135(2):243-7.
1341. Ramirez-Anguiano J, Yamamoto-Furusho JK, Barquera R, Beltran O, Granados J. Association of HLA-DR3 and HLA-DR4 with sinonasal polyposis in Mexican Mestizos. Otolaryngology - Head & Neck Surgery. 2006;135(1):90-3.
1342. Fruth K, Best N, Amro M, Ingel K, Gosepath J, Mann WJ, et al. No evidence for a correlation of glutathione S-tranferase polymorphisms and chronic rhinosinusitis. Rhinology. 2011 Jun;49(2):180-4.
1343. Platt MP, Soler Z, Metson R, Stankovic KM. Pathways analysis of molecular markers in chronic sinusitis with polyps. Otolaryngology--head and neck surgery

: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 May;144(5):802-8.

1344. Kerem E. Atypical CF and CF related diseases. Paediatric Respiratory Reviews. [Review]. 2006;7(SUPPL. 1):S144-S6.
1345. Cuppens H, Marynen P, De Boeck C, Cassiman JJ. Detection of 98.5% of the mutations in 200 Belgian cystic fibrosis alleles by reverse dot-blot and sequencing of the complete coding region and exon/intron junctions of the CFTR gene. Genomics. 1993 Dec;18(3):693-7.
1346. Davidson TM, Stearns G. Extended indications for endoscopic sinus surgery. Ear, nose, & throat journal. 1994 Jul;73(7):467-8, 73-4.
1347. Stern RC, Boat TF, Wood RE, Matthews LW, Doershuk CF. Treatment and prognosis of nasal polyps in cystic fibrosis. American journal of diseases of children (1960). 1982 Dec;136(12):1067-70.
1348. Kerrebijn JD, Poublon RM, Overbeek SE. Nasal and paranasal disease in adult cystic fibrosis patients. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1992 Nov;5(10):1239-42.
1349. De Gaudemar I, Contencin P, Van den Abbeele T, Munck A, Navarro J, Narcy P. Is nasal polyposis in cystic fibrosis a direct manifestation of genetic mutation or a complication of chronic infection? Rhinology. 1996 Dec;34(4):194-7.
1350. Jorissen MB, De Boeck K, Cuppens H. Genotype-phenotype correlations for the paranasal sinuses in cystic fibrosis. American journal of respiratory and critical care medicine. 1999 May;159(5 Pt 1):1412-6.
1351. Wang X, Moylan B, Leopold DA, Kim J, Rubenstein RC, Togias A, et al. Mutation in the gene responsible for cystic fibrosis and predisposition to chronic rhinosinusitis in the general population. JAMA. 2000 Oct 11;284(14):1814-9.
1352. Singh M, Das RR. Zinc for the common cold. Cochrane database of systematic reviews (Online). 2011(2):CD001364.
1353. Wu T, Zhang J, Qiu Y, Xie L, Liu GJ. Chinese medicinal herbs for the common cold. Cochrane database of systematic reviews (Online). 2007(1):CD004782.
1354. Zalmanovici A, Yaphe J. Steroids for acute sinusitis. Cochrane database of systematic reviews (Online). 2007(2):CD005149.
1355. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, Varonen H, Rautakorpi UM, Williams JW, Jr., et al. Antibiotics for acute maxillary sinusitis. Cochrane database of systematic reviews (Online). 2008(2):CD000243.
1356. Lissiman E, Bhasale AL, Cohen M. Garlic for the common cold. Cochrane database of systematic reviews (Online). 2009(3):CD006206.
1357. Kim SY, Chang YJ, Cho HM, Hwang YW, Moon YS. Non-steroidal anti-inflammatory drugs for the common cold. Cochrane database of systematic reviews (Online). 2009(3):CD006362.
1358. Jefferson T, Del Mar C, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane database of systematic reviews (Online). 2010(1):CD006207.
1359. Kassel JC, King D, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. Cochrane database of systematic reviews (Online). 2010(3):CD006821.
1360. Guppy MP, Mickan SM, Del Mar CB, Thorning S, Rack A. Advising patients to increase fluid intake for treating acute respiratory infections. Cochrane database of systematic reviews (Online). 2011(2):CD004419.
1361. Albalawi ZH, Othman SS, Alfaleh K. Intranasal ipratropium bromide for the common cold. Cochrane database of systematic reviews (Online). 2011(7):CD008231.
1362. Hao Q, Lu Z, Dong BR, Huang CQ, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane database of systematic reviews (Online). 2011;9:CD006895.
1363. De Sutter AI, van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. Cochrane database of systematic reviews (Online). 2012;2:CD004976.
1364. Singh M. Heated, humidified air for the common cold. Cochrane database of systematic reviews (Online). 2011(5):CD001728.
1365. Arroll B. Common cold. Clinical evidence. 2011;2011.
1366. Douglas RM, Hemila H, Chalker E, Treacy B. Vitamin C for preventing and treating the common cold. Cochrane database of systematic reviews (Online). 2007(3):CD000980.
1367. Keith PK, Dymek A, Pfaar O, Fokkens WJ, Kirbye SY. A randomised placebo-controlled study: fluticasone furoate nasal spray reduces symptoms of uncomplicated acute rhinosinusitis. Primary Care Respiratory Journal. 2012;in press.
1368. Pilan RR, Pinna F, Bezerra TFP, Renata Lopes Mori RL, Voegels R. Prevalence of Chronic Rhinosinusitis in São Paulo. Rhinology. 2012;50(in press).
1369. Natvig K, Larsen TE. Mucocele of the paranasal sinuses. A retrospective clinical and histological study. J Laryngol Otol. 1978 Dec;92(12):1075-82.
1370. Lund VJ, Henderson B, Song Y. Involvement of cytokines and vascular adhesion receptors in the pathology of fronto-ethmoidal mucocoeles. Acta Otolaryngol. 1993 Jul;113(4):540-6.
1371. Lund VJ. Anatomical considerations in the aetiology of fronto-ethmoidal mucoceles. Rhinology. 1987 Jun;25(2):83-8.
1372. Lloyd G, Lund VJ, Savy L, Howard D. Optimum imaging for mucoceles. J Laryngol Otol. 2000 Mar;114(3):233-6.
1373. Lund VJ, Milroy CM. Fronto-ethmoidal mucocoeles: a histopathological analysis. J Laryngol Otol. 1991 Nov;105(11):921-3.
1374. Kennedy DW, Josephson JS, Zinreich SJ, Mattox DE, Goldsmith MM. Endoscopic sinus surgery for mucoceles: a viable alternative. The Laryngoscope. 1989 Sep;99(9):885-95.
1375. Moriyama H, Nakajima T, Honda Y. Studies on mucocoeles of the ethmoid and sphenoid sinuses: analysis of 47 cases. J

Laryngol Otol. 1992 Jan;106(1):23-7.

1376. Benninger MS, Marks S. The endoscopic management of sphenoid and ethmoid mucoceles with orbital and intranasal extension. Rhinology. 1995 Sep;33(3):157-61.
1377. Lund VJ. Endoscopic management of paranasal sinus mucocoeles. J Laryngol Otol. 1998 Jan;112(1):36-40.
1378. Conboy PJ, Jones NS. The place of endoscopic sinus surgery in the treatment of paranasal sinus mucocoeles. Clinical otolaryngology and allied sciences. 2003 Jun;28(3):207-10.
1379. Khong JJ, Malhotra R, Selva D, Wormald PJ. Efficacy of endoscopic sinus surgery for paranasal sinus mucocele including modified endoscopic Lothrop procedure for frontal sinus mucocele. J Laryngol Otol. 2004 May;118(5):352-6.
1380. Bockmuhl U, Kratzsch B, Benda K, Draf W. Surgery for paranasal sinus mucocoeles: efficacy of endonasal micro-endoscopic management and long-term results of 185 patients. Rhinology. 2006 Mar;44(1):62-7.
1381. Beasley N JN. Paranasal sinus mucocoeles, modern management. American journal of rhinology. 1995(9):251-6.
1382. Bolger WE, Leonard D, Dick EJ, Jr., Stierna P. Gram negative sinusitis: a bacteriologic and histologic study in rabbits. American journal of rhinology. 1997 Jan-Feb;11(1):15-25.
1383. Khalid AN, Hunt J, Perloff JR, Kennedy DW. The role of bone in chronic rhinosinusitis. The Laryngoscope. 2002 Nov;112(11):1951-7.
1384. Giacchi RJ, Lebowitz RA, Yee HT, Light JP, Jacobs JB. Histopathologic evaluation of the ethmoid bone in chronic sinusitis. American journal of rhinology. 2001 May-Jun;15(3):193-7.
1385. Jang YJ, Koo TW, Chung SY, Park SG. Bone involvement in chronic rhinosinusitis assessed by 99mTc-MDP bone SPECT. Clinical otolaryngology and allied sciences. 2002 Jun;27(3):156-61.
1386. Biedlingmaier JF, Whelan P, Zoarski G, Rothman M. Histopathology and CT analysis of partially resected middle turbinates. The Laryngoscope. 1996 Jan;106(1 Pt 1):102-4.
1387. Kim HY, Dhong HJ, Lee HJ, Chung YJ, Yim YJ, Oh JW, et al. Hyperostosis may affect prognosis after primary endoscopic sinus surgery for chronic rhinosinusitis. Otolaryngology - Head & Neck Surgery. 2006;135(1):94-9.
1388. Georgalas C, Videler W, Freling N, Fokkens W. Global Osteitis Scoring Scale and chronic rhinosinusitis: a marker of revision surgery. Clin Otolaryngol. 2010 Dec;35(6):455-61.
1389. Eggesbo HB. Radiological imaging of inflammatory lesions in the nasal cavity and paranasal sinuses. European radiology. 2006 Apr;16(4):872-88.
1390. Lund VJ, Lloyd GA. Radiological changes associated with benign nasal polyps. J Laryngol Otol. 1983 Jun;97(6):503-10.
1391. Som PM, Lawson W, Lidov MW. Simulated aggressive skull base erosion in response to benign sinonasal disease. Radiology. 1991 Sep;180(3):755-9.
1392. Lund VJ, Lloyd G, Savy L, Howard D. Fungal rhinosinusitis. J Laryngol Otol. 2000 Jan;114(1):76-80.
1393. Lundgren S, Andersson S, Sennerby L. Spontaneous bone formation in the maxillary sinus after removal of a cyst: coincidence or consequence? Clin Implant Dent Relat Res. 2003;5(2):78-81.
1394. Maitra S, Gupta D, Radojkovic M, Sood S. Osseous metaplasia of the maxillary sinus with formation of a well-developed haversian system and bone marrow. Ear, nose, & throat journal. 2009 Sep;88(9):1115-20.
1395. Kim YK, Kim HJ, Kim J, Chung SK, Kim E, Ko YH, et al. Nasal polyps with metaplastic ossification: CT and MR imaging findings. Neuroradiology. 2010 Dec;52(12):1179-84.
1396. Kurimoto T, Tonari M, Ishizaki N, Matsuo J, Oku H, Sugasawa J, et al. A case of eosinophilic chronic rhinosinusitis associated with optic neuropathy. Clin Ophthalmol. 2011;5:853-6.
1397. Bizzoni A, Bolzoni Villaret A, Lombardi D, Tomenzoli D, Danzi P, Semeraro F, et al. Isolated sphenoid inflammatory diseases associated with visual impairment: 15-year experience at a single institution. Rhinology. 2011 Jun;49(2):202-6.
1398. Hens G, Hellings PW. The nose: gatekeeper and trigger of bronchial disease. Rhinology. 2006 Sep;44(3):179-87.
1399. Johansson A, Bende M, Millqvist E, Bake B. Nasobronchial relationship after cold air provocation. Respiratory medicine. 2000 Nov;94(11):1119-22.
1400. Koskela HO, Koskela AK, Tukiaineu HO. Bronchoconstriction due to cold weather in COPD. The roles of direct airway effects and cutaneous reflex mechanisms. Chest. 1996 Sep;110(3):632-6.
1401. Hens G, Raap U, Vanoirbeek J, Meyts I, Callebaut I, Verbinnen B, et al. Selective Nasal Allergen Provocation Induces Substance P-mediated Bronchial Hyperresponsiveness. Am J Respir Cell Mol Biol. 2010 Jun 10.
1402. Denburg JA, Keith PK. Systemic aspects of chronic rhinosinusitis. Immunology and allergy clinics of North America. 2004 Feb;24(1):87-102.
1403. Barnes KC. Genetic epidemiology of health disparities in allergy and clinical immunology. The Journal of allergy and clinical immunology. 2006 Feb;117(2):243-54; quiz 55-6.
1404. Braunstahl GJ, Hellings PW. Nasobronchial interaction mechanisms in allergic airways disease. Current opinion in otolaryngology & head and neck surgery. 2006 Jun;14(3):176-82.
1405. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Gaffey TA, Tarara JE, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? The Journal of allergy and clinical immunology. 2003 Nov;112(5):877-82.
1406. Matsuno O, Ono E, Takenaka R, Okubo T, Takatani K, Ueno T, et al. Asthma and sinusitis: association and implication. Int Arch Allergy Immunol. 2008;147(1):52-8.
1407. ten Brinke A, Grootendorst DC, Schmidt JT, De Bruine FT, van Buchem MA, Sterk PJ, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. The Journal of allergy and clinical immunology. 2002 Apr;109(4):621-6.

1408. Hellings PW, Hens G, Meyts I, Bullens D, Vanoirbeek J, Gevaert P, et al. Aggravation of bronchial eosinophilia in mice by nasal and bronchial exposure to Staphylococcus aureus enterotoxin B. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2006 Aug;36(8):1063-71.

1409. Kountakis SE, Bradley DT. Effect of asthma on sinus computed tomography grade and symptom scores in patients undergoing revision functional endoscopic sinus surgery. American journal of rhinology. 2003 Jul-Aug;17(4):215-9.

1410. Nishioka GJ, Cook PR, Davis WE, McKinsey JP. Functional endoscopic sinus surgery in patients with chronic sinusitis and asthma. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1994 Jun;110(6):494-500.

1411. Dinis PB, Gomes A. Sinusitis and asthma: how do they interrelate in sinus surgery? American journal of rhinology. 1997 Nov-Dec;11(6):421-8.

1412. Dhong HJ, Jung YS, Chung SK, Choi DC. Effect of endoscopic sinus surgery on asthmatic patients with chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2001 Jan;124(1):99-104.

1413. Proimos E, Papadakis CE, Chimona TS, Kiagiadaki D, Ferekidis E, Yiotakis J. The effect of functional endoscopic sinus surgery on patients with asthma and CRS with nasal polyps. Rhinology. 2010 Sep;48(3):331-8.

1414. Senior BA, Kennedy DW, Tanabodee J, Kroger H, Hassab M, Lanza DC. Long-term impact of functional endoscopic sinus surgery on asthma. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1999 Jul;121(1):66-8.

1415. Manning SC, Wasserman RL, Silver R, Phillips DL. Results of endoscopic sinus surgery in pediatric patients with chronic sinusitis and asthma. Archives of otolaryngology--head & neck surgery. 1994 Oct;120(10):1142-5.

1416. Ikeda K, Tanno N, Tamura G, Suzuki H, Oshima T, Shimomura A, et al. Endoscopic sinus surgery improves pulmonary function in patients with asthma associated with chronic sinusitis. The Annals of otology, rhinology, and laryngology. 1999 Apr;108(4):355-9.

1417. Dejima K, Hama T, Miyazaki M, Yasuda S, Fukushima K, Oshima A, et al. A clinical study of endoscopic sinus surgery for sinusitis in patients with bronchial asthma. International archives of allergy and immunology. [10.1159/000088430]. 2005;138(2):97-104.

1418. Goldstein MF, Grundfast SK, Dunsky EH, Dvorin DJ, Lesser R. Effect of functional endoscopic sinus surgery on bronchial asthma outcomes. Archives of otolaryngology--head & neck surgery. 1999 Mar;125(3):314-9.

1419. Amar YG, Frenkiel S, Sobol SE. Outcome analysis of endoscopic sinus surgery for chronic sinusitis in patients having Samter's triad. J Otolaryngol. 2000 Feb;29(1):7-12.

1420. Batra PS, Kern RC, Tripathi A, Conley DB, Ditto AM, Haines GK, 3rd, et al. Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma. The Laryngoscope. 2003 Oct;113(10):1703-6.

1421. Chambers DW, Davis WE, Cook PR, Nishioka GJ, Rudman DT. Long-term outcome analysis of functional endoscopic sinus surgery: correlation of symptoms with endoscopic examination findings and potential prognostic variables. The Laryngoscope. 1997 Apr;107(4):504-10.

1422. Ragab S, Scadding GK, Lund VJ, Saleh H. Treatment of chronic rhinosinusitis and its effects on asthma. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2006 Jul;28(1):68-74.

1423. Ragab A, Clement P, Vincken W. Objective assessment of lower airway involvement in chronic rhinosinusitis. American journal of rhinology. 2004 Jan-Feb;18(1):15-21.

1424. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. The Journal of allergy and clinical immunology. 2003 May;111(5):913-21; quiz 22.

1425. 1425. Uri N, Cohen-Kerem R, Barzilai G, Greenberg E, Doweck I, Weiler-Ravell D. Functional endoscopic sinus surgery in the treatment of massive polyposis in asthmatic patients. J Laryngol Otol. 2002 Mar;116(3):185-9.

1426. Ehnhage A, Olsson P, Kolbeck KG, Skedinger M, Dahlen B, Alenius M, et al. Functional endoscopic sinus surgery improved asthma symptoms as well as PEFR and olfaction in patients with nasal polyposis. Allergy. 2009 May;64(5):762-9.

1427. Ragab SM, Hassanin MZ. Optimizing the surgical field in pediatric functional endoscopic sinus surgery: a new evidence-based approach. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 Jan;142(1):48-54.

1428. Marshak T, Rivlin Y, Bentur L, Ronen O, Uri N. Prevalence of rhinosinusitis among atypical cystic fibrosis patients. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2011 Apr;268(4):519-24.

1429. Godoy JM, Godoy AN, Ribalta G, Largo I. Bacterial pattern in chronic sinusitis and cystic fibrosis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Oct;145(4):673-6.

1430. Kovell LC, Wang J, Ishman SL, Zeitlin PL, Boss EF. Cystic fibrosis and sinusitis in children: outcomes and socioeconomic status. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Jul;145(1):146-53.

1431. Hurst JR, Wilkinson TM, Donaldson GC, Wedzicha JA. Upper airway symptoms

and quality of life in chronic obstructive pulmonary disease (COPD). Respiratory medicine. 2004 Aug;98(8):767-70.

