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European Position Paper on Rhinosinusitis and Nasal Polyps 2007

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ABSTRACT

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Rhinosinusitis is a significant and increasing health problem which results in a large financial burden on society. This evidence based
position paper describes what is known about rhinosinusitis and nasal polyps, offers evidence based recommendations on diagnosis
and treatment, and considers how we can make progress with research in this area.

Rhinitis and sinusitis usually coexist and are concurrent in most individuals; thus, the correct terminology is now rhinosinusitis.
Rhinosinusitis (including nasal polyps) 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 polyps and/or mucopurulent discharge primarily
from middle meatus and/or; oedema/mucosal obstruction primarily in middle meatus, and/or CT changes showing mucosal changes
within the ostiomeatal complex and/or sinuses.

The paper gives different definitions for epidemiology, first line and second line treatment and for research.

Furthermore the paper describes the anatomy and (patho)physiology, epidemiology and predisposing factors, inflammatory mecha-
nisms, evidence based diagnosis, medical and surgical treatment in acute and chronic rhinosinusitis and nasal polyposis in adults and
children. Evidence based schemes for diagnosis and treatment are given for the first and second line clinicians. Moreover attention is
given to complications and socio-economic cost of chronic rhinosinusitis and nasal polyps. Last but not least the relation to the lower
airways is discussed.

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European Position Paper on Rhinosinusitis and Nasal Polyps 2007

CONTENTS

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 [1-3]. Data on (chronic) rhinosinusitis are limited and the disease entity is badly defined. Therefore, the available data are difficult to interpret and extrapolate.

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 [4-7]. In 2005 the first European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) was published [8, 9]. 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 can make progress with research in this area. The paper has been approved by the European Rhinologic Society.

Evidence-based medicine is an important method of preparing guidelines [10, 11]. Moreover, the implementation of guidelines is equally important.

Table 1-1. Category of evidence [11]

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

Since the preparation of the first EP3OS document an increasing amount of evidence on the pathophysiology, diagnosis and treatment has been published (Figure 1).

Figure 1. Randomized controlled trials in chronic rhinosinusitis with or without nasal polyps. The number of trials in the last 5-6 years equals the number ever published before.
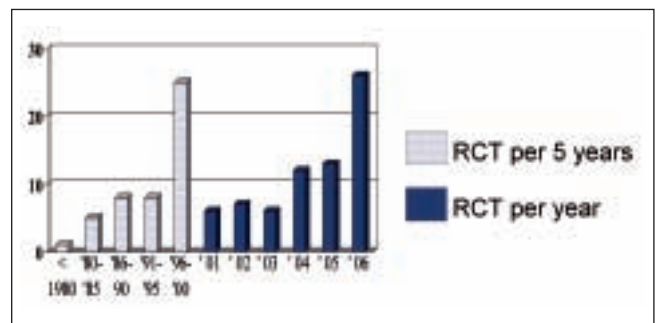
This revision is intended to be a state-of-the art review for the specialist as well as for the general practitioner:
- to update their knowledge of rhinosinusitis and nasal polyposis;
- to provide an evidence-based documented review of the diagnostic methods;
- to provide an evidence-based review of 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.

In this revision new data have led to considerable increase in amount of available evidence and therefore to considerable changes in the schemes for diagnosis and treatment.
Moreover the whole 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 attributed to our knowledge and understanding.

2. Definition of rhinosinusitis and nasal polyps

2-1 Introduction

Rhinitis and sinusitis usually coexist and are concurrent in most individuals; thus, the correct terminology is now rhinosinusitis. The diagnosis of rhinosinusitis is made by a wide variety of practitioners, including allergologists, otolaryngologists, pulmonologists, primary care physicians and many others. Therefore, an accurate, efficient, and accessible definition of rhinosinusitis is required. A number of groups have published reports on rhinosinusitis and its definition. In most of these reports definitions are based on symptomatology and duration of disease and a single definition is aimed at all practitioners [4, 5, 12, 13].

Due to the large differences in technical possibilities to diagnose and treat rhinosinusitis/nasal polyps by various disciplines, the need to differentiate between subgroups varies. On 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 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

2-2-1 Clinical definition of rhinosinusitis/nasal polyps

2-2-1-1 Bacteria
Rhinosinusitis (including nasal polyps) 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:
  - 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 Severity of the disease
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:

HOW TROUBLESOME ARE YOUR SYMPTOMS OF RHINOSINUSITIS?

10 cm

Not troublesome   Worst thinkable troublesome
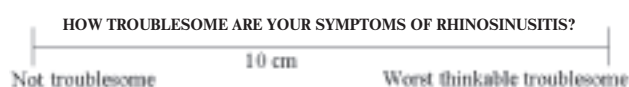
A VAS > 5 affects patient QOL [14].

2-2-3 Duration of the disease

Acute
  < 12 weeks
  complete resolution of symptoms.
Chronic
  > 12 weeks symptoms
  without complete resolution of symptoms.

Chronic rhinosinusitis may also be subject to exacerbations

2-3 Definition for use in epidemiology studies/General Practice

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

Acute rhinosinusitis (ARS) 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.

Acute rhinosinusistis 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 acute rhinosinusitis.

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

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

Chronic rhinosinusitis with or without nasal polyps 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.

2-4 Definition for research

For research purposes acute rhinosinusitis is defined as above. Bacteriology (antral tap, middle meatal tap) and/or radiology (X-ray, CT) are advised, but not obligatory.

For research purposes chronic rhinosinusitis (CRS) is defined as above. CRS is the major finding and nasal polyposis (NP) is considered a subgroup of this entitiy. For the purpose of a study, the differentiation between CRS and NP must be based on out-patient endoscopy. The research definition is based on the presence of polyps and prior surgery.

2-4-1 Definition of chronic rhinosinusitis when no earlier sinus surgery has been performed

Chronic rhinosinusitis with nasal polyposis:
polyps bilateral, endoscopically visualised in middle meatus
Chronic rhinosinusitis without nasal polyps:
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 IgE or SPT's.

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 and/or nasal polyposis:
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. Chronic rhinosinusitis with or without nasal polyps

3-1 Anatomy and (patho)physiology

The nose and paranasal sinuses constitute a collection of air-filled spaces within the anterior skull. The paranasal sinuses communicate with the nasal cavity through small apertures. The nasal cavity and its adjacent paranasal sinuses are lined by pseudostratified columnar ciliated epithelium. This contains goblet cells and nasal glands, producers of nasal secretions that keep the nose moist and form a "tapis roulant" of mucus. Particles and bacteria can be caught in this mucus, rendered harmless by enzymes like lysozyme and lactoferrin, and be transported down towards the oesophagus. Cilia play an important role in mucus transport. All paranasal sinuses are normally cleared by this mucociliary transport, even though transport from large areas of sinuses passes through small openings towards the nasal cavity.

A fundamental role in the pathogenesis of rhinosinusitis is played by the ostiomeatal complex, a functional unit that comprises maxillary sinus ostia, anterior ethmoid cells and their ostia, ethmoid infundibulum, hiatus semilunaris and middle meatus. The key element is the maintenance of the ostial patency. Specifically, ostial patency significantly affects mucus composition and secretion; moreover, an open ostium allows mucociliary clearance to easily remove particulate matter and bacteria. Problems occur if the orifice is too small for the amount of mucus, if mucus production is increased, for instance during an upper respiratory tract infection (URTI), or if ciliary function is impaired. Stasis of secretions follows and bacterial export ceases, causing or exacerbating inflammation of the mucosa whilst aeration of the mucosa is decreased, causing even more ciliary dysfunction. This vicious cycle can be difficult to break, and if the condition persists, it can result as chronic rhinosinusitis. In chronic rhinosinusitis the role of ostium occlusion seems to be less pronounced than in ARS.

3-2 Rhinosinusitis

Rhinosinusitis is an inflammatory process involving the mucosa of the nose and one or more sinuses. The mucosa of the nose and sinuses form a continuum and thus more often than not the mucous membranes of the sinus are involved in diseases which are primarily caused by an inflammation of the nasal mucosa. Chronic rhinosinusitis is a multifactorial disease [15]. Factors contributing can be mucociliairy impairment [16, 17], (bacterial) infection [18], allergy [19], swelling of the mucosa for another reason, or rarely physical obstructions caused by morphological/anatomical variations in the nasal cavity or paranasal sinuses [20, 21]. A role in the pathogenesis of rhinosinusitis is certainly played by the ostiomeatal complex, a func-tional unit that comprises maxillary sinus ostia, anterior ethmoid cells and their ostia, ethmoid infundibulum, hiatus semilunaris and middle meatus. The key element is the maintenance of the ostial patency. An in depth discussion on factors contributing to chronic rhinosinusitis and nasal polyps can be found in chapter 4.

3-3 Chronic rhinosinusitis with or without nasal polyps

Chronic rhinosinusitis with or without nasal polyps is often taken together as one disease entity, because it seems impossible to clearly differentiate both entities [22-24]. Chronic rhinosinusitis with nasal polyps (CRS without NP) is considered a subgroup of chronic rhinosinusitis (CRS) (Figure 3-1).
The question remains as to why "ballooning" of mucosa develops in polyposis patients and not in all rhinosinusitis patients. Nasal polyps have a strong tendency to recur after surgery even when aeration is improved [25]. This may reflect a distinct property of the mucosa of polyp patients which has yet to be identified. Some studies have tried to divide chronic rhinosinusitis and nasal polyps based on inflammatory markers [26-30]. Although these studies point to a more pronounced eosinophilia and IL-5 expression in nasal polyps than that found in patients with chronic rhinosinusitis, these studies also point to a continuum in which differences might be found at the ends of the spectrum but at the moment no clear cut division can be made.

Figure 3-1. The spectrum of chronic rhinosinusitis and nasal polyps
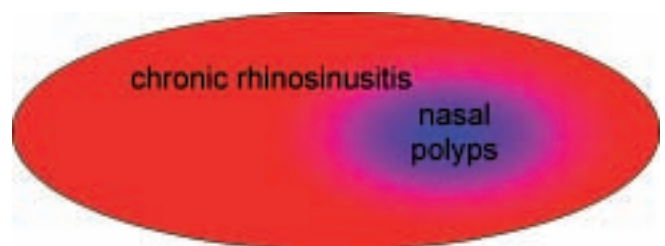
Nasal polyps appear as grape-like structures in the upper nasal cavity, originating from within the ostiomeatal complex. They consist of loose connective tissue, oedema, inflammatory cells and some glands and capillaries, and are covered with varying types of epithelium, mostly respiratory pseudostratified epithelium with ciliated cells and goblet cells. Eosinophils are the most common inflammatory cells in nasal polyps, but neutrophils, mast cells, plasma cells, lymphocytes and monocytes are also present, as well as fibroblasts. IL-5 is the predominant cytokine in nasal polyposis, reflecting activation and prolonged survival of eosinophils [31].

The reason why polyps develop in some patients and not in others remains unknown. There is a definite relationship in patients with 'Samter triad': asthma, NSAID sensitivity and nasal polyps. However, not all patients with NSAID sensitivity have nasal polyps, and vice-versa. In the general population, the prevalence of nasal polyps is 4% [32]. In patients with asthma, a prevalence of 7 to 15% has been noted whereas, in NSAID sensitivity, nasal polyps are found in 36 to 60% of patients [33, 34]. It had long been assumed that allergy predisposed to nasal polyps because the symptoms of watery rhinorrhoea and mucosal swelling are present in both diseases, and eosinophils are abundant. However, epidemiological data provide no evidence for this relationship: polyps are found in 0.5 to 1.5% of patients with positive skin prick tests for common allergens [34, 35].

4. Epidemiology and predisposing factors

4-1 Introduction

Rhinosinusitis 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.

The incidence of acute viral rhinosinusitis (common cold) is very high. It has been estimated that adults suffer 2 to 5 colds per year, and school children may suffer 7 to 10 colds per year. The exact incidence is difficult to measure because most patients with common cold do not consult a doctor. Recently a case control study in the Dutch population concluded that an estimated 900000 consultations take place annually for acute respiratory tract infection. Rhinovirus (24%) and Influenzae (11%) were the most common agents isolated. [36]. More reliable data are available on ARS. As mentioned earlier acute non-viral rhinosinusitis (ARS) is defined as an increase of symptoms after 5 days or persistent symptoms after 10 days after a sudden onset of two or more of the symptoms: nasal blockage/congestion, anterior discharge/postnasal drip, facial pain/pressure, and/or reduction/loss of smell. It is estimated that only 0.5% to 2% of viral URTIs are complicated by bacterial infection; however, the exact incidence is unknown given the difficulty distinguishing viral from bacterial infection without invasive sinus-puncture studies. Bacterial culture results in suspected cases of acute community-acquired sinusitis are positive in only 60% of cases [37]. Signs and symptoms of bacterial infection may be mild and often resolve spontaneously [38, 39].

In spite of the high incidence of ARS and prevalence and significant morbidity of chronic rhinosinusitis (CRS), with and without nasal polyps, there is only limited accurate data on the epidemiology of these conditions. This observation mainly relates to the lack of a uniformly accepted definition for CRS. In addition, patient selection criteria greatly differ between epidemiologic studies complicating comparison of studies. When interpreting epidemiologic data, one should be aware of a significant selection bias of the different studies presented below. The purpose of this section of the EP3OS document is to give an updated overview of the currently available epidemiologic data on ARS and CRS with and without nasal polyps, and illustrate the factors which are believed to predispose to their development.

4-2 Acute bacterial rhinosinusitis.

When describing the incidence of acute bacterial rhinosinusitis there has been a lot of debate about the actual definition of the condition. For example in the Cochrane Review on antibiotics for ARS, studies were included if sinusitis was proven by a consistent clinical history, and radiographic or aspiration evidence of ARS [40]. However, most guidelines on the diagnosis of acute bacterial rhinosinusitis base the diagnosis on symptoms and clinical examination. However, if the diagnosis is based on clinical examination alone, the rate of false positive results is high. In patients with a clinical diagnosis of ARS, less than half have significant abnormalities at X-ray examination [41]. Based on sinus puncture/aspiration (considered the most accurate), 49-83% of symptomatic patients had ARS [42]. Compared with puncture/aspiration, radiography offered moderate ability to diagnose sinusitis Using sinus opacity or fluid as the criterion for sinusitis, radiography had sensitivity of 0.73 and specificity of 0.80 [42].

An average of 8.4 % of the Dutch population reported at least one episode of ARS per year in 1999 [43]. The incidence of visits to the general practitioner for acute sinusitis in the Netherlands in 2000 was 20 per 1000 men and 33.8 per 1000 women [44]. According to National Ambulatory Medical Care Survey (NAMCS) data in the USA, sinusitis is the fifth most common diagnosis for which an antibiotic is prescribed. Written in 2002, sinusitis accounted for 9% and 21% of all paediatric and adult antibiotic prescriptions respectively [4].

4-3 Factors associated with acute rhinosinusitis.

4-3-1 Pathogens
Superinfection by bacteria on mucosa damaged by viral infection (common cold) is the most important cause of ARS. The most common bacterial species isolated from the maxillary sinuses of patients with ARS are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*, the latter being more common in children [45, 46]. Other *streptococcal species, anaerobic bacteria* and *Staphylococcus aureus* cause a small percentage of cases. Resistance patterns of the predominant pathogens vary considerably [47, 48]. The prevalence and degree of antibacterial resistance in common respiratory pathogens are increasing worldwide. In France, increases in resistance have been observed during the last twenty years in the same geographical area for *H. influenzae* and *S. pneumoniae* [49]. The association between inappropriate antibiotic consumption and the prevalence of resistance is widely assumed based on in vitro experience [50]. Pathogens may also influence the severity of symptomatology [51].

4-3-2 Ciliary impairment
Normal mucociliary flow is a significant non-specific defence mechanism in the prevention of ARS. Viral rhinosinusitis

results in the loss of cilia and ciliated cells, reaching a maximum around one week after the infection. Three weeks after the beginning of the infection the number of cilia and ciliated cells increases to nearly normal. However, as a sign of regeneration, immature short cilia (0.7 to 2.5 μm in length) were often seen [52]. The impaired mucociliary function during viral rhinosinusitis results in an increased sensitivity to bacterial infection.

Also in animal experiments it was shown that shortly after exposure to pathogenic bacteria, like *Streptococcus pneumoniae, Hemophilus influenzae, Pseudomonas aeruginosa*, a significant loss of ciliated cells from sinus mucosa and a corresponding disruption of normal mucociliary flow occurred [53].

4-3-3 Allergy

Review articles on sinusitis have suggested that atopy predisposes to rhinosinusitis [54]. This theory is attractive given the popularity of the concept that disease in the ostiomeatal area contributes to the development of sinus disease. Mucosa in an individual with allergic rhinitis might be expected to be swollen and therefore more liable to obstruct sinus ostia, reduce ventilation, leading to mucus retention which in turn might be more prone to 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 reflected in the term 'rhinosinusitis' [55]. However, the number of studies determining the occurrence of ARS in patients with and without allergy are very limited.

Savolainen studied the occurrence of allergy in 224 patients with verified ARS by means of an allergy questionnaire, skin testing, and nasal smears. Allergy was found in 25% of the patients and considered probable in another 6.5%. The corresponding percentages in the control group were 16.5 and 3, respectively. There were no differences between allergic and non-allergic patients in the number of previous ARS episodes nor of previously performed sinus irrigations. Bacteriological and radiological findings did not differ significantly between the groups [56]. Alho showed that subjects with allergic IgE-mediated rhinitis had more severe paranasal sinus changes on CT scanning than non-allergic subjects during viral colds. These changes indicate impaired sinus functioning and may increase the risk of bacterial sinusitis [57]. Alho studied cellular modifications during acute viral rhinitis in three different groups (allergic, recurrent sinusitis, and healthy patients). No significant difference in inflammatory cells was found in any group during acute (D0) and convalescent (D21) phases.

In a small prospective study, no difference in prevalence of purulent rhinosinusitis was found between patients with and without allergic rhinitis [58]. Furthermore, allergy was found in 31.5% of patients with verified acute maxillary sinusitis and there were no differences between allergic and non-allergic patients in the number of prior ARS episodes [56]. Newman et

al. reported that whilst 39% of patients with CRS had asthma, raised specific IgE or an eosinophilia, only 25% had true markers to show they were atopic [59]. Finally, Emanuel et al. [60] found relatively lower percentages of allergic patients in the group of patients with the most severe sinus disease on CT scan and Iwens et al. [61] reported that the prevalence and extent of sinus mucosa involvement on CT was not determined by the atopic state.

Radiologic studies are unhelpful in unravelling the correlation between allergy and rhinosinusitis. High percentages of sinus mucosa abnormalities are found on radiologic images of allergic patients, e.g. 60% incidence of abnormalities on CT scans among subjects with ragweed allergy during the season [62]. However, one should interpret this data with caution in view of the fact that high percentages of incidental findings are found on radiologic images of the sinus mucosa in individuals without nasal complaints, ranging from 24.7 % to 49.2 % [63-66], that the normal nasal cycle induces cyclical changes in the nasal mucosa volume [67], and that radiological abnormalities do not correlate well with patient's symptoms [62].

Holzmann reported an increased prevalence of allergic rhinitis in children with orbital complications of ARS, and these complications occurred especially during the pollen season [68]. In a study involving 8723 children, Chen and colleagues found the prevalence of sinusitis to be significantly higher in children with allergic rhinitis than in children without allergies [69].

In conclusion, although an attractive hypothesis, we can repeat the statement made a decade ago that there are no published prospective reports on the incidence of infective rhinosinusitis in populations with and without clearly defined allergic rhinosinusitis [70].

4-3-4 Helicobacter pylori and laryngopharyngeal reflux

Very few articles can be found in the literature regarding the role of the laryngopharyngeal reflux (LPR) and/or *Helicobacter pylori* infection in the pathogenesis of ARS. More have investigated a possible role in CRS but without significant results. Wise described a correlation between LPR (detected either with pH sensor and/or with symptom scores), and postnasal drip without the typical findings of CRS, a problem which might predispose a subject to an acute bacterial infection [71]. In a case report, Dinis underlines the presence of *Helicobacter* in the sphenoid sinus of a patient with severe sphenoid sinusitis that was also treated with *Helicobacter pylori* therapy [72]. Therefore, even if there is no clear correlation between reflux disease and/or Helicobacter pylori infection and ARS, this is undoubtedly a field for future investigation when one considers the increase of this gastrointestinal problem in developed countries and the fact that the acid content of reflux and the Helicobacter infection itself can cause mucociliary impairment.

4-3-5 Other risk factors : ventilation, naso-gastric tube
Nosocomial sinusitis are frequently observed in intensive care [73, 74] and have been generally linked to naso-tracheal intubation [75] or presence of naso-gastric tube [76]. The maxillary sinus is frequently involved. Endoscopy of the middle meatus is useful to determine the presence of purulence in the middle meatus and if the culture is possible. Bacteriology differs from community acquired cases with a more frequent isolation of anaerobic bacteria [77]. Treatment may include, complementary to adjustment of antibiotic treatment, drainage, daily lavage and removal of the grastic tube [78].

4-4 Chronic rhinosinusitis (CRS) without nasal polyps

The paucity of accurate epidemiologic data on CRS with or without nasal polyps 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 [79], 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 [80]. However, the prevalence of doctor-diagnosed CRS is much lower; a prevalence of 2% was found using ICD-9 codes as an identifier [81]. Corroboration of the definitive diagnosis of CRS should be done with nasal endoscopy [82] or CT [83]. As the diagnosis of CRS has primarily been based on symptoms, often excluding dysosmia, this means that the diagnosis of CRS is often overestimated [83]. The majority of primary care physicians do not have the training or equipment to perform nasal endoscopy that also leads to overdiagnosis [84].

Interestingly, the prevalence rate of CRS was substantially higher in females with a female/male ratio of 6/4 [79]. 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 [85]. 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% [85]. 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% [86], 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. [87] 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) [88]. Not withstanding the shortcomings of epidemiologic studies on CRS, it represents a common disorder of multifactorial origin. A list of factors will be discussed in the following chapter which are believed to be etiologically linked to CRS.

4-5 Factors associated with chronic rhinosinusitis (CRS) without nasal polyps

4-5-1 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 chronic rhinosinusitis, and is probably reversible, although restoration takes some time [89]. 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. Nasal polyps are present in about 40% of patients with CF [90]. These polyps are generally more neutrophilic than eosinophilic in nature but may respond to steroids nonetheless, as inhaled steroids in patients with CF reduce neutrophilic inflammation [91-93].

4-5-2 Allergy
Review articles on rhinosinusitis have suggested that atopy predisposes to its development [54, 94]. 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 [95, 96] and are frequently associated.

It has been postulated [97] 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. Futhermore, 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 [55]. However, critical analysis of the papers linking atopy as a risk factor to infective rhinosinusitis (chronic or acute) reveal that whilst many of the studies suggest a higher prevalence of allergy in patients presenting with symptoms consistent with sinusitis 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 [30, 98-102]. 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 [103]. Among CRS patients undergoing sinus surgery, the prevalence of positive skin prick tests ranges from 50% to 84% [56, 60, 104], of which the majority (60%) have multiple sensitivities [60]. As far back as 1975, Friedman reported an incidence of atopy in 94% of patients undergoing sphenoethmoidectomies [105].

However, the role of allergy in CRS is questioned by other epidemiologic studies showing no increase in the incidence of infectious rhinosinusitis during the pollen season in pollen-sensitized patients [70]. 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 [106]. 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 [106].

4-5-3 Asthma

Recent evidence suggests that allergic inflammation in the upper and lower airways coexist and should be seen as a continuum of inflammation, with inflammation in one part of the airway influencing its counterpart at a distance. The arguments and consequences of this statement are summerized in the ARIA document [107]. Rhinosinusitis and asthma are also frequently associated in the same patients, but their inter-relationship is poorly understood. The evidence that treatment of rhinosinusitis improves asthma symptoms and hence reduces the need for medication to control asthma, mainly results from research in children and will be discussed below (Chapter 9-7). In short, improvements in both asthma symptoms and medication have been obtained after surgery for rhinosinusitis in children with both conditions [108-110].

Studies on radiographic abnormalities of the sinuses in asthmatic patients have shown a high prevalence of abnormal sinus mucosa [111, 112]. All patients with steroid-dependant asthma had abnormal mucosal changes on CT compared to 88% with mild to moderate asthma [113]. Again caution should be exercised in the interpretation of these studies. Radiographically detected sinus abnormalities in sensitized patients may reflect inflammation related to the allergic state rather than to sinus infection.

4-5-4 Immunocompromised state

Among conditions associated with dysfunction of the immune system, congenital immunodeficiencies manifest themselves with symptoms early in life and will be dealt with in the paedi-

atric CRS section (see Chapter 7-6). 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. found an unexpectedly high incidence of immune dysfunction [114]. Of the 60 patients with in vitro T-lymphocyte function testing, 55% showed abnormal proliferation in response to recall antigens. Low immunoglobulin G, A, and M 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. [115] reported that sinusitis 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. [116] reported a lower incidence of rhinosinusitis (34%), but with a good correlation between low CD4+ cell count and the probability of rhinosinusitis. 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 [117].

4-5-5 Genetic factors

Although chronic sinus disease 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 (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 [118]. The most common mutation, F508, is found in 70 to 80% of all CFTR genes in Northern Europe [119, 120]. Upper airway manifestations of CF patients include chronic rhinosinusitis and nasal polyps, which are found in 25 to 40 % of CF patients above the age of 5 [121-124]. Interestingly, Jorissen et al. [125] 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 [126].

4-5-6 Pregnancy and endocrine state

During pregnancy, nasal congestion occurs in approximately one-fifth of women [127]. 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 like vascular changes may be involved. Whether pregnancy rhinitis predisposes to the development of sinusitis, is not clear. In a small prospective study, Sobol et al. [128] 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% [129]. In addition, thyroid dysfunction has been implicated in CRS, b there is only limited data on the prevalence of CRS in patients with hypothyroidism.

4-5-7 Local host factors
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 [130]. However, some studies that have made this assertion have equated mucosal thickening on CT with CRS [131] when it has been shown that incidental mucosal thickening occurs in approximately a third of an asymptomatic population [20]. However, Bolger et al. [132] found no correlation between CRS and bony anatomic variations in the nose. Holbrook et al. also found no correlation between sinus opacification, anatomical variations and symptom scores [133]. However, 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 [134] there are several studies that show the prevalence of anatomical variations is no more common in patients with rhinosinusitis or polyposis than in a control population [20, 21, 135]. 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. [136, 137]. 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 [138, 139] whilst others have not [21, 137, 140]. Taken together, there is no evidence for a causal correlation between nasal anatomic variations in general and the incidence of CRS. In spite of the observation that sinonasal complaints often resolve after surgery, this does not necessarily imply that anatomic variation is etiologically involved.

CRS of dental origin should not be overlooked when considering the etiology 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.

4-5-8 Micro-organisms

4-5-8-1 Bacteria
Although it is often hypothesized that CRS evolves from ARS, this has never been proven. Furthermore, the role of bacteria in CRS is far from clear. A number of authors have described the microbiology of the middle meatus and sinuses. However if and which of these pathogen are contributory to the disease remains a matter of debate. Bhattacharyya (2005) found that both anaerobes and aerobic species could be recovered from both diseased and the non-diseased contralateral side of patients with chronic rhinosinusitis casting doubt on the aetiologic role of bacteria in CRS [141]. Anaerobes are more prevalent in infections secondary to dental problems.

Arouja isolated aerobes from 86% of the middle meatus samples of CRS patients, whereas anaerobes were isolated in 8%. The most frequent microorganisms were *Staphylococcus aureus* (36%), *coagulase-negative Staphylococcus* (20%), and *Streptococcus pneumoniae* (17%). Middle meatus and maxillary sinus cultures presented the same pathogens in 80% of cases. In healthy individuals, *coagulase-negative Staphylococcus* (56%), *S. aureus* (39%), and *S. pneumoniae* (9%) were the most frequent isolates. [142]. Some authors suggest that as chronicity develops, the aerobic and facultative species are gradually replaced by anaerobes [143, 144]. This change may result from the selective pressure of antimicrobial agents that enable resistant organisms to survive and from the development of conditions appropriate for anaerobic growth, which include the reduction in oxygen tension and an increase in acidity within the sinus. Often polymicrobial colonisation is found; the contribution to the disease of the different pathogens remains unclear. The presence of intracellular *S. aureus* in epithelial cells of the nasal mucosa has been suggested to pay a significant risk factor for recurrent episodes of rhinosinusitis due to persistent bacterial clonotypes, which appear refractory to antimicrobial and surgical therapy [145].

4-5-8-2 Fungi
Fungi have been cultured from human sinuses [146]. Their presence may be relatively benign, colonizing normal sinuses or forming saprophytic crusts. They may also cause a range of pathology, ranging from non-invasive fungus balls to invasive, debilitating disease [147].

There is an increasing interest in the concept that the most common form of sinus disease induced by fungus may be caused by the inflammation stimulated by airborne fungal antigens. In 1999 it was proposed that most patients with CRS exhibit eosinophilic infiltration and the presence of fungi by histology or culture [148]. This assertion was based on finding positive fungal culture by using a new culture technique in 202 of 210 (96%) patients with CRS who prospectively were evaluated in a cohort study. No increase in type I sensitivity was found in patients as compared with controls. The term "eosinophilic

chronic rhinosinusitis" was proposed to replace previously used nomenclature (allergic chronic rhinosinusitis). Using this new culture technique, the same percentage of positive fungi cultures was also found in normal controls [149].

Pant et al. suggest that fungal-specific immunity is characterised by serum IgG3 and not IgE distinguished patients with CRS and eosinophilic mucus from healthy controls, regardless of whether fungi were found within the mucus. They found no differences between those with CRS and the eosinophilic mucus group and a group with allergic fungal rhinosinusitis [150].

Some authors suggest that non IgE mediated mechanisms to fungal spores might be responsible for eosinophilic inflammation seen in some individuals [151] Shin et al. found that patients with CRS had an exaggerated humoral and TH1 and TH2 cellular response to common airborne fungi, particularly Alternaria. No increase in type I sensitivity was found in patients as compared with controls [152]. In another study no correlation was found between fungal parameters and the clinical parameters of CRS or the presence of eosinophilia [153] and the use of quantitative PCR produced a recovery rate of fungi of 46% in a group with CRS and a control group [154].

A broad array of fungi has been identified in the sinus cavities of patients with sinusitis through varied staining and culture techniques [148, 149]. As with the isolation of bacteria in sinus cavities in these patients, the presence of fungi does not prove that these pathogens directly create or perpetuate disease. The use of topical or systemic antifungal agents have not consistently been shown to help patients with CRS [155, 156].

4-5-9 "Osteitis"—the role of bone

Areas of increased bone density and irregular bony thickening are frequently seen on CT in areas of chronic inflammation and may be a marker of the chronic inflammatory process [157]. However, the effect during the initial phases of a severe CRS frequently appears as rarefaction of the bony ethmoid partitions. Although to date bacterial organisms have not been identified in the bone in either humans or animal models of CRS, it has been suggested that that this irregular bony thickening is a sign of inflammation of the bone which in turn might maintain mucosal inflammation [158].

In rabbit studies it was demonstrated that not only the bone adjacent to the involved maxillary sinus become involved, but that the inflammation typically spreads through the Haversian canals and may result in bone changes consistent with some degree of chronic osteomyelitis at a distance from the primary infection [159, 160]. It is certainly possible that these changes, if further confirmed in patients, may at least in part, explain why CRS is relatively resistant to therapy.

4-5-10 Environmental factors

Cigarette smoking was associated with a higher prevalence of rhinosinusitis in Canada [85], whereas this observation was not confirmed in a nationwide survey in Korea [86]. Other lifestyle-related factors are undoubtedly involved in the chronic inflammatory processes of rhinosinusitis. For instance, low income was associated with a higher prevalence of CRS [85]. In spite of in vitro data on the toxicity of pollutants on respiratory epithelium, there exists no convincing evidence for the etiologic role of pollutants and toxins such as ozone in CRS.

4-5-11 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 [161]. 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 [162].

4-5-12 Helicobacter pylori and laryngopharyngeal reflux

Heliobacter pylori DNA has been detected in between 11% [163] and 33% [164] of sinus samples from patients with CRS but not from controls. However, as in ARS this does not prove a causal relationship.

4-6 Chronic rhinosinusitis with nasal polyps

Epidemiologic studies rely on nasal endoscopy and/or questionnaires to report on the prevalence of nasal polyps (NP). Large NP can be visualized by anterior rhinoscopy, whereas nasal endoscopy is warranted for the diagnosis of smaller NP. Nasal endoscopy appears to be 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 [165]. Therefore, 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 [166].

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 CRS with NP do not seek medical advice for their sinonasal symptoms [167]. Compared to

patients with CRS with NP not seeking medical attention, those actively seeking medical care for CRS with NP had more extensive NP with more reduction of peak nasal inspiratory flow and greater impairment of the sense of smell [168].

In a population-based study in Skövde, Sweden, Johansson et al. [165] 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 [136]. Based on a postal questionnaire survey in Finland, Hedman et al. [32] 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. [167] reported a prevalence of NP of 2.1% in France.

From autopsy studies, a prevalence of 2% has been found using anterior rhinoscopy [169]. After removing whole naso-ethmoidal blocks, nasal polyps were found in 5 of 19 cadavers [170], and in 42% of 31 autopsy samples combining endoscopy with endoscopic sinus surgery [171]. 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 [172]. In a prospective study on the incidence of symptomatic NP, Larsen and Tos [173] 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% [174], with a higher prevalence (6.7%) in the asthmatic patients.

In general, NP occur in all races and becomes more common with age [167, 175-178]. The average age of onset is approximately 42 years, which is 7 years older than the average age of the onset of asthma [179-181]. NP are uncommon under the age of 20 [182] and are more frequently found in men than in women [32, 173, 183], except in the studies by Settipane [174] and Klossek [167].

4-7 Factors associated with chronic rhinosinusitis with nasal polyps

4-7-1 Allergy
From 0.5 to 4.5% of subjects with allergic rhinitis have NP [34, 35, 184], which compares with the normal population [172]. In children the prevalence of CRS with NP has been reported to be 0.1% [34] and Kern found NP in 25.6% of patients with allergy com-

pared to 3.9% in a control population [185]. On the other hand, the prevalence of allergy in patients with NP has been reported as varying from 10% [186], to 54% [187] and 64% [188]. Contrary to reports that have implicated atopy as being more prevalent in patients with NP, others have failed to show this [34, 184, 189-191]. Recently, Bachert et al. [192] 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% [193] and 81% [194] of NP patients compared to respectively 34% and 11% of controls. Based on questionnaires, food allergy was reported by 22% [167] and 31% [177] of patients with NP, which was significantly higher than in non-NP controls [167]. 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 [194]. Further research is needed to investigate a possible role for food allergy in the initiation and perpetuation of NP.

4-7-2 Asthma
Bronchial symptoms are associated with NP in a subgroup of patients [195]. Wheezing and respiratory discomfort are present in 31% and 42% of patients with NP, and asthma is reported by 26% of patients with NP, compared to 6% of controls [167]. Alternatively, 7% of asthmatic patients have NP [34], with a prevalence of 13% in non-atopic asthma (skin prick test and total and specific IgE negative) and 5% in atopic asthma [182]. Late onset asthma is associated with the development of nasal polyps in 10-15% [34]. Asthma develops first in approximately 69% of patients with both asthma and CRS with NP. NP take between 9 and 13 years to develop, only two years in aspirin induced asthma [196] Ten percent develop both polyps and asthma simultaneously and the remainder develop polyps first and asthma later (between 2 and 12 years) [175]. Generally NP are twice as prevalent in men although the proportion of those with polyps and asthma is twice that in women than men. Women that have nasal polyps are 1.6 times more likely to be asthmatic and 2.7 times to have allergic rhinitis [178].

4-7-3 Aspirin sensitivity
In patients with aspirin sensitivity 36-96% have CRS with NP [35, 182, 197-202] and up to 96% have radiographic changes affecting their paranasal sinuses [203]. 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 [204]. Concerning hereditary factors, HLA A1/B8 has been reported as having a higher incidence in patients with asthma and aspirin sensitivity [205] although Klossek et al [167] found no difference between gender in 10033 patients. Zhang found that IgE antibodies to enterotoxins can be found in the majority of patients polyps who are aspirin sensitive [206].

4-7-4 Genetics predisposition of chronic rhinosinusitis with nasal polyps

Although the mechanisms involved in the pathogenesis of nasal polyps (NP) remain largely unclear, there are reports suggesting an underlying genetic predisposition. This concept is supported by some clinical data and genetic studies. This chapter does not include NP in cystic fibrosis (CF), which is known to be a hereditary disease with multi-systemic involvement with genetic variations, presenting with defect in chloride transport across membranes and dehydrated secretions.

4-7-4-1 Family and twin studies

An interesting observation is that NP are frequently found to run in families, suggesting a hereditary or with shared environmental factor. In the study by Rugina et al. [177], more than half of 224 NP patients (52%) had a positive family history of NP. The presence of NP was considered when NP had been diagnosed by an ENT practitioner or the tients had undergone sinus surgery for NP. A lower percentage (14%) of familial occurrence of NP was reported earlier by Greisner et al. [86] in smaller group (n = 50) of adult patients with NP. Thus, these results strongly suggest the existence of a hereditary factor in the pathogenesis of NP.

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 [207, 208]. NPs 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 [209].

4-7-4-2 Linkage analysis and association studies

In the literature, some studies were able to show linkage of certain phenotypes of NP to candidate gene polymorphisms. Karjalainen et al. reported that subjects with a single G-to-T polymorphism in exon 5 at +4845 of the gene encoding IL-1alpha (IL-1A) were found to have less risk of developing NP as compared to subjects with common G/G genotype [210]. 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 [211].

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. [212] reported an association between HLA-A74 and NPs, whereas Molnar-Gabor et al. [213] 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 [214]. 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 [215].

4-7-4-3 Multiple gene expressions in nasal polyps

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 (Table 4-1). With the advance of microassay technique, expression profiles of over 10000 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 [216]. In another study [217], 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. Same as for 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.

4-7-5 Environmental factors

The role of environmental factors in the development of CRS with NP is unclear. No difference in the prevalence of CRS with NP has been found related to the patient's habitat or pollution at work [177]. One study found that a significantly smaller proportion of the population with polyps were smokers compared to an unselected population (15% vs. 35%) [177], whereas this was not confirmed by others [167]. One study reports on the association between the use of a woodstove as a primary source of heating and the development of NP [218].

4-8 Epidemiology and predisposing factors for rhinosinusitis in children

4-8-1 Epidemiology

Few prospective population studies exist (see Table 4.1). The first longitudinal study was performed by Maresh and Washburn [219] who followed 100 healthy children from birth to maturity, looking at history, physical examination and routine postero-anterior radiograph of the paranasal sinuses 4 times a year. Postero-anterior standard X-ray of the sinuses in a child gives only information about the maxillary sinuses. There existed a relatively constant percentage (30 %) of "pathologic" antra in the films taken between 1 and 6 years of age. From 6 to 12 years, this percentage dropped steadily to approximately 15%. Variations in size of the sinuses occurred frequently, without any relation to infections. When there was an upper respiratory tract infection ("URTI") in the previous 2 weeks, less than 50% showed clear sinuses. Tonsillectomy had no demonstrable effect on the radiographic appearance of the sinuses.

Since the introduction of CT scanning, it has become clear that a runny nose in a child is not only due to limited rhinitis or adenoid hypertrophy, but that in the majority of the cases the sinuses are involved as well – 64% in a CT scan study of children with a history of chronic purulent rhinorrhea and nasal obstruction [220]. In an MRI study of a non-ENT paediatric population [87] it was shown that the overall prevalence of sinusitis signs in children was 45%. This prevalence increased in the presence of a history of nasal obstruction to 50%, to 80% when bilateral mucosal swelling was present on rhinoscopy, to 81% after a recent upper respiratory tract infection (URI), and to 100% in the presence of purulent secretions. Kristo et al

found a similar overall percentage (50 %) of abnormalities on MRI in 24 school children [221]. At follow-up after 6 to 7 months about half of the abnormal sinuses on MRI findings had resolved or improved without any intervention.

Therefore, in younger children with CRS, there exists a spontaneous tendency towards recovery after the age of 6 to 8 years. A decrease in prevalence of rhinosinusitis in older children was also confirmed by other authors in patient populations [223].