1432. Hens G, Vanaudenaerde BM, Bullens DM, Piessens M, Decramer M, Dupont LJ, et al. Sinonasal pathology in nonallergic asthma and COPD: 'united airway disease' beyond the scope of allergy. Allergy. 2008 Mar;63(3):261-7.
1433. Guilemany JM, Angrill J, Alobid I, Centellas S, Pujols L, Bartra J, et al. United airways again: high prevalence of rhinosinusitis and nasal polyps in bronchiectasis. Allergy. 2009 May;64(5):790-7.
1434. Guilemany JM, Marino-Sanchez FS, Angrill J, Alobid I, Centellas S, Pujols L, et al. The importance of smell in patients with bronchiectasis. Respiratory medicine. 2011 Jan;105(1):44-9.
1435. Bulgarelli R, De Maestri A, Vento R. [The bronchosinusal syndrome in children. Chronic or recurrent sinusitis and bronchitis. Sinusitis and bronchial asthma. Kartagener's syndrome. Mounier-Kahn syndrome. The bronchosinusal syndrome in pancreatic cystic fibrosis and in agammaglobulinemia]. Minerva Pediatr. 1961 Sep 15;13:1163-96.
1436. Wise SK, Kingdom TT, McKean L, DelGaudio JM, Venkatraman G. Presence of fungus in sinus cultures of cystic fibrosis patients. American journal of rhinology. 2005;19(1):47-51.
1437. Hansen SK, Rau MH, Johansen HK, Ciofu O, Jelsbak L, Yang L, et al. Evolution and diversification of Pseudomonas aeruginosa in the paranasal sinuses of cystic fibrosis children have implications for chronic lung infection. The ISME journal. 2012 Jan;6(1):31-45.
1438. Aanaes K, Rickelt LF, Johansen HK, von Buchwald C, Pressler T, Hoiby N, et al. Decreased mucosal oxygen tension in the maxillary sinuses in patients with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2011 Mar;10(2):114-20.
1439. Owens JM, Shroyer KR, Kingdom TT. Expression of cyclooxygenase and lipoxygenase enzymes in sinonasal mucosa of patients with cystic fibrosis. Archives of otolaryngology--head & neck surgery. 2008 Aug;134(8):825-31.
1440. Roca-Ferrer J, Pujols L, Gartner S, Moreno A, Pumarola F, Mullol J, et al. Upregulation of COX-1 and COX-2 in nasal polyps in cystic fibrosis. Thorax. 2006;61(7):592-6.
1441. Schraven SP, Wehrmann M, Wagner W, Blumenstock G, Koitschev A. Prevalence and histopathology of chronic polypoid sinusitis in pediatric patients with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2011 May;10(3):181-6.
1442. Wu X, Amorn MM, Aujla PK, Rice S, Mimms R, Watson AM, et al. Histologic characteristics and mucin immunohistochemistry of cystic fibrosis sinus mucosa. Archives of otolaryngology--head & neck surgery. 2011 Apr;137(4):383-9.
1443. Knipping S, Holzhausen HJ, Riederer A, Bloching M. Cystic fibrosis: ultrastructural changes of nasal mucosa. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2007 Dec;264(12):1413-8.
1444. Woodworth BA, Wood R, Baatz JE, Schlosser RJ. Sinonasal surfactant protein A1, A2, and D gene expression in cystic fibrosis: a preliminary report. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 Jul;137(1):34-8.
1445. Seifert CM, Harvey RJ, Mathews JW, Meyer TA, Ahn C, Woodworth BA, et al. Temporal bone pneumatization and its relationship to paranasal sinus development in cystic fibrosis. Rhinology. 2010 Jun;48(2):233-8.
1446. Feuillet-Fieux MN, Lenoir G, Sermet I, Elie C, Djadi-Prat J, Ferrec M, et al. Nasal polyposis and cystic fibrosis(CF): review of the literature. Rhinology. 2011 Aug;49(3):347-55.
1447. Castellani C, Quinzii C, Altieri S, Mastella G, Assael BM. A pilot survey of cystic fibrosis clinical manifestations in CFTR mutation heterozygotes. Genet Test. 2001 Fall;5(3):249-54.
1448. Raman V, Clary R, Siegrist KL, Zehnbauer B, Chatila TA. Increased prevalence of mutations in the cystic fibrosis transmembrane conductance regulator in children with chronic rhinosinusitis. Pediatrics. 2002 Jan;109(1):E13.
1449. Wang X, Kim J, McWilliams R, Cutting GR. Increased prevalence of chronic rhinosinusitis in carriers of a cystic fibrosis mutation. Archives of Otolaryngology -- Head & Neck Surgery. 2005;131(3):237-40.
1450. Babinski D, Trawinska-Bartnicka M. Rhinosinusitis in cystic fibrosis: not a simple story. Int J Pediatr Otorhinolaryngol. 2008 May;72(5):619-24.
1451. Cimmino M, Nardone M, Cavaliere M, Plantulli A, Sepe A, Esposito V, et al. Dornase alfa as postoperative therapy in cystic fibrosis sinonasal disease. Archives of Otolaryngology -- Head & Neck Surgery. 2005;131(12):1097-101.
1452. Mainz JG, Schiller I, Ritschel C, Mentzel HJ, Riethmuller J, Koitschev A, et al. Sinonasal inhalation of dornase alfa in CF: A double-blind placebo-controlled cross-over pilot trial. Auris Nasus Larynx. 2011 Apr;38(2):220-7.
1453. Lim M, Citardi MJ, Leong JL. Topical antimicrobials in the management of chronic rhinosinusitis: a systematic review. American journal of rhinology. 2008 Jul-Aug;22(4):381-9.
1454. Wagner JA, Nepomuceno IB, Messner AH, Moran ML, Batson EP, Dimiceli S, et al. A phase II, double-blind, randomized, placebo-controlled clinical trial of tgAAVCF using maxillary sinus delivery in patients with cystic fibrosis with antrostomies. Hum Gene Ther. 2002 Jul 20;13(11):1349-59.
1455. Moss RB, King VV. Management of sinusitis in cystic fibrosis by endoscopic surgery and serial antimicrobial lavage. Reduction in recurrence requiring surgery. Archives of otolaryngology--head & neck surgery. 1995 May;121(5):566-72.
1456. Khalid AN, Mace J, Smith TL. Outcomes of sinus surgery in adults with cystic fibrosis. Otolaryngology--head and neck surgery

: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009 Sep;141(3):358-63.

1457. Cho DY, Hwang PH. Results of endoscopic maxillary mega-antrostomy in recalcitrant maxillary sinusitis. American journal of rhinology. 2008 Nov-Dec;22(6):658-62.
1458. Coste A, Idrissi F, Beautru R, Lenoir G, Reinert P, Manach Y, et al. [Endoscopic endonasal ethmoidectomy in severe sinusitis of cystic fibrosis. Mid-term results in 12 patients]. Ann Otolaryngol Chir Cervicofac. 1997;114(4):99-104.
1459. Holzmann D, Speich R, Kaufmann T, Laube I, Russi EW, Simmen D, et al. Effects of sinus surgery in patients with cystic fibrosis after lung transplantation: a 10-year experience. Transplantation. 2004 Jan 15;77(1):134-6.
1460. Duplechain JK, White JA, Miller RH. Pediatric sinusitis. The role of endoscopic sinus surgery in cystic fibrosis and other forms of sinonasal disease. Archives of otolaryngology--head & neck surgery. 1991 Apr;117(4):422-6.
1461. Jones JW, Parsons DS, Cuyler JP. The results of functional endoscopic sinus (FES) surgery on the symptoms of patients with cystic fibrosis. Int J Pediatr Otorhinolaryngol. 1993 Dec;28(1):25-32.
1462. Samter M, Beers RF, Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. Ann Intern Med. 1968 May;68(5):975-83.
1463. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2002 Nov;89(5):474-8.
1464. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) - classification, diagnosis and management: review of the EAACI/ENDA(#) and GA2LEN/HANNA*. Allergy. 2011 Jul;66(7):818-29.
1465. Settipane G. Nasal polyps: Epidemiology, pathology, immunology , and treatment. American journal of rhinology & allergy. 1987(1):119-26.
1466. Kowalski ML. Aspirin-sensitive rhinosinusitis and asthma. Clin Allergy Immunol. 2007;19:147-75.
1467. Vento SI, Ertama LO, Hytonen ML, Wolff CH, Malmberg CH. Nasal polyposis: clinical course during 20 years. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2000 Sep;85(3):209-14.
1468. Kowalski M. Nasal Polyposis In aspirin-hypersensitive patients with asthma and aspirin-tolerant patients J World Allergy org. 2003(15):246-50.
1469. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. Br Med J. 1975 Jan 11;1(5949):67-9.
1470. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. The Journal of allergy and clinical immunology. 2006 Oct;118(4):773-86; quiz 87-8.
1471. Kowalski ML, Sliwinska-Kowalska M, Igarashi Y, White MV, Wojciechowska B, Brayton P, et al. Nasal secretions in response to acetylsalicylic acid. The Journal of allergy and clinical immunology. 1993 Feb;91(2):580-98.
1472. Fischer AR, Rosenberg MA, Lilly CM, Callery JC, Rubin P, Cohn J, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. The Journal of allergy and clinical immunology. 1994 Dec;94(6 Pt 1):1046-56.
1473. Nasser S, Christie PE, Pfister R, Sousa AR, Walls A, Schmitz-Schumann M, et al. Effect of endobronchial aspirin challenge on inflammatory cells in bronchial biopsy samples from aspirin-sensitive asthmatic subjects. Thorax. 1996 Jan;51(1):64-70.
1474. Kowalski ML, Grzegorczyk J, Wojciechowska B, Poniatowska M. Intranasal challenge with aspirin induces cell influx and activation of eosinophils and mast cells in nasal secretions of ASA-sensitive patients. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1996 Jul;26(7):807-14.
1475. Picado C, Ramis I, Rosello J, Prat J, Bulbena O, Plaza V, et al. Release of peptide leukotriene into nasal secretions after local instillation of aspirin in aspirin-sensitive asthmatic patients. Am Rev Respir Dis. 1992 Jan;145(1):65-9.
1476. Pawliczak R, Lewandowska-Polak A, Kowalski ML. Pathogenesis of nasal polyps: An update. Current Allergy & Asthma Reports. [Review]. 2005;5(6):463-71.
1477. Jankowski R. Eosinophils in the Pathophysiology of Nasal Polyposis. Acta Otolaryngol. 1996;116(2):160-3.
1478. Kowalski ML, Lewandowska A, Wozniak J, Makowska J, Jankowski A, DuBuske L. Inhibition of nasal polyp mast cell and eosinophil activation by desloratadine. Allergy. 2005;60(1):80-5.
1479. Varga EM, Jacobson MR, Masuyama K, Rak S, Till SJ, Darby Y, et al. Inflammatory cell populations and cytokine mRNA expression in the nasal mucosa in aspirin-sensitive rhinitis. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1999 Sep;14(3):610-5.
1480. Pods R, Ross D, van Hulst S, Rudack C, Maune S. RANTES, eotaxin and eotaxin-2 expression and production in patients with aspirin triad. Allergy. 2003 Nov;58(11):1165-70.
1481. Bachert C. Nasal polyposis- a new concept on the formation of polyps. ACI International. 1999;11(4):130-5.
1482. Kowalski ML, Grzegorczyk J, Pawliczak R, Kornatowski T, Wagrowska-Danilewicz M, Danilewicz M. Decreased apoptosis and distinct profile of infiltrating cells in the nasal polyps of patients with aspirin hypersensitivity. Allergy. 2002 Jun;57(6):493-500.
1483. Suh YJ, Yoon SH, Sampson AP, Kim HJ, Kim SH, Nahm DH, et al. Specific immunoglobulin E for staphylococcal enterotoxins in nasal polyps from patients

with aspirin-intolerant asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2004 Aug;34(8):1270-5.

1484. Perez-Novo CA, Kowalski ML, Kuna P, Ptasinska A, Holtappels G, van Cauwenberge P, et al. Aspirin sensitivity and IgE antibodies to Staphylococcus aureus enterotoxins in nasal polyposis: studies on the relationship. Int Arch Allergy Immunol. 2004 Mar;133(3):255-60.
1485. Perez-Novo AA, Jedrzejczak-Czechowicz M, Lewandowska-Polak A, Claeys C, Holtappels G, van Cauwenberge P, et al. T cell inflammatory response, Foxp3 and TNFRS18-L regulation of peripheral blood mononuclear cells from patients with nasal polyps-asthma after staphylococcal superantigen stimulation. Clinical & Experimental Allergy. 2010;40:1323-32.
1486. Pawankar R. Nasal polyposis: an update: editorial review. Curr Opin Allergy Clin Immunol. 2003 Feb;3(1):1-6.
1487. Mudd PA, Katial RK, Alam R, Hohensee S, Ramakrishnan V, Kingdom TT. Variations in expression of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in nasal mucosa of aspirin-sensitive versus aspirin-tolerant patients with nasal polyposis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2011 Oct;107(4):353-9.
1488. Sekigawa T, Tajima A, Hasegawa T, Hasegawa Y, Inoue H, Sano Y, et al. Gene-expression profiles in human nasal polyp tissues and identification of genetic susceptibility in aspirin-intolerant asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2009 Jul;39(7):972-81.
1489. Cheong HS, Park SM, Kim MO, Park JS, Lee JY, Byun JY, et al. Genome-wide methylation profile of nasal polyps: relation to aspirin hypersensitivity in asthmatics. Allergy. 2011 May;66(5):637-44.
1490. Zander KA, Saavedra MT, West J, Scapa V, Sanders L, Kingdom TT. Protein microarray analysis of nasal polyps from aspirin-sensitive and aspirin-tolerant patients with chronic rhinosinusitis. American journal of rhinology & allergy. 2009 May-Jun;23(3):268-72.
1491. Kim TH, Lee JY, Park JS, Park SW, Jang AS, Byun JY, et al. Fatty Acid binding protein 1 is related with development of aspirin-exacerbated respiratory disease. PLoS One. 2011;6(8):e22711.
1492. Szczeklik A, Gryglewski RJ, Olszewski E, Dembinska-Kiec A, Czerniawska-Mysik G. Aspirin-sensitive asthma: the effect of aspirin on the release of prostaglandins from nasal polyps. Pharmacol Res Commun. 1977 May;9(5):415-25.
1493. Kowalski ML, Pawliczak R, Wozniak J, Siuda K, Poniatowska M, Iwaszkiewicz J, et al. Differential metabolism of arachidonic acid in nasal polyp epithelial cells cultured from aspirin-sensitive and aspirin-tolerant patients. American journal of respiratory and critical care medicine. 2000 Feb;161(2 Pt 1):391-8.
1494. Picado C, Bioque G, Roca-Ferrer J, Pujols L, Mullol J, Benitez P, et al. Nuclear factor-kappaB activity is down-regulated in nasal polyps from aspirin-sensitive asthmatics. Allergy. 2003 Feb;58(2):122-6.
1495. Pujols L, Mullol J, Alobid I, Roca-Ferrer J, Xaubet A, Picado C. Dynamics of COX-2 in nasal mucosa and nasal polyps from aspirin-tolerant and aspirin-intolerant patients with asthma. Journal of Allergy & Clinical Immunology. 2004;114(4):814-9.
1496. Yoshimura T, Yoshikawa M, Otori N, Haruna S, Moriyama H. Correlation between the prostaglandin D(2)/E(2) ratio in nasal polyps and the recalcitrant pathophysiology of chronic rhinosinusitis associated with bronchial asthma. Allergol Int. 2008 Dec;57(4):429-36.
1497. Ying S, Meng Q, Scadding G, Parikh A, Corrigan CJ, Lee TH. Aspirin-sensitive rhinosinusitis is associated with reduced E-prostanoid 2 receptor expression on nasal mucosal inflammatory cells. Journal of Allergy & Clinical Immunology. 2006;117(2):312-8.
1498. Yamashita T, Tsuji H, Maeda N, Tomoda K, Kumazawa T. Etiology of nasal polyps associated with aspirin-sensitive asthma. Rhinol Suppl. 1989;8:15-24.
1499. Jung TT, Juhn SK, Hwang D, Stewart R. Prostaglandins, leukotrienes, and other arachidonic acid metabolites in nasal polyps and nasal mucosa. The Laryngoscope. 1987 Feb;97(2):184-9.
1500. Perez-Novo C, Watelet JB, Claeys C, van Cauwenberge P, Bachert C. Prostaglandin, leukotriene, and lipoxin balance in chronic rhinosinusitis with and without nasal polyposis. The Journal of allergy and clinical immunology. 2005;115(6):1189-96.
1501. Owens JM, Shroyer KR, Kingdom TT. Expression of cyclooxygenase and lipoxygenase enzymes in nasal polyps of aspirin-sensitive and aspirin-tolerant patients. Archives of Otolaryngology -- Head & Neck Surgery. 2006;132(6):579-87.
1502. Adamjee J, Suh HJ, Park HS, Choi JH, Penrose JF, Lam BK, et al. Expression of 5-lipoxygenase and cyclooxygenase pathway enzymes in nasal polyps of patients with aspirin-intolerant asthma. Journal of Pathology. 2006;209(3):392-9.
1503. Corrigan C, Mallett K, Ying S, Roberts D, Parikh A, Scadding G, et al. Expression of the cysteinyl leukotriene receptors cysLT<inf>1</inf> and cysLT<inf>2</inf> in aspirin-sensitive and aspirin-tolerant chronic rhinosinusitis. Journal of Allergy & Clinical Immunology. 2005;115(2):316-22.
1504. Kim JE, Kountakis SE. The prevalence of Samter's triad in patients undergoing functional endoscopic sinus surgery. Ear, nose, & throat journal. 2007 Jul;86(7):396-9.
1505. Lumry WR, Curd JG, Zeiger RS, Pleskow WW, Stevenson DD. Aspirin-sensitive rhinosinusitis: the clinical syndrome and effects of aspirin administration. The Journal of allergy and clinical immunology. 1983 Jun;71(6):580-7.
1506. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczynska M, Picado C, Scadding G, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. Allergy. 2007 Oct;62(10):1111-8.
1507. McDonald JR, Mathison DA, Stevenson DD. Aspirin intolerance in asthma.

Detection by oral challenge. The Journal of allergy and clinical immunology. 1972 Oct;50(4):198-207.