4-8-2 Predisposing factors

These include day care [224, 225], nasal obstruction and passive smoking [226-228]). No protective effect of breast-feeding has been demonstrated [229, 230]. Urban atmospheric pollution in Sao Paulo was associated with a higher prevalence of rhinitis, sinusitis and URTIs in 1000 schoolchildren aged 7-14 years than that seen in 1000 rural children [231]. Children with tonsillitis or otitis media are more likely to suffer from sinusitis than those without suggesting that immunological deficiencies are involved [232]. CRS is more common in children with mucociliary dysfunction due to CF (often plus NP) or primary ciliary dyskinesia and in those with humoral immune deficiencies [233]. Heterozygotes for CF genes occur more commonly than expected in the CRS population suggesting that this may be a predisposing factor [234]. Anatomical variations of the lateral nasal wall are common in children but bear no relationship to sinusitis [235].

4-9 Conclusion

The overview of the currently available literature illustrates the paucity of accurate information on the epidemiology of ARS, and CRS with and without NP, 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 ARS, CRS and NP, and well-defined inclusion criteria for epidemiologic research, will it be possible to obtain accurate epidemiologic data on the natural evolution of CRS and NP, the influence of ethnic background and genetic factors on CRS and NP, and the factors associated with the disease manifestation. Such studies need to be performed in order to make significant progress in the development of diagnostic and therapeutic strategies for affected patients.

Table 4-1. Results of epidemiologic studies in rhinosinusitis is children.

author/year	included group	examination method	result	conclusion
Maresh, Washburn, 1940 [219]	100 healthy children from birth to maturity	ENT-examination and pa-Xray of sinuses	30% "pathologic antra" overall >50% "pathologic antra" with previous upper airway infection (URTI) in the last two weeks	high rate of pathology, can be under or over estimated because of the examination technique
Bagatsch, 1980 [222]	24,000 children in the area of Rostock followed up for 1 year		one or more URTI in the year: 0-2 years: 84% 4-6 years: 74% > 7 years: 80%	increased between November and February

5. Inflammatory mechanisms in acute and chronic rhinosinusitis with or without nasal polyposis

5-1 Introduction

Rhinosinusitis is a heterogeneous group of diseases, with different underlying aetiologies and pathomechanisms, and may indeed represent an umbrella, covering different disease entities. It is currently not understood whether acute recurrent rhinosinusitis necessarily develops into chronic rhinosinusitis, which then possibly gives rise to polyp growth, or whether these entities develop independently from each other. All of these items may be referred to as "rhinosinusitis", meaning "inflammation of the nose and sinuses"; however, for didactic reasons and for future clinical and research purposes, a differentiation of these entities is preferred. For this purpose, we differentiate between acute rhinosinusitis (ARS), chronic rhinosinusitis (CRS) without polyps and chronic rhinosinusitis with nasal polyposis (NP), and omit an ill-defined group of "hyperplastic chronic rhinosinusitis", which might be included in CRS, or represent an overlap between CRS and NP.

5-2 Acute rhinosinusitis

The pathophysiology of ARS remains underexplored because of the difficulty of obtaining mucosal samples during the course of the disease. Few experimental models have been dedicated to bacterial infections though experimental models of viral rhinosinusitis in animals and man exist.[236-238]. The common cold is commonly presumed to be implicated in opportunistic bacterial infections due to impairment of mechanical, humoral and cellular defences and epithelial damage. Usually two phases of reaction are described: a non-specific phase where the mucus and its contents (eg: lysozyme, defensin) play a major role and a second including the immune response and inflammatory reaction. Common cold symptoms are usually short- lived with a peak of severity at 48 hours; the course of bacterial infection appears longer. Some previous studies have confirmed preferential association and cooperation between virus and bacteria eg, Influenzae A virus and streptococcal infection, HRV-14 and *S. pneumoniae* [239]. The mechanism of this superinfection may be in relation to viral replication which increases bacterial adhesion. However rhinovirus, the most frequent cause of the common cold is not associated with major epithelial destruction nor immunosuppression. An initial mechanism involving release of IL-6 and IL-8 and overexpression of ICAM may be relevant.

5-2-1 Histopathology: inflammatory cells and mediators
From single case reports or a single study including 10 patients with complications, neutrophils are mainly found in the mucosa and the sinus fluid [240]. Epithelial cells are the first barrier in contact with virus or bacteria. These release and express several mediators and receptors to initiate different viral elimination mechanisms Recently evidence of biofilms has been suggested in experimentally-induced bacterial (*Pseudomonas*) sinusitis in rabbits [241].

5-2-1-1 Epithelial cells
No specific studies are available concerning the role of epithelial cells in ARS. In cases of experimental induced viral rhinosinusitis, epithelial damage is observed. In vitro release of Il-6 after rhinovirus innoculation has been found [242]. Epithelial cells in contact with human rhinovirus express intracellular adhesion molecule 1 (ICAM-1) which belongs to the immunoglobulin supergene family. Membranous (m-ICAM) and circulating (s-ICAM) forms are detected during common colds and expressed in vitro by epithelial cells [243].

5-2-1-2 Granulocytes
Neutrophils are responsible for proteolytic degradation due to the action of protease [244]. In vitro leucocytes produce lactic acid during *S. pneumoniae* induced rhinosinusitis [245]. Neutrophils are a likely source of IL-8 and TNF-α [246].

5-2-1-3 T lymphocytes
These are stimulated during ARS by pro-inflammatory cytokines such as IL-1ß, IL-6 and TNF-α [247]. Experimentally, antigen stimulated TH2 seems active in the augmented response to bacterial with *S. pneumoniae* in allergic mice [236].

5-2-1-4 Cytokines
Mucosal tissue sampled from the maxillary sinus in ARS (n=10), demonstrated significantly elevated IL-8 concentrations compared to 7 controls [240]. IL-8 belongs to the CXC-chemokine group and is a potent neutrophil chemotactic protein, which is constantly synthesized in the nasal mucosa [247]. Similar results, though not reaching significance, were obtained for IL-1ß and IL-6, whereas other cytokines such as GM-CSF, IL-5 and IL-4 were not upregulated. Another study confirm that some specific cytokines were more implicated in ARS (IL-12, IL-4, IL-10, IL-13) [248]. Recently, IL-8, TNF-α and total protein content were increased in nasal lavage from subjects with ARS compared to controls and allergic rhinitis subjects [246]. The cytokine pattern found in ARS resembles that in lavage from naturally acquired viral rhinitis [249].

5-2-1-5 Adhesion molecules

Human rhinoviruses use intercellular adhesion molecule-1 (ICAM-1) as their cellular receptor [250]. Expression of cell adhesion molecules are induced by pro-inflammatory cytokines [251].

5-2-1-6 Neuromediators

The role of the nervous system in ARS is not documented but probably needs further investigation [252]. Human axon responses are considered as an immediate protective mucosal defense mechanism but no specific investigation has been performed during ARS [253].

5-3 Chronic rhinosinusitis without nasal polyps

5-3-1 Histopathology and inflammatory cells

In the sinus fluid of patients with chronic rhinosinusitis undergoing surgery, the inflammatory cells are predominantly neutrophils, as observed in ARS, but a small number of eosinophils, mast cells and basophils may also be found [254, 255]. The mucosal lining in chronic rhinosinusitis is characterized by basement membrane thickening, goblet cell hyperplasia, subepithelial oedema, and mononuclear cell infiltration. In a recent study evaluating the percentage of eosinophils (out of 1000 inflammatory cells counted per vision field), 31 patients with untreated chronic rhinosinusitis without nasal polyps all had less than 10% eosinophils (overall mean 2%), whereas in 123 untreated nasal polyp specimen, 108 samples showed more than 10% eosinophils (overall mean 50%) [256]. These observations suggest that tissue eosinophilia is not a hallmark of chronic rhinosinusitis without polyp formation, and that there are major differences in the pathophysiology of these sinus diseases.

5-3-1-1 Lymphocytes

T cells, in particular CD4+ T helper cells, participate in the CRS pathophysiology by being predominant at the initiation and regulation of inflammation [257]. Epithelial cells from CRS express functional B7 co-stimulatory molecules (B7-H1, B7-H2, B7-H3, and B7-DC) and may contribute in the regulation of lymphocytic activity at mucosal surfaces [258].

5-3-1-2 Eosinophils

Tissue eosinophilia in CRS has been widely reported as a marker of inflammation [259], and also shows some relationship to severity [260] and prognosis [261]. CRS is also accompanied by 3-nitrotyrosine formation, largely restricted to the eosinophils [262] while Br-Tyr, a molecular footprint predominantly formed by eosinophil peroxidase-catalyzed tissue damage, may serve as an objective index of sinus disease activity when compared to healthy mucosa [263]. However, biopsies from paediatric CRS patients show less eosinophilic inflammation, basement membrane thickening, and mucous gland hyperplasia than in adults (see section 9) [264].

The association between eosinophil inflammation and the presence of fungi in CRS has recently been a matter of considerable interest and investigation [148, 149]. Eosinophil infiltration on mucus cytology is correlated with the clinical diagnosis, the presence of fungal elements on cytology, and serum IgE [265]. No significant correlations between the fungal culture, middle meatal eosinophilia and clinical parameters of CRS were found [266]. In addition, a chronic eosinophilic inflammatory response to *Aspergillus fumigatus* is also evoked in a murine model of CRS, mimicking the human eosinophilic disease [267].

CRS has lower levels of eosinophilic markers [eosinophils, eotaxin, and eosinophil cationic protein (ECP)] compared with nasal polyps [268, 269], while round cell infiltration, eosinophils and plasma cells also differ in CRS and nasal polyp patients [270]. All these findings suggest that CRS without and with nasal polyps

Table 5-1. Inflammatory cells and mediators in acute rhinosinusitis

author/year	tissue/patients	cells	mediators	technique	conclusions
Rudack, 1998 [240]	sinus mucosa acute RS surgical cases	no	IL-8, IL-1β, IL-6, IL-5	ELISA	increase IL-8, IL-1β, IL-6 during ARS
Ramadan, 2002 [237]	virus-induced ARS reovirus	B cells T cells	no	histology	B and Tcells interactions are still present after D14 and D21 confirming delayed immune response
Passariello, 2002 [239]	cell culture epithelial pneumocyst		IL-6, IL-8, ICAM-1	ELISA	HRV promotes internalisation of *S. aureus* due to the action of cytokines and ICAM-1
Yu, 2004 [236]	mice: S.Pneumoniae-induced ARS and allergic sensitsation	eosinophils, polymorpho-nuclear cells		histology	interference of TH2 cells with immun response in experimental ARS
Riechelmann, 2005 [248]	nasal secretion human ARS		IL-12, IL-4, IL-I0, IL-13	IHC	differential profile between ARS and CRS : IL-12, IL-4, IL-10, IL-13
Perloff, 2005 [241]	maxillary mucosa rabbits	infection with pseudomonas	no	electronic microscopy	presence of biofilm on mucosa of maxillary sinus
Khoury, 2006 [238]	sinusonasal mucosa mice S.pneumoniae mice	T lymphocyte eosinophil	bacterials counts	nasal lavage	increase bacterial count when sensitisation present

might be two different disease entities, although they may also be interpreted as different degrees of inflammation.

5-3-1-3 Macrophages (CD68+ cells)

There is an increase in the number of macrophages in CRS and nasal polyps [269] with different phenotypes of macrophages present in the diseases. The macrophage mannose receptor (MMR), capable of phagocytosis of invaders and signal transduction for pro-inflammatory mechanisms, might be of importance in CRS immune interactions since MMR shows a higher expression in CRS than in nasal polyps and controls [271].

5-3-1-4 Mast Cells

Both mast cells (tryptase) and eosinophils (ECP) are involved in non-allergic and allergic forms of chronic nasal inflammation including CRS [272]. Mast cell, eosinophil, and IgE+ cell numbers are raised in patients with CRS when compared with controls [273].

5-3-1-5 Neutrophils

In one study, tissue infiltration in CRS was dominated by lymphocytes and neutrophils [274]. In another study, eosinophils dominated in the middle meatal lavages of asthma patients while neutrophils dominate in the nasal cytology of patients with small airway disease. Their correlation with lung function suggests an involvement of the lower airways in CRS [266].

5-3-2 Pathomechanisms and inflammatory mediators

A range of mediators and cytokines, namely IL-1, IL-6, IL-8, TNF-α, IL-3, GM-CSF, ICAM-1, MPO and ECP, have been described as increased in CRS versus control tissue, mostly from inferior turbinates [278-281]. Interestingly, VCAM-1, an adhesion molecule involved in selective eosinophil recruitment, and IL-5, a key cytokine for eosinophil survival and activity, were not increased [278, 280]. This cytokine and mediator profile resembles the profile found in viral rhinitis or ARS, with the exception of a small though significant increase of ECP. This profile is different from the pattern in nasal polyposis.

5-3-2-1 Cytokines

author/year	tissue/patients	cell type	technique	conclusions
Bernardes 2004 [262]	sinonasal mucosa (CRS) healthy nasal mucosa	eosinophils	IHC	CRS: increase of eosinophil activation
Claeys, 2004 [275]	sinonasal mucosa (CRS without NP and wNP)	macrophages	RT-PCR	CRS without NP: MMR mRNA expression is higher than in NP and controls
Chan, 2004 [264]	sinonasal mucosa (CRS children & adults)	eosinophils lymphocytes	histology	CRS in children: eosinophilc inflammation lower than in adult CRS
Kramer, 2004 [272]	nasal secretions (CRS patients)	mast cells	uniCAP system	mast cells are involved in CRS inflammation
Muluk, 2004 [257]	sinonasal mucosa (CRS)	healthy turbinate	T lymphocytes	IHC CRS: increase in T lymphocytes numbers
Rudack 2004 [276]	sinunasal mucosa (CRS)	neutrophils	IHC	neutrophils dominate in CRS inflammation
Kim, 2005 [258]	sinonasal mucosa	nasalepithelial primary cells	IHC	expression of functional B7 costimulatory molecules
Polzehl, 2005 [270]	sinonasal mucosa (CRS without NP and wNP)	eosinophils, mast cells, macrophages, B cells, T cells	IHC	differencial infiltration of inflammatory cells in both patient's groups
Ragab, 2005 [266]	nasal middle meatal lavage (CRS)	neutrophils	nasal cytology	neutrophils dominate in nasal mucosa of patients with small airway disease
Seiberling, 2005 [277]	sinonasal mucosa (CRS without NP and wNP)	eosinophils	histology, ELISA	CRS without NP: lower eosinophilc inflammation than CRS with NP
Carney, 2006 [273]	infundibular nasosinusal mucosa (CRS)	mast cells	IHC	CRS: increase of mast cell numbers compared to controls
Citardi, 2006 [263]	sinonasal mucosa (CRS) normal ethmoid mucosa	eosinophils	mass spectrometry	CRS: increase of eosinophil activation
Hafidh, 2006 [265]	nasal mucosa (CRS patients & healthy subjects)	fungal spores (mucus) eosinophils (cytology)	histology	CRS: correlation between nasal eosinophilia and fungal presence
Lindsay, 2006 [267]	mice sensitised to Aspergillus fumigatus	eosinophils	histology	murine CRS model: eosinophil inflammation mimicks human CRS
Ragab, 2006 [153]	nasal lavages (CRS patients) during FESS	eosinophils	histology (H&E, GMS)	CRS: No correlation of fungal culture with eosinophilia, and clinical parameters
Van Zele, 2006 [269]	sinonasal mucosa (CRS without NP and wNP)	eosinophils, T cells	IHC	CRS without NP: increased T cells and decreased eosinophils, compared to NP

Table 5-2. Inflammatory cells in chronic rhinosinusitis without nasal polyps

IHC:immunohistochemistry; RT-PCR: reverse-transcriptase protein chain reaction; ELISA: enzyme-linked immunosorbent assay; CRS without NP: chronic rhinosinusitis without nasal polyps; CRS with NP: chronic rhinosinusitis with nasal polyps; H&E: hematoxilin & eosin; GMS: Giemsa)

IL-8, a highly potent chemoattractant for neutrophils, has been demonstrated in chronic rhinosinusitis tissue [282] and IL-8 protein concentrations in nasal discharge from chronic rhinosinusitis patients were significantly higher than in allergic rhinitis patients in a study also involving immunohistochemistry and in situ hybridization [283]. In a study measuring cytokine protein concentrations including IL-3, IL-4, IL-5, IL-8 and GM-CSF in tissue homogenates, IL-8 was found to be significantly increased in ARS, and IL-3 in chronic rhinosinusitis mucosa compared to inferior turbinate samples [278]. IL-3 might be involved in the local defense and repair of chronically inflamed sinus mucosa by supporting various cell populations and indirectly contributing to fibrosis and thickening of the mucosa [284].

In patients with CRS, IL-5, IL-6, and IL-8, and expression in nasal mucosa is elevated in comparison with healthy subjects [285]. Reports of different types and quantities of inflammatory mediators also support the hypothesis that CRS and nasal polyps may constitute two different disease entities. Albumin and IL-5 levels, but not IL-8, are lower in patient with CRS without than with nasal polyps [286]. CRS without nasal polyps is characterized by a Th1 polarization with high levels of IFN-γ and TGF-β, while CRS with nasal polyps shows a Th2 polarization with increased IL-5 and IgE concentrations [269].

By assessing biomarker profiles of disease, lower levels of IgE and IL-5 were found in CRS than in nasal polyps [248]. While no differences were found in IL-6, IL-8, and IL-11, TGF-β was found to be 3 times greater in patients with nasal polyps, as well as responding more to IL-4, than in patients with CRS alone [287]. Levels of IL-5 and ECP were lower in CRS than in nasal polyps, and correlated directly with peptide-LTs and inversely with PGE2 [288].

Patients with CRS show exaggerated humoral and cellular responses, both of Th1 and Th2 (IL-5, IL-13) types, to common airborne fungi, particularly *Alternaria* [152]. Using the YAMIK sinus catheter, both saline or betamethasone decreased IL-1α and IL-8 levels after the 2nd and 3rd weeks of therapy in CRS patients while TNF-α level decreased only in patients treated with betamethasone [289]. Besides the improvement of CRS symptoms and amelioration of asthma, elevated serum Th2 cytokines (IL-4 and IL-5) were normalized after sinus surgery [290]. *Staphylococcus aureus* exotoxin B increased IL-6 levels in nasal epithelial cell from patients with CRS [291].

Toll-like receptors (TLR) and the alternate pathway of complement are important components of innate immunity that are expressed in human sinonasal epithelium. Detectable levels of TLR mRNA were found in human sinonasal tissue from CRS patients [292].

An increased expression of TLR2 and proinflammatory cytokines (RANTES and GM-CSF) was also found in CRS patients compared with controls [293].

5-3-2-2 Chemokines
In patients with CRS, chemokines have a different expression in atopic (increased CCR4+ and EG2+ cells) and non-atopic (decreased CCR5+ cells), suggesting a potential association of eosinophil and Th2 cell infiltration in atopic rhinosinusitis [294]. Other chemokines such as growth-related oncogene-alpha (GRO-α) and granulocyte chemotactic protein-2 (GCP-2), mainly produced by gland and epithelial cells, contribute to neutrophil chemotaxis in CRS, whereas IL-8 and ENA-78 appear to be of secondary importance [286].

In addition, CCL-20 expression was localized to the epithelial and submucosal glandular and increased in CRS patients [295].

5-3-2-3 Adhesion molecules
In patients with maxillary CRS, eosinophilia and vessels expressing endothelial L-selectin ligands increased during chronic rhinosinusitis compared with uninflamed control tissue, correlating with the severity of the inflammation [296].

5-3-2-4 Eicosanoids
In CRS patients without NP, COX-2 mRNA and PGE2 were found to be higher than CRS with nasal polyps while 15-Lipoxygenase and lipoxin A [4] were increased in all CRS groups compared with healthy mucosa. LTC4 synthase, 5-lipoxygenase mRNA, and peptide-LT levels were increased in proportion to disease severity [288]. CysLT1 receptor expression is decreased in CRS compared to nasal polyps whereas CysLT2 is enhanced in both groups compared to healthy controls. Both receptor levels were correlated to eosinophil numbers, sol-IL-5Rα, ECP, and peptide-LTs. PGE2 protein concentrations and prostanoid receptors (EP1 and EP3) are up-regulated in CRS compared to nasal polyps, whereas EP2 and EP4 expression is enhanced in both diseased groups compared to controls [297].

5-3-2-5 Metalloproteinases and TGF-β
The expression of transforming growth factor beta 1 (TGF-β1) at protein and RNA level is significantly higher in CRS without NP versus CRS with NP and linked to a fibrotic cross anatomy [298]. In CRS, MMP-9 and TIMP-1, a natural antagonist, but not MMP-7 are increased [299], probably resulting in a low MMP-9 activity.

In patients with CRS, MMP-9 concentrations in nasal fluid are paralleled by MMP-9 in extracellular matrix (ECM) and independently predicted by the number of neutrophils and macrophages in the tissue, but not related to fibrosis, number of myofibroblasts, or TGF-β1 expression [300].

Several findings also suggest different histopathological characters between CRS and nasal polyps. CRS is histologically characterized by fibrosis and reflected by an increased expression of TGF-β1 compared with nasal polyps, suggesting a potential differentiation between these two entities [301]. In CRS and nasal polyp tissues, the expression of TGF-β1, MMP-7, MMP-9, and TIMP-1 was increased compared with controls while TGF-β1 and TIMP-1 were higher in CRS and MMP-7 in nasal polyps [302]. After sinus surgery, MMP-9 and TGF-β1 were initially increased and healing quality correlated to preoperative MMP-9 levels in nasal secretions. MMP-9 was also lower in patients

with good healing compared to those with poor healing, suggesting MMP-9 as a potential factor to predict and monitor healing quality after sinus surgery [303]. Clarithromycin therapy also reduces cellular expression of TGF-β and NFκB in biopsies from CRS patients [304].

5-3-2-6 Immunoglobulin

IgE+ cell numbers are raised in patients with allergic, fungal, and eosinophilic CRS when compared with controls [273]. In a clinical trial, preoperative total IgE levels showed a significant correlation with the extent of disease on sinus CT, without any change one year after sinus surgery [308]. IgG antibodies to

Table 5-3. Inflammatory mediatos (cytokines, chemokines, toll-like receptors, adhesion molecules, eicosanoids, and matrix metalloproteinases) in chronic rhinosinusitis without nasal polyps

author, year	tissue, patient	marker	technique	conclusion
Ruback, 2004 [276]	sinonasal mucosa (biopsies)	IL-5, IL-8	ELISA	CRS without NP: lower levels of IL-5 but not IL-8 than in NP
Shin 2004 [152]	PBMC from CRS (in vitro)	IFN-γ, IL-5, IL-13	ELISA	exposure to Alternaria increase cytokine levels
Van der Meer, 2004 [292]	sinonasal mucosa	toll-like receptors (TLR)	RT-PCR	TLR are expressed in CRS
Wallwork, 2004 [304]	CRS nasal mucosa (in vivo & in vitro)	TGF-β1, NFkB	IHC	clarythromycin inhibits TGF-β1 and NFkB only in vitro
Watelet, 2004 [301]	sinonasal mucosa (FESS)	TGF-β1	IHC	CRS without NP: increased expression of TGF-β1 compared to NP
Watelet, 2004 [303]	sinonasal mucosa (FESS)	MMP-9, TGF-β1	IHC	correlation with the tissue healing quality
Bradley, 2005 [287]	sinunasal mucosa (FESS)	TGF-β	RT-PCR	CRS without NP: lower expression of TGF-β than in NP
Elhini,2005 [294]	ethmoidal sinus mucosa	CCR4+, CCR5+	IHC Real Time PCR	CRS patients: increase of CCR4+ in atopics and decrease of CCR5+ in non-atopics
Furukido, 2005 [289]	sinus lavage (with YAMIK catheter)	IL-1β, IL-8, TNF-α	ELISA	betamethasone and Saline decrease cytokine levels
Pérez-Novo, 2005 [288]	sinonasal mucosa	IL-5	ELISA	CRS without NP: lower levels of IL-5 and ECP than in NP
Riechelmann, 2005 [248]	nasal secretions	15 cytokines (IL-5)	ELISA	CRS without NP: lower levels of IL-5 than in NP
Toppila-Salmi, 2005 [296]	maxillary sinus mucosa (surgery)	L-selectin ligands	IHC	increased expression in CRS endothelial cells
Damm, 2006 [291]	CRS primary epithelial cells (cultures)	IL-6	ELISA	SA enterotoxin B increases IL-6 in CRS
Lane, 2006 [293]	ethmoidal mucosa (surgery)	TLR2, RANTES, GM-CSF	real time PCR	increase in CRS compared to healthy controls
Lee, 2006 [295]	sinonasal mucosa	CCL 20	IHC Real Time PCR	increased expression of CCL-20 in CRS without NP
Lin, 2006 [305]	sinunasal mucosa (FESS)	IL-4, IL-5	ELISA	sinus surgery increases cytokine levels
Rudack, 2006 [286]	sinonasal mucosa	GRO-α, GCP-2, IL-8, ENA-78	HPLC + bioassay	expression of GRO-α and GCP-2 in CRS
Pérez-Novo, 2005 [288]	sinonasal mucosa	COX-2 PGE2	real time PCR ELISA	CRS without NP: COX-2 and PGE2 are more expressed than in NP
Pérez-Novo, 2006 [297]	nasal mucosa	CysLT receptors EP Receptors	real time PCR	CRS without NP: CysLT and EP receptors are more expressed than in NP
Watelet, 2006 [306]	sinonasal mucosa (FESS)	MMP-9	IHC	there exists a correlation between MMP-9 expression and tissue healing quality
Lu, 2005 [302]	sinonasal mucosa (surgery)	MMP-7, MMP-9, TIMP-1, TGF-β1	ELISA	there exists a diffeernt profile expression in CRSwo NP, nasal polyps, and healthy mucosa
Van Zele, 2006 [307]	sinonasal mucosa	INF-γ, TGF-β	ELISA UniCAP system	There is a TH1 polarization in CRS without NP
Xu, 2006 [285]	sinonasal mucosa	IL-5, IL-6, IL-8, NFkB	ELISA RT-PCR	cytokines are increased in CRS compared to healthy controls

FESS: functional endoscopic sinus surgery; Immunohistochemistry: CRS without NP: chronic rhinosinusitis without nasal polyps, CRS with NP:chronic rhinosinusitis with nasal polyps; RT-PCR: reverse-transcriptase protein chain reaction; ELISA: enzymo-linked immunosorbent assay

Alternaria and *Cladosporium* are clearly increased in patients with CRS compared with normal individuals while less than 30% of CRS patients have specific IgE antibodies to *Alternaria* or *Cladosporium* [152]. Fungal-specific IgG (IgG3) and IgA levels (to *Alternaria alternata* and *Aspergillus fumigatus*), but not IgE, are higher in CRS with eosinophilic mucus compared with healthy volunteers, challenging the presumption of a unique pathogenic role of fungal allergy in "allergic fungal sinusitis" [150].

5-3-2-7 Nitric Oxide (NO)
CRS epthelial cells show a stronger expression of TLR-4 and iNOS than controls, iNOS being upregulated in nasal epithelium and correlated with TLR-4 [309]. In a prospective randomized trial in patients with CRS who had failed initial medical therapy with nasal corticosteroids, the rise in nNO seen on both medical and surgical treatments correlated with symptom score, saccharin clearance time, endoscopic changes, and polyp size, suggesting that nNO provides a non-invasive objective measure of the response of CRS to therapy on an individual basis [310]. However, some contradictory results on the role of nNO on nasal inflammation have been recently assessed [311].

5-3-2-8 Neuropeptides
Neurogenic inflammation may play a potential role on the manifestation of chronic rhinosinusitis [312]. In addition, CGRP (trigeminal sensory) and VIP (parasympathetic) levels in saliva were significantly elevated between attacks in patients with the diagnosis of allergic CRS and migraine compared to controls , returning to baseline after pseudoephedrine therapy but only in CRS patients [313].

5-3-2-9 Mucins
Airway mucus is overproduced in CRS. Mucins are the major components of mucus and the macromolecules that impart rheologic properties to airway mucus. MUC5AC and MUC5B are

Table 5-4. Inflammatory mediators (immunoglubulins, nitric oxide, neuropeptides, mucins, and others) in Chronic Rhinosinusitis without nasal polyps

author, year	tissue, patient	marker	technique	conclusion
Kim, 2004 [314]	maxillary sinonasal mucosa	MUC5AC, MUC5B	RT-PCR	increased in CRS compared to healthy controls
Lee, 2004 [317]	maxillary sinonasal mucosa	MUC8	RT-PCR	MUC8 is upregulated in CRS compared to controls
Maniscalco, 2004 [324]	allergic rhinitis patients	nasal NO	chemi-luminescence	nNO during humming is a reliable marker of sinus patency
Shin, 2004 [152]	PBMC from CRS (in vitro)	fungal IgG	UniCAP system	IgG is increased in CRS compared to healthy controls
Wang, 2004 [309]	sinonasal mucosa	TLR4, iNOS	in-situ hybridization	TLR4 and iNOS are increased in CRS compared to healthy controls
Ali, 2005 [316]	CRS patients (sinusal mucus)	MUC5AC, MUC2	ELISA	increase of MUC5AC and decrease of MUC2 in CRS
Pant, 2005 [150]	CRS patients (serum)	fungal IgG, IgA	ELISA	IgG3 and IgA are increased in CRS
Sun, 2005 [321]	CRS patients (sinus effusions, nasal secretions, serum)	VEGF	ELISA	VEGF expression is higher in the sinus mucosa than in nasal mucosa and serum
Bellamy, 2006 [313]	allergic CRS (saliva)	VIP, CGRP	radioimmuno-assay	neuropetides are increased in acute attacks
Carney, 2006 [273]	infundibular sinonasal mucosa	IgE+ cells	immuno-histochemistry	IgE+ cells are increased in CRS compared to healthy controls
Lal, 2006 [308]	CRS patients (serum)	total IgE	ELISA	correlation of IgE levels with the CRS extent
Martínez, 2006 [319]	sinonasal mucosa (FESS)	MUC1, MUC2, MUC4 MUC5AC, MUC5B	IHC In situ hybridization	there exist different MUC expression patterns depending on the sinonasal disease
Pena, 2006 [320]	children with CRS (sinonasal mucosa)	MUC5AC	IHC	MUC5AC is expressed in the epithelium but not in submucosal glands
Ragab SM, 2006 [310]	CRS patients	nasal NO	chemi-luminescence	medial and surgical treatments increase nNO, with correlation with nasal symptoms
Viswanathan, 2006 [315]	CRS patients (nasal mucus)	MUC5AC, MUC5B	ELISA	increased in CRS compared to healthy controls
Hu, 2007 [322]	children with CRS (sinonasal mucosa)	VEGF	IHC	CRS without NP: lower expression of VGEF compared to NP
Lee, 2006 [323]	sinonasal mucosa (FESS)	surfactant protein-A	RT-PCR	increased expression of SP-A in CRS compared to healthy controls

FESS: functional endoscopc sinus surgery; IHC:immunohistochemistry; CRS without NP:chronic rhinosinusitis without nasal polyps; CRS with NP:chronic rhinosinusitis with nasal polyps; RT-PCR: reverse-transcriptase protein chain reaction; ELISA: enzymo-linked immunosorbent assay

Table 5-5. Biofilms in chronic rhinosinusitis		
author, year	*population*	*evidence for biofilms in CRS*
Cryer, 2004 [329]	Adults with CRS (n=16) Biopsies of mucosa	Morphological evidence of EPS seen on four of the specimens and of bacteria in one on SEM
Perloff, 2004 [330]	Frontal recess stents from post FESS adults (n=6)	All six had biofilm morphology on SEM and five had cultures with S.aureus
Ferguson, 2005 [331, 467]	Adults with CRS (n=4) TEM of Biospies of mucosa	Morphologic evidence of biofilm in two of the samples on TEM
Palmer, 2005 [332]	Rabbit model of *P.aeruginosa* (type IV pili mutants) maxillary sinusitis (n=4) SEM of mucosa	Biofilm not seen in sinusitis model with bacteria defective with type IV pili (impaired attachement). Increased CBF seen in response.
Perloff, [241]	Rabbit model of *P.aeruginosa* maxillary sinusitis (n=22)	All clinically had sinusitis. 21 cultured *P.aeruginosa*. Morphological evidence of biofilm seen in all on SEM No biofilm seen in the 22 contraleteral controls
Ramadan, [333]	Adults with CRS (n=5) SEM of Mucosal biopsies	All 5 had morphological evidence of biofilms based on SEM
Sanclement, [334]	Adults with CRS (n=30) controls (n=4) SEM/TEM of mucosal biopsies	Morphological evidence of biofilms seen in 24 patients. No controls positive.
Bendouah, 2006 [335]	Adults with CRS (n=19) Semi quantitative in vitro culture assessment	22 of 31 isolates of *S. Aureus, Coagulase negative Staphylococcal Species, P. aeruginosa* demonstrated biofilm forming capacity *in vitro*
Bendouah, 2006 [336]	Adults with CRS (n=19) Semi quantitative *in vitro* culture assessment	Correlates above data with a dichotomous outcome of 'poor or favourable' based on symptoms and endoscopic signs. Poor outcome overrepresented in patients with biofilm forming isolates
Sanderson, [337]	Adults with CRS (n=18) controls (n=5) FISH visualised with confocal microscopy of mucosal biopsies	FISH for *S. pneumoniae, S. aureus, H. influenza* and *P. aeruginosa* and standard cultures 14 of 18 had evidence of biofilm and 2 of 5 controls. Cultures did not correlate.
Zuliani, [338]	Children with CRS and OSA (n=16) Adenoid samples	All 8 CRS patients had biofilms in the adenoids. No control demonstrated significant biofilm coverage.
FESS: functional endoscopic sinus surgery; SEM:scanning electron microscopy; TEM:transmission electron microscopy; OSA:obstructibe sleep apnoea FISH:fluorescent in situ hybridisation		

increased in CRS compared with healthy sinus mucosa [314, 315]. MUC5AC and MUC5B represent the major mucin component in sinus while MUC5B and MUC2 predominated in healthy mucosa. In CRS, upregulation of MUC5AC was associated with downregulation of MUC2 and vice versa [316]. MUC8 expression is also increased in CRS compared with healthy maxillary sinus mucosa [317]. In a comparative study between different upper airways pathologies CRS with nasal polyps had a different pattern of mucin expression (increased MUC1 and MUC4, and decreased MUC5AC) compared to healthy mucosa while cystic fibrosis CRS (increased MUC5B) and antrochoanal polyps (decreased MUC2) also expressed a different pattern from CRS with nasal polyps [318, 319]. Moreover, the number of goblet cells expressing MUC5AC mucin does not differ in children with and without CRS [320].

5-3-2-10 Other mediators
Vascular endothelial-cell growth factor (VEGF) is produced in paranasal sinuses and nasal mucosa and it has been found to be increased in patients with CRS. Hypoxia is associated with VEGF production by nasal fibroblasts and TNF-α and endotoxin may synergistically enhance VEGF production in paranasal sinuses under hypoxic conditions [321]. In children,

VEGF expression was shown to be lower within CRS mucosa than in nasal polyps [322]. Surfactant protein A (SP-A), a protein that appears to play an important role in mammalian first-line host defense, was found to be increased in sinus mucosa of CRS patients compared with healthy sinus mucosa [323].

5-3-2-11 Biofilms
The conversion of free-floating planktonic bacterial forms into complex sessile communities has been extensively investigated. Biofilms are structured, specialised communities of adherent micro-organisms encased in a complex extra-cellular polymeric substance (EPS) [325].There is no one common biofilm structure with bacteria responding to environment and intrinsic genetic programming. These influences and cell-cell signalling that exists between bacteria in close proximity (quorum sensing) facilitates the development of the biofilm phenotype [326]. Although the bacteria per se may be susceptible to antibiotics, the adoption of a biofilm strategy is protective resulting in chronic and recalcitrant infectious processes. Biofilms have been found in otitis media, cholesteatoma and tonsillitis [327]. There are presently 11 papers in the literature showing evidence for biofilm formation in CRS [328].

5-4 Chronic rhinosinusitis with nasal polyps

5-4-1 Histopathology and inflammatory cells

Histomorphological characterisation of polyp tissue reveals frequent epithelial damage, a thickened basement membrane, and oedematous to sometimes fibrotic stromal tissue, with a reduced number of vessels and glands, but virtually no neural structure [339-341]. The stroma of mature polyps is mainly characterised by its oedematous nature and consists of supporting fibroblasts and infiltrating inflammatory cells, localized around "empty" pseudocyst formations. Among the inflammatory cells, EG2 (activated) eosinophils are a prominent and characteristic feature in about 80% of European polyps [342], whereas lymphocytes and neutrophils are the predominant cells in cystic fibrosis and in CRS without NP. Eosinophils are localised around the vessels, glands, and directly beneath the mucosal epithelium [340]. However, neutrophils are also a constant finding in nasal polyps, and their number is increased compared to controls [269]. Furthermore, increased numbers of activated T-cells and plasma cells characterize the typical cell composition.

In small polyps, not larger than 5 mm, growing on normal looking mucosa of the middle turbinate in patients with bilateral polyposis, the early processes of polyp growth have been studied [343]. Numerous subepithelial EG2+ eosinophils were present in the luminal compartment of the early stage polyp, forming a cap over the central pseudocyst area. In contrast, mast cells were scarce in the polyp tissue, but were normally distributed in the pedicle and the adjacent mucosa, which had a normal appearance. This contrasts to mature polyps, where degranulated mast cells and eosinophils are often diffusely distributed in the polyp tissue. Fibronectin deposition was noticed around the eosinophils in the luminal compartment of the early stage polyp, was accumulated subepithelially, and formed a network-like structure in the polyp centre and within the pseudocysts. The presence of myofibroblasts was limited to the central pseudocyst area. Interestingly, albumin and probably other plasma proteins were deposited within the pseudocysts, adjacent to the eosinophil infiltration. These observations suggest a central deposition of plasma proteins, regulated by the subepithelial eosinophilic inflammation, as a pathogenetic principle of polyp formation and growth.

5-4-1-1 Lymphocytes

Nasal polyps show a significantly increased number of T-lymphocytes (CD3) and activated T-lymphocytes (CD25) compared to control patients [269]. In non-allergic CRS with nasal polyps a tendency to fewer CD4+ cells in the epithelium and more CD8+ cells in the lamina propria was found [344]. An inverse median ratio of CD4+/CD8+ T cells as compared to the middle turbinate of control subjects was found in one recent study [345]. Functional studies on T-cells, especially T regulatory cells, are lacking so far. Interestingly, there were almost no naïve B-lymphocytes (CD20) present in the tissue, although a significantly higher number of plasma cells (CD138) was present in NP versus controls and CRS without polyps [269, 346]. This fact is reflected by a significant increase in immunoglobulin A, G and E synthesis (van Zele, unpublished).

S. aureus superantigens (SAgs) bind the Vβ-region of the T-cell receptor (TCR) outside the peptide-binding site. Approximately 50 distinct Vβ-domains exist in the human repertoire, and distinct SAgs will bind only particular domains, generating a pattern of Vβ-enrichment in lymphocytes dependent on the binding characteristics of a given toxin. Flow cytometry was used to analyze the Vβ-repertoire of polyp-derived CD4+ and CD8+ lymphocytes in the light of the known skewing associated with SAg exposure. Seven of 20 subjects exhibited skewing in Vβ-domains with strong associations to *S. aureus* SAgs. This study establishes evidence of *S. aureus* SAg-T-cell interactions in polyp lymphocytes of 35% of CRS with NP patients [347].

5-4-1-2 Eosinophils

An increased number of eosinophils, demonstrated by HE staining or EG2 IHC, is a hallmark of Caucasian NPs. Eosinophil numbers are significantly higher in NP tissue compared to CRS [348] and other sinus disease and control mucosa, and are further increased in patients with co-morbid asthma and/or aspirin sensitivity, but independent from atopy [192, 349]. In a study evaluating the percentage of eosinophils (out of 1000 inflammatory cells counted per vision field), 31 patients with untreated chronic sinusitis without nasal polyps all had less than 10% eosinophils (overall mean 2%), whereas in 123 untreated nasal polyp specimen, 108 samples showed more than 10% eosinophils (overall mean 50%) [350]. Generally, the differences in ECP measurement between diseases are more pronounced than the cell numbers, indicating a more intense activation of eosinophils in polyps. However, the eosinophilic inflammation in nasal polyp tissue from China, as measured by ECP and cytokine/chemokine levels (IL-5, eotaxin), was not significantly different from control tissue, and was significantly lower compared to Caucasian polyps. The semi-quantitative scores for EG2+ eosinophils were 0,45+1.15 for the Chinese polyp patients and 1,95 ± 2,85 for the Caucasian polyp patients, being significantly different [346]. Furthermore, eosinophil numbers are not different from controls and cystic fibrosis polyps [269].