1508. Stevenson DD. Approach to the patient with a history of adverse reactions to aspirin or NSAIDs: diagnosis and treatment. Allergy and asthma proceedings : the official journal of regional and state allergy societies. 2000 Jan-Feb;21(1):25-31.
1509. Bianco. Aspirin induced tolerance in aspirin asthma detectected by a new challenge test IRCS J Med Sci. 1977;5:129.
1510. Dahlen B, Zetterstrom O. Comparison of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1990 May;3(5):527-34.
1511. Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A. Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2000 May;15(5):863-9.
1512. Milewski M, Mastalerz L, Nizankowska E, Szczeklik A. Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. The Journal of allergy and clinical immunology. 1998 May;101(5):581-6.
1513. Casadevall J, Ventura PJ, Mullol J, Picado C. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. Thorax. 2000 Nov;55(11):921-4.
1514. Kowalski ML, Makowska J. Use of nonsteroidal anti-inflammatory drugs in patients with aspirin hypersensitivity : safety of cyclo-oxygenase-2 inhibitors. Treatments in respiratory medicine. 2006;5(6):399-406.
1515. Ragab S, Parikh A, Darby YC, Scadding GK. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2001 Sep;31(9):1385-91.
1516. Dahlen B. The Swedish-Polish treatment study with the 5-lipoxygenase inhibitor Zileuton in aspirin-intolerant asthmatics. J Resp Crit Care Med. 1995;151(A):376-0.
1517. McFadden EA, Woodson BT, Fink JN, Toohill RJ. Surgical treatment of aspirin triad sinusitis. American journal of rhinology. 1997 Jul-Aug;11(4):263-70.
1518. Awad OG, Fasano MB, Lee JH, Graham SM. Asthma outcomes after endoscopic sinus surgery in aspirin-tolerant versus aspirin-induced asthmatic patients. American journal of rhinology. 2008 Mar-Apr;22(2):197-203.
1519. Awad OG, Lee JH, Fasano MB, Graham SM. Sinonasal outcomes after endoscopic sinus surgery in asthmatic patients with nasal polyps: a difference between aspirin-tolerant and aspirin-induced asthma? The Laryngoscope. 2008 Jul;118(7):1282-6.
1520. Katotomichelakis M, Riga M, Davris S, Tripsianis G, Simopoulou M, Nikolettos N, et al. Allergic rhinitis and aspirin-exacerbated respiratory disease as predictors of the olfactory outcome after endoscopic sinus surgery. American journal of rhinology & allergy. 2009 May-Jun;23(3):348-53.
1521. Mendelsohn D, Jeremic G, Wright ED, Rotenberg BW. Revision rates after endoscopic sinus surgery: a recurrence analysis. The Annals of otology, rhinology, and laryngology. 2011 Mar;120(3):162-6.
1522. Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS. Aspirin desensitization in aspirin-sensitive asthmatic patients: clinical manifestations and characterization of the refractory period. The Journal of allergy and clinical immunology. 1982 Jan;69(1 Pt 1):11-9.
1523. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. The Journal of allergy and clinical immunology. 2003 Jan;111(1):180-6.
1524. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. The Journal of allergy and clinical immunology. 1996 Oct;98(4):751-8.
1525. Lee RU, Stevenson DD. Aspirin-exacerbated respiratory disease: evaluation and management. Allergy Asthma Immunol Res. 2011 Jan;3(1):3-10.
1526. Forer B, Kivity S, Sade J, Landsberg R. Aspirin desensitization for ASA triad patients--prospective study of the rhinologist`s perspective. Rhinology. 2011 Mar;49(1):95-9.
1527. Scadding GK, Hassab M, Darby YC, Lund VJ, Freedman A. Intranasal lysine aspirin in recurrent nasal polyposis. Clinical otolaryngology and allied sciences. 1995 Dec;20(6):561-3.
1528. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: A controlled trial. The Laryngoscope. 2005;115(8):1385-90.
1529. Ogata N, Darby Y, Scadding G. Intranasal lysine-aspirin administration decreases polyp volume in patients with aspirin-intolerant asthma. J Laryngol Otol. 2007 Dec;121(12):1156-60.
1530. Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2010 Aug;105(2):130-5.
1531. Alqudah M, Graham SM, Ballas ZK. High prevalence of humoral immunodeficiency patients with refractory chronic rhinosinusitis. American journal of rhinology & allergy. 2010 Nov-Dec;24(6):409-12.
1532. Vanlerberghe L, Joniau S, Jorissen M. The prevalence of humoral immunodeficiency in refractory rhinosinusitis: a retrospective analysis. B-ENT. 2006;2(4):161-6.
1533. Carr TF, Koterba AP, Chandra R, Grammer LC, Conley DB, Harris KE, et al. Characterization of specific antibody deficiency in adults with medically

refractory chronic rhinosinusitis. American journal of rhinology & allergy. 2011 Jul-Aug;25(4):241-4.

1534. Urschel S, Kayikci L, Wintergerst U, Notheis G, Jansson A, Belohradsky BH. Common variable immunodeficiency disorders in children: delayed diagnosis despite typical clinical presentation. J Pediatr. 2009 Jun;154(6):888-94.
1535. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol. 2007 May;27(3):308-16.
1536. Joshi AY, Iyer VN, Hagan JB, St Sauver JL, Boyce TG. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clinic proceedings Mayo Clinic. 2009;84(1):16-22.
1537. Aghamohammadi A, Moazzami K, Rezaei N, Karimi A, Movahedi M, Gharagozlou M, et al. ENT manifestations in Iranian patients with primary antibody deficiencies. J Laryngol Otol. 2008 Apr;122(4):409-13.
1538. Cheng YK, Decker PA, O'Byrne MM, Weiler CR. Clinical and laboratory characteristics of 75 patients with specific polysaccharide antibody deficiency syndrome. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2006 Sep;97(3):306-11.
1539. Stiehm ER. The four most common pediatric immunodeficiencies. Journal of immunotoxicology. 2008 Apr;5(2):227-34.
1540. Oksenhendler E, Gerard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2008 May 15;46(10):1547-54.
1541. Kainulainen L, Suonpaa J, Nikoskelainen J, Svedstrom E, Vuorinen T, Meurman O, et al. Bacteria and viruses in maxillary sinuses of patients with primary hypogammaglobulinemia. Archives of otolaryngology--head & neck surgery. 2007 Jun;133(6):597-602.
1542. Bondioni MP, Duse M, Plebani A, Soresina A, Notarangelo LD, Berlucchi M, et al. Pulmonary and sinusal changes in 45 patients with primary immunodeficiencies: computed tomography evaluation. J Comput Assist Tomogr. 2007 Jul-Aug;31(4):620-8.
1543. Rose MA, Schubert R, Schmitt-Grohe S, Reichenbach J, Zielen S. Immunoglobulins and inflammatory cytokines in nasal secretions in humoral immunodeficiencies. The Laryngoscope. 2006 Feb;116(2):239-44.
1544. Khalid AN, Mace JC, Smith TL. Outcomes of sinus surgery in ambulatory patients with immune dysfunction. American journal of rhinology & allergy. 2010 May-Jun;24(3):230-3.
1545. Moon BJ, Han JH, Jang YJ, Lee BJ, Chung YS. Effect of chronic rhinosinusitis on liver transplant patients. American journal of rhinology & allergy. 2009 Sep-Oct;23(5):492-6.
1546. Tomazic P, Neuschitzer A, Koele W, Lang-Loidolt D. Feasibility of routine paranasal sinus CT-scans in preoperative transplant patients. Annals of transplantation : quarterly of the Polish Transplantation Society. 2011 Jun 30;16(2):31-5.
1547. DelGaudio JM, Martinez EJ. Endoscopic sinus surgery in patients with chronic hepatic failure awaiting liver transplant. American journal of rhinology. 2004;18(4):253-8.
1548. Sun HY, Forrest G, Gupta KL, Aguado JM, Lortholary O, Julia MB, et al. Rhino-orbital-cerebral zygomycosis in solid organ transplant recipients. Transplantation. 2010 Jul 15;90(1):85-92.
1549. Thompson AM, Couch M, Zahurak ML, Johnson C, Vogelsang GB. Risk factors for post-stem cell transplant sinusitis. Bone marrow transplantation. 2002 Feb;29(3):257-61.
1550. Ortiz E, Nakamura E, Magalhaes R, Souza CA, Chone CT, Vigorito AC, et al. Prognostic value of sinus CT scans in hematopoietic stem cell transplantation. Brazilian journal of otorhinolaryngology. 2010 Sep-Oct;76(5):618-22.
1551. Moeller CW, Martin J, Welch KC. Sinonasal evaluation preceding hematopoietic transplantation. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 May;144(5):796-801.
1552. Won YW, Yi SY, Jang JH, Kim K, Kim SJ, Kim WS, et al. Retrospective analysis of paranasal sinusitis in patients receiving hematopoietic stem cell transplantation. International journal of hematology. 2011 Mar;93(3):383-8.
1553. Arulrajah S, Symons H, Cahoon EK, Tekes A, Huisman TA, Izbudak I. Relationship between clinical sinusitis symptoms and sinus CT severity in pediatric post bone marrow transplant and immunocompetent patients. European journal of pediatrics. 2012 Feb;171(2):375-81.
1554. Chen CY, Sheng WH, Cheng A, Chen YC, Tsay W, Tang JL, et al. Invasive fungal sinusitis in patients with hematological malignancy: 15 years experience in a single university hospital in Taiwan. BMC infectious diseases. 2011;11:250.
1555. Zappasodi P, Rossi M, Castagnola C, Pagella F, Matti E, Cavanna C, et al. Resolution of invasive fungal sinusitis in immunocompromised patients: neutrophil count is crucial beside a combined medical and surgical approach. Annals of hematology. 2010 Jul;89(7):737-9.
1556. Kontoyiannis DP. Antifungal prophylaxis in hematopoietic stem cell transplant recipients: the unfinished tale of imperfect success. Bone marrow transplantation. 2011 Feb;46(2):165-73.
1557. Lionakis MS, Kontoyiannis DP. Sinus zygomycosis in a patient receiving voriconazole prophylaxis. British journal of haematology. 2005 Apr;129(1):2.
1558. Miziara ID, Araujo Filho BC, De La Cortina RC, Romano FR, Lima AS. Chronic rhinosinusitis in HIV-infected patients: Radiological and clinical evaluation. Revista Brasileira de Otorrinolaringologia. 2005;71(5):604-8.

1559. Belafsky PC, Amedee R, Moore B, Kissinger PJ. The association between sinusitis and survival among individuals infected with the human immunodeficiency virus. American journal of rhinology. 2001 Sep-Oct;15(5):343-5.

1560. Pinheiro Neto CD, Weber R, Araujo-Filho BC, Miziara ID. Rhinosinusitis in HIV-infected children undergoing antiretroviral therapy. Brazilian journal of otorhinolaryngology. 2009 Jan-Feb;75(1):70-5.

1561. Parikh SL, Venkatraman G, DelGaudio JM. Invasive fungal sinusitis: a 15-year review from a single institution. American journal of rhinology. 2004 Mar-Apr;18(2):75-81.

1562. Gillespie MB, Huchton DM, O'Malley BW. Role of middle turbinate biopsy in the diagnosis of fulminant invasive fungal rhinosinusitis. The Laryngoscope. 2000 Nov;110(11):1832-6.

1563. DelGaudio JM. Computed tomographic findings in patients with invasive fungal sinusitis. Archives of otolaryngology--head & neck surgery. 2003;129(2):236-40.

1564. Groppo ER, El-Sayed IH, Aiken AH, Glastonbury CM. Computed tomography and magnetic resonance imaging characteristics of acute invasive fungal sinusitis. Archives of otolaryngology--head & neck surgery. 2011 Oct;137(10):1005-10.

1565. Ruping MJ, Heinz WJ, Kindo AJ, Rickerts V, Lass-Florl C, Beisel C, et al. Forty-one recent cases of invasive zygomycosis from a global clinical registry. The Journal of antimicrobial chemotherapy. 2010 Feb;65(2):296-302.

1566. DelGaudio JM, Clemson LA. An early detection protocol for invasive fungal sinusitis in neutropenic patients successfully reduces extent of disease at presentation and long term morbidity. The Laryngoscope. 2009 Jan;119(1):180-3.

1567. Robey AB, O'Brien EK, Richardson BE, Baker JJ, Poage DP, Leopold DA. The changing face of paranasal sinus fungus balls. The Annals of otology, rhinology, and laryngology. 2009 Jul;118(7):500-5.

1568. Lackner A, Stammberger H, Buzina W, Freudenschuss K, Panzitt T, Schosteritsch S, et al. Fungi: a normal content of human nasal mucus. American journal of rhinology. 2005 Mar-Apr;19(2):125-9.

1569. Ghegan MD, Lee FS, Schlosser RJ. Incidence of skull base and orbital erosion in allergic fungal rhinosinusitis (AFRS) and non-AFRS. Otolaryngology - Head & Neck Surgery. [Review]. 2006;134(4):592-5.

1570. Wise SK, Ghegan MD, Gorham E, Schlosser RJ. Socioeconomic factors in the diagnosis of allergic fungal rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2008 Jan;138(1):38-42.

1571. Pant H, Kette FE, Smith WB, Wormald PJ, Macardle PJ. Fungal-specific humoral response in eosinophilic mucus chronic rhinosinusitis. The Laryngoscope. 2005;115(4):601-6.

1572. Rupa V, Jacob M, Mathews MS, Seshadri MS. A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal sinusitis. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2010 Feb;267(2):233-8.

1573. Kinsella JB, Bradfield JJ, Gourley WK, Calhoun KH, Rassekh CH. Allergic fungal sinusitis. Clinical otolaryngology and allied sciences. 1996 Oct;21(5):389-92.

1574. Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: our experience. Archives of otolaryngology--head & neck surgery. 1998 Oct;124(10):1179-80.

1575. Schubert MS. Allergic fungal sinusitis: pathogenesis and management strategies. Drugs. 2004;64(4):363-74.

1576. Schubert MS, Goetz DW. Evaluation and treatment of allergic fungal sinusitis. II. Treatment and follow-up. The Journal of allergy and clinical immunology. 1998 Sep;102(3):395-402.

1577. Kupferberg SB, Bent JP, 3rd, Kuhn FA. Prognosis for allergic fungal sinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1997 Jul;117(1):35-41.

1578. deShazo RD, Swain RE. Diagnostic criteria for allergic fungal sinusitis. The Journal of allergy and clinical immunology. 1995 Jul;96(1):24-35.

1579. Ikram M, Abbas A, Suhail A, Onali MA, Akhtar S, Iqbal M. Management of allergic fungal sinusitis with postoperative oral and nasal steroids: a controlled study. Ear, nose, & throat journal. 2009;88(4):E8-11.

1580. Greenhaw B, deShazo RD, Arnold J, Wright L. Fungal immunotherapy in patients with allergic fungal sinusitis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2011 Nov;107(5):432-6.

1581. Mabry RL, Marple BF, Folker RJ, Mabry CS. Immunotherapy for allergic fungal sinusitis: three years' experience. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1998 Dec;119(6):648-51.

1582. Folker RJ, Marple BF, Mabry RL, Mabry CS. Treatment of allergic fungal sinusitis: a comparison trial of postoperative immunotherapy with specific fungal antigens. The Laryngoscope. 1998 Nov;108(11 Pt 1):1623-7.

1583. Marple B, Newcomer M, Schwade N, Mabry R. Natural history of allergic fungal rhinosinusitis: a 4- to 10-year follow-up. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002 Nov;127(5):361-6.

1584. Seiberling K, Wormald PJ. The role of itraconazole in recalcitrant fungal sinusitis. American journal of rhinology & allergy. 2009 May-Jun;23(3):303-6.

1585. Sacks PL, Harvey RJ, Rimmer J, Gallagher RM, Sacks R. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. Cochrane database of systematic reviews (Online). 2011(8):CD008263.

1586. Schubert MS. Antileukotriene therapy for allergic fungal sinusitis. The Journal of allergy and clinical immunology. 2001 Sep;108(3):466-7.

1587. Thamboo A, Philpott C, Javer A, Clark A. Single-blind study of manuka honey in allergic fungal rhinosinusitis. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2011 Jun 1;40(3):238-43.

1588. Marple BF, Mabry RL. Allergic fungal sinusitis: learning from our failures. American journal of rhinology. 2000 Jul-Aug;14(4):223-6.

1589. Champagne JP, Antisdel JL, Woodard TD, Kountakis SE. Epidemiologic factors affect surgical outcomes in allergic fungal sinusitis. The Laryngoscope. 2010 Nov;120(11):2322-4.

1590. Marple BF. Allergic fungal rhinosinusitis: current theories and management strategies. The Laryngoscope. 2001 Jun;111(6):1006-19.

1591. Glasier CM, Ascher DP, Williams KD. Incidental paranasal sinus abnormalities on CT of children: clinical correlation. AJNR Am J Neuroradiol. 1986 Sep-Oct;7(5):861-4.

1592. Diament. Prevalence of incidental paranasal sinuses opacification in pediatric patients: a CT study. J Comput Assist Tomogr 1987;11(3):426-31.

1593. Hill M, Bhattacharyya N, Hall TR, Lufkin R, Shapiro NL. Incidental paranasal sinus imaging abnormalities and the normal Lund score in children. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2004 Feb;130(2):171-5.

1594. Bhattacharyya N, Jones DT, Hill M, Shapiro NL. The diagnostic accuracy of computed tomography in pediatric chronic rhinosinusitis. Archives of Otolaryngology -- Head & Neck Surgery. 2004;130(9):1029-32.

1595. Rachelefsky. Diseases of paranasal sinuses in children. In Bierman W, Pearlman D (eds): Management of Upper Respiratory Tract Disease. Philadelphia, WB Saunders. 1980.

1596. Van der Veken P, Clement PA, Buisseret T, Desprechins B, Kaufman L, Derde MP. [CAT-scan study of the prevalence of sinus disorders and anatomical variations in 196 children]. Acta Otorhinolaryngol Belg. 1989;43(1):51-8.

1597. Nguyen KL, Corbett ML, Garcia DP, Eberly SM, Massey EN, Le HT, et al. Chronic sinusitis among pediatric patients with chronic respiratory complaints. The Journal of allergy and clinical immunology. 1993 Dec;92(6):824-30.

1598. Bagatsch. Morbidates analyse der unspezifisch-infektbedingten acute Erkrankungen der Respirationtraktes und der Mittelohrräume des Kindesalterns in einem Ballungsgebiet mit modernen Wohnbedingungen. HNO Praxis. 1980;5:1-8.

1599. Van Buchem F. Maxillary sinusitis in children. Clin Otolaryngol 1992;17(1):49-53.

1600. Celedon JC, Litonjua AA, Weiss ST, Gold DR. Day care attendance in the first year of life and illnesses of the upper and lower respiratory tract in children with a familial history of atopy. Pediatrics. 1999 Sep;104(3 Pt 1):495-500.

1601. Cunningham JM, Chiu EJ, Landgraf JM, Gliklich RE. The health impact of chronic recurrent rhinosinusitis in children. Archives of otolaryngology--head & neck surgery. 2000 Nov;126(11):1363-8.

1602. Kay DJ, Rosenfeld RM. Quality of life for children with persistent sinonasal symptoms. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2003 Jan;128(1):17-26.

1603. Terrell AM, Ramadan HH. Correlation between SN-5 and computed tomography in children with chronic rhinosinusitis. The Laryngoscope. 2009 Jul;119(7):1394-8.

1604. Rudnick EF, Mitchell RB. Long-term improvements in quality-of-life after surgical therapy for pediatric sinonasal disease. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2007 Dec;137(6):873-7.

1605. Sivasli E, Sirikci A, Bayazyt YA, Gumusburun E, Erbagci H, Bayram M, et al. Anatomic variations of the paranasal sinus area in pediatric patients with chronic sinusitis. Surg Radiol Anat. 2003 Feb;24(6):400-5.

1606. Al-Qudah M. The relationship between anatomical variations of the sino-nasal region and chronic sinusitis extension in children. Int J Pediatr Otorhinolaryngol. 2008 Jun;72(6):817-21.

1607. Muntz HR, Lusk RP. Bacteriology of the ethmoid bullae in children with chronic sinusitis. Archives of otolaryngology--head & neck surgery. 1991 Feb;117(2):179-81.

1608. Brook I. Bacteriologic features of chronic sinusitis in children. JAMA. 1981 Aug 28;246(9):967-9.

1609. Hsin CH, Su MC, Tsao CH, Chuang CY, Liu CM. Bacteriology and antimicrobial susceptibility of pediatric chronic rhinosinusitis: a 6-year result of maxillary sinus punctures. Am J Otolaryngol. 2010 May-Jun;31(3):145-9.

1610. McNeil JC, Hulten KG, Mason EO, Jr., Kaplan SL. Serotype 19A is the most common Streptococcus pneumoniae isolate in children with chronic sinusitis. Pediatr Infect Dis J. 2009 Sep;28(9):766-8.

1611. Zuliani G, Carlisle M, Duberstein A, Haupert M, Syamal M, Berk R, et al. Biofilm density in the pediatric nasopharynx: recurrent acute otitis media versus obstructive sleep apnea. The Annals of otology, rhinology, and laryngology. 2009 Jul;118(7):519-24.

1612. Zuliani G, Carron M, Gurrola J, Coleman C, Haupert M, Berk R, et al. Identification of adenoid biofilms in chronic rhinosinusitis. International Journal of Pediatric Otorhinolaryngology. 2006;70(9):1613-7.

1613. Elwany S, El-Dine AN, El-Medany A, Omran A, Mandour Z, El-Salam AA. Relationship between bacteriology of the adenoid core and middle meatus in children with sinusitis. J Laryngol Otol. 2011 Mar;125(3):279-81.

1614. Shin KS, Cho SH, Kim KR, Tae K, Lee SH, Park CW, et al. The role of adenoids in pediatric rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2008 Nov;72(11):1643-50.