5-4-1-3 Macrophages and dendritic cells

Macrophage numbers seem to be slightly increased in nasal polyps, and these cells express increased amounts of macrophage mannose receptors (MMR), an innate pattern recognizing receptor, capable of phagocytosis of invaders and signal transduction for proinflammatory mechanisms [275]. There also is a higher number of macrophages in patients with CF than in patients with CRS or in controls [351]. Our knowledge on dendritic cells is very limited; they are present in nasal polyps, and express the high affinity IgE receptor [344, 352].

Table 5-6. Inflammatory cells in Chronic Rhinosinusitis with nasal polyps (IHC; immunohistochemistry; RT-PCR; reverse-transcriptase protein chain reaction; ELISA: enzymo-linked immunosorbent assay)

author, year	tissue, patients	cell type	technique	conclusion
Fokkens, 1990 [344]	nasal polyps healthy nasal mucosa allergic rhinitis nasal mucosa	T lymphocytes B lymphocytes eosinophils neutrophils dendritic cells Ig+ cells	IHC	
Jankowski, 1996 [350]	nasal polyps sinonasal mucosa (CRS)	eosinophils	IHC	CRS with NP: more than 10% eosinophils compared to CRS without NP
Drake-Lee, 1997 [354]	nasal polyps inferior turbinate	mast cells	IHC	greater mast cell degranulation in CRS with NP compared to healthy inferior turbinate
Haas, 1997 [352]	nasal polyps healthy nasal mucosa	dendritic cell	IHC	dendritic cells are present in NP
Jahnsen, 1997 [361]	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 [353]	nasal polyps healthy nasal mucosa	mast cells	fluorescence microscopy	number of mast cells is not different between controls and CRS with NP
Seong, 2002 [359]	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 [351]	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 [362]	nasal polyps healthy nasal mucosa	endothelial cells	IHC	VPF/VEGF expression was higher in NP than in healthy nasal mucosa
Shin, 2003 [356]	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 [364]	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 [271]	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 [358]	nasal polyps	epithelial cells	IHC	clinical efficacy of glucocorticoids on NP epithelial GM-CSF production, which prolongs eosinophil survival.
Gosepath, 2005 [363]	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 [355]	nasal polyps	epithelial cells, stem cell factor (SCF)	ELISA RT-PCR	epithelial cells release stem cell factor (SCF)
Conley, 2006 [365]	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 [345]	nasal polyps healthy nasal mucosa	T lymphocytes	IHC	inverse median ratio of CD4+/CD8+ T cells as compared to the middle turbinate
Schaefer, 2006 [357]	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
Van Zele, 2006 [269]	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 [366]	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

5-4-1-4 Mast Cells

The number of mast cells is not different between controls and nasal polyps, these cells are however more often IgE-positive, especially in asthmatics, independent of atopy [353]. There was greater mast cell degranulation in the nasal polyp compared to inferior turbinate [354]. The density of mast cells in the epithelial and stromal layers of nasal polyps correlated with the expression of SCF mRNA and protein in the supernatants of NP epithelial cells [355].

5-4-1-5 Neutrophils

There is an increased number of neutrophils and higher concentrations of MPO protein in nasal polyps vs. controls, but not compared to CRS without polyps, and both parameters are even higher in CF NPs [269, 351] indicating a massive activation in CF- NPs compared to non-CF-NPs. The role of neutrophils currently is not understood in NPs.

5-4-1-6 Epithelial cells

Human nasal epithelial cells contain and secrete IL-8, GM-CSF, eotaxin, eotaxin-2 and RANTES, and thus may provide enough growth factors to attract eosinophils [356, 357], with GM-CSF being important for the survival of those cells [358]. Epithelial cells also release stem cell factor (SCF), a cytokine with chemotactic and survival activity for mast cells, with the expression of SCF mRNA correlating to SCF protein, and with the density of mast cells in epithelial and stromal layers of nasal polyps [355].

Inflammatory mediators may lead to over-expression of MUC8 mRNA in nasal polyps and downregulation of MUC5AC mRNA expression, and influence the composition of mucus in polyp disease [359]. Nasal polyp epithelial cells also express increased amounts of LL-37, an antimicrobial peptide [360], but down-regulate the level of TLR9 expression [347], and are thus directly involved in innate immunity functions.

5-4-1-7 Endothelial cells (See also adhesion molecules)

Endothelial cells express VCAM-1, induced by IL-4 and IL-13, which plays an important role for the preferential recruitment of eosinophils and T lymphocytes [361]. However, a key phenomenon in nasal polyps is the remarkable oedema, which awaits explanation. Vascular permeability/vascular endothelial growth factor (VPF/VEGF) plays an important role in inducing angiogenesis and modulating capillary permeability. In fact, the expression of VPF/VEGF in specimens of nasal polyps was significantly stronger than in specimens of healthy nasal mucosa of controls [362]. VPF/VEGF in polypous tissue was mainly localized in vascular endothelial cells, in basal membranes and perivascular spaces, and in epithelial cells. The markedly increased expression in nasal polyps as opposed to healthy nasal mucosa suggests that VPF/VEGF may play a significant role in both the formation of nasal polyps and in the induction of heavy tissue oedema [363].

5-4-2 Pathomechanisms and Inflammatory Mediators

5-4-2-1 Cytokines

A large body of studies has focused on eosinophilic mediators in nasal polyp tissue, and demonstrated that different cell types generate these mediators. Early studies by Denburg et al [367] demonstrated that conditioned medium, derived from cultured nasal polyp epithelial cells, contained potent eosinophil colony-stimulating activities, as well as an interleukin-3-like activity. The authors suggested that accumulation of eosinophils in polyps may partly be a result of differentiation of progenitor cells stimulated by soluble haemopoietic factors derived from mucosal cell populations. An increased synthesis of GM-CSF by epithelial cells, fibroblasts, monocytes, and eosinophils was suggested later [99, 368-370]. According to Hamilos et al [30], polyp tissue samples from patients with or without allergy contained different cytokine profiles. Other studies involving protein measurements in tissue homogenates could not support these findings [31, 278].

In contrast, IL-5 was found to be significantly increased in nasal polyps, compared to healthy controls, and the concentration of IL-5 was independent of the atopic status of the patient. Indeed, the highest concentrations of IL-5 were found in subjects with non-allergic asthma and aspirin sensitivity. Furthermore, eosinophils were positively stained for IL-5, suggesting a possible autocrine role for this cytokine in the activation of eosinophils, and a strong correlation between concentrations of IL-5 protein and eosinophilic cationic protein (ECP) was demonstrated later [192]. The key role of IL-5 was supported by the finding that treatment of eosinophil-infiltrated polyp tissue with neutralizing anti-IL-5 monoclonal antibody (mAB), but not anti-IL-3 or anti-GM-CSF mAbs in vitro, resulted in eosinophil apoptosis and decreased tissue eosinophilia [371].

Collectively, these studies suggest that increased production of IL-5 is likely to influence the predominance and activation of eosinophils in nasal polyps independent of atopy. The lack of difference in the amounts of cytokines detected in polyps from allergic or non-allergic patients was meanwhile supported by several other studies [372, 373]. Furthermore, Wagenmann et al [374] demonstrated that both Th1 and Th2 type cytokines were upregulated in eosinophilic NP, irrespective of allergen skin test results.

Recently, the regulation of the IL-5 receptor, which exists in the soluble and transmembrane isoform, has been investigated [375]. Whereas the probably antagonistic soluble isoform is upregulated, the signal transducing transmembrane isoform is down-regulated in nasal polyps, especially if associated with asthma.

5-4-2-2 Chemokines

Recent studies have also shown that nasal polyps also express high levels of RANTES and eotaxin, the predominant recognised eosinophil chemoattractants. Bartels and colleagues [376] demonstrated that expression of eotaxin- and RANTES

mRNA, but not MCP-3 mRNA, was elevated in non-atopic and atopic nasal polyps, when compared to normal nasal mucosa. Similarly, several publications demonstrated an increased mRNA expression for eotaxin, eotaxin-2, eotaxin-3, and MCP-4 [357, 377-379]. The expression of eotaxin-2, a CCR3-specific chemokine, was found to be the most prominent of the three chemokines investigated. According to other data [31, 192, 343], it appears that eotaxin, rather than RANTES, in cooperation with IL-5, plays a key role in chemo-attraction and activation of eosinophils in NP tissue. This is in accordance with the findings of a recent extensive study of about 950 non-allergic and allergic polyp patients, which has also suggested that nasal polyp eosinophilic infiltration and activation may correlate mainly with increased eotaxin gene expression, rather than with RANTES expression [380]. The excessive production of eotaxin in nasal polyps was recently confirmed in comparison to controls and CRS patients [269].

5-4-2-3 Adhesion molecules

Studies of cell adhesion molecules are relatively few. Early studies by Symon and colleagues [381] demonstrated that ICAM-1, E-selectin and P-selectin were well expressed by nasal polyp endothelium, whereas VCAM-1 expression was weak or absent. An elegant study by Jahnsen et al [382], employing three-colour immunofluorescence staining, has however demonstrated that both the number of eosinophils and the proportion of vessels positive for VCAM-1 were significantly increased in nasal polyps compared with the turbinate mucosa of the same patients. Moreover, treatment with topical glucocorticosteroids decreases the density of eosinophils and the expression of VCAM-1 in polyps [383]. The interaction between VLA-4 on eosinophils and VCAM-1 on endothelial cells may not only be of particular importance for transendothelial migration of eosinophils, but may also modify their activation and effector functions [384].

5-4-2-4 Eicosanoids

Levels of leukotrienes and their receptors have been shown to be up-regulated in nasal polyp tissue [385, 386], more pronounced in patients with intolerance to aspirin [288, 387, 388]. A recent study suggested that high levels of LTC4 synthase are directly linked to the manifestation of aspirin intolerance [389], and polymorphisms linked to this enzyme have been suggested to cause the syndrome [390]. However, up-regulation of cysteinyl-leukotrienes (CysLTs) does occur in chronic rhinosinusitis even in the absence of clinical aspirin sensitivity and appears to be closely related to the severity of eosinophilic inflammation (IL-5 and ECP), a hallmark of nasal polyp disease [288]. Increased expression of the CysLT1 and CysLT2 receptors have been demonstrated on inflammatory cells in nasal polyp tissue [297, 391, 392], but also inflammatory cells in nasal lavage from patients with allergic rhinitis [393]. Thus, the regulation of CysLTs does not seem to be a pathognomonic feature of aspirin intolerance.

The regulation of the cyclo-oxygenases and their products, the prostaglandins, in nasal polyps is characterized by a deficit in the production of PGE2 compared to CysLT levels [297, 393-395]. This phenomenon was also observed in nasal polyp tissue and peripheral blood from aspirin-intolerant subjects [396], and cyclo-oxygenase (COX)-2 mRNA expression and NF-kB activity were markedly lower in nasal polyp tissue from aspirin intolerant subjects compared to tolerant patients [397, 398]. However, our recent data indicate that levels of PGE2 inversely correlate with the degree of eosinophilic inflammation in nasal tissue from aspirin intolerant, but also tolerant patients. These findings support previous studies [395, 399], and suggest that this down-regulation may again represent a bystander phenomenon linked to the severity of the inflammatory process. Of interest, research on prostanoid E (EP) receptor regulation has recently been performed, with controversial results. A down-regulation of EP1 and EP3 and an up–regulation of EP2 and EP4 receptors in nasal polyp tissue compared to normal nasal mucosa was shown [297]. It is known that EP2 and EP4 are highly expressed on eosinophils and a deficiency of PGE2 production may up-regulate the expression of these receptors. However, the expression of EP2 and EP4 receptors did not correlate with eosinophil numbers or eosinophil activation markers, indicating that the regulation of these receptors may involve other cellular sources. This was recently confirmed by Ying et al. who showed the expression of EP receptors in a variety of inflammatory cells in the nasal mucosa [400]. These authors found a down-regulation of the EP2 receptor in aspirin intolerant patients and speculated on the effects on the production of inflammatory mediators. However, PGD2 may also mediate eosinophil chemotaxis and activation and the production of cytokines such as interleukins IL-4, IL-5, and IL-13 by human Th2 inflammatory cells via different receptors, e.g. via the CRTH2 receptor [401, 402]. The relative contributions of EP and other PG receptors is far from being unravelled, and so far, little points to a specific change in PG regulation in aspirin-intolerant subjects.

Finally, lipoxins are generally associated with anti-inflammatory effects and have been reported to reduce leukocyte infiltration [403]. However, certain di- hydroxyeicosatetraenoic acids (HETEs), which are precursors of these molecules, may have also pro-inflammatory effects, specifically neutrophilic and eosinophilic chemotaxis [404]. Nasal polyp tissue has been shown to have a high capacity to produce LXA4 after incubation with exogenous LTA4 in the presence of polymorphonuclear granulocytes [405]. In addition, severity of asthma has been associated with increased expression and activation of the 15-LO (lipoxygenase) enzyme, collagen deposition and eosinophil accumulation [406]. Interestingly, the capacity to produce lipoxins is decreased in epithelial cells from patients with aspirin intolerance [407]. These results are in line with those showing that basal levels of this enzyme are increased in nasal polyp tissue of aspirin-tolerant, but down- regulated in aspirin intolerant subjects. 15-LO and LXA4 levels were increased in all chronic sinus disease groups, but significantly down-regulated in

patients with aspirin intolerance, suggesting a specific regulation in this subgroup [297].

Summarizing, eicosanoid changes in paranasal sinus diseases are generally characterized by an up- regulation of CysLTs, LXA4 and PGD2 and a down- regulation of COX-2 and PGE2. Eosinophilic markers such as ECP and IL-5 correlate directly with LTC4/D4/E4 and inversely with PGE2 concentrations, demonstrating the close relationship to severity of inflammation. In the sinus mucosa of aspirin intolerant subjects, these changes might be extreme, as the degree of inflammation is maximal, and the clinically apparent aspirin intolerance triad may be dependent on severe inflammation in the airways. In contrast, specific changes such as a relative down-regulation of lipoxin LXA4 in those patients is less obvious, as they possibly only unfold under the pre-condition of severe inflammation.

5-4-2-5 Metalloproteinases and TGF-β

The expression of TGF-β1 and TGF-β2, predominantly by eosinophils, and their putative effects on fibroblast activity and pathogenesis of nasal polyps have been suggested in several studies [222-224]. These studies compared protein levels in tissue homogenates from patients with nasal polyps who were either untreated or treated with oral corticosteroid, and control subjects. Patients with untreated polyp samples and controls showed significantly higher concentrations of IL-5, eotaxin, ECP and albumin, and significantly lower concentrations of TGF-β1. In contrast, corticosteroid treatment significantly reduced IL-5, ECP and albumin concentrations, whereas TGF-β1 was increased [205].

These observations suggest that IL-5 and TGF-β1 represent cytokines with counteracting activities, with a low TGF-β1 protein concentration in IL-5 driven nasal polyps. Furthermore, they support the deposition of albumin and other plasma proteins as a possible pathogenic principle of polyp formation, caused by the lack of upregulation/production of TGF-β1. The lack of TGF also may prevent the upregulation of TIMPs, thus failing to prevent ECM breakdown by metallo-proteinases. The relative down-regulation of ECM is especially apparent in comparison to CRS, demonstrating a significantly increased TGF versus controls [269].

TGF-β1 is a potent fibrogenic cytokine that stimulates extracellular matrix formation, acts as a chemoattractant for fibroblasts, but inhibits the synthesis of IL-5 and abrogates the survival-prolonging effect of haematopoietins (IL-5 and GM-CSF) on eosinophils [225]. Staphylococcal enterotoxins may induce a further down-regulation of TGF in specific populations of patients [346].

Oedema and pseudocyst formation characterize NP, with a few areas of fibrosis. An imbalance of metallo-proteinases with an upregulation of MMP-7 and MMP-9, but not TIMP-1, in nasal polyps has been recently demonstrated [408]. This results in the enhancement of MMP-9 in NP, which may account for oedema formation with albumin retention. The therapeutic effect of macrolide antibiotics may partially be related to the suppression of MMPs in the airways [409].

5-4-2-6 Nitric Oxide (NO)

Inducible nitric oxide synthase (iNOS) expression is upregulated in nasal polyp epithelium, especially in patients with asthma and aspirin–exacerbated respiratory disease [410]. The role of NO in nasal polyp formation and the possible diagnostic use are currently evaluated.

5-4-3 Impact of Staphylococcus aureus enterotoxins (SAEs)

Early studies have shown that tissue IgE concentrations and the number of IgE positive cells may be raised in nasal polyps, suggesting the possibility of local IgE production [411]. The local production of IgE is a characteristic feature of nasal polyposis, with a more than tenfold increase of IgE producing plasma cells in NP versus controls. Analysis of specific IgE revealed a multiclonal IgE response in nasal polyp tissue and IgE antibodies to *Staphylococcus aureus* enterotoxins (SAEs) in about 30-50% of the patients and in about 60-80% of nasal polyp subjects with asthma [192, 343, 348, 412-414]. A recent prospective study revealed that colonization of the middle meatus with *Staphylococcus aureus* is significantly more frequent in NP (63.6%) compared to CRS (27.3%, p < 0.05), and is related to the prevalence of IgE antibodies to classical enterotoxins (27.8 vs 5.9%) [415]. If aspirin sensitivity, including asthma, accompanied nasal polyp disease, the *S. aureus* colonization rate was as high as 87.5%, and IgE antibodies to enterotoxins were found in 80% of cases.

Total and specific IgE as well as ECP in polyp homogenates are only partially reflected in the serum of the patients, however, the likelyhood is clearly increased in patients with nasal polyps and asthma. Staining of NP tissue revealed follicular structures characterised by B- and T-cells, and lymphoid agglomerates with diffuse plasma cell infiltration, demonstrating the organization of secondary lymphoid tissue with consecutive local IgE production in NP [416].

The classical SAEs, especially TSST-1 and Staphylococcus protein A (SPA), are excellent candidates to induce multiclonal IgE synthesis by increasing the release of IL-4 as well as the expression of CD40 ligand on T-cells and B7.2 on B-cells cells cells [417, 418]. SPA furthermore interacts with the VH3-family of immunoglobulin heavy chain variable gene products and thus preferentially selects plasma cells presenting such immunoglobulins on their surface, which leads to a VH3 bias [419]. In fact, follicle-like aggregates can be found in nasal polyps, expressing CD20+ B-cells, CD3+ T-cells and IgE plasma cells, but largely lacking CD1a+ dendritic antigen presenting cells, supporting the concept of a superantigen stimulation [416]. SAEs furthermore stimulate T-cells by binding to the variable beta-chain of the T-cell receptor, which induces cytokine production of IL-4 and IL-5, directly activate eosinophils and prolong their survival and also may directly activate epithelial cells to release chemokines [420]. SAEs also activate antigen-presenting cells to increase antigen uptake.

In vivo animal models support the pivotal role of SAEs in airway disease (421), with SAEs inducing eosinophilic inflammatory responses in sensitized mice in both, the upper and the

Table 5-7. 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 ensodcopic sinus surgery)

author, year	tissue, patient	marker	technique	conclusion
Camilos, 1993 [99]	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 [370]	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 [427]	nasal polyps sinonasal mucosa	IL-8, GM-CSF, IL-1β, IL-6, IL-8, TNF-α	ELISA RT-PCR	nasal polyps may represent a more active inflammatory tissue (more cytokines) than healthy nasal mucosa
Bartels, 1997 [376]	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 [26]	nasal polyps sinonasal mucosa	IL-1 β, 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 [372]	nasal polyps healthy sinonasal mucosa allergic rhinitis mucosa	IL-4, IL-5, IFN-γ mRNA	RT-PCR Southern blot	NP and allergic rhinitis may differ in the mechanism by which IL-4 and IL-5 are increased
Simon, 1997 [371]	nasal polyps	IL-5	ELISA RT-PCR	IL-5 is an important cytokine that may delay the death process in NP eosinophils
Bachert, 1998 [278]	nasal polyps	Th1, Th2 cytokines	Elispot	Th1 and Th2 type cytokines are upregulated in NP, irrespective of allergen skin test results.
Bachert, 2001 [428]	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 ImmunoCAP	association between increased levels of total IgE, specific IgE, and eosinophilic inflammation in NP
Gevaert, 2003 [375]	nasal polyps sinonasal mucosa	Soluble IL-5Rα	RT-PCR	antagonistic soluble isoform is upregulated, the signal transducing transmembrane isoform is down-regulated in nasal polyps, mainly in asthma.
Wallwork, 2004 [304]	CRS nasal mucosa (in vivo & in vitro)	TGF-β1, NFkB	IHC	clarythromycin inhibits TGF-β1 and NFκB only in vitro
Watelet, 2004a [303]	sinonasal mucosa (FESS)	MMP-9, TGF-β1	IHC ELISA	correlation with the tissue healing quality
Watelet, 2004b [408]	sinonasal mucosa (FESS)	TGF-β1	IHC ELISA	CRS without NP: increased expression of TGF-β1 compared to NP
Elhini, 2005 [294]	ethmoidal sinus mucosa	CCR4+, CCR5+	IHC real time PCR	CRS patients: increase of CCR4+ in atopics and decrease of CCR5+ in non-atopics
Lu, 2005 [302]	sinonasal mucosa (surgery)	MMP-7, MMP-9, TIMP-1, TGF-β1	ELISA	different profile expression in CRS, NP, and healthy mucosa
Pérez-Novo, 2005 [288]	sinonasal mucosa	COX-2 PGE2	real time PCR ELISA	CRS: COX-2 and PGE2 are more expressed than in NP
Toppila-Salmi, 2005 [296]	maxillary sinus mucosa (surgery)	L-selectin ligands	IHC	increased expression in CRS endothelial cells
Lane, 2006 [429]	ethmoidal mucosa (surgery)	TLR2, RANTES, GM-CSF	real time PCR	CRS: increase compared to healthy controls
Lee, 2006 [295]	sinonasal mucosa	CCL-20	IHC real time PCRS	increased expression of CCL20 in CR
Olze, 2006 [378]	nasal polyps turbinate mucosa	eotaxin, eotaxin-2, and -3	ELISA	eotaxin is expressed in CRS
Pérez-Novo, 2006 [297]	nasal mucosa	CysLT receptors EP Receptors	real time PCR	CRS: CysLT and EP receptors are more expressed than in NP
Rudack, 2006 [286]	sinonasal mucosa	GRO-α, GCP-2, IL-8, ENA-78	HPLC + bioassay	expression of GRO-α and GCP-2 in CRS
Watelet, 2006 [306]	sinonasal mucosa (FESS)	MMP-9	IHC	correlation between MMP-9 expression and tissue healing quality

lower airways, when applied in either of those locations [422]. In fact, when comparing SAE-IgE positive nasal polyps to SAE-IgE negative, the number of IgE positive cells and eosinophils is significantly increased. The more severe inflammation is also reflected by significantly increased levels of IL-5, ECP and total IgE. Furthermore, a possible link to aspirin sensitivity has been proposed, with SAEs creating a severe inflammation possibly serving as a basis for the specific changes seen in aspirin sensitivity [412, 414]. A review on the current knowledge on the impact of SAEs on nasal polyp disease and lower airway disease was recently published [206]. IgE antibody formation to SAE can be seen in nasal polyp tissue, but rarely in CRS without polyps.

In conclusion, SAEs are able to induce a more severe eosinophilic inflammation as well as the synthesis of a multiclonal IgE response with high total IgE concentrations in the tissue, which would suggest that SAEs are at least modifiers of disease in CRS with nasal polyps [206, 420]. Interestingly, similar findings have recently been reported in asthma, which is known to be associated with NP [349], and in COPD [423], thus providing a link between upper and lower airways.

5-4-4 Nasal polyps in cystic fibrosis

NPs and CF-NPs share the remodelling pattern, i.e. they can be discriminated from CRS without polyps and controls by the oedema formation. Different to NPs, CF-NP display a very prominent neutrophilic inflammation, with abnormally increased concentrations of IL-1β, IL-8 and MPO [269] and an increased activity of NFκB [424], whereas macrophages, but not eosinophils, are significantly increased over control mucosa. Furthermore, there seems to be a reactive imbalance in innate immunity markers, with mRNA expression of HBD 2 and of TLR2 being significantly higher in CF-NP compared to non-CF-NP [425].

The calcium-activated chloride channel hCLCA1 is thought to regulate the expression of soluble gel-forming mucins, and is upregulated by IL-9. Increased expression of IL-9 and IL-9R, as well as upregulation of hCLCA1, in mucus-overproducing epithelium of patients with cystic fibrosis supports the hypothesis that IL-9 contributes to mucus overproduction in cystic fibrosis [426].

5-4-5 CRS with or without nasal polyps

When searching through the literature, it is apparent that definitions do matter; especially in older literature, the term CRS was confused by "hyperplastic CRS" or "hyperplastic CRS with polyp formation", which would probably be equivalent to NPs rather than CRS. However, because of a lack of clinical data provided in those papers, the distinction between these diseases can often not be made, and the interpretation from those studies has to be done with caution. For the purpose of this chapter, we have used clearly defined patient populations.

Whereas NPs are characterized by oedema formation, with an increased VPF/VEGF, an upregulation of MMPs, but not

TIMP, and a low level or decrease in TGF-β1, CRS shows a fibrotic remodelling pattern with a balanced MMP system and a significantly increased TGF-β protein content [269]. This fundamental difference has been linked to the predominant type of inflammation: eosinophilic or neutrophilic; however, this notion has to be challenged in the light of 1) the fact that NPs and NPs in CF both show oedema formation, but are characterized by either abundant eosinophils or neutrophils and their products; and 2) the fact that NPs from different parts of the world do not show the same degree of eosinophilic inflammatory pattern [346]. It is important to note that also in NPs, the number of neutrophils is increased versus controls, and the frequent impression of a predominantly "eosinophilic" inflammation neglects those cells.

Both chronic sinus diseases, CRS and NPs, show increased numbers and activation of T-cells, while only NPs display a significant increase in plasma cells and consecutive immunoglobulin synthesis [269]. The role of this observation is unclear, and may reflect a constant microbial trigger.

NP have significantly higher levels of eosinophilic markers (eosinophils, eotaxin and ECP) compared to CRS and controls in Caucasians, in whom CRS is characterized by proinflammatory cytokines (IL-1β and TNF-α), a Th1 polarisation with high levels of IFN-γ, and a significant increase in profibrotic TGF-β, while NPs show a Th2 polarisation with high IL-5 and IgE concentrations and a decrease in TGF-β [269]. Further studies will have to investigate TH1 and TH2-specific transduction signals, as well as the role of T regulatory cells, to fully understand the stability of these patterns; studies in non-caucasian populations may further be helpful to differentiate primary from secondary phenomena.

5-5 Aspirin sensitivity – Inflammatory mechanisms in acute and chronic rhinosinusitis

5-5-1 Introduction

The presence of aspirin-intolerance in a patient with rhinosinusitis with or without nasal polyposis is associated with a particularly persistent and treatment-resistant form of disease, coexisting usually with severe asthma and referred to as the "aspirin triad" [430]. 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 [34]. 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 [25, 431, 432]. Rhinosinusitis in aspirin hypersensitive patients with nasal polyposis is characterized by involvement of all sinuses and nasal passages and higher thickness of hypertrophic mucosa as has been documented with computer tomography [433].

5-5-2 Mechanisms of acute ASA-induced reactions

In ASA-sensitive patients acute nasal symptoms (sneezing, rhinorrhea and congestion) may be induced by challenge with

oral or intranasal aspirin but also with other cross-reacting nonsteroidal anti-inflammatory drugs (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 [434, 435]. 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 [388]. Concomitant release of both mast cell (tryptase, histamine) and eosinophil (ECP) specific mediators into nasal washes clearly indicate activation of both types of cells [436-438]. 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 [439]. In parallel with inflammatory mediator release an influx of leucocytes into nasal secretions occurred with significant enrichment in eosinophils [436].

5-5-3 Chronic rhinosinusitis with nasal polyps
Although the pathogenesis of chronic eosinophilic inflammation of the airway mucosa and nasal polyps 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 with nasal polyps in aspirin-sensitive patients may be different from that in aspirin tolerant patients [440].

5-5-3-1 Cells and cytokine profile
A high degree of marked tissue eosinophilia is a prominent feature of rhinosinusits with nasal polypos in ASA-hypersensitive patients and accordingly significantly more ECP was released from non-stimulated or stimulated nasal polyp dispersed cells from ASA-sensitive patients [350, 441]. An increased number of eosinophils in the tissue has been linked to a distinctive profile of cytokine expression with upregulation of several cytokines related to eosinophil activation and survival (eg. IL-5, GM-CSF, RANTES, eotaxin) [442-444]. 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. 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 [445]. Bachert at al [192] 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 [412].

Not only activated eosinophils but also mast cells are abundant in the nasal polyps tissue from ASA-sensitive patients [355, 446]. The density of mast cells was correlated with the number of polypectomies, implicating an important role for these cells in the pathogenesis of CRS with nasal polyps. 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 [355].

5-5-3-2 Arachidonic acid metabolites
Since Szczeklik et al [447] 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 PGE_2 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 [398, 448]. Low expression of COX-2 mRNA in nasal polyps from ASA-sensitive patients was in turn linked to a downregulation of NF-κB activity and to abnormal regulation of COX-2 expression mechanisms at the transcriptional level [449, 450]. Since PGE_2 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 PGE_2 could contribute to development of more severe eosinophilic inflammation in aspirin-sensitive patients. Although a significant deficit of PGE_2 was demonstrated in polyp tissue of ASA-sensitive as compared to ASA-tolerant patients, decreased expression of COX-2mRNA and PGE production seem to be a feature of CRS with nasal polyps also in patients without ASA-sensitivity representing more general mechanism involved in the growth of nasal polyps. On the other hand the percentages of neutrophils, mast cells, eosinophils, and T cells expressing prostaglandin EP2, but not EP1, EP3, or 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 [400, 451] but these observations could not be reproduced in vivo when nasal washes were analysed [388, 452]. Similarly when nasal polyp dispersed cells were cultured basal and stimulated release of LTC4 was found to be similar in nasal polyp cells from from ASA-sensitive and ASA-tolerant patients [355]. Whole blood cells from aspirin sensitive and tolerant patients did not differ in their ability to generate cyclooygenase and lipoxygenase

products [453]. 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 [288, 439, 454]. 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 [389, 392]. More recently other arachidonic acid metabolites generated on 15-LOX pathway have been associated with CRS with nasal polyps in ASA-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 [448]. 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 [288].

5-6 Conclusion

Although far from being completely understood, pathomechanisms in ARS, CRS and NP are better understood today and begin to allow us to differentiate these diseases via their cytokine profile, their pattern of inflammation as well as remodeling processes.

6. Diagnosis

6-1 Assessment of rhinosinusitis symptoms

6-1-1 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 [24, 455-459]. It is interesting to note that only a small proportion of patients with purulent rhinosinusitis, without coexisting chest disease, complain of cough [460].

The symptoms are principally the same in acute and chronic rhinosinusitis as well as in CRS with nasal polyps, but the symptom pattern and intensity may vary. Acute forms of infections, both acute and acute exacerbations of chronic rhinosinusitis, have usually more distinct and often more severe symptoms.

Simple nasal polyps may cause constant non-periodic nasal blockage , which can have a valve-like sensation allowing better airflow in only one direction. Nasal polyps may cause nasal congestion, which can be a feeling of pressure and fullness in the nose and paranasal cavities. This is typical for ethmoidal polyposis, which in severe cases can cause widening of the nasal and paranasal cavities demonstrated radiologically and in extreme cases, hyperteliorism. Disorders of smell are more prevalent in patients with nasal polyps than in other chronic rhinosinusitis patients [25].

6-1-2 Subjective assessment of the symptoms
Subjective assessment of the symptoms should consider the strength or degree of the symptoms, the duration of the symptom. During the last decade more attention has been paid not only to symptoms but also to their effect on the patient's quality of life (QoL) [461, 462].
The assessment of subjective symptoms is done using questionnaires or in clinical studies recorded in logbooks. Evaluation frequency depends on the aims of the study, usually once or twice daily. Continuous recording devices are also available.

The degree or strength of the symptoms can be estimated using many different grading tools.
- recorded as such: severe, moderate, slight and no symptom;
- recorded as numbers: from 0 to 4 or as many degrees as needed;
- recorded as VAS score on a line giving a measurable continuum (0 – 10 cm).

Terms such as mild, moderate or severe may include both symptom severity estimation, but also an estimate of duration i.e. "moderate symptom severity" can mean an intense symptom but only for a short time in the recorded period or less severe symptom but lasting for most of the recording period.

A recent study has considered the relationship between subjective assessment instruments in chronic rhinosinusitis and has shown that 'mild' equates to a visual analogue score of 3 or less, 'moderate' to > 3-7 and 'severe' to > 7-10 [14].

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. It provides the possibility to record time periods (eg. days) without symptoms, which can be reliably compared between testees (inter-patient) and from study to study.

These criteria are inconsistent and not always comparable when considering rhinosinusitis. [459], where the symptoms may fluctuate from time to time. Nevertheless in many randomised, controlled and prospective rhinosinusitis intervention studies, both allergic and infective, these methods of recording symptoms have given statistically significant results.

In a study correlating nasosinal symptoms with topographic distribution of chronic rhinosinuitis as demonstrated by CT scanning, the symptoms of nasal obstruction, anterior and posterior nasal discharge, sneezing and facial congestion failed to discriminate site of disease. By contrast loss of smell and flavour were correlated with what the authors refer to as 'diffuse rhinosinusitis' ie mainly CRS with nasal polyps, whereas cacosmia and facial pain correlated with 'localised or anterior sinusitis' ie mainly sinusitis of dental or foreign body origin. [84]

6-1-3 Validation of subjective symptoms assessment
Validation of the rhinosinusitis symptoms to show the relevance in distinguishing disease modalities and repeatabilty between ratings of the same patient (intrapatient, longitudinal validity) and between different patients (interpatient, cross-sectional validity) have been done. Lately, more specific and validated subjective symptom scoring tools have become available

with the development of quality of life (QoL) evaluations. These are either assess general health evaluating [463, 464] or are disease specific [461, 462, 465].

6-1-3-1 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 varies from true mechanical obstruction of airflow to the sensation of fullness in the midface.

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, hyperreactivity or infective rhinitis [466-470]. However, there are also some studies where this correlation is not seen [471] or the correlation was poor [472, 473].

The interpatient variation in subjective scoring suggests that every nose is "individually calibrated", which makes interpatient comparisons less reliable but still significant [466, 468].

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 [470, 474].

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.

6-1-3-2 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 [475] and in "autonomic (previously termed vasomotor) rhinitis" [476].

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.

6-1-3-3 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 alter-

ations 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 and other disease conditions [477-480] as well as numerous clinical studies concerning other diseases than rhinosinusitis (Evidence level Ib).

6-1-3-4 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 [455] or paranasal sinus radiographs [481]. The importance of facial pain as a cardinal sign of chronic rhinosinusitis has also been called into question [482] where the symptoms are more diffuse and fluctuate rendering the clinical correlation of facial pain and pressure scorings against objective assessments unconvincing. 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 [483]. However, rhinosinusitis disease specific quality of life studies also include facial pain-related parameters, which have been validated [465].

6-1-3-5 Overall rating of rhinosinusitis severity

Overall rating of rhinosinusitis severity can be obtained as such or by total symptoms scores, which are summed scores of the individual symptoms scores. These are both commonly used, but according to an old validation study for measuring the severity of rhinitis, scores indicating the course of individual symptoms should not be combined into a summed score, rather the patient's overall rating of the condition should be used [484]. QoL methods have produced validated questionnaires which measure the impact of overall rhinosinusitis symptoms on everyday life [461].

6-1-3-6 Chronic Sinusitis Survey (CSS)

This is a 6-item duration based monitor of sinusitis specific outcomes which has both systemic and medication-based sections [485]. In common with other questionnaires, it is rather better at determining the relative impact of chronic rhinosinusitis compared to other diseases than as a measure of improvement following therapeutic intervention but can be a useful tool [462, 486] [Evidence Level IIb]. Mean scores one year after endoscopic frontal sinus surgery showed a significant improvement in symptoms of pain, congestion, and drainage and medication use was also significantly reduced [487].

6-1-3-7 The Chronic Rhinosinusitis Type Specific Questionnaire

This test contains three forms. Form 1 collects data on nasal and sinus symptoms prior to treatment, Form 2 collects data

Table 6-1. Endoscopic appearances scores

characteristic	Baseline & Follow-up
polyp left (0,1,2,3)	
polyp, right (0,1,2,3)	
oedema, left (0,1,2,)	
oedema, right (0,1,2,)	
discharge, left (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	

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.

on the clinical classification of sinus disease and Form 3 data on nasal and sinus symptoms after sinus surgery. Hoffman et al have used this in combination with an SF-36 to look at patient outcomes after surgical management of chronic rhinosinusitis though it is somewhat time consuming to complete [488].

6-2 Examination

6-2-1 Anterior rhinoscopy
Anterior rhinoscopy alone is inadequate, but remains the first step in examining a patient with these diseases.

6-2-2 Endoscopy
This may be performed without and with decongestion and semi-quantitative scores [457] for polyps, oedema, discharge, crusting and scarring (post-operatively) can be obtained (Table 6-1) at baseline and at regular intervals following therapeutic

interventions eg at 3, 6, 9 and 12 months. This has a high inter-rater concordance [489]. A number of staging systems for polyps have been proposed [490-492]. Johansson showed good correlation between a 0 - 3 scoring system and their own system in which they estimated the percentage projection of polyps from the lateral wall and the percentage of the nasal cavity volume occupied by polyps. However, they did not find a correlation between size of polyps and symptoms. (Level III).

6-2-3 Nasal cytology, biopsy and bacteriology
Generally cytology has not proved a useful tool in diagnosis of rhinosinusitis although a biopsy may be indicated to exclude more sinister and severe conditions such as neoplasia and the vasculitides.

Several microbiology studies [494-498] [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 6-2). 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 [499].

6-2-4 Imaging
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 [501-503]. Nevertheless it can be useful to prove ARS in studies.

Transillumination was advocated in the 1970's as an inexpensive and efficacious screening modality for sinus pathology [504]. The insensitivity and unspecificity makes it unreliable for the diagnosis of rhinosinusitis [505].

Sinus ultrasound is also insensitive and of limited usefulness for the diagnosis of rhinosinusitis 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 [41, 506, 507].

Table 6-2. Bacteriology of Rhinosinusitis; Correlation of middle meatus versus maxillary sinus

author	no of samples	type of rhinosinusitis	technique	concordance
Gold & Tami, 1997 [495]	21	chronic	endoscopic tap (MM) v maxillary aspiration during ESS	85.7%
Klossek et al, 1998 [494]	65	chronic	endoscoic swab (MM) v maxillary aspiration during ESS	73.8%
Vogan et al, 2000 [496]	16	acute	endoscoic swab (MM) v maxillary sinus tap	93%
Casiano et al, 2001 [497]	29	acute (intensive care)	endoscopic tissue culture (MM) v maxillary sinus tap	60%
Talbot et al, 2001 [500]	46	acute	endoscopic swab (MM) v maxillary sinus tap	90.6%
Joniau et al 2005 [498]	26	acute	endoscopic swab (MM) v maxillary sinus tap	88.5%

MM: middle meatus; ESS: endoscopic sinus surgery

CT scanning is the imaging modality of choice confirming 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. The demonstration of the complex sinonasal anatomy has been regarded as at least as important as confirmation of inflammatory change[508-510]. Considerable ethnic as well as individual differences may be encountered [511]. Many protocols have been described and interest has recently centred on improving definition whilst reducing radiation dose [512].

MRI is not the primary imaging modality in chronic rhinosinusitis and is usually reserved in combination with CT for the investigation of more serious conditions such as neoplasia.