1615. Bercin AS, Ural A, Kutluhan A, Yurttas V. Relationship between sinusitis and adenoid size in pediatric age group.

The Annals of otology, rhinology, and laryngology. 2007 Jul;116(7):550-3.

1616. Eun YG, Park DC, Kim SG, Kim MG, Yeo SG. Immunoglobulins and transcription factors in adenoids of children with otitis media with effusion and chronic rhinosinusitis. Int J Pediatr Otorhinolaryngol. 2009 Oct;73(10):1412-6.
1617. Shin SY, Choi GS, Park HS, Lee KH, Kim SW, Cho JS. Immunological investigation in the adenoid tissues from children with chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009 Jul;141(1):91-6.
1618. Baroody F. Eosinophilia in chronic childhood sinusitis. Archives of otolaryngology--head & neck surgery. 1991(117):179-81.
1619. Driscoll PV, Naclerio RM, Baroody FM. CD4+ lymphocytes are increased in the sinus mucosa of children with chronic sinusitis. Archives of otolaryngology--head & neck surgery. 1996 Oct;122(10):1071-6.
1620. Chan KH, Abzug MJ, Coffinet L, Simoes EAF, Cool C, Liu AH. Chronic rhinosinusitis in young children differs from adults: A histopathology study. Journal of Pediatrics. 2004;144(2):206-12.
1621. Coffinet L, Chan KH, Abzug MJ, Simoes EA, Cool C, Liu AH. Immunopathology of chronic rhinosinusitis in young children. J Pediatr. 2009 May;154(5):754-8.
1622. Berger G, Kogan T, Paker M, Berger-Achituv S, Ebner Y. Pediatric chronic rhinosinusitis histopathology: differences and similarities with the adult form. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Jan;144(1):85-90.
1623. Ramadan HH, Fornelli R, Ortiz AO, Rodman S. Correlation of allergy and severity of sinus disease. American journal of rhinology. 1999 Sep-Oct;13(5):345-7.
1624. Tantimongkolsuk C, Pornrattanarungsee S, Chiewvit P, Visitsunthorn N, Ungkanont K, Vichyanond P. Pediatric sinusitis: Symptom profiles with associated atopic conditions. Journal of the Medical Association of Thailand. 2005;88(SUPPL. 8):S149-S55.
1625. Iwens P, Clement PA. Sinusitis in allergic patients. Rhinology. 1994 Jun;32(2):65-7.
1626. Leo G, Piacentini E, Incorvaia C, Consonni D, Frati F. Chronic rhinosinusitis and allergy. Pediatr Allergy Immunol. 2007 Nov;18 Suppl 18:19-21.
1627. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinus disease with associated reactive airway disease in children. Pediatrics. 1984 Apr;73(4):526-9.
1628. Tosca MA, Cosentino C, Pallestrini E, Caligo G, Milanese M, Ciprandi G. Improvement of clinical and immunopathologic parameters in asthmatic children treated for concomitant chronic rhinosinusitis. Annals of Allergy, Asthma, & Immunology. 2003;91(1):71-8.
1629. Phipps CD, Wood WE, Gibson WS, Cochran WJ. Gastroesophageal reflux contributing to chronic sinus disease in children: a prospective analysis. Archives of otolaryngology--head & neck surgery. 2000 Jul;126(7):831-6.
1630. El-Serag HB, Gilger M, Kuebeler M, Rabeneck L. Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects. Gastroenterology. 2001 Dec;121(6):1294-9.
1631. Bothwell MR, Parsons DS, Talbot A, Barbero GJ, Wilder B. Outcome of reflux therapy on pediatric chronic sinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1999 Sep;121(3):255-62.
1632. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics. 1991 Mar;87(3):311-6.
1633. Sethi DS, Winkelstein JA, Lederman H, Loury MC. Immunologic defects in patients with chronic recurrent sinusitis: diagnosis and management. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1995 Feb;112(2):242-7.
1634. Ramesh S, Brodsky L, Afshani E, Pizzuto M, Ishman M, Helm J, et al. Open trial of intravenous immune serum globulin for chronic sinusitis in children. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 1997 Aug;79(2):119-24.
1635. Sleigh MA. Primary ciliary dyskinesia. Lancet. 1981 Aug 29;2(8244):476.
1636. Rollin M, Seymour K, Hariri M, Harcourt J. Rhinosinusitis, symptomatology & absence of polyposis in children with primary ciliary dyskinesia. Rhinology. 2009 Mar;47(1):75-8.
1637. Gysin C, Alothman GA, Papsin BC. Sinonasal disease in cystic fibrosis: clinical characteristics, diagnosis, and management. Pediatr Pulmonol. 2000 Dec;30(6):481-9.
1638. Manning SC, Merkel M, Kriesel K, Vuitch F, Marple B. Computed tomography and magnetic resonance diagnosis of allergic fungal sinusitis. The Laryngoscope. 1997 Feb;107(2):170-6.
1639. Orobello PW, Jr., Park RI, Belcher LJ, Eggleston P, Lederman HM, Banks JR, et al. Microbiology of chronic sinusitis in children. Archives of otolaryngology--head & neck surgery. 1991 Sep;117(9):980-3.
1640. Hsin CH, Tsao CH, Su MC, Chou MC, Liu CM. Comparison of maxillary sinus puncture with endoscopic middle meatal culture in pediatric rhinosinusitis. American journal of rhinology. 2008 May-Jun;22(3):280-4.
1641. Park AH, Muntz HR, Smith ME, Afify Z, Pysher T, Pavia A. Pediatric invasive fungal rhinosinusitis in immunocompromised children with cancer. Otolaryngology - Head & Neck Surgery. 2005;133(3):411-6.
1642. Krzeski A, Kapiszewska-Dzedzej D, Gorski NP, Jakubczyk I. Cystic fibrosis in rhinologic practice. American journal of rhinology. 2002 May-Jun;16(3):155-60.
1643. Mullol J, Xaubet A, Lopez E, Roca-Ferrer J, Picado C. Comparative study of the effects of different glucocorticosteroids on eosinophil survival primed by cultured epithelial cell supernatants obtained from nasal mucosa and nasal polyps. Thorax. [Comparative Study. In Vitro. Research Support, Non-U.S. Gov't]. 1995

Mar;50(3):270-4.

1644. Mullol J, Lopez E, Roca-Ferrer J, Xaubet A, Pujols L, Fernandez-Morata JC, et al. Effects of topical anti-inflammatory drugs on eosinophil survival primed by epithelial cells. Additive effect of glucocorticoids and nedocromil sodium. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1997 Dec;27(12):1432-41.

1645. Mullol J, Xaubet A, Lopez E, Roca-Ferrer J, Carrion T, Rosello-Catafau J, et al. [Eosinophil activation by epithelial cells of the respiratory mucosa. Comparative study of normal mucosa and inflammatory mucosa]. Med Clin (Barc). 1997 May 31;109(1):6-11.

1646. Mullol J, Xaubet A, Gaya A, Roca-Ferrer J, Lopez E, Fernandez JC, et al. Cytokine gene expression and release from epithelial cells. A comparison study between healthy nasal mucosa and nasal polyps. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1995 Jul;25(7):607-15.

1647. Mullol J, Roca-Ferrer J, Xaubet A, Raserra J, Picado C. Inhibition of GM-CSF secretion by topical corticosteroids and nedocromil sodium. A comparison study using nasal polyp epithelial cells. Respiratory medicine. 2000 May;94(5):428-31.

1648. Roca-Ferrer J, Mullol J, Lopez E, Xaubet A, Pujols L, Fernandez JC, et al. Effect of topical anti-inflammatory drugs on epithelial cell-induced eosinophil survival and GM-CSF secretion. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1997 Jul;10(7):1489-95.

1649. Xaubet A, Mullol J, Roca-Ferrer J, Pujols L, Fuentes M, Perez M, et al. Effect of budesonide and nedocromil sodium on IL-6 and IL-8 release from human nasal mucosa and polyp epithelial cells. Respiratory medicine. 2001 May;95(5):408-14.

1650. Leung DY, Bloom JW. Update on glucocorticoid action and resistance. The Journal of allergy and clinical immunology. [Research Support, Non-U.S. Gov't Review]. 2003 Jan;111(1):3-22; quiz 3.

1651. Ito K, Chung KF, Adcock IM. Update on glucocorticoid action and resistance. The Journal of allergy and clinical immunology. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review]. 2006 Mar;117(3):522-43.

1652. Pujols L, Mullol J, Roca-Ferrer J, Torrego A, Xaubet A, Cidlowski JA, et al. Expression of glucocorticoid receptor alpha- and beta-isoforms in human cells and tissues. Am J Physiol Cell Physiol. [Research Support, Non-U.S. Gov't]. 2002 Oct;283(4):C1324-31.

1653. Oakley RH, Sar M, Cidlowski JA. The human glucocorticoid receptor beta isoform. Expression, biochemical properties, and putative function. J Biol Chem. [Research Support, Non-U.S. Gov't]. 1996 Apr 19;271(16):9550-9.

1654. Pujols L, Mullol J, Benitez P, Torrego A, Xaubet A, de Haro J, et al. Expression of the glucocorticoid receptor alpha and beta isoforms in human nasal mucosa and polyp epithelial cells. Respiratory medicine. [Research Support, Non-U.S. Gov't]. 2003 Jan;97(1):90-6.

1655. Hamilos DL, Leung DY, Muro S, Kahn AM, Hamilos SS, Thawley SE, et al. GRbeta expression in nasal polyp inflammatory cells and its relationship to the anti-inflammatory effects of intranasal fluticasone. The Journal of allergy and clinical immunology. [Research Support, Non-U.S. Gov't]. 2001 Jul;108(1):59-68.

1656. Knutsson PU, Bronnegard M, Marcus C, Stierna P. Regulation of glucocorticoid receptor mRNA in nasal mucosa by local administration of fluticasone and budesonide. The Journal of allergy and clinical immunology. [Comparative Study Research Support, Non-U.S. Gov't]. 1996 Feb;97(2):655-61.

1657. Pujols L, Mullol J, Perez M, Roca-Ferrer J, Juan M, Xaubet A, et al. Expression of the human glucocorticoid receptor alpha and beta isoforms in human respiratory epithelial cells and their regulation by dexamethasone. Am J Respir Cell Mol Biol. 2001 Jan;24(1):49-57.

1658. Harvey RJ, Goddard JC, Wise SK, Schlosser RJ. Effects of endoscopic sinus surgery and delivery device on cadaver sinus irrigation. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2008 Jul;139(1):137-42.

1659. Snidvongs K, Chaowanapanja P, Aeumjaturapat S, Chusakul S, Praweswararat P. Does nasal irrigation enter paranasal sinuses in chronic rhinosinusitis? American journal of rhinology. 2008 Sep-Oct;22(5):483-6.

1660. Hyo N, Takano H, Hyo Y. Particle deposition efficiency of therapeutic aerosols in the human maxillary sinus. Rhinology. 1989 Mar;27(1):17-26.

1661. Wormald PJ, Cain T, Oates L, Hawke L, Wong I. A comparative study of three methods of nasal irrigation. The Laryngoscope. 2004;114(12):2224-7.

1662. Olson DE, Rasgon BM, Hilsinger RL, Jr. Radiographic comparison of three methods for nasal saline irrigation. The Laryngoscope. 2002 Aug;112(8 Pt 1):1394-8.

1663. Grobler A, Weitzel EK, Buele A, Jardeleza C, Cheong YC, Field J, et al. Pre- and postoperative sinus penetration of nasal irrigation. The Laryngoscope. 2008 Nov;118(11):2078-81.

1664. Valentine R, Athanasiadis T, Thwin M, Singhal D, Weitzel EK, Wormald PJ. A prospective controlled trial of pulsed nasal nebulizer in maximally dissected cadavers. American journal of rhinology. 2008 Jul-Aug;22(4):390-4.

1665. Merkus P, Ebbens FA, Muller B, Fokkens WJ. The 'best method' of topical nasal drug delivery: comparison of seven techniques. Rhinology. 2006 Jun;44(2):102-7.

1666. Beule A, Athanasiadis T, Athanasiadis E, Field J, Wormald PJ. Efficacy of different techniques of sinonasal irrigation after modified Lothrop procedure. American journal of rhinology & allergy. [Comparative Study]. 2009 Jan-Feb;23(1):85-90.

1667. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, Kennedy DW, et al. Adult chronic rhinosinusitis:

definitions, diagnosis, epidemiology, and pathophysiology. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. [Research Support, Non-U.S. Gov't Review]. 2003 Sep;129(3 Suppl):S1-32.

1668. Dijkstra MD, Ebbens FA, Poublon RM, Fokkens WJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2004 Sep;34(9):1395-400.
1669. Furukido K, Takeno S, Ueda T, Yajin K. Cytokine profile in paranasal effusions in patients with chronic sinusitis using the YAMIK sinus catheter with and without betamethasone. European Archives of Oto-Rhino-Laryngology. 2005;262(1):50-4.
1670. Lavigne F, Cameron L, Renzi PM, Planet JF, Christodoulopoulos P, Lamkioued B, et al. Intrasinus administration of topical budesonide to allergic patients with chronic rhinosinusitis following surgery. The Laryngoscope. 2002 May;112(5):858-64.
1671. Lund VJ, Black JH, Szabo LZ, Schrewelius C, Akerlund A. Efficacy and tolerability of budesonide aqueous nasal spray in chronic rhinosinusitis patients. Rhinology. 2004 Jun;42(2):57-62.
1672. Parikh A, Scadding GK, Darby Y, Baker RC. Topical corticosteroids in chronic rhinosinusitis: a randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray. Rhinology. 2001 Jun;39(2):75-9.
1673. Sykes DA, Wilson R, Chan KL, Mackay IS, Cole PJ. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis. A controlled study. Lancet. 1986 Aug 16;2(8503):359-60.
1674. Jorissen M, Bachert C. Effect of corticosteroids on wound healing after endoscopic sinus surgery. Rhinology. 2009 Sep;47(3):280-6.
1675. Giger R, Pasche P, Cheseaux C, Cantini L, Rossetti A, Landis BN, et al. Comparison of once- versus twice-daily use of beclomethasone dipropionate aqueous nasal spray in the treatment of allergic and non-allergic chronic rhinosinusitis. European Archives of Oto-Rhino-Laryngology. 2003;260(3):135-40.
1676. Cuenant G, Stipon JP, Plante-Longchamp G, Baudoin C, Guerrier Y. Efficacy of endonasal neomycin-tixocortol pivalate irrigation in the treatment of chronic allergic and bacterial sinusitis. ORL J Otorhinolaryngol Relat Spec. 1986;48(4):226-32.
1677. Dijkstra MD, Ebbens FA, Poublon RML, Fokkens WJ. Fluticasone propionate aqueous nasal spray does not influence the recurrence rate of chronic rhinosinusitis and nasal polyps 1 year after functional endoscopic sinus surgery. Clinical & Experimental Allergy. 2004;34(9):1395-400.
1678. Lal D, Hwang PH. Oral corticosteroid therapy in chronic rhinosinusitis without polyposis: a systematic review. International forum of allergy & rhinology. 2011;1(2):136-43.
1679. Subramanian HN, Schechtman KB, Hamilos DL. A retrospective analysis of treatment outcomes and time to relapse after intensive medical treatment for chronic sinusitis. American journal of rhinology. 2002 Nov-Dec;16(6):303-12.
1680. Lal D, Scianna JM, Stankiewicz JA. Efficacy of targeted medical therapy in chronic rhinosinusitis, and predictors of failure. American journal of rhinology & allergy. [Comparative Study]. 2009 Jul-Aug;23(4):396-400.
1681. Namyslowski G, Misiolek M, Czecior E, Malafiej E, Orecka B, Namyslowski P, et al. Comparison of the efficacy and tolerability of amoxycillin/clavulanic acid 875 mg b.i.d. with cefuroxime 500 mg b.i.d. in the treatment of chronic and acute exacerbation of chronic sinusitis in adults. J Chemother. 2002 Oct;14(5):508-17.
1682. Legent F, Bordure P, Beauvillain C, Berche P. A double-blind comparison of ciprofloxacin and amoxycillin/clavulanic acid in the treatment of chronic sinusitis. Chemotherapy. 1994;40 Suppl 1:8-15.
1683. Huck W, Reed BD, Nielsen RW, Ferguson RT, Gray DW, Lund GK, et al. Cefaclor vs amoxicillin in the treatment of acute, recurrent, and chronic sinusitis. Arch Fam Med. 1993 May;2(5):497-503.
1684. Kudoh S, Kimura H, Uetake T, et al. Clinical effect of low-dose, long-term macrolide antibiotic chemotherapy on diffuse panbronchiolitis. Jpn J Thorac Dis. 1984;22:254-54.
1685. Nagai H, Shishido H, Yoneda R, Yamaguchi E, Tamura A, Kurashima A. Long-term low-dose administration of erythromycin to patients with diffuse panbronchiolitis. Respiration. 1991;58(3-4):145-9.
1686. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. American journal of respiratory and critical care medicine. 1998 Jun;157(6 Pt 1):1829-32.
1687. Equi AC, Davies JC, Painter H, Hyde S, Bush A, Geddes DM, et al. Exploring the mechanisms of macrolides in cystic fibrosis. Respiratory medicine. 2006 Apr;100(4):687-97.
1688. Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, et al. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA. 2003 Oct 1;290(13):1749-56.
1689. Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. Thorax. 2002 Mar;57(3):212-6.
1690. Black PN, Blasi F, Jenkins CR, Scicchitano R, Mills GD, Rubinfeld AR, et al. Trial of roxithromycin in subjects with asthma and serological evidence of infection with Chlamydia pneumoniae. American journal of respiratory and critical care medicine. 2001;164(4):536-41.
1691. Kostadima E, Tsiodras S, Alexopoulos EI, Kaditis AG, Mavrou I, Georgatou N, et al.

Clarithromycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2004 May;23(5):714-7.

1692. Kraft M, Cassell GH, Pak J, Martin RJ. Mycoplasma pneumoniae and Chlamydia pneumoniae in asthma: effect of clarithromycin. Chest. 2002 Jun;121(6):1782-8.

1693. Shoji T, Yoshida S, Sakamoto H, Hasegawa H, Nakagawa H, Amayasu H. Anti-inflammatory effect of roxithromycin in patients with aspirin-intolerant asthma. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 1999 Jul;29(7):950-6.

1694. Banerjee D, Khair OA, Honeybourne D. The effect of oral clarithromycin on health status and sputum bacteriology in stable COPD. Respiratory medicine. 2005 Feb;99(2):208-15.

1695. Banerjee D, Honeybourne D, Khair OA. The effect of oral clarithromycin on bronchial airway inflammation in moderate-to-severe stable COPD: a randomized controlled trial. Treatments in respiratory medicine. 2004;3(1):59-65.

1696. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. The New England journal of medicine. 2011 Aug 25;365(8):689-98.

1697. Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: a double-blind, placebo-controlled study. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1997 May;10(5):994-9.

1698. Tsang KW, Ho PI, Chan KN, Ip MS, Lam WK, Ho CS, et al. A pilot study of low-dose erythromycin in bronchiectasis. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1999 Feb;13(2):361-4.

1699. Yalcin E, Kiper N, Ozcelik U. Effects of clarithromycin on inflammatory parameters and clinical conditions in chil- dren with bronchiectasis. Journal of Clinical Pharmacy and Therapeutics. 2006;31:49-55.

1700. Nishi K, Mizuguchi M, Tachibana H, Ooka T, Amemiya T, Myou S, et al. [Effect of clarithromycin on symptoms and mucociliary transport in patients with sino-bronchial syndrome]. Nippon Kyobu Shikkan Gakkai Zasshi. 1995;33(12):1392-400.