A range of staging systems based on CT scanning have been described using stages 0-4 and of varying complexity [59, 490, 513-517].

The Lund-Mackay system relies on a score of 0-2 dependent upon the absence, partial or complete opacification of each sinus system and of the ostiomeatal complex, deriving a maximum score of 12 per side (Table 6-3) [490].

Table 6-3. CT scoring system [490]

sinus system	left	right
maxillary (0,1,2)		
anterior ethmoids (0,1,2)		
posterior ethmoids (0,1,2)		
sphenoid (0,1,2)		
frontal (0,1,2)		
ostiomeatal complex (0 or 2 only)*		
total points		

0-no abnormalities; 1-partial opacification; 2-total opacification.
*0-not occluded; 2-occluded

This has been validated in several studies [518] [Evidence Level IIb] and was adopted by the Rhinosinusitis Task Force Committee of the American Academy of Otolaryngology Head and Neck Surgery in 1996 [5]. CT and endoscopic scores correlate well [519] but the correlation between CT findings and symptom scores has generally been shown to be poor and is not a good indicator of outcome [133, 520, 521] [Evidence Level IIb]. However, Wabnitz and colleagues did find a correlation between VAS and CT score though not between CT score and QoL as measured with the Chronic Sinusitis Score [522]. Bhattacharyya compared three staging systems with the Rhinosinusitis Symptom Inventory [523] and found the Lund score to correlate best with nasal scores but the degree of correlation remained low.

It should be noted that incidental abnormalities are found on scanning in up to a fifth of the 'normal' population [64]. A mean LM score of 4.26 in adults [524] and 2.81 in children aged 1-18 years [525] have been reported. In addition for ethical reasons a CT scan is generally only performed post-operatively when there are persistent problems and therefore CT staging or scoring can only be considered as an inclusion criterion for studies and not as an outcome assessment.

6-2-5 Mucociliary function

6-2-5-1 Nasomucociliary clearance
The use of saccharin, dye or radioactive particles to measure mucociliary transit time has been available for nearly thirty years [526-528]. It allows if altered one to recognize early alterations of rhinosinusal 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 normals, hypertrophied inferior turbinates and septal deviation [529].

6-2-5-2 Ciliary beat frequency
Specific measurements of ciliary activity using a phase contrast microscope with photometric cell [530, 531] have been used in a number of studies to evaluate therapeutic success [532, 533] [Evidence Level IIb]. The normal range from the inferior turbinate is over 8 Hz but these techniques are available in only a few centres to which children suspected of primary ciliary dyskinesia (PCD) should be referred. The final gold standard of ciliary function involves culture techniques for 6 weeks [534].

6-2-5-3 Electron microscopy
This may be used to confirm the presence of specific inherited disorders of the cilia as in PCD.

6-2-5-4 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 sig-

nificant sinus obstruction eg severe CRS with nasal polyps. Conversely elevated levels suggest nasal inflammation but ostiomeatal patency [535] [Evidence Level IIb]. It can potentially be used, as an outcome measure after therapy [536] [Evidence Level IIa] However, some contradictory results on the role of nNO on nasal inflammation have been recently assessed [311].

6-2-6 Nasal airway assessment

6-2-6-1 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 polyps and compares well with rhinomanometry [537, 538] [Evidence Level IIb]. Normative data is now available in an adult Caucasian population [539]. Expiratory peak flow is less often used as mucus is expelled into the mask and the technique may be associated with eustachian dysfunction.
Furthemore in non-allergic, non-infectitious perennial rhinitis versus controls, repeated PNIF resulted in a brief but statistically significant increase in nasal airway resistance in the rhinitic patients suggesting a neuronal mechanism [540]

6-2-6-2 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 with and without nasal polyps 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 [532] [Evidence Level IIb].

6-2-6-3 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. It can be used to demonstrate subtle changes, both as a result of medical and surgical intervention [536, 538, 541, 542] [Evidence Level IIa].

6-2-6-4 Rhinostereometry
This also measures subtle changes in mucosal swelling, largely in the inferior turbinates [543, 544] [Level IIb] and is therefore not directly applicable to assessment of chronic rhinosinusitis.

6-2-7 Olfaction

6-2-7-1 Threshold Testing
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 [533, 541, 545-547] [Evidence Level IIb].

6-2-7-2 Other quantitative olfactory testing
Scratch and sniff test using patches impregnated with micro-

encapsulated odorants are available [548] and have been utilised in studies of both chronic rhinosinusitis with and without nasal polyps [538]. A cruder screening test, the Zurich Smell Diskette test may also be used and has the advantage of pictorial representation of the items [549, 550]. 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 [480]. More complex tests exist [551] e.g. 'Sniff 'n' sticks' which limit their application to the research setting. A combined supra-threshold detection and identification test has been devised as a cross-cultural tool in the European population, the results of which are presented in the appendix [552] [Evidence Level III].

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

6-2-8 Aspirin and other challenges
Objective experiments to differentiate patient groups according to rhinosinusitis severity or aetiology have been done using nasal provocation with histamine or metacholine [553, 554] which test mucosal hyper-reactivity. The tests can differentiate subpopulations with statistical significance, but because of considerable overlap of results, these tests have not achieved the equivalent position in rhinitis severity evaluations as the corresponding bronchial tests i.e in asthma diagnosis.

Establishing a diagnosis of aspirin hypersensitivity is important since it provides the patient with a long list of common drugs that must not be taken in view of the risk of a severe reaction. It diagnoses a particular type of asthma and sinonasal disease and allows choice of a specific therapy, i.e. aspirin desensitization.
The oral aspirin challenge test was introduced to clinical practice in the early 1970's [555]. Over the following years it was validated and more frequently used [556-558]. An inhalation test was introduced in 1977 by S Bianco. This challenge is safer and faster to perform than the oral one, although less sensitive [559-561]. Contrary to the oral challenge it does not produce systemic reactions. The nasal provocation test was employed in the late 1980's [562, 563]. It is recommended especially for patients with predominantly nasal symptoms and 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 only truly soluble form of aspirin must be used for both respiratory routes. Test procedures have recently been reviewed in detail [564]. The sensitivity and specificity of the tests are shown in Table 6-4.

Table 6-4. Diagnosis of aspirin sensitivity

history ±	challenge sensitivity (%)	specificity (%)
oral	77	93
bronchial	77	93
nasal	73	94

6-2-9 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 [565]. 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) [566].

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 [567].
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 exclude bacterial infection. [566].

6-3 Quality of Life

During the last decade more attention has been paid to not only symptoms but also to patient's quality of life (QoL) [462] or more accurately health-related quality of life (HRQoL). The QoL questionnaires can provide either general (generic) or disease specific health assessment. However, it is of interest that the severity of nasal symptoms or findings do not always correlate with QoL scales [522, 568]. [Evidence Level IIb].

6-3-1 General (generic) health status instruments
General (generic) measurements enable the comparison of patients suffering from chronic rhinosinusitis with other patient groups. Of these the Medical Outcomes Study Short Form 36 (SF36) [463] is by far the most widely used and well validated and this has been used both pre- and post-operatively in chronic rhinosinusitis. [536, 569] [Evidence Level IIa,IIb]. It includes eight domains: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role-functioning emotional and mental health. Many other generic measurements are also available [464]. For example EuroQOL, Short Form-12 and Quality of Well-Being Scale have been used in sinusitis studies [570].
The Glasgow Benefit Inventory has also been applied to chronic rhinosinusitis and its treatment [571] as has the EuroQol and McGill pain questionnaires [572, 573].

6-3-2 Disease specific health status instruments (see also appendix)
Several disease specific questionnaires for evaluation of quality of life in chronic rhinosinusitis have been published. In these questionnaires specific symptoms for rhinosinusitis are included. Such areas include headache, facial pain or pressure, nasal discharge or postnasal drip, and nasal congestion. Disease specific questionnaires are usually used to measure effects within the disease in response to interventions. They are usually more sensitive than general health status instruments.

6-3-2-1 Rhinosinusitis outcome measure (RSOM) and Sinonasal Outcome Test-20
RSOM contains 31 items classified into 7 domains and takes approximately 20 minutes to complete [574]. RSOM has been well-validated and allows measurement of symptom severity and importance to the patient. The severity and importance scales, however, make it somewhat difficult for the patient to fill the questionnaire [575] RSOM-31 has been used in medical studies [576].

6-3-2-2 Sinonasal Outcome Test 20
A modified instrument referred to as the Sinonasal Outcome Test 20 (SNOT 20) is validated and easy to use [465]. This has been used in a number of studies both medical and surgical [536, 577] [Evidence Levels Ib, IIb]. However, the lack of the SNOT-20 is that it does no contain questions on nasal obstruction and loss of smell and taste. These questions are included in the SNOT-22 questionnaire which however is not validated. This test was the primary outcome in the largest audit to date of surgery for chronic rhinosinusitis with or without nasal polyps [520].

6-3-2-3 Sinonasal Outcome Test 16
The Sinonasal Outcome Test 16 (SNOT 16) is also a rhinosinusitis specific quality of life health related instrument [578].

6-3-2-4 Rhinosinusitis Disablity Index (RSDI)
In this 30 item validated questionnaire, the patient is asked to relate nasal and sinus symptoms to specific limitations on daily functioning [461, 579]. It is similar to the RSOM 31 in the types of questions it contains. It can be completed easily and quickly but does not allow the patient to indicate their most important symptoms. However, it does have some general questions similar to the SF-36.

6-3-2-5 Rhinoconjunctivitis quality of life questionnaire (RQLQ)
This is a well-validated questionnaire but specifically focuses on allergy and is not validated in acute and CRS with or without NP [580].
A newer standardized version RQLQ(S) is also available and it has been used for example in a nasal lavage study in chronic rinosinusitis [581].

6-3-2-6 RhinoQOL
The RhinoQol is a sinusitis specific instrument which measures symptom frequency, bothersomeness and impact. It can be used for acute and chronic sinusitis [582].

6-3-2-7 Rhinitis Symptom Utility Index (RSUI)
This consists of ten questions on the severity and frequency of

a stuffy or blocked nose, runny nose, sneezing, itching, watery eyes and itching nose or throat. The RSUI is designed for cost-effectiveness studies. The two-week reproducibility of the RSUI was weak, probably reflecting the day to day variability of rhinitis [583].

6-3-2-8 SN-5

SN-5 is a validated HRQoL instrument that can be used to measure child's QoL in relation to chronic sinonasal symptoms [584, 585]. The SN-5 domains are sinus infection, nasal obstruction, allergy symptoms, emotional distress, and activity limitations. The information for the questionnaire is given by a child's caregiver.

6-3-3 Results

6-3-3-1 General (generic) questionnaires

In three generic SF-36 surveys the scores of chronic rhinosinusitis patients were compared to those of a healthy population. The results showed statistically significant differences in seven of eight domains [572, 586, 587]. Two studies have reported that patients with chronic rhinosinusitis have more bodily pain and worse social functioning than for example patients with chronic obstructive pulmonary disease, congestive heart failure, diabetes, or back pain [572, 588].

The EuroQol, SF-36 and McGill pain questionnaire were used to assess 56 patients with refractory CRS in an RCT investigating use of filgrastim. Baseline results confirmed that patient QOL was below normal and suggested an improvement (though not significant) in the actively treated group [572].

The effect of surgical treatment was studied with generic questionnaires preoperatively and usually 3, 6 or 12 months after the operation [512, 573, 587]. Following endoscopic sinus surgery, the SF-36 questionnaire demonstrated a return to normality in all eight domains six months post-operatively which was maintained at twelve months [569]. In a study by Gliklich and Metson after the sinus surgery significant improvements were found in reduction of the symptoms and medications needed [486]. Significant improvements in general health status were noted in six of eight categories, and most attained near-normative levels. Oral steroid treatment also had a similar effect on HRQoL as surgery as measured by SF-36 [587].

Radenne et al. have studied the QoL of nasal polyposis patients using a generic SF-36 questionnaire [568]. Polyposis impaired the QoL more than for example perennial rhinitis. Treatment significantly improved the symptoms and the QoL of the polyposis patients. FESS surgery on asthmatic patients with massive nasal polyposis improved nasal breathing and QoL, and also the use of asthma medications was significantly reduced [589].

In a recent study evaluating the effect of radical surgery on QoL, the SF36 and McGill Pain questionnaires were used on 23 patients who underwent Denker's procedures. Both ques-

tionnaires demonstrated improvement in most domains when post-opertaive results at 1 and 2 years were compared with baseline [573].

6-3-3-2 Disease specific questionnaires

A disease-specific questionnaire seems to be more sensitive than a general questionnaire in following patients after ethmoid sinus surgery [485]. 76% patients reported relief of the symptoms at least in two of the domains studied after FESS surgery [459].

Despite similarities in objective disease measures, female patients reported significantly worse QoL scores before and after FESS surgery as measured with RSDI questionnaire [590].

The RSOM questionnaire was used in a study where the effect 50 mg prednisolone or placebo daily for 14 days was compared [576]. Significant improvement was noted in total RSOM score with both active and placebo treatments (53% vs. 21%). However, the subset of nasal-spesific RSOM scores (6 parameters) showed significant improvement only in the prednisolone group.

In a recent randomised study of patients with chronic rhinosinusitis/nasal polyposis, treatment was either endoscopic sinus surgery or three months of a macrolide antibiotic such as erythromycin [536]. Patients were followed up at 3, 6, 9 and 12 months with a variety of parameters including visual analogue scores of nasal symptoms, SNOT 20, SF-36, nitric oxide measurements of upper and lower respiratory tract expired air, acoustic rhinometry, saccharine clearance test and nasal endoscopy. Ninety patients were randomised, with 45 in each arm and at the end of one year, 38 were available for analysis in the medical arm and 40 in the surgical arm. The study showed that there had been improvement in all subjective and objective parameters (p < 0.01) but there was no difference between the medical and surgical groups except that total nasal volume as measured by acoustic rhinometry was greater in the surgical group. This study shows the usefulness of objective measurement in confirming subjective impressions (Evidence Level 1b).

In a prospective multicentre cohort study of 3128 adults undergoing surgery for chronic rhinosinusitis/nasal polyposis health-related quality of life was compared at 12 and 36 months after surgery using a SNOT-22 questionnaire. This is a non-validated modification of the SNOT-20 by the addition of two questions on nasal blockage and sense of taste and smell and was useful in demonstrating significant improvement following surgery which did not change between 12 and 36 months [520]. However, it was not possible with this outcome measure to show advantage of extended sinus clearance over 'simple' polypectomy.

Nowadays there are many generic and disease specific HRQoL questionnaires available to rhinosinusitis studies. However, most of the questionnaires are not yet validated. QoL measurement is quite a new tool evaluating the impact of disease and the efficacy of treatment. In rhinosinusitis studies, when the effect of medical treatment or surgery has been evaluated, QoL has been considered to be an important outcome measurement as distinct from classic rhinosinusitis symptom parameters. In a number of studies, chronic rhinosinusitis has been shown to significantly impair QoL [Level Ib] [465, 572, 584, 591, 592] and this has also been shown to improve significantly with treatment [Level IIb] [459, 486, 585, 587, 593, 594].

7. Management

7-1 Treatment of rhinosinusitis with corticosteroids

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 [370, 427, 595, 596] or indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells [368, 597-599]. The potency of these effects is lower in nasal polyps than in nasal mucosa suggesting an induced inflammatory resistance to steroid treatment in chronic rhinosinusitis / nasal polyposis [596, 597].

The biological action of glucocorticoids is mediated through activation of intracellular glucocorticoid receptors (GR) [600], expressed in many tissues and cells [601] 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 [602]. Upon hormone binding, GRα enhances anti-inflammatory or represses proinflammatory 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 antiinflammatory effects of glucocorticoids, including an overexpression of GRβ or a downexpression of GRα . Increased expression of GRβ has been reported in patients with nasal polyps [603, 604] while downregulation of GR* levels after treatment with glucocorticoids [605, 606] has also been postulated to be one of the possible explanations for the secondary glucocorticoid resistance phenomenon.

The anti-inflammatory effect of corticosteroids could, theoretically, be expected as well in non-allergic (i.e. infectious) as in allergic rhinosinusitis. Tissue eosinophilia is thus also seen in CRS [259].

Indications for corticosteroids in rhinosinusitis:
- Acute rhinosinusitis;
- Prophylactic treatment of acute recurrent rhinosinusitis;
- Chronic rhinosinusitis without NP;
- Chronic rhinosinusitis with NP;
- Postoperative treatment of chronic rhinosinusitis with or without NP.

7-1-1 Acute rhinosinusitis

Most studies on corticosteroids in ARS determine the effect of topical corticosteroids as adjunct therapy to antibiotics. Very recently a study is published in which topical corticosteroid treatment as monotherapy is compared to antibiotics

7-1-1-1 Topical corticosteroid as monotherapy in acute rhinosinusitis

Recently mometasone furoate (MF) has been used and compared to amoxicillin and placebo in ARS [607]. MF 200 g twice daily was significantly superior to placebo and amoxicillin at improving symptom score. Used once daily MF was also superior to placebo but not to amoxicillin. This randomized study was done double-blind, double-dummy on 981 subjects. This is the first study to show topical steroids when used twice daily are effective in ARS as monotherapy and more effective than amoxicillin when used twice daily.

7-1-1-2 Topical corticosteroid as adjunct therapy in acute rhinosinusitis

Qvarnberg et al [608] measured the clinical effect of budesonide (BUD)/placebo as a complement to erythromycin and sinus washout in a randomized, double-blind study on patients referred for sinus surgery due to chronic or recurrent acute maxillary sinusitis. Three months treatment was given to 20 subjects in 2 groups, all without NP. Treatment with BUD resulted in a significant improvement of nasal symptoms, facial pain and sensitivity. No significant improvement was seen in mucosal thickening on x-ray. The final clinical outcome did not differ between the groups. No side effects of treatment were noted. It is not possible in this study to distinguish chronic from ARS but all cases were reported to have intermittent "episodes of sinusitis for the last two years".

In a multicentre study Meltzer et al [609] used flunisolide as adjunctive therapy to amoxicillin clavulanate potassium in patients with ARS or CRS for three weeks and an additional four weeks on only flunisolide. The overall score for global assessment of efficacy was greater in patients treated with flunisolide than placebo (p=0.007) after 3 weeks and after 4 additional weeks p=0.08. No difference was seen on x-ray but inflammatory cells were significantly reduced in flunisolide group compared to placebo.

Barlan et al [610] used BUD as adjunctive therapy to amoxillin clavulanate potassium for three weeks in a randomized, placebo controlled study in children with ARS. Improvement in cough and nasal secretion were seen at the end of the second week of treatment in the BUD group, $p < 0.05$ for both symptoms compared to placebo. At the end of week three there were no differences between the groups.

Melzer et al [611] gave mometasone furoate (MF) 400 g to 200

patients and placebo to 207 patients with ARS as adjunctive therapy to amoxicillin/clavulanate potassium for 21 days. Total symptom score and individual symptom scores as congestion, facial pain, headache and rhinorrhea improved significantly, but not postnasal drip in the MF group. The effect was most obvious after 16 days treatment. Improvement on CT was seen in MF group but was not statistically significant. No side effects of treatment were seen.

In a study by Dolor et al [612] 200 g FP daily was used as adjunctive therapy for 3 weeks (to cefuroxime for 10 days and xylometazoline for 3 days) in a double blind placebo controlled multicentre trial (n=47 in FP group and 48 in control group) in patients with ARS. Time was measured to clinical success. After two weeks, success was seen in 73.9 and 93.5% in placebo and FP group respectively (p=0.009). Time to clinical success was 9.5 and 6.0 days respectively (p=0.01)

Nayak et al [613] compared MF 200 and 400 g to placebo in 325, 318 and 324 patients with ARS (no NP) as adjunctive therapy to amoxicillin/clavulanate potassium for 21 days treatment. Total symptom score (TSS) was improved from day 4 and at the end of the study (21 days) in both MF groups compared to placebo. Improvement compared to the situation before treatment was 50 and 51% for MF groups and 44% in placebo group, p < 0,017. Individual nasal symptom scores such as nasal congestion, facial pain, rhinorrhea and postnasal drip improved in both MF-groups compared to placebo. CT was

improved, but not statistically significant in MF groups compared to placebo. No side effects of treatment were seen.