1701. Scadding GK, Lund VJ, Darby YC. The effect of long-term antibiotic therapy upon ciliary beat frequency in chronic rhinosinusitis. J Laryngol Otol. 1995 Jan;109(1):24-6.

1702. Ichimura K, Shimazaki Y, Ishibashi T, Higo R. Effect of new macrolide roxithromycin upon nasal polyps associated with chronic sinusitis. Auris Nasus Larynx. 1996;23:48-56.

1703. Hashiba M, Baba S. Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. Acta Otolaryngol Suppl (Stockh). 1996;525:73-8.

1704. Suzuki H, Shimomura A, Ikeda K, Oshima T, Takasaka T. Effects of long-term low-dose macrolide administration on neutrophil recruitment and IL-8 in the nasal discharge of chronic sinusitis patients. Tohoku J Exp Med. 1997;182(2):115-24.

1705. Rubin BK, Druce H, Ramirez OE, Palmer R. Effect of clarithromycin on nasal mucus properties in healthy subjects and in patients with purulent rhinitis. American journal of respiratory and critical care medicine. 1997;155(6):2018-23.

1706. Cervin A, Kalm O, Sandkull P, Lindberg S. One-year low-dose erythromycin treatment of persistent chronic sinusitis after sinus surgery: clinical outcome and effects on mucociliary parameters and nasal nitric oxide. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002 May;126(5):481-9.

1707. Piromchai P, Thanaviratananich S, Laopaiboon M. Systemic antibiotics for chronic rhinosinusitis without nasal polyps in adults. Cochrane database of systematic reviews (Online). 2011(5):CD008233.

1708. Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. The Laryngoscope. 2006 Feb;116(2):189-93.

1709. Videler WJ, Badia L, Harvey RJ, Gane S, Georgalas C, van der Meulen FW, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. Allergy. 2011 Sep 2;66(11):1457-68.

1710. Suzuki H, Ikeda K, Honma R, Gotoh S, Oshima T, Furukawa M, et al. Prognostic factors of chronic rhinosinusitis under long-term low-dose macrolide therapy. ORL J Otorhinolaryngol Relat Spec. 2000;62(3):121-7.

1711. Newman LJ, Platts-Mills TA, Phillips CD, Hazen KC, Gross CW. Chronic sinusitis. Relationship of computed tomographic findings to allergy, asthma, and eosinophilia [published erratum appears in JAMA 1994 Sep 21;272(11):852] [see comments]. Jama. 1994;271(5):363-7.

1712. Videler WJ, van Hee SM, Reinartz C, Georgalas FW, Meulen, KFokkens WD. Long-term, low-dose antibiotics in recalcitrant chronic rhinosinusitis: A retrospective analysis. Rhinology. 2012;50(1):45-55.

1713. Haruna S, Shimada C, Ozawa M, Fukami S, Moriyama H. A study of poor responders for long-term, low-dose macrolide administration for chronic sinusitis. Rhinology. 2009 Mar;47(1):66-71.

1714. Maruyama S, Yoshioka H, Fujita K, Takimoto M, Satake Y. Sensitivity of group A streptococci to antibiotics. Prevalence of resistance to erythromycin in Japan. American journal of diseases of children (1960). 1979 Nov;133(11):1143-5.

1715. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci

in Finland. Finnish Study Group for Antimicrobial Resistance. The New England journal of medicine. 1997 Aug 14;337(7):441-6.

1716. Esther CR, Jr., Esserman DA, Gilligan P, Kerr A, Noone PG. Chronic Mycobacterium abscessus infection and lung function decline in cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2010 Mar;9(2):117-23.
1717. Roux AL, Catherinot E, Ripoll F, Soismier N, Macheras E, Ravilly S, et al. Multicenter study of prevalence of nontuberculous mycobacteria in patients with cystic fibrosis in france. J Clin Microbiol. 2009 Dec;47(12):4124-8.
1718. Renna M, Schaffner C, Brown K, Shang S, Tamayo MH, Hegyi K, et al. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. J Clin Invest. 2011 Sep 1;121(9):3554-63.
1719. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet. 2007 Feb 10;369(9560):482-90.
1720. Kamijyo A, Matsuzaki Z, Kikushima K, Ogino J, Nozawa I, Matsuoka T, et al. Fosfomycin nebulizer therapy to chronic sinusitis. Auris Nasus Larynx. 2001 Aug;28(3):227-32.
1721. Kobayashi T, Baba S. Topical use of antibiotics for paranasal sinusitis. Rhinol Suppl. 1992;14:77-81.
1722. Scheinberg PA, Otsuji A. Nebulized antibiotics for the treatment of acute exacerbations of chronic rhinosinusitis. Ear, nose, & throat journal. 2002 Sep;81(9):648-52.
1723. Vaughan WC, Carvalho G. Use of nebulized antibiotics for acute infections in chronic sinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002 Dec;127(6):558-68.
1724. Leonard DW, Bolger WE. Topical antibiotic therapy for recalcitrant sinusitis. The Laryngoscope. 1999 Apr;109(4):668-70.
1725. Solares CA, Batra PS, Hall GS, Citardi MJ. Treatment of chronic rhinosinusitis exacerbations due to methicillin-resistant Staphylococcus aureus with mupirocin irrigations. Am J Otolaryngol. 2006 May-Jun;27(3):161-5.
1726. Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2001 Sep;125(3):265-9.
1727. Videler WJ, van Drunen CM, Reitsma JB, Fokkens WJ. Nebulized bacitracin/colimycin: a treatment option in recalcitrant chronic rhinosinusitis with Staphylococcus aureus? A double-blind, randomized, placebo-controlled, cross-over pilot study. Rhinology. 2008 Jun;46(2):92-8.
1728. Chiu AG, Antunes MB, Palmer JN, Cohen NA. Evaluation of the in vivo efficacy of topical tobramycin against Pseudomonas sinonasal biofilms. The Journal of antimicrobial chemotherapy. 2007 Jun;59(6):1130-4.
1729. Spisek R, Brazova J, Rozkova D, Zapletalova K, Sediva A, Bartunkova J. Maturation of dendritic cells by bacterial immunomodulators. Vaccine. 2004 Jul 29;22(21-22):2761-8.
1730. Bowman LM, Holt PG. Selective enhancement of systemic Th1 immunity in immunologically immature rats with an orally administered bacterial extract. Infect Immun. 2001 Jun;69(6):3719-27.
1731. Heintz B, Schlenter WW, Kirsten R, Nelson K. Clinical efficacy of Broncho-Vaxom in adult patients with chronic purulent sinusitis--a multi-centric, placebo-controlled, double-blind study. Int J Clin Pharmacol Ther Toxicol. 1989 Nov;27(11):530-4.
1732. Rotenberg BW, Bertens KA. Use of complementary and alternative medical therapies for chronic rhinosinusitis: a canadian perspective. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2010 Oct;39(5):586-93.
1733. Yakirevitch A, Bedrin L, Migirov L, Wolf M, Talmi YP. Use of alternative medicine in Israeli chronic rhinosinusitis patients. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2009 Aug;38(4):517-20.
1734. Newton JR, Santangeli L, Shakeel M, Ram B. Use of complementary and alternative medicine by patients attending a rhinology outpatient clinic. American journal of rhinology & allergy. 2009 Jan-Feb;23(1):59-63.
1735. Guo R, Canter PH, Ernst E. Herbal medicines for the treatment of rhinosinusitis: a systematic review. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2006 Oct;135(4):496-506.
1736. Harvey R, Hannan SA, Badia L, Scadding G. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane database of systematic reviews (Online). 2007(3):CD006394.
1737. Pynnonen MA, Mukerji SS, Kim HM, Adams ME, Terrell JE. Nasal saline for chronic sinonasal symptoms: a randomized controlled trial. Archives of otolaryngology--head & neck surgery. 2007 Nov;133(11):1115-20.
1738. Freeman SR, Sivayoham ES, Jepson K, de Carpentier J. A preliminary randomised controlled trial evaluating the efficacy of saline douching following endoscopic sinus surgery. Clin Otolaryngol. 2008 Oct;33(5):462-5.
1739. Lee JM, Nayak JV, Doghramji LL, Welch KC, Chiu AG. Assessing the risk of irrigation bottle and fluid contamination after endoscopic sinus surgery. American journal of rhinology & allergy. 2010 May-Jun;24(3):197-9.
1740. Welch KC, Cohen MB, Doghramji LL, Cohen NA, Chandra RK, Palmer JN, et al.

Clinical correlation between irrigation bottle contamination and clinical outcomes in post-functional endoscopic sinus surgery patients. American journal of rhinology & allergy. 2009 Jul-Aug;23(4):401-4.

1741. Williams GB, Ross LL, Chandra RK. Are bulb syringe irrigators a potential source of bacterial contamination in chronic rhinosinusitis? American journal of rhinology. 2008 Jul-Aug;22(4):399-401.
1742. Raza T, Elsherif HS, Zulianello L, Plouin-Gaudon I, Landis BN, Lacroix JS. Nasal lavage with sodium hypochlorite solution in Staphylococcus aureus persistent rhinosinusitis. Rhinology. 2008 Mar;46(1):15-22.
1743. Weissman JD, Fernandez F, Hwang PH. Xylitol nasal irrigation in the management of chronic rhinosinusitis: a pilot study. The Laryngoscope. 2011 Nov;121(11):2468-72.
1744. Hai PV, Lidstone C, Wallwork B. The effect of endoscopic sinus surgery on bacterial biofilms in chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2010 Mar;142(3 Suppl 1):S27-32.
1745. Le T, Psaltis A, Tan LW, Wormald PJ. The efficacy of topical antibiofilm agents in a sheep model of rhinosinusitis. American journal of rhinology. 2008 Nov-Dec;22(6):560-7.
1746. Chiu AG, Palmer JN, Woodworth BA, Doghramji L, Cohen MB, Prince A, et al. Baby shampoo nasal irrigations for the symptomatic post-functional endoscopic sinus surgery patient. American journal of rhinology. 2008 Jan-Feb;22(1):34-7.
1747. Mukerji SS, Pynnonen MA, Kim HM, Singer A, Tabor M, Terrell JE. Probiotics as adjunctive treatment for chronic rhinosinusitis: a randomized controlled trial. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2009 Feb;140(2):202-8.
1748. Pincus RL, Kim HH, Silvers S, Gold S. A study of the link between gastric reflux and chronic sinusitis in adults. Ear, nose, & throat journal. 2006 Mar;85(3):174-8.
1749. Wong IW, Omari TI, Myers JC, Rees G, Nair SB, Jamieson GG, et al. Nasopharyngeal pH monitoring in chronic sinusitis patients using a novel four channel probe. The Laryngoscope. 2004 Sep;114(9):1582-5.
1750. Jecker P, Orloff LA, Wohlfeil M, Mann WJ. Gastroesophageal reflux disease (GERD), extraesophageal reflux (EER) and recurrent chronic rhinosinusitis. European Archives of Oto-Rhino-Laryngology. 2006;263(7):664-7.
1751. DiBaise JK, Olusola BF, Huerter JV, Quigley EM. Role of GERD in chronic resistant sinusitis: a prospective, open label, pilot trial. Am J Gastroenterol. 2002 Apr;97(4):843-50.
1752. Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. Pediatrics. 2006 May;117(5):e817-20.
1753. Laheij RJ, Van Ijzendoorn MC, Janssen MJ, Jansen JB. Gastric acid-suppressive therapy and community-acquired respiratory infections. Aliment Pharmacol Ther. 2003 Oct 15;18(8):847-51.
1754. Smith GCS, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ (Clinical research ed). [10.1136/bmj.327.7429.1459]. 2003;327(7429):1459-61.
1755. Khalil H, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. In: The Cochrane C, Khalil H, editors. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006.
1756. Hartog B, van Benthem PP, Prins LC, Hordijk GJ. Efficacy of sinus irrigation versus sinus irrigation followed by functional endoscopic sinus surgery. The Annals of otology, rhinology, and laryngology. 1997;106(9):759-66.
1757. Hopkins C, Browne JP, Slack R, Lund V, Topham J, Reeves B, et al. The national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. Clin Otolaryngol. 2006 Oct;31(5):390-8.
1758. Hopkins C, Slack R, Lund V, Brown P, Copley L, Browne J. Long-term outcomes from the English national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis. The Laryngoscope. 2009 Dec;119(12):2459-65.
1759. Chester AC, Antisdel JL, Sindwani R. Symptom-specific outcomes of endoscopic sinus surgery: a systematic review. Otolaryngol Head Neck Surg. 2009;140(5):633-9.
1760. Croy I, Hummel T, Pade A, Pade J. Quality of life following nasal surgery. The Laryngoscope. [10.1002/lary.20824]. 2010;120(4):826-31.
1761. Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. The Laryngoscope. 2005 Dec;115(12):2199-205.
1762. Deal RT, Kountakis SE. Significance of nasal polyps in chronic rhinosinusitis: Symptoms and surgical outcomes. The Laryngoscope. 2004;114(11 I):1932-5.
1763. Javer AR, Genoway KA. Patient quality of life improvements with and without computer assistance in sinus surgery: outcomes study. The Journal of Otolaryngology. 2006;35(6):373-9.
1764. Lund VJ. The results of inferior and middle meatal antrostomy under endoscopic control. Acta Otorhinolaryngol Belg. 1993;47(1):65-71.
1765. Penttilä MA, Rautiainen ME, Pukander JS, Karma PH. Endoscopic versus Caldwell-Luc approach in chronic maxillary sinusitis: comparison of symptoms at one-year follow-up. Rhinology. 1994;32(4):161-5.
1766. Kuehnemund M, Lopatin A, Amedee RG, Mann WJ. Endonasal sinus surgery: extended versus limited approach. American journal of rhinology. 2002;16(4):187-92.
1767. Jankowski R, Pigret D, Decroocq F, Blum A, Gillet P. Comparison of radical (nasalisation) and functional ethmoidectomy in patients with severe sinonasal polyposis. A retrospective

study. Rev Laryngol Otol Rhinol (Bord). 2006;127(3):131-40.

1768. Havas TE, Lowinger DS. Comparison of functional endonasal sinus surgery with and without partial middle turbinate resection. The Annals of otology, rhinology, and laryngology. 2000;109(7):634-40.
1769. Marchioni D, Alicandri-Ciufelli M, Mattioli F, Marchetti A, Jovic G, Massone F, et al. Middle turbinate preservation versus middle turbinate resection in endoscopic surgical treatment of nasal polyposis. Acta Oto-Laryngologica. 2008;128(9):1019-26.
1770. Soler ZM, Hwang PH, Mace J, Smith TL. Outcomes after middle turbinate resection: revisiting a controversial topic. The Laryngoscope. [10.1002/lary.20812]. 2010;120(4):832-7.
1771. Myller J, Dastidar P, Torkkeli T, Rautiainen M, Toppila-Salmi S. Computed tomography findings after endoscopic sinus surgery with preserving or enlarging maxillary sinus ostium surgery. Rhinology. 2011 Oct;49(4):438-44.
1772. Batra PS, Ryan MW, Sindwani R, Marple BF. Balloon catheter technology in rhinology: Reviewing the evidence. The Laryngoscope. [10.1002/lary.21114]. 2011;121(1):226-32.
1773. Tomazic PV, Stammberger H, Koele W, Gerstenberger C. Ethmoid roof CSF-leak following frontal sinus balloon sinuplasty. Rhinology. [10.4193/Rhin09.129]. 2010;48(2):247-50.
1774. Gliklich RE, Metson R. Effect of sinus surgery on quality of life. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1997 Jul;117(1):12-7.
1775. arks SC, Shamsa F. Evaluation of prognostic factors in endoscopic sinus surgery. American journal of rhinology. 1997;11(3):187-91.
1776. Wang P-C, Chu C-C, Liang S-C, Tai C-J. Outcome predictors for endoscopic sinus surgery. Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002;126(2):154-9.
1777. Kim HY, Dhong H-J, Chung SK, Chung Y-J, Kim M-G. Clinical characteristics of chronic rhinosinusitis with asthma. Auris, Nasus, Larynx. [10.1016/j.anl.2006.05.002]. 2006;33(4):403-8.
1778. Ramadan HH. Surgical causes of failure in endoscopic sinus surgery. The Laryngoscope. 1999;109(1):27-9.
1779. McMains KC, Kountakis SE. Revision functional endoscopic sinus surgery: Objective and subjective surgical outcomes. American journal of rhinology. 2005;19(4):344-7.
1780. Cohen NA, Kennedy DW. Revision Endoscopic Sinus Surgery. Otolaryngologic clinics of North America. [Review]. 2006;39(3):417-35.
1781. Mechor B, Javer AR. Revision endoscopic sinus surgery: the St. Paul's Sinus Centre experience. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2008;37(5):676-80.
1782. Videler WJM, van Drunen CM, van der Meulen FW, Fokkens WJ. Radical surgery: effect on quality of life and pain in chronic rhinosinusitis. Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery. [10.1016/j.otohns.2006.08.010]. 2007;136(2):261-7.
1783. King JM, Caldarelli DD, Pigato JB. A review of revision functional endoscopic sinus surgery. The Laryngoscope. [10.1288/00005537-199404000-00002]. 1994;104(4):404-8.
1784. Chu CT, Lebowitz RA, Jacobs JB. An analysis of sites of disease in revision endoscopic sinus surgery. American journal of rhinology. 1997;11(4):287-91.
1785. Bhattacharyya N. Clinical outcomes after revision endoscopic sinus surgery. Archives of otolaryngology--head & neck surgery. [10.1001/archotol.130.8.975]. 2004;130(8):975-8.
1786. Litvack JR, Griest S, James KE, Smith TL. Endoscopic and quality-of-life outcomes after revision endoscopic sinus surgery. The Laryngoscope. [10.1097/MLG.0b013e31814539e8]. 2007;117(12):2233-8.
1787. Schlosser RJ. Surgical salvage for the non-functioning sinus. Otolaryngologic clinics of North America. [10.1016/j.otc.2010.02.015]. 2010;43(3):591-604, ix-x-591-604, ix-x.
1788. Ferguson BJ, Otto BA, Pant H. When surgery, antibiotics, and steroids fail to resolve chronic rhinosinusitis. Immunology and allergy clinics of North America. 2009 Nov;29(4):719-32.
1789. Aukema AA, Mulder PG, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. The Journal of allergy and clinical immunology. 2005 May;115(5):1017-23.
1790. Bross-Soriano D, Arrieta-G??mez JR, Prado-Calleros H. Infections after endoscopic polypectomy using nasal steroids. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2004;130(3):319-22.
1791. Chalton R, Mackay I, Wilson R, Cole P. Double blind, placebo controlled trial of betamethasone nasal drops for nasal polyposis. Br Med J (Clin Res Ed). 1985 Sep 21;291(6498):788.
1792. Dingsor G, Kramer J, Olsholt R, S??derstr??m T. Flunisolide nasal spray 0.025% in the prophylactic treatment of nasal polyposis after polypectomy. A randomized, double blind, parallel, placebo controlled study. Rhinology. 1985;23(1):49-.
1793. Drettner B, Ebbesen A, Nilsson M. Prophylactive treatment with flunisolide after polypectomy. Rhinology. 1982;20(3):149-58.
1794. Filiaci F, Passali D, Puxeddu R, Schrewelius C. A randomized controlled trial showing efficacy of once daily intranasal budesonide in nasal polyposis. Rhinology. 2000;38(4):185-90.
1795. Hartwig S, Linden M, Laurent C, Vargo AK, Lindqvist N. Budesonide nasal spray as prophylactic treatment after polypectomy. (A double blind clinical trial). Journal of Laryngol Otol. 1988;102(2):148-51.
1796. Holmberg K, Juliusson S, Balder B, Smith

DL, Richards DH, Karlsson G. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. Annals of Allergy, Asthma and Immunology. 1997;78(3):270-6.

1797. Holmstrom M. Clinical performance of fluticasone propionate nasal drops. Allergy: European Journal of Allergy and Clinical Immunology. 1999;Supplement 54(53):21-5.
1798. Holopainen E, Grahne B, Malmberg H. Budesonide in the treatment of nasal polyposis. European Journal of Respiratory Diseases. 1982;63(Suppl 122):221-8.
1799. Jankowski R, Klossek JM, Attali V, Coste A, Serrano E. Long-term study of fluticasone propionate aqueous nasal spray in acute and maintenance therapy of nasal polyposis. Allergy. 2009;64(6):944-50.
1800. Johansen L, Illum P, Kristensen S, Winther L, Petersen S, Synnerstad B. The effect of budesonide (Rhinocort¬Æ) in the treatment of small and medium-sized nasal polyps. Clinical Otolaryngology & Allied Sciences. 1993;18(6):524-7.
1801. Johansson L, Holmberg K, Mel?©n I, Stierna P, Bende M. Sensitivity of a new grading system for studying nasal polyps with the potential to detect early changes in polyp size after treatment with a topical corticosteroid (budesonide). Acta oto-laryngologica2002. p. 49-53.
1802. Keith P, Nieminen J, Hollingworth K, Dolovich J. Efficacy and tolerability of fluticasone propionate nasal drops 400 mug daily compared with placebo for the treatment of bilateral polyposis in adults. Clinical and Experimental Allergy. 2000;30(10):1460-8.
1803. Land DA, McNeill J. Double blind controlled study of effect of topical steroids on nasal polyps. Clinical Otolaryngology. 1983;8:139-.
1804. Lildholdt T, Rundcrantz H, Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. Clinical otolaryngology and allied sciences. 1995 Feb;20(1):26-30.
1805. Mastalerz L, Milewski M, Duplaga M, Nizankowska E, Szczeklik A. Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. Allergy. 1997 Sep;52(9):895-900.
1806. Mygind N, Pedersen CB, Prytz S, S??rensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. Clinical Allergy. 1975;5(2):159-64.
1807. Passali D, Bernstein JM, Passali FM, Damiani V, Passali GC, Bellussi L. Treatment of recurrent chronic hyperplastic sinusitis with nasal polyposis. Archives of otolaryngology--head & neck surgery. 2003;129(6):656-9.
1808. Penttila M, Poulsen P, Hollingworth K, Holmstrom M. Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 mug once daily and twice daily in the treatment of bilateral nasal polyposis: A placebo-controlled randomized study in adult patients. Clinical and Experimental Allergy. 2000;30(1):94-102.
1809. Ruhno J, Andersson B, Denburg J, Anderson M, Hitch D, Lapp P, et al. A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. The Journal of allergy and clinical immunology. 1990 Dec;86(6 Pt 1):946-53.
1810. Small CB, Hernandez J, Reyes A, Schenkel E, Damiano A, Stryszak P, et al. Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. The Journal of allergy and clinical immunology. 2005 Dec;116(6):1275-81.
1811. Stjarne P, Blomgren K, Caye-Thomasen P, Salo S, Soderstrom T. The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: A randomized, double-blind, placebo-controlled study. Acta Oto-Laryngologica. 2006;126(6):606-12.
1812. Stjarne P, Olsson P, Alenius M. Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. Archives of otolaryngology--head & neck surgery. 2009 Mar;135(3):296-302.
1813. Tos M, Svendstrup F, Arndal H, Orntoft S, Jakobsen J, Borum P, et al. Efficacy of an aqueous and a powder formulation of nasal budesonide compared in patients with nasal polyps. American journal of rhinology. 1998;12(3):183-9.
1814. Vlckova I, Navratil P, Kana R, Pavlicek P, Chrbolka P, Djupesland PG. Effective treatment of mild-to-moderate nasal polyposis with fluticasone delivered by a novel device. Rhinology. 2009;47(4):419-26.
1815. Jankowski R, Schrewelius C, Bonfils P, Saban Y, Gilain L, Prades JM, et al. Efficacy and tolerability of budesonide aqueous nasal spray treatment in patients with nasal polyps. Archives of otolaryngology--head & neck surgery. [Clinical Trial Randomized Controlled Trial]. 2001 Apr;127(4):447-52.
1816. Stjarne P, Mosges R, Jorissen M, Passali D, Bellussi L, Staudinger H, et al. A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. Archives of otolaryngology--head & neck surgery. 2006 Feb;132(2):179-85.
1817. Berggren F, Johansson L. Cost effectiveness of nasal budesonide versus surgical treatment for nasal polyps. Pharmacoeconomics. 2003;21(5):352-6.
1818. el Naggar M, Kale S, Aldren C, Martin F. Effect of Beconase nasal spray on olfactory function in post-nasal polypectomy patients: a prospective controlled trial. J Laryngol Otol. 1995 Oct;109(10):941-4.
1819. Jurkiewicz D, Zielnik-Jurkiewicz B, Wojdas A. Effectiveness of fluticasone propionate in nasal polyps treatment. International Review of Allergology and Clinical Immunology. 2004;10(1):22-4.
1820. Karlsson G, Rundcrantz H. A randomized trial in intranasal beclomethasone dipropionate after polypectomy. Rhinology. 1982;20(3):144-8.
1821. Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. Rhinology. 2005;43(1):2-10.

1822. Chur V, Small CB, Stryszak P, Teper A. Mometasone furoate nasal spray is safe for the treatment of nasal polyps in pediatric subjects 6-17 years of age. Journal of Allergy & Clinical Immunology. 2010;25(2 Suppl 2):AB101-AB.

1823. Hansen FS, Djupesland PG, Fokkens WJ. Preliminary efficacy of fluticasone delivered by a novel device in recalcitrant chronic rhinosinusitis. Rhinology. 2010 Sep;48(3):292-9.

1824. Patriarca G, Bellioni P, Nucera E, Schiavino D, Papa G, Schinco G, et al. Intranasal treatment with lysine acetylsalicylate in patients with nasal polyposis. Ann Allergy. 1991 Dec;67(6):588-92.

1825. Stevenson DD, Pleskow WW, Simon RA, Mathison DA, Lumry WR, Schatz M, et al. Aspirin-sensitive rhinosinusitis asthma: a double-blind crossover study of treatment with aspirin. The Journal of allergy and clinical immunology. 1984 Apr;73(4):500-7.

1826. Benninger MS. Epistaxis and its relationship to handedness with use of intranasal steroid spray. Ear, nose, & throat journal. 2008 Aug;87(8):463-5.

1827. Kumar SD, Brieva JL, Danta I, Wanner A. Transient effect of inhaled fluticasone on airway mucosal blood flow in subjects with and without asthma. American Journal of Respiratory & Critical Care Medicine. 2000;161(3 Pt 1):918-21.

1828. Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. Drug Saf. 2003;26(12):863-93.

1829. Lund VJ, Preziosi P, Hercberg S, Hamoir M, Dubreuil C, Pessey JJ, et al. Yearly incidence of rhinitis, nasal bleeding, and other nasal symptoms in mature women. Rhinology. [Multicenter Study Research Support, Non-U.S. Gov't]. 2006 Mar;44(1):26-31.

1830. Lanier B, Kai G, Marple B, Wall GM. Pathophysiology and progression of nasal septal perforation. Annals of Allergy, Asthma, & Immunology. [Research Support, Non-U.S. Gov't Review]. 2007 2007 Dec Dec;99(6):473-9; quiz 80-1.

1831. Mygind N. Effects of beclomethasone dipropionate aerosol on nasal mucosa. Br J Clin Pharmacol. 1977;4 Suppl 3:287S-91S.

1832. Holm AF, Fokkens WJ, Godthelp T, Mulder PG, Vroom TM, Rijntjes E. A 1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. Clinical otolaryngology and allied sciences. [Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 1998 Feb;23(1):69-73.

1833. Mygind N, Sorensen H, Pedersen CB. The nasal mucosa during long-term treatment with beclomethasone dipropionate aerosol. A light-and scanning electron microscopic study of nasal polyps. Acta Otolaryngol. 1978 May-Jun;85(5-6):437-43.

1834. Klemi PJ, Virolainen E, Puhakka H. The effect of intranasal beclomethasone dipropionate on the nasal mucosa. Rhinology. [Clinical Trial Randomized Controlled Trial]. 1980 Mar;18(1):19-24.

1835. Lindqvist N, Balle VH, Karma P, Karja J, Lindstrom D, Makinen J, et al. Long-term safety and efficacy of budesonide nasal aerosol in perennial rhinitis. A 12-month multicentre study. Allergy. [Clinical Trial]. 1986 Apr;41(3):179-86.

1836. Baroody FM, Cheng CC, Moylan B, deTineo M, Haney L, Reed KD, et al. Absence of nasal mucosal atrophy with fluticasone aqueous nasal spray. Archives of Otolaryngology -- Head & Neck Surgery. [Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S.]. 2001 Feb;127(2):193-9.

1837. Klossek JM, Lalibert, x00E, F., F. M, Mounedji N, et al. Local safety of intranasal triamcinolone acetonide: clinical and histological aspects of nasal mucosa in the long-term treatment of perennial allergic rhinitis. Rhinology. [Clinical Trial Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't]. 2001 Mar;39(1):17-22.

1838. Minshall E, Ghaffar O, Cameron L, O'Brien F, Quinn H, Rowe-Jones J, et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1998 May;118(5):648-54.

1839. Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. Allergy. [Comparative Study Research Support, Non-U.S. Gov't eview]. 2008 Oct;63(10):1292-300.

1840. Bielory L, Blaiss M, Fineman SM, Ledford DK, Lieberman P, Simons FE, et al. Concerns about intranasal corticosteroids for over-the-counter use: position statement of the Joint Task Force for the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. [Review]. 2006 Apr;96(4):514-25.

1841. Skoner D. Update of growth effects of inhaled and intranasal corticosteroids. Curr Opin Allergy Clin Immunol. 2002 Feb;2(1):7-10.

1842. Lildholdt T, Fogstrup J, Gammelgaard N, Kortholm B, Ulsoe C. Surgical versus medical treatment of nasal polyps. Acta Oto-Laryngologica. 1988;105(1-2):140-3.

1843. Martinez-Anton A, De BC, Alobid I et al. Corticosteroid therapy increases membrane-tethered while decreases secreted mucin expression in nasal polyps. Allergy: European Journal of Allergy and Clinical Immunology. 2008;63(10):1368-76.

1844. Vaidyanathan S, Barnes M, Williamson P, Hopkinson P, Donnan PT, Lipworth B. Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids: a randomized trial. Ann Intern Med. 2011 Mar 1;154(5):293-302.

1845. Schalek P, Petras P, Klement V, Hahn A. Short-term antibiotics treatment in patients with nasal polyps and enterotoxins producing Staphylococcus aureus strains. European archives of

oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2009 Dec;266(12):1909-13.

1846. Yamada T, Fujieda S, Mori S, Yamamoto H, Saito H. Macrolide treatment decreased the size of nasal polyps and IL-8 levels in nasal lavage. American journal of rhinology. 2000 May-Jun;14(3):143-8.
1847. Guglielmo M, Gulotta C, Mancini F, Sacchi M, Tarantini F. Recalcitrant nasal polyposis: achievement of total remission following treatment with omalizumab. J Investig Allergol Clin Immunol. 2009;19(2):158-9.
1848. Grundmann SA, Hemfort PB, Luger TA, Brehler R. Anti-IgE (omalizumab): a new therapeutic approach for chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2008 Jan;121(1):257-8.
1849. Penn R, Mikula S. The role of anti-IgE immunoglobulin therapy in nasal polyposis: a pilot study. American journal of rhinology. 2007 Jul-Aug;21(4):428-32.
1850. Vennera Mdel C, Picado C, Mullol J, Alobid I, Bernal-Sprekelsen M. Efficacy of omalizumab in the treatment of nasal polyps. Thorax. 2011 Sep;66(9):824-5.
1851. Cox L, Lieberman P, Wallace D, Simons FE, Finegold I, Platts-Mills T, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. The Journal of allergy and clinical immunology. 2011 Jul;128(1):210-2.
1852. Omalizumab: a second look in severe persistent asthma: new adverse effects. Prescrire Int. 2011 Apr;20(115):90-2.
1853. Mepolizumab: 240563, anti-IL-5 monoclonal antibody - GlaxoSmithKline, anti-interleukin-5 monoclonal antibody - GlaxoSmithKline, SB 240563. Drugs R D. 2008;9(2):125-30.
1854. Walsh GM. Reslizumab, a humanized anti-IL-5 mAb for the treatment of eosinophil-mediated inflammatory conditions. Curr Opin Mol Ther. 2009 Jun;11(3):329-36.
1855. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. American journal of respiratory and critical care medicine. 2011 Nov 15;184(10):1125-32.
1856. Haye R, Aanesen JP, Burtin B, Donnelly F, Duby C. The effect of cetirizine on symptoms and signs of nasal polyposis. J Laryngol Otol. 1998 Nov;112(11):1042-6.
1857. Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: perioperative management, prevention of recurrence, and role of steroids and antifungal agents. Otolaryngologic clinics of North America. 2000 Apr;33(2):419-33.
1858. Stankiewicz JA, Musgrave BK, Scianna JM. Nasal amphotericin irrigation in chronic rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2008 Feb;16(1):44-6.
1859. Ebbens FA, Georgalas C, Fokkens WJ. Fungus as the cause of chronic rhinosinusitis: the case remains unproven. Current opinion in otolaryngology & head and neck surgery. 2009 Feb;17(1):43-9.
1860. Jen A, Kacker A, Huang C, Anand V. Fluconazole nasal spray in the treatment of allergic fungal sinusitis: A pilot study. Ear, nose, & throat journal. 2004;83(10):692-5.
1861. Kennedy DW, Kuhn FA, Hamilos DL, Zinreich SJ, Butler D, Warsi G, et al. Treatment of chronic rhinosinusitis with high-dose oral terbinafine: A double blind, placebo-controlled study. The Laryngoscope. 2005;115(10 I):1793-9.
1862. Rains BM, 3rd, Mineck CW. Treatment of allergic fungal sinusitis with high-dose itraconazole. American journal of rhinology. 2003 Jan-Feb;17(1):1-8.
1863. Chan KO, Genoway KA, Javer AR. Effectiveness of itraconazole in the management of refractory allergic fungal rhinosinusitis. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2008 Dec;37(6):870-4.
1864. Inhaled frusemide and asthma. Lancet. 1990 Apr 21;335(8695):944-6.
1865. Cavaliere F, Masieri S. Furosemide protective effect against airway obstruction. Curr Drug Targets. 2002 Jun;3(3):197-201.
1866. Passali D, Mezzedimi C, Passali GC, Bellussi L. Efficacy of inhalation form of furosemide to prevent postsurgical relapses of rhinosinusal polyposis. ORL J Otorhinolaryngol Relat Spec. 2000 Nov-Dec;62(6):307-10.
1867. Kroflic B, Coer A, Baudoin T, Kalogjera L. Topical furosemide versus oral steroid in preoperative management of nasal polyposis. European Archives of Oto-Rhino-Laryngology. 2006;263(8):767-71.
1868. Corrigan CJ. Asthma refractory to glucocorticoids: the role of newer immunosuppressants. Am J Respir Med. 2002;1(1):47-54.
1869. Schaper C, Noga O, Koch B, Ewert R, Felix SB, Glaser S, et al. Anti-inflammatory properties of montelukast, a leukotriene receptor antagonist in patients with asthma and nasal polyposis. J Investig Allergol Clin Immunol. 2011;21(1):51-8.
1870. Kieff DA, Busaba NY. Efficacy of montelukast in the treatment of nasal polyposis. Annals of Otology, Rhinology & Laryngology. 2005;114(12 I):941-5.
1871. Parnes SM, Chuma AV. Acute effects of antileukotrienes on sinonasal polyposis and sinusitis. Ear, nose, & throat journal. 2000 Jan;79(1):18-20, 4-5.
1872. Nonaka M, Sakanushi A, Kusama K, Ogihara N, Yagi T. One-year evaluation of combined treatment with an intranasal corticosteroid and montelukast for chronic rhinosinusitis associated with asthma. J Nippon Med Sch. 2010;77(1):21-8.
1873. Mostafa BE, Hay HA, Mohammed HE, Yamani M. Role of leukotriene inhibitors in the postoperative management of nasal polyps. Orl. 2005;67(3):148-53.
1874. Pauli C, Fintelmann R, Klemens C, Hilgert E, Jund F, Rasp G, et al. [Polyposis nasi--improvement in quality of life by the influence of leukotrien receptor antagonists]. Laryngorhinootologie. 2007 Apr;86(4):282-6.
1875. Stewart RA, Ram B, Hamilton G, Weiner

J, Kane KJ. Montelukast as an adjunct to oral and inhaled steroid therapy in chronic nasal polyposis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2008 Nov;139(5):682-7.

1876. Rizk H. Role of aspirin desensitization in the management of chronic rhinosinusitis. Current opinion in otolaryngology & head and neck surgery. 2011 Jun;19(3):210-7.
1877. Kamani T, Sama A. Management of nasal polyps in 'aspirin sensitive asthma' triad. Current opinion in otolaryngology & head and neck surgery. 2011 Feb;19(1):6-10.
1878. Rozsasi A, Polzehl D, Deutschle T, Smith E, Wiesmiller K, Riechelmann H, et al. Long-term treatment with aspirin desensitization: a prospective clinical trial comparing 100 and 300 mg aspirin daily. Allergy. 2008 Sep;63(9):1228-34.
1879. Zheng C, Wang Z, Lacroix JS. Effect of intranasal treatment with capsaicin on the recurrence of polyps after polypectomy and ethmoidectomy. Acta Oto-Laryngologica. 2000;120(1):62-6.
1880. Baudoin T, Kalogjera L, Hat J. Capsaicin significantly reduces sinonasal polyps. Acta Otolaryngol. 2000 Mar;120(2):307-11.
1881. Filiaci F, Zambetti G, Luce M, Ciofalo A. Local treatment of nasal polyposis with capsaicin: preliminary findings. Allergol Immunopathol (Madr). 1996 Jan-Feb;24(1):13-8.
1882. Johansson L, Oberg D, Melen I, Bende M. Do topical nasal decongestants affect polyps? Acta Oto-Laryngologica. 2006;126(3):288-90.
1883. Pigret D, Jankowski R. Management of post-ethmoidectomy crust formation: randomized single-blind clinical trial comparing pressurized seawater versus antiseptic/mucolytic saline. Rhinology. 1996 Mar;34(1):38-40.
1884. Pinto JM, Elwany S, Baroody FM, Naclerio RM. Effects of saline sprays on symptoms after endoscopic sinus surgery. American journal of rhinology. 2006;20(2):191-6.
1885. Poetker DM, Mendolia-Loffredo S, Smith TL. Outcomes of endoscopic sinus surgery for chronic rhinosinusitis associated with sinonasal polyposis. American journal of rhinology. 2007 Jan-Feb;21(1):84-8.
1886. Dalziel K, Stein K, Round A, Garside R, Royle P. Systematic review of endoscopic sinus surgery for nasal polyps. Health Technol Assess. 2003;7(17):iii, 1-159.
1887. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. The Laryngoscope. 2004 May;114(5):811-3.
1888. Bhattacharyya N. Influence of polyps on outcomes after endoscopic sinus surgery. The Laryngoscope. 2007 Oct;117(10):1834-8.
1889. Alobid I, Benitez P, Bernal-Sprekelsen M, Roca J, Alonso J, Picado C, et al. Nasal polyposis and its impact on quality of life: comparison between the effects of medical and surgical treatments. Allergy. 2005;60(4):452-8.
1890. Schapowal AG, Simon HU, Schmitz-Schumann M. Phenomenology, pathogenesis, diagnosis and treatment of aspirin-sensitive rhinosinusitis. Acta Otorhinolaryngol Belg. 1995;49(3):235-50.
1891. Masterson L, Tanweer F, Bueser T, Leong P. Extensive endoscopic sinus surgery: does this reduce the revision rate for nasal polyposis? European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2010 Oct;267(10):1557-61.
1892. Silverman JB, Prasittivatechakool K, Busaba NY. An evidence-based review of endoscopic frontal sinus surgery. American journal of rhinology & allergy. 2009 Nov-Dec;23(6):e59-62.
1893. Chan Y, Melroy CT, Kuhn CA, Kuhn FL, Daniel WT, Kuhn FA. Long-term frontal sinus patency after endoscopic frontal sinusotomy. The Laryngoscope. 2009 Jun;119(6):1229-32.
1894. Friedman M, Bliznikas D, Vidyasagar R, Joseph NJ, Landsberg R. Long-term results after endoscopic sinus surgery involving frontal recess dissection. The Laryngoscope. 2006 Apr;116(4):573-9.
1895. Lee JY, Lee SH, Hong HS, Lee JD, Cho SH. Is the canine fossa puncture approach really necessary for the severely diseased maxillary sinus during endoscopic sinus surgery? The Laryngoscope. 2008 Jun;118(6):1082-7.
1896. Seiberling K, Ooi E, MiinYip J, Wormald PJ. Canine fossa trephine for the severely diseased maxillary sinus. American journal of rhinology & allergy. 2009 Nov-Dec;23(6):615-8.
1897. Sathananthar S, Nagaonkar S, Paleri V, Le T, Robinson S, Wormald PJ. Canine fossa puncture and clearance of the maxillary sinus for the severely diseased maxillary sinus. The Laryngoscope. 2005 Jun;115(6):1026-9.
1898. Wright ED, Agrawal S. Impact of perioperative systemic steroids on surgical outcomes in patients with chronic rhinosinusitis with polyposis: evaluation with the novel Perioperative Sinus Endoscopy (POSE) scoring system. The Laryngoscope. 2007 Nov;117(11 Pt 2 Suppl 115):1-28.
1899. Wormald PJ. Salvage frontal sinus surgery: the endoscopic modified Lothrop procedure. The Laryngoscope. 2003 Feb;113(2):276-83.
1900. Georgalas C, Hansen F, Videler WJ, Fokkens WJ. Long terms results of Draf type III (modified endoscopic Lothrop) frontal sinus drainage procedure in 122 patients: a single centre experience. Rhinology. 2011 Jun;49(2):195-201.
1901. Anderson P, Sindwani R. Safety and efficacy of the endoscopic modified Lothrop procedure: a systematic review and meta-analysis. The Laryngoscope. 2009 Sep;119(9):1828-33.
1902. Dalziel K, Stein K, Round A, Garside R, Royle P. Endoscopic sinus surgery for the excision of nasal polyps: A systematic review of safety and effectiveness. American journal of rhinology. 2006;20(5):506-19.
1903. Hopkins C, Browne JP, Slack R, Lund VJ, Topham J, Reeves BC, et al. Complications of surgery for nasal polyposis and chronic rhinosinusitis: The results of a national audit in England and Wales. The Laryngoscope. 2006;116(8):1494-9.

1904. Ecevit MC, Sutay S, Erdag TK. The microdebrider and its complications in endoscopic surgery for nasal polyposis. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale. 2008 Apr;37(2):160-4.

1905. Devars du Mayne M, Pruliere-Escabasse V, Zerah-Lancner F, Coste A, Papon JF. Polypectomy compared with ethmoidectomy in the treatment of nasal polyposis. Archives of otolaryngology--head & neck surgery. 2011 Feb;137(2):111-7.

1906. Bajaj Y, Sethi N, Carr S, Knight LC. Endoscopic sinus surgery as day-case procedure. J Laryngol Otol. 2009 Jun;123(6):619-22.

1907. Lee JY, Lee SW. Influence of age on the surgical outcome after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. The Laryngoscope. [10.1097/MLG.0b013e318058197a]. 2007;117(6):1084-9.

1908. Reh DD, Mace J, Robinson JL, Smith TL. Impact of age on presentation of chronic rhinosinusitis and outcomes of endoscopic sinus surgery. American journal of rhinology. 2007 Mar-Apr;21(2):207-13.

1909. Sil A, Mackay I, Rowe-Jones J. Assessment of predictive prognostic factors for functional endoscopic sinus surgery in a 5-year prospective outcome study. American journal of rhinology. 2007;21(3):289-96.

1910. Akhtar S, Ikram M, Azam I, Dahri T. Factors associated with recurrent nasal polyps: a tertiary care experience. JPMA The Journal of the Pakistan Medical Association. 2010 Feb;60(2):102-4.

1911. Ramadan HH, VanMetre R. Endoscopic sinus surgery in geriatric population. American journal of rhinology. 2004;18(2):125-7.

1912. Jiang RS, Hsu CY. Endoscopic sinus surgery for the treatment of chronic sinusitis in geriatric patients. Ear, nose, & throat journal. 2001;80(4):230-2.

1913. Ban JH, Kwon HJ, Lee KC. Outcomes of endoscopic sinus surgery in an elderly population: comparison with those in an adult population. Clin Otolaryngol. 2010 Aug;35(4):300-6.

1914. Hopkins C, Gillett S, Slack R. Are men really more full of SNOT? Clin Otolaryngol. 2009 Jun;34(3):267-8.

1915. Busaba NY, Sin HJ, Salman SD. Impact of gender on clinical presentation of chronic rhinosinusitis with and without polyposis. J Laryngol Otol. 2008 Nov;122(11):1180-4.

1916. Nakayama T, Yoshikawa M, Asaka D, Okushi T, Matsuwaki Y, Otori N, et al. Mucosal eosinophilia and recurrence of nasal polyps - new classification of chronic rhinosinusitis. Rhinology. 2011 Oct;49(4):392-6.

1917. Punekar YS, Ahmad A, Saleh HA. Estimating the effect of nasal steroid treatment on repeat polypectomies: survival time analysis using the General Practice Research Database. Rhinology. 2011 Jun;49(2):190-4.

1918. Lee JY, Lee SW, Lee JD. Comparison of the surgical outcome between primary and revision endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. Am J Otolaryngol. 2008 Nov-Dec;29(6):379-84.

1919. Poznanovic SA, Kingdom TT. Total IgE levels and peripheral eosinophilia: correlation with mucosal disease based on computed tomographic imaging of the paranasal sinus. Archives of otolaryngology--head & neck surgery. 2007 Jul;133(7):701-4.

1920. Tosun F, Arslan HH, Karslioglu Y, Deveci MS, Durmaz A. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. The Annals of otology, rhinology, and laryngology. 2010 Jul;119(7):455-9.

1921. Seybt MW, McMains KC, Kountakis SE. The prevalence and effect of asthma on adults with chronic rhinosinusitis. Ear, nose, & throat journal. 2007 Jul;86(7):409-11.

1922. Lin DC, Chandra RK, Tan BK, Zirkle W, Conley DB, Grammer LC, et al. Association between severity of asthma and degree of chronic rhinosinusitis. American journal of rhinology & allergy. 2011 Jul-Aug;25(4):205-8.

1923. Zhang Z, Linkin DR, Finkelman BS, O'Malley BW, Jr., Thaler ER, Doghramji L, et al. Asthma and biofilm-forming bacteria are independently associated with revision sinus surgeries for chronic rhinosinusitis. The Journal of allergy and clinical immunology. 2011 Jul;128(1):221-3 e1.

1924. Dunlop G, Scadding GK, Lund VJ. The effect of endoscopic sinus surgery on asthma: management of patients with chronic rhinosinusitis, nasal polyposis, and asthma. American journal of rhinology. 1999;13(4):261-5.

1925. Dixon AE, Kaminsky DA, Holbrook JT, Wise RA, Shade DM, Irvin CG. Allergic rhinitis and sinusitis in asthma differential: Effects on symptoms and pulmonary function. Chest. 2006;130(2):429-35.

1926. Young J, Frenkiel S, Tewfik MA, Mouadeb DA. Long-term outcome analysis of endoscopic sinus surgery for chronic sinusitis. American journal of rhinology. 2007 Nov-Dec;21(6):743-7.

1927. Jarvis D, Newson R, Lotvall J, Hastan D, Tomassen P, Keil T, et al. Asthma in adults and its association with chronic rhinosinusitis: The GA(2) LEN survey in Europe. Allergy. 2012 Jan;67(1):91-8.

1928. Lund VJ. The effect of sinonasal surgery on asthma. Allergy. 1999;54(Suppl 57):141-5.

1929. Scadding G. The effect of medical treatment of sinusitis upon concomitant asthma. Allergy. 1999;54(Suppl 57):136-40.

1930. Senior BA, Kennedy DW. Management of sinusitis in the asthmatic patient. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 1996;77(1):6-15; quiz -9.

1931. Park AH, Lau J, Stankiewicz J, Chow J. The role of functional endoscopic sinus surgery in asthmatic patients. J Otolaryngol. 1998;27(5):275.

1932. Palmer JN, Conley DB, Dong RG, Ditto AM, Yarnold PR, Kern RC. Efficacy of endoscopic sinus surgery in the management of patients with asthma and chronic sinusitis. American journal of rhinology. 2001 Jan-Feb;15(1):49-53.

1933. Riechelmann H, Mewes T, Weschta M,

Gropper G. Nasal allergen provocation with Dermatophagoides pteronyssinus in patients with chronic rhinitis referred to a rhinologic surgical center. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2002;88(6):624.

1934. Gosepath J, Pogodsky T, Mann WJ. Characteristics of recurrent chronic rhinosinusitis after previous surgical therapy. Acta Otolaryngol. 2008 Jul;128(7):778-84.
1935. Walker C, Williams H, Phelan J. Allergic rhinitis history as a predictor of other future disqualifying otorhinolaryngological defects. Aviat Space Environ Med. 1998;69(10):952-6.
1936. Ferguson BJ, Johnson JT. Allergic rhinitis and rhinosinusitis. Is there a connection between allergy and infection? PostgradMed. 1999;105(4):55.
1937. Pinto JM, Baroody FM. Chronic sinusitis and allergic rhinitis: at the nexus of sinonasal inflammatory disease. J Otolaryngol. 2002;31(Suppl 1):S10-7.
1938. Smart BA. The impact of allergic and nonallergic rhinitis on pediatric sinusitis. Current Allergy & Asthma Reports. 2006;6(3):221-7.
1939. Gutman M, Torres A, Keen KJ, Houser SM. Prevalence of allergy in patients with chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2004 May;130(5):545-52.
1940. Suzuki M, Watanabe T, Suko T, Mogi G. Comparison of sinusitis with and without allergic rhinitis: characteristics of paranasal sinus effusion and mucosa. Am J Otolaryngol. 1999;20(3):143-50.
1941. Nishioka GJ, Cook PR, Davis WE, McKinsey JP. Immunotherapy in patients undergoing functional endoscopic sinus surgery. Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery. 1994;110(4):406-12.
1942. Bertrand B, Eloy P, Rombeaux Pl. Allergy and sinusitis. Acta Otorhinolaryngol Belg. 1997;51(4):227-37.
1943. Giger R, Dulguerov P, Quinodoz D, Leuba D, Landis BN, Lacroix JS, et al. Chronic panrhinosinusitis without nasal polyps: Long-term outcome after functional endoscopic sinus surgery. Otolaryngology - Head & Neck Surgery. 2004;131(4):534-41.
1944. Bonfils P, Malinvaud D. Influence of allergy in patients with nasal polyposis after endoscopic sinus surgery. Acta Otolaryngol. 2008 Feb;128(2):186-92.
1945. Bergoin C, Gosset P, Lamblin C, Bolard F, Turck D, Tonnel AB, et al. Cell and cytokine profile in nasal secretions in cystic fibrosis. J CystFibros. 2002;1(3):110.
1946. Osborn AJ, Leung R, Ratjen F, James AL. Effect of endoscopic sinus surgery on pulmonary function and microbial pathogens in a pediatric population with cystic fibrosis. Archives of otolaryngology--head & neck surgery. 2011 Jun;137(6):542-7.
1947. Halvorson DJ, Dupree JR, Porubsky ES. Management of chronic sinusitis in the adult cystic fibrosis patient. The Annals of otology, rhinology, and laryngology. 1998;107(11 Pt 1):946-52.
1948. Rowe-Jones JM, Mackay IS. Endoscopic sinus surgery in the treatment of cystic fibrosis with nasal polyposis. The Laryngoscope. 1996 Dec;106(12 Pt 1):1540-4.
1949. Friedman M, Landsberg R, Tanyeri H, Schults RA, Kelanic S, Caldarelli DD. Endoscopic sinus surgery in patients infected with HIV. The Laryngoscope. 2000;110(10 Pt 1):1613.
1950. Murphy C, Davidson TM, Jellison W, Austin S, Mathews WC, Ellison DW, et al. Sinonasal disease and olfactory impairment in HIV disease: endoscopic sinus surgery and outcome measures. The Laryngoscope. 2000;110(10 Pt 1):1707-10.
1951. Hunt SM, Miyamoto RC, Cornelius RS, Tami TA. Invasive fungal sinusitis in the acquired immunodeficiency syndrome. OtolaryngolClin North Am. 2000;33(2):335.
1952. Anselmo-Lima WT, Lopes RP, Valera FCP, Demarco RC. Invasive fungal rhinosinusitis in immunocompromised patients. Rhinology. 2004;42(3):141-4.
1953. Savage DG, Taylor P, Blackwell J, Chen F, Szydlo RM, Rule SA, et al. Paranasal sinusitis following allogeneic bone marrow transplant. Bone marrow transplantation. 1997;19(1):55-9.
1954. Imamura R, Voegels R, Sperandio F, Sennes LU, Silva R, Butugan O, et al. Microbiology of sinusitis in patients undergoing bone marrow transplantation. OtolaryngolHead Neck Surg. 1999;120(2):279.
1955. Kennedy CA, Adams GL, Neglia JP, Giebink GS. Impact of surgical treatment on paranasal fungal infections in bone marrow transplant patients. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1997;116(6 Pt 1):610-6.
1956. Sterman BM. Sinus surgery in bone marrow transplantation patients. American journal of rhinology. 1999;13(4):315.
1957. Buehring I, Friedrich B, Schaaf J, Schmidt H, Ahrens P, Zielen S. Chronic sinusitis refractory to standard management in patients with humoral immunodeficiencies. Clin Exp Immunol. 1997;109(3):468-72.
1958. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34.
1959. Sneller MC. Common variable immunodeficiency. Am J Med Sci. 2001;321(1):42.
1960. Scadding GK, Lund VJ, Darby YC, Navas-Romero J, Seymour N, Turner MW. IgG subclass levels in chronic rhinosinusitis. Rhinology. 1994;32(1):15-9.
1961. Jiang RS, Hsu CY. Serum immunoglobulins and IgG subclass levels in sinus mycetoma. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2004 May;130(5):563-6.
1962. Buckley RH. Immunoglobulin G subclass deficiency: fact or fancy? Curr Allergy Asthma Rep. 2002;2(5):356.
1963. Maguire GA, Kumararatne DS, Joyce HJ. Are there any clinical indications for

measuring IgG subclasses? Ann Clin Biochem. 2002;39(Pt 4):374.

1964. 1964. Seppanen M, Suvilehto J, Lokki ML, Notkola IL, Jarvinen A, Jarva H, et al. Immunoglobulins and complement factor C4 in adult rhinosinusitis. Clinical & Experimental Immunology. 2006;145(2):219-27.

1965. Tahkokallio O, Seppala IJ, Sarvas H, Kayhty H, Mattila PS. Concentrations of serum immunoglobulins and antibodies to pneumococcal capsular polysaccharides in patients with recurrent or chronic sinusitis. The Annals of otology, rhinology, and laryngology. 2001;110(7 Pt 1):675-81.

1966. Lusk RP, Polmar SH, Muntz HR. Endoscopic ethmoidectomy and maxillary antrostomy in immunodeficient patients. Archives of otolaryngology--head & neck surgery. 1991;117(1):60-3.

1967. Chester AC, Sindwani R, Smith TL, Bhattacharyya N. Fatigue improvement following endoscopic sinus surgery: a systematic review and meta-analysis. The Laryngoscope. 2008 Apr;118(4):730-9.

1968. Sauter. The effects of endoscopic sinus surgery on level of fatigue in patients with chronic rhinosinusitis. American journal of rhinology & allergy. 2008;22(4):420-6.

1969. Soler ZM, Mace J, Smith TL. Fibromyalgia and chronic rhinosinusitis: outcomes after endoscopic sinus surgery. American journal of rhinology. 2008 Jul-Aug;22(4):427-32.

1970. Zhang Z, Kofonow JM, Finkelman BS, Doghramji L, Chiu AG, Kennedy DW, et al. Clinical factors associated with bacterial biofilm formation in chronic rhinosinusitis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Mar;144(3):457-62.

1971. Singhal D, Psaltis AJ, Foreman A, Wormald P-J. The impact of biofilms on outcomes after endoscopic sinus surgery. American journal of rhinology & allergy. [10.2500/ajra.2010.24.3462]. 2010;24(3):169-74.

1972. Das S, Becker AM, Perakis H, Prosser JD, Kountakis SE. The effects of smoking on short-term quality of life outcomes in sinus surgery. The Laryngoscope. 2007 Dec;117(12):2229-32.

1973. Das S, Khichi SS, Perakis H, Woodard T, Kountakis SE. Effects of smoking on quality of life following sinus surgery: 4-year follow-up. The Laryngoscope. 2009 Nov;119(11):2284-7.

1974. Naidoo Y, Wen D, Bassiouni A, Keen M, Wormald PJ. Long-term results after primary frontal sinus surgery. International forum of allergy & rhinology. 2012 Jan 17.

1975. Moscato G, Pala G, Boillat MA, Folletti I, Gerth van Wijk R, Olgiati-Des Gouttes D, et al. EAACI position paper: prevention of work-related respiratory allergies among pre-apprentices or apprentices and young workers. Allergy. 2011 Sep;66(9):1164-73.

1976. Hox V, Delrue S, Scheers H, Adams E, Keirsbilck S, Jorissen M, et al. Negative impact of occupational exposure on surgical outcome in patients with rhinosinusitis. Allergy. 2012 Jan 9.

1977. Otten FW, Grote JJ. Treatment of chronic maxillary sinusitis in children. Int J Pediatr Otorhinolaryngol. 1988 Sep;15(3):269-78.

1978. Otten HW, Antvelink JB, Ruyter de Wildt H, Rietema SJ, Siemelink RJ, Hordijk GJ. Is antibiotic treatment of chronic sinusitis effective in children? Clinical otolaryngology and allied sciences. 1994 Jun;19(3):215-7.

1979. Don DM, Yellon RF, Casselbrant ML, Bluestone CD. Efficacy of a stepwise protocol that includes intravenous antibiotic therapy for the management of chronic sinusitis in children and adolescents. Archives of otolaryngology--head & neck surgery. 2001 Sep;127(9):1093-8.

1980. Adappa ND, Coticchia JM. Management of refractory chronic rhinosinusitis in children. Am J Otolaryngol. 2006 Nov-Dec;27(6):384-9.

1981. Gawchik S, Goldstein S, Prenner B, John A. Relief of cough and nasal symptoms associated with allergic rhinitis by mometasone furoate nasal spray. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2003 Apr;90(4):416-21.

1982. Ratner PH, Meltzer EO, Teper A. Mometasone furoate nasal spray is safe and effective for 1-year treatment of children with perennial allergic rhinitis. Int J Pediatr Otorhinolaryngol. 2009 May;73(5):651-7.

1983. Schenkel EJ, Skoner DP, Bronsky EA, Miller SD, Pearlman DS, Rooklin A, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. Pediatrics. 2000 Feb;105(2):E22.

1984. Ozturk F, Bakirtas A, Ileri F, Turktas I. Efficacy and tolerability of systemic methylprednisolone in children and adolescents with chronic rhinosinusitis: a double-blind, placebo-controlled randomized trial. The Journal of allergy and clinical immunology. 2011 Aug;128(2):348-52.

1985. Michel O, Essers S, Heppt WJ, Johannssen V, Reuter W, Hommel G. The value of Ems Mineral Salts in the treatment of rhinosinusitis in children: Prospective study on the efficacy of mineral salts versus xylometazoline in the topical nasal treatment of children. International Journal of Pediatric Otorhinolaryngology. 2005;69(10):1359-65.

1986. Wei JL, Sykes KJ, Johnson P, He J, Mayo MS. Safety and efficacy of once-daily nasal irrigation for the treatment of pediatric chronic rhinosinusitis. The Laryngoscope. 2011 Sep;121(9):1989-2000.

1987. Brietzke SE, Brigger MT. Adenoidectomy outcomes in pediatric rhinosinusitis: a meta-analysis. Int J Pediatr Otorhinolaryngol. 2008 Oct;72(10):1541-5.

1988. Ramadan HH, Tiu J. Failures of adenoidectomy for chronic rhinosinusitis in children: for whom and when do they fail? The Laryngoscope. 2007 Jun;117(6):1080-3.

1989. Ramadan HH, Cost JL. Outcome of adenoidectomy versus adenoidectomy with maxillary sinus wash for chronic rhinosinusitis in children. The Laryngoscope. 2008 May;118(5):871-3.

1990. Criddle MW, Stinson A, Savliwala M, Coticchia J. Pediatric chronic rhinosinusitis: a retrospective review. Am

J Otolaryngol. 2008 Nov-Dec;29(6):372-8.

1991. Ramadan HH. Revision endoscopic sinus surgery in children: surgical causes of failure. The Laryngoscope. 2009 Jun;119(6):1214-7.
1992. Ramadan HH, Terrell AM. Balloon catheter sinuplasty and adenoidectomy in children with chronic rhinosinusitis. The Annals of otology, rhinology, and laryngology. 2010 Sep;119(9):578-82.
1993. Hebert RL, 2nd, Bent JP, 3rd. Meta-analysis of outcomes of pediatric functional endoscopic sinus surgery. The Laryngoscope. 1998 Jun;108(6):796-9.
1994. Bothwell MR, Piccirillo JF, Lusk RP, Ridenour BD. Long-term outcome of facial growth after functional endoscopic sinus surgery. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2002 Jun;126(6):628-34.
1995. Chang PH, Lee LA, Huang CC, Lai CH, Lee TJ. Functional endoscopic sinus surgery in children using a limited approach. Archives of Otolaryngology -- Head & Neck Surgery. [Review]. 2004;130(9):1033-6.
1996. Walner DL, Falciglia M, Willging JP, Myer CM, 3rd. The role of second-look nasal endoscopy after pediatric functional endoscopic sinus surgery. Archives of otolaryngology--head & neck surgery. 1998 Apr;124(4):425-8.
1997. Ramadan HH. Corticosteroid therapy during endoscopic sinus surgery in children: is there a need for a second look? Archives of otolaryngology--head & neck surgery. 2001 Feb;127(2):188-92.
1998. Younis RT. The pros and cons of second-look sinonasal endoscopy after endoscopic sinus surgery in children. Archives of Otolaryngology -- Head & Neck Surgery. [Review]. 2005;131(3):267-9.
1999. Lee TJ, Liang CW, Chang PH, Huang CC. Risk factors for protracted sinusitis in pediatrics after endoscopic sinus surgery. Auris Nasus Larynx. 2009 Dec;36(6):655-60.
2000. van Oene CM, van Reij EJ, Sprangers MA, Fokkens WJ. Quality-assessment of disease-specific quality of life questionnaires for rhinitis and rhinosinusitis: a systematic review. Allergy. 2007 Dec;62(12):1359-71.
2001. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg. 1995;113(1):104-9.
2002. Piccirillo J. Psychometric and clinimetric validity of the 31-item rhinosinusitis outcome measure. American journal of rhinology. 1995(9):297-306.
2003. Mortuaire G, Vandeville S, Chevalier D. Psychometric evaluation of the SinoNasal Outcome Test-16 for quality of life in chronic rhinosinusitis with nasal polyps. European annals of otorhinolaryngology, head and neck diseases. 2010 Jun;127(3):91-6.
2004. Anderson ER, Murphy MP, Weymuller EA, Jr. Clinimetric evaluation of the Sinonasal Outcome Test-16. Student Research Award 1998. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1999 Dec;121(6):702-7.
2005. Majima Y, Kurono Y, Hirakawa K, Suzaki H, Haruna S, Kawauchi H, et al. Reliability and validity assessments of a Japanese version of QOL 20-Item Sino-Nasal Outcome Test for chronic rhinosinusitis. Auris Nasus Larynx. 2010 Aug;37(4):443-8.
2006. Zuo KJ, Fang JQ, Piccirillo JF, Wang H, Xu G. [Development of the Sino-Nasal Outcome Test-20 Chinese version (SNOT-20 CV)]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2008 Oct;43(10):751-6.
2007. Bezerra TF, Piccirillo JF, Fornazieri MA, de MPRR, Abdo TR, de Rezende Pinna F, et al. Cross-Cultural Adaptation and Validation of SNOT-20 in Portuguese. Int J Otolaryngol. 2011;2011:306529.
2008. Baumann I, Blumenstock G, DeMaddalena H, Piccirillo JF, Plinkert PK. [Quality of life in patients with chronic rhinosinusitis: validation of the Sino-Nasal Outcome Test-20 German Adapted Version]. Hno. 2007 Jan;55(1):42-7.
2009. Tahamiler R, Edizer DT, Canakcioglu S. [The validity of the Rhinosinusitis Disability Index in chronic sinusitis]. Kulak Burun Bogaz Ihtis Derg. 2007;17(3):138-42.
2010. Marro M. French validation of the NOSE and RhinoQOL questionnaires in the management of nasal obstruction. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011;144(6):988-93.
2011. Atlas SJ, Gallagher PM, Wu YA, Singer DE, Gliklich RE, Metson RB, et al. Development and validation of a new health-related quality of life instrument for patients with sinusitis. Quality of Life Research. [Review]. 2005;14(5):1375-86.
2012. Lange B, Thilsing T, Al-kalemji A, Baelum J, Martinussen T, Kjeldsen A. The Sino-Nasal Outcome Test 22 validated for Danish patients. Dan Med Bull. 2011 Feb;58(2):A4235.
2013. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009 Oct;34(5):447-54.
2014. Schalek P, Otruba L, Hahn A. Quality of life in patients with chronic rhinosinusitis: a validation of the Czech version of SNOT-22 questionnaire. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2010 Mar;267(3):473-5.
2015. Lu W, Qi F, Gao ZQ, Feng GD, Yuan XD, Jin XF. [Quality of life survey on patients with chronic rhinosinusitis by using Chinese version of the 22-item sinonasal outcome test (SNOT-22)]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2008 Jan;43(1):18-21.
2016. Sahlstrand-Johnson P, Ohlsson B, Von Buchwald C, Jannert M. A multi-centre study on quality of life and absenteeism in patients with CRS referred for endoscopic surgery. Rhinology. 2011 Oct;49(4):420-8.
2017. Stavem K, Rossberg E, Larsson PG. Reliability, validity and responsiveness of a Norwegian version of the Chronic Sinusitis Survey. BMC ear, nose, and throat disorders. 2006;6:9.
2018. Gliklich RE, Metson R. Techniques for outcomes research in chronic sinusitis. The Laryngoscope. 1995 Apr;105(4 Pt

1):387-90.

2019. Wang PC, Tai CJ, Chu CC, Liang SC. Translation and validation assessment of the Chinese version of the chronic sinusitis survey. Chang Gung Med J. 2002 Jan;25(1):9-15.

2020. Fairley JW. Reliability and validity of a nasal symptom questionnaire for use as an outcome measure in clinical research and audit of FESS. Clinical Otolaryngology. 1993;40(4):195-7.

2021. Fahmy FF, McCombe A, McKiernan DC. Sino nasal assessment questionnaire, a patient focused, rhinosinusitis specific outcome measure. Rhinology. 2002 Dec;40(4):195-7.

2022. Garbutt J, Spitznagel E, Piccirillo J. Use of the modified SNOT-16 in primary care patients with clinically diagnosed acute rhinosinusitis. Archives of otolaryngology--head & neck surgery. 2011 Aug;137(8):792-7.

2023. Revicki D, Margolis M, Thompson C, Meltzer E, Sandor D, Shaw J. Major Symptom Score Utility Index for patients with acute rhinosinusitis. American journal of rhinology & allergy. 2011 Apr 8.

2024. Garbutt JM, Gellman EF, Littenberg B. The development and validation of an instrument to assess acute sinus disease in children. Qual Life Res. 1999 May;8(3):225-33.

2025. Teul I, Zbislawski W, Baran S, Czerwinski F, Lorkowski J. Quality of life of patients with diseases of sinuses. Journal of physiology and pharmacology : an official journal of the Polish Physiological Society. 2007 Nov;58 Suppl 5(Pt 2):691-7.

2026. Durr DG, Desrosiers MY, Dassa C. Impact of rhinosinusitis in health care delivery: the Quebec experience. J Otolaryngol. 2001 Apr;30(2):93-7.

2027. Winstead W, Barnett SN. Impact of endoscopic sinus surgery on global health perception: an outcomes study. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1998 Nov;119(5):486-91.

2028. Gillett S, Hopkins C, Slack R, Browne JP. A pilot study of the SNOT 22 score in adults with no sinonasal disease. Clin Otolaryngol. 2009 Oct;34(5):467-9.

2029. Chester AC. Symptom outcomes following endoscopic sinus surgery. Current opinion in otolaryngology & head and neck surgery. 2009 Feb;17(1):50-8.

2030. Ray NF. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. The Journal of allergy and clinical immunology. 1999;103(3):408-14.

2031. Murphy MP, Fishman P, Short SO, Sullivan SD, Yueh B, Weymuller EA, Jr. Health care utilization and cost among adults with chronic rhinosinusitis enrolled in a health maintenance organization. Otolaryngol Head Neck Surg. 2002;127(5):367-76.

2032. Agthoven v. Cost analysis of regular and filgrastim treatment in patients with refractory chronic rhinosinusitis. Rhinology. 2002;40(2):69-74.

2033. Bhattacharyya N. Assessing the additional disease burden of polyps in chronic rhinosinusitis. The Annals of otology, rhinology, and laryngology. 2009 Mar;118(3):185-9.

2034. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. The Annals of otology, rhinology, and laryngology. 2011 Jul;120(7):423-7.

2035. Bhattacharyya N, Orlandi RR, Grebner J, Martinson M. Cost burden of chronic rhinosinusitis: a claims-based study. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2011 Mar;144(3):440-5.

2036. Anand VK. Epidemiology and economic impact of rhinosinusitis. Annals of Otology, Rhinology & Laryngology. [Conference Paper]. 2004;113(5 II):3-5.

2037. Lang HC. Outpatient drug expenditures and prescription policies for diseases with high cost to the National Health Insurance system in Taiwan. J Formos Med Assoc. 2004;103(4):280-5.

2038. Bhattacharyya N, Kepnes LJ. Additional disease burden from hay fever and sinusitis accompanying asthma. The Annals of otology, rhinology, and laryngology. 2009 Sep;118(9):651-5.

2039. Goetzel RZ, Hawkins K, Ozminkowski RJ, Wang S. The health and productivity cost burden of the "top 10" physical and mental health conditions affecting six large U.S. employers in 1999. J Occup Environ Med. 2003 Jan;45(1):5-14.

2040. Bhattacharyya N. The economic burden and symptom manifestations of chronic rhinosinusitis. American journal of rhinology. 2003 Jan-Feb;17(1):27-32.

2041. Stankiewics J. Impact of chronic rhinosinusitis on work productivity through one-year follow-up after baloon dilation of the ethmoid infundibulum. Int Forum of Allery and Rhinology. 2011(1):38-45.

2042. Stull DE, Roberts L, Frank L, Heithoff K. Relationship of nasal congestion with sleep, mood, and productivity. Curr Med Res Opin. 2007 Apr;23(4):811-9.

2043. 2043. Bramley TJ, Lerner D, Sames M. Productivity losses related to the common cold. J Occup Environ Med. 2002 Sep;44(9):822-9.

2044. Hellgren J, Cervin A, Nordling S, Bergman A, Cardell LO. Allergic rhinitis and the common cold--high cost to society. Allergy. 2010 Jun 1;65(6):776-83.

2045. Drake-Lee, A. and J. Price (1997). "Mast cell ultrastructure in the inferior turbinate and stroma of nasal polyps." J Laryngol Otol 111(4): 340-345.

2046. Jahnsen, F., P. Brandtzaeg, et al. (1997). "Expression of functional VCAM-1 by cultured nasal polyp-derived microvascular endothelium." Am J Pathol. 150(6): 2113-2123.

2047. Loesel, L. (2001). "Immunopathologic study of chronic sinusitis: a proposal for atopic and non-atopic IgE-activated mast cell allergic inflammation." Ann Otol Rhinol Laryngol. 110(5 Pt 1): 447-452.

2048. Seong, J., J. Koo, et al. (2002). "Upregulation of MUC8 and downregulation of MUC5AC by inflammatory mediators in human nasal polyps and cultured nasal epithelium." Acta Otolaryngol. 122(4): 401-407.

2049. Chen, P. and S. Fang (2004). "Expression of human beta-defensin 2 in human

nasal mucosa." Eur Arch Otorhinolaryngol. 261(5): 238-241.

2050. Gosepath, J., J. Brieger, et al. (2005). "Expression, localization, and significance of vascular permeability/vascular endothelial growth factor in nasal polyps " American Journal ofvRhinology. 19(1): 7-13.
2051. Watelet, J. B., C. Claeys, et al. (2004). "Predictive and monitoring value of matrix metalloproteinase-9 for healing quality after sinus surgery." Wound Repair & Regeneration 12(4): 412-418.
2052. Elhini, A., S. Abdelwahab, et al. (2005). "Th1 and Th2 cell population in chronic ethmoidal rhinosinusitis: A chemokine receptor assay." Laryngoscope 115(7): 1272-1277.
2053. Rudack, C., F. Sachse, et al. (2006). "Primary role of growth-related oncogene-a and granulocyte chemotactic protein-2 as neutrophil chemoattractants in chronic rhinosinusitis." Clinical & Experimental Allergy 36(6): 748-759.
2054. Watelet, J. B., P. Demetter, et al. (2006). "Wound healing after paranasal sinus surgery: Neutrophilic inflammation influences the outcome." Histopathology 48(2): 174-181.
2055. Erbek, S. S., H. Erinanc, et al. (2010). "Expression of a disintegrin and metalloproteinase 33 protein in nasal polyposis: an immunohistochemical study." Am J Rhinol Allergy 24(3): 79-82.
2056. Okano, M., T. Fujiwara, et al. (2011). "Role of fungal antigens in eosinophilia-associated cellular responses in nasal polyps: a comparison with enterotoxin." Clin Exp Allergy 41(2): 171-178.
2057. Agayev A, Yilmaz S. Images in clinical medicine. Cavernous sinus thrombosis. The New Eng Land DA, McNeill Land DA, McNeill journal of medicine. 2008 Nov 20;359(21):2266.
2058. Razek AA, Castillo M. Imaging lesions of the cavernous sinus. AJNR American journal of neuroradiology. 2009 Mar;30(3):444-52.
2059. Absoud M, Hikmet F, Dey P, Joffe M, Thambapillai E. Bilateral cavernous sinus thrombosis complicating sinusitis. Journal of the Royal Society of Medicine. 2006 Sep;99(9):474-6.
2060. Parmar H, Gandhi D, Mukherji SK, Trobe JD. Restricted diffusion in the superior ophthalmic vein and cavernous sinus in a case of cavernous sinus thrombosis. Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society. 2009 Mar;29(1):16-20.
2061. Bachert C, Zhang N, van Zele T, Gevaert P, Patou J, van Cauwenberge P. Staphylococcus aureus enterotoxins as immune stimulants in chronic rhinosinusitis. Clin Allergy Immunol. 2007;20:163-75.
2062. Fokkens WJ, Holm AF, Rijntjes E, Mulder PG, Vroom TM. Characterization and quantification of cellular infiltrates in nasal mucosa of patients with grass pollen allergy, non-allergic patients with nasal polyps and controls. Int Arch Allergy Appl Immunol. 1990;93(1):66-72.
2063. Ming YL, Rhee C. Inflammatory cytokine expression on nasal polyps developed in allergic and infectious rhinitis. Acta Otolaryngol Suppl. 1997;117:302.
2064. Venkatachalam VP, Jain A. Comparative evaluation of functional endoscopic sinus surgery and conventional surgery in the management of chronic sinusitis. Journal of the Indian Medical Association. 2002;100(2):78-9, 82-3-78-9, 82-3.
2065. Ahmed J, Pal S, Hopkins C, Jayaraj S. Functional endoscopic balloon dilation of sinus ostia for chronic rhinosinusitis. Cochrane database of systematic reviews (Online). [10.1002/14651858.CD008515.pub2]. 2011(7):CD008515-CD.
2066. Rupa V, Jacob M, Mathews MS, Seshadri MS. A prospective, randomised, placebo-controlled trial of postoperative oral steroid in allergic fungal sinusitis. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2010 Feb;267(2):233-8.
2067. Alobid I, Benitez P, Pujols L, Maldonado M, Bernal-Sprekelsen M, Morello A, et al. Severe nasal polyposis and its impact on quality of life. The effect of a short course of oral steroids followed by long-term intranasal steroid treatment. Rhinology. 2006;44(1):8-13.
2068. Hissaria P, Smith W, Wormald PJ, Taylor J, Vadas M, Gillis D, et al. Short course of systemic corticosteroids in sinonasal polyposis: A double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. Journal of Allergy & Clinical Immunology. 2006;118(1):128-33.
2069. Ferguson BJ. Categorization of eosinophilic chronic rhinosinusitis. Current Opinion in Otolaryngology & Head & Neck Surgery. [Review]. 2004;12(3):237-42.
2070. Asplund MS, Hagberg H, Holmstrom M. Chemotherapy in severe nasal polyposis--a possible beneficial effect? A report of three cases. Rhinology. 2010 Sep;48(3):374-6.
2071. Buyukozturk S, Gelincik A, Aslan I, Aydin S, Colakoglu B, Dal M. Methotrexate: can it be a choice for nasal polyposis in aspirin exacerbated respiratory disease? J Asthma. 2009 Dec;46(10):1037-41.

CONTENT

With thanks to our sponsors:

NeilMed®

Bionorica®

HPH

HARTINGTON PHARMACEUTICAL

ERS

EAACI

EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

Medtronic

REGENERON

SANOFI

Grupo Uriach