All these studies were on study groups where intranasal steroids have been used as an additional treatment to antibiotics. Only the Meltzer study compares topical corticosteroid as monotherapy to antibiotics. The findings by Meltzer et al [607] are of great interest but one might argue that objective references of bacterial infection were lacking (sinus aspirates for culture) as well as CT or x-ray. There might be a high number of viral infections but the results are in favour of a more restricted attitude to antibiotics in ARS. The evidence level as monotherapy and as adjunctive therapy to systemic antibiotics is I.

7-1-1-3 Oral corticosteroid as adjunct therapy in acute rhinosinusitis

Gehanno et al [614] 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 headace and facial pain in the steroid group.

In a multicentre study Klossek et al [615] assessed in a double

Table 7-1. Treatment with nasal corticosteroids in acute rhinosinusitis

study	*drug*	*antibiotic*	*number*	*effect*	*X-ray*	*level of evidence*
Qvarnberg, 1992 [608]	budesonide	erythromycin	20	significant effect on nasal symptoms, facial pain and sensitivity; final clinical outcome did not differ	mucosal thickening = no effect	Ib
Meltzer, 1993 [609]	flunisolide	amox/clav	180	significant effect: overall score for global assessment of efficacy was greater in the group whith flunisolide	no effect on x-ray	Ib
Barlan, 1997 [610]	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, 2000 [611]	mometasone furoate	amox/clav	407	significant effect in congestion, facial pain, headache and rhinorrhea. No significant effect in postnasal drip	no statistical difference in CT outcome	Ib
Dolor, 2001 [612]	fluticasone propionate	cefuroxime axetil	95	significant effect. effect measured as clinical success depending on patients self-judgment of symptomatic improvement	not done	Ib
Nayak, 2002 [613]	mometasone furoate	amox/clav	967	total symptom score (TSS) was improved (nasal congestion, facial pain, rhinorrhea and postnasal drip)	no statistical difference in CT outcome	Ib
Meltzer, 2005 [607]	mometasone furoate		981	significant effect on total symptoms score, nasal congestion, facial pain, sinus headache. significantly superior to placebo and amoxicillin	not done	Ib

Table 7-2. Treatment with oral corticosteroids in acute rhinosinusitis

study	drug	antibiotic	number	effect	effect at end of treatment	level of evidence
Gehanno, 2000 [614]	8 mg metylpred-nisolone TDS	amoxicillin clavulanate	417	significant reduction of headace and facial pain	no statistical difference at 14 days	Ib
Klossek, 2004 [615]	oral prednisone	cefpodoxime	289	improvement in pain, nasal obstruc-tion and consumption of paracetamol during first 3 days	no statistical difference at end of study	Ib

blind, randomised study in parallel groups the efficacy and toler-ance to prednisone administered for 3 days in addition to cefpo-doxime in adult patients presenting with an acute bacterial rhi-nosinusitis (proven by culture) with severe pain. The assess-ments made during the first 3 days of treatment showed a statis-tically significant difference in favour of the prednisone group regarding pain, nasal obstruction and consumption of paraceta-mol. 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. Evidence level for steroids as pain reliever: I but there is no evidence for a more positive long term outcome compared to placebo.

7-1-2 Prophylactic treatment of recurrent episodes of acute rhinos-inusitis

In a study by Puhakka et al [616] FP (200 g 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 positive for rhi-novirus, based on x-ray, was 18.4% and 34.9% in FP and place-bo group respectively (p = 0.07) thus indicating a non-signifi-cant effect of FP.

Cook et al. randomized, as a continuation of an acute episode of rhinosinusitis, patients with at least 2 episodes of rhinosi-nusitis in the previous 6 months or at least 3 episodes in the last 12 months for a double blind, placebo-controlled study with FP, 200 mcg QD. 227 subjects were included. Additionally cefuroxime axetil 250 mg BID was used for the first 20 days. 39% had a recurrence in the placebo group and 25% in the FP group (p = 0.016) during the seven week follow-up period.

Mean number of days to first recurrence was 97.5 and 116.6 respectively (p = 0.011) [617].

There is very low evidence for a prophylactic effect of nasal corticosteroids to prevent recurrence of ARS episodes.

7-1-3 Chronic rhinosinusitis without nasal polyps

7-1-3-1 Topical corticosteroid chronic rhinosinusitis without nasal polyps
Parikh et al [618] performed a randomized, double blind, place-bo-controlled trial on patients with chronic RS on two groups with respectively 9 and 13 subjects (2 subjects in each group with nasal polyps) to test fluticasone propionate for 16 weeks. No significant improvement was seen, as measured by symp-tom scores, diary card, acoustic rhinometry or endoscopy. No side effects were seen in either group.

In another double blind placebo controlled study on patients with CRS (without NP) with allergy to house dust mite and who had recently been operated on but still had signs of chronic RS, 256 ug budesonide (BUD) or placebo was instilled into the maxillary sinus once a day through a sinus catheter for three weeks [619]. A regression of more than 50% of total nasal symptom scores was seen in 11/13 in the BUD group and 4/13 in placebo group. The effect was more long term in BUD group, i.e. 2-12 months compared with less than 2 months in the placebo group (who had experienced an effect during the catheter period). A significant decrease was also seen in BUD group after three weeks treatment for CD-3, eosinophils and cells expressing IL-4 and IL-5.

In a study by Cuenant et al [620] tixocortol pivalate was given as endonasal irrigation in combination with neomycin for 11 days in a double blind placebo controlled in patients with chronic RS. Maxillary ostial patency and nasal obstruction was signifi-

Table 7-3. Treatment with nasal corticosteroids in prophylaxis of acute rhinosinusitis

study	drug	number	time (weeks)	effect	comments	level of evidence
Puhakka, 1998 [616]	FP	199	1	N.S.	common cold	Ib
Cook, 2002 [617]	FP	227	7	increased time to first recurrence. decreased frequency of ARS		Ib

cantly improved in the tixocortol group compared to placebo. Patients with CRS without allergy responded better to topical steroids than those with allergy.

Sykes et al [621] looked on 50 patients with mucopurulent CRS and allocated them to 3 groups for local treatment with sprays with either dexamethasone + tramazoline + neomycin/dexamethasone + tramazoline/placebo 4 times daily for 4 weeks and evaluation was performed double blinded. Treatment in both active groups was more effective than placebo (discharge, blockage and facial pain and x-ray) but no difference was seen with the addition of neomycin to dexamethasone.

A recent multicentre double-blinded placebo-controlled randomised trial of 134 patients with CRS without nasal polyps treated with topical budesonide for 20 weeks showed significant improvement in a number of parameters including symptom score and nasal inspiratory peak flow [622]. Quality of life assessments did not change however.

There is some evidence for an effect of topical intranasal steroids in CRS, particularly with intramaxillary instillation of steroids. No side effects were seen, including no increased signs of infection with intranasal corticosteroid treatment.

7-1-3-2 Oral corticosteroid chronic rhinosinusitis without nasal polyps

There are no data showing efficacy of oral corticosteroids in chronic rhinosinusitis without nasal polyps.

7-1-4 Chronic rhinosinusitis with NP

In studies on the treatment of NP, 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. Only placebo controlled studies will be referred to.

7-1-4-1 Topical corticosteroid chronic rhinosinusitis with

nasal polyps

Mygind et al [623] showed that beclomethasone dipropionate (BDP) 400 g daily for three weeks reduced nasal symptoms in 19 patients with NP compared to a control group of 16 patients treated with placebo aerosol. Reduction of polyp size did not differ in this short treatment study.

In another study with BDP 400 g daily for four weeks (double blind, cross over with 9 and 11 subjects in each group), Deuschl and Drettner [624] found a significant improvement in nasal symptoms of blockage and nasal patency as measured with rhinomanometry. Difference in size of polyps was, however, not seen.

Holopainen et al [625] showed in a randomized, double blind, paralell, placebo controlled study with 400 g budesonide (n=19) for 4 months that total mean score and nasal peak flow were in favour for budesonide. Polyps also decreased in size in the budesonide group.

Tos et al [626] also showed that budesonide in spray (128 g) and powder (140 g) were both significantly more effective than placebo (multicentre) concerning reduction of polyp size, improvement of sense of smell, reduction of symptom score and overall assessment compared to placebo.

Vendelo Johansen [627] tested BUD 400 g daily compared to placebo for three months in a multicentre, randomized, double blind study in patients with small and medium-sized eosinophilic nasal polyps (grade 1-2). Polyps decreased in the BUD group while an increase was seen in the placebo group. The difference in polyp score between the groups was significant ($p < 0.01$). Both nasal symptoms (blockage, runny nose, sneezing) and peak nasal inspiratory flow (PNIF) improved significantly in BUD group.

Lildholt et al [491] compared BUD 400 or 800 g daily with place-

Table 7-4. Treatment with nasal corticosteroids in chronic rhinosinusitis without nasal polyposis

study	drug	number	time	symptoms	other effects	level of evidence
Cuenant, 1986 [620]	tixocortol irrigation	60	11 days	nasal obstruction significantly improved	maxillary ostial patency significantly improved	Ib
Sykes, 1986 [621]	dexamethasone + tramazoline	50	4 wks	discharge, obstruction and facial pain significantly improved	plain x-ray and nasal airway resistance and mucociliary clearance significant improved	IIa
Parikh, 2001 [618]	fluticasone propionate	22	16 wks	not significant	acoustic rhinometry not significant.	Ib
Lavigne, 2002 [619]	intrasinus budesonide	26	3 wks	total symptom score significant improved	T-cells, eosinophils mRNA for IL-4, and IL-5 significantly improved	Ib
Lund et al 2004 [622]	budesonide	134	20 wks	significant symptom improvement	significant improvement in airway using PNIF	Ib

bo for four weeks (n=40, 34, 42 respectively). Symptom relief was significant in both BUD groups compared to placebo but there was no significant difference in polyp size between the groups as measured by the investigators. Peak nasal expiratory flow (PNEF) was significantly improved in the BUD groups and increased during the study. No difference was noted for sense of smell. No dose-response correlation was seen.

Holmberg et al [628] used FP 400 g, BDP 400 g and placebo for 26 weeks in a double blind, parallel group, single centre study. Patients with bilateral polyps, grade 1-2, n=19, 18 and 18 respectively in each group were investigated. There was a significant improvement in symptoms and PNIF for both steroid groups compared to placebo. No statistically significant differences between the two active groups were seen.

Keith et al [629] compared fluticasone propionate (FP) nasal drops (FPND) 400 g daily to placebo in a placebo controlled, parallel-group, multicentre, randomized study (n=52 in both groups) for 12 weeks. Polyp reduction was not significant but nasal blockage and PNIF were significantly improved in FPND group. A few more cases of epistaxis in the FPND group were seen. No other side effects were reported.

Penttila et al [630] tried FPND 400 and 800 g and placebo daily for 12 days in a randomized, double-blind, multi-centre study for a dose-response analysis. Nasal symptoms were significantly reduced in both FP groups as well as PNIF. 800 g FP improved PNIF more than the lower dose and reduced polyp size significantly ($p < 0.01$) which was not seen in the 400 g group.

Lund et al [538] compared FP 400 g, BDP 400 g and placebo (n=10, 10, 9) for 12 weeks in a double-blind, randomized, parallel-group, single-centre study. Polyp score was significantly improved in FP group. Nasal cavity volume measured with acoustic rhinometry improved in both active groups. Morning PNIF improved in both active groups but was quicker with FP. Overall rhinitis symptoms did not differ statistically between the groups after 12 weeks treatment.

Hadfield et al [631] looked at treatment of NP in patients with cystic fibrosis in a randomised, double-blind, placebo controlled study. Betamethasone drops were used in 46 patients for 6 weeks out of which 22 completed the course. There was a significant reduction in polyp size in the group treated with betametasone but no significant difference was seen in the placebo group.

Mometasone furoate (MF) has been tried in a number of studies as reported by Small et al [632]. 354 subjects were divided in three groups to have either MF 200 g once or twice daily or placebo for four months. In both MF groups significant polyp reduction was seen as well as improvement in loss of smell, rhinorrhea and congestion. Twice daily was superior to once daily regarding congestion/obstruction and both doses significantly increased PNIF

A comparable study was performed by Stjärne et al [633], finding 200 g twice daily had a significant effect in reducing polyp size while 200 g once daily was not statistically effective compared to placebo. Both MF doses significantly improved congestion/obstruction as well as PNIF but no improvement in sense of smell was seen after four months.

A third study also by Stjärne et al [634] compared in 298 subjects with mild-to-moderate nasal polyposis, treatment with mometasone furoate nasal spray (MFNS) 200 g once daily (QD) in the morning during 16 weeks with placebo. They found a significantly decrease in nasal congestion, polyp size, and improved sense of smell, peak nasal inspiratory flow and quality of life.

Aukema et al. [635] sought to investigate in a 12-week, double-blind, placebo-controlled study whether treatment with fluticasone propionate nasal drops (FPNDs) can reduce the need for surgery, as measured by signs and symptoms of nasal polyposis and chronic rhinosinusitis, in fifty-four patients with severe nasal polyposis/chronic rhinosinusitis who were on the waiting list for functional endoscopic sinus surgery (FESS). FESS was no longer required in 13 of 27 patients treated with FPNDs versus 6 of 27 in the placebo group ($p < 0,05$). Six patients from the placebo group dropped out versus 1 from the FPND group. Symptoms of nasal obstruction, rhinorrhea, postnasal drip, and loss of smell were reduced in the FPND group ($p < 0,05$). Peak nasal inspiratory flow scores increased significantly ($p < 0,01$).

Topical corticosteroids sprays have a documented effect on bilateral NP and also on symptoms associated with NP such as nasal blockage, secretion and sneezing but the effect on the sense of smell is not high. There is a high evidence level (Ia) for effect on polyp size and nasal symptoms associated with nasal polyposis . For individual symptoms blockage responds best to corticosteroids but improvement in sense of smell is not so obvious. Nasal drops are more effective than nasal spray and have a significant positive effect on smell (Ib).

7-1-4-2 Side effects of topical corticosteroid for chronic rhinosinusitis with nasal polyps
Intranasal administration of corticosteroids is associated with minor nose bleeding in a small proportion of recipients. This effect has been attributed to the vasoconstrictor activity of the corticosteroid molecules, and is considered to account for the very rare occurrence of nasal septal perforation [636]. 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 [637]. Nasal biopsy studies do not

Table 7-5. Treatment with nasal corticosteroids in chronic rhinosinusitis with nasal polyposis

study	drug	number	treatment time (weeks)	effect on nasal symptoms (*stat sig)	objective measures (*stat sig)	effect on polyps	level of evidence
Mygind, 1975 [623]	BDP	35	3	total symptom score*		n.s.	Ib
Deuschl, 1977 [624]	BDP	20	2x4weeks	blockage*	rhinomanometry*	n.s.	Ib
Holopainen, 1982 [625]	Bud	19	16	total symptom score*	nasal peak flow* eosinophilia*	yes	Ib
Vendelo Johansen, 1993 [627]	Bud	91	12	blockage* sneezing* secretion* sense of smell N.S.	nasal peak inspiratory flow *	yes	Ib
Lildholt, 1995 [491]	Bud	116	4	blockage* sneezing* secretion* sense of smell N.S.	nasal peak expiratory flow*	yes	Ib
Holmberg, 1997 [628]	FP/BDP	55	26	over all assessment*	nasal peak inspiratory flow*	yes in BDP	Ib
Tos , 1998 [626]	Bud	138	6	total symptom score* sense of smell*		yes	Ib
Lund, 1998 [538]	FP/BDP	29	12	blockage* rhinitis N.S.	nasal peak inspiratory flow* acoustic rhinometry*	yes FP	Ib
Keith, 2000 [629]	FPND	104	12	blockage* rhinitis* sense of smell N.S.	nasal peak inspiratory flow* olfactory test N.S.	n.s.	Ib
Penttilä, 2000 [630]	FP	142	12	blockage* rhinitis* sense of smell N.S.	nasal peak inspiratory flow* olfactory test*	yes	Ib
Hadfield, 2000 [631]	betametasone	46 CF children	6	N.S.		yes	Ib
Aukema 2005 [635]	fluticasone propionate nasal drops	54	12	nasal obstruction * rhinorrhea * postnasal drip * and loss of smell *	nasal peak inspiratory flow* CT scan	yes	Ib
Small et al 2005 [632]	Mometasone	354	16	obstruction* loss of smell* rhinorrhea*	nasal peak inspiratory flow*	yes	Ib
Stjärne et al 2006 [633]	Mometasone	310	16	obstruction* loss of smell N.S. rhinorrhea*	nasal peak inspiratory flow*	200ug OD no 200ug BID yes	Ib
Stjärne et al 2006 [634]	Mometasone	298	16	obstruction* loss of smell * rhinorrhea* QOL	nasal peak inspiratory flow*	yes	Ib

show any detrimental structural effects within the nasal mucosa with long-term administration of intranasal corticosteroids [638]. 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 [636]. 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 [639]. 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 [640]. 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.

7-1-4-3 Systemic corticosteroids in chronic rhinosinusitis with nasal polyps

Traditionally systemic steroids have been used in patients with

NP although no placebo-controlled studies or dose-effect studies have supported the concept. The clinical acceptance that systemic steroids have a significant effect on NP are supported by open studies where a single injection of 14 mg betametasone have been compared with snare polypectomy surgery [493, 641]. 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 topical treatment since both treatments were used at the same time. The control groups underwent surgery during the study period.

In another open study oral prednisolone was given in doses of 60 mg to 25 patients with severe polyposis for four days and for each of the following 12 days the dose was reduced by 5 mg daily. Antibiotics and antacids were also given. 72% experienced a clear improvement due to involution of polyps [642] and in 52% a clear improvement was seen on CT. In particular nasal obstruction and the sense of smell were reported to improve. Out of 22 subjects treated, 10 were polyp free based on anterior rhinoscopy 2 weeks – 2 months after therapy.

Damm et al. [643] showed a good effect with combined treatment using topical steroids (budesonide, unknown doses) and oral treatment with fluocortolone 560 mg or 715 mg in 2 different groups of patients with 20 severe cases of CRS with NP. This study was not controlled. A large improvement of symptoms was seen (80%) and improvement on MRI (> 30% reduction of MRT-pathology) was observed in 50%.

Recently, however, two well designed studies have shown effect of systemic steroids in NP. Benitez et al [644] 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 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.

In a double-blind randomized, placebo controlled study, Hissaria et al compared 50 mg prednisolone daily for 14 days with placebo [576]. A significant improvement was found in nasal symptoms (obstruction, secretion, sneezing, sense of smell), endoscopic findings of polyp size and MRI scores supporting the effect of systemic steroids on NP.

There is no study available on depot injection of corticosteroids or local injection into polyps or the inferior turbinate. These types of treatment are actually obsolete, because of the risk of fat necrosis at the site of the injection or blindness following endonasal injection.

Studies on systemic steroids in NP has recently been published giving support to the clinical impression that they are effective after two weeks use in doses acceptable for a majority of patients. As well as symptom relief, an effect on polyp size and MRI changes are seen. Evidence level:Ib.

7-1-4-4 Side effects of systemic corticosteroids in 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.

As a guide for oral treatment, the approximate equivalent doses of the main corticosteroids in terms of their glucocorticoid (or anti-inflammatory) properties are listed below [645].

7-1-5 Postoperative treatment with topical corticosteriods for chronic rhinosinusitis with NP to prevent recurrence of polyps
There are a couple of studies on nasal steroids used after surgical resection of polyps.
Drettner et al [646] used flunisolide 200   g daily for 3 months in a double-blind, placebo controlled study with 11 subjects in both groups. A statistically significant effect was seen on nasal symptoms but not on polyp score.

Table 7-6. Treatment with systemic corticosteroids in chronic rhinosinusitis with NP

study	drug	number	dose/time	effect symptoms	effect polyps	level of evidence
Lildholt, 1988 [641]	betametamethasone/BDP	53	?/52 weeks	yes	yes	III
Lildholt, 1997 [493]	betametamethasone/budesonide	16	14mg/52 weeks	yes	yes	III
van Camp, 1994 [642]	prednisolone 60 mg	25	2 weeks	72%	yes (10/22)	III
Lildholt, 1997 [493]	betametamethasone/budesonide	16	14mg/52 weeks	yes	yes	III
Damm, 1999 [643]	budesonide + fluocortolone	20	?	yes	?	III
Benitez , 2006 [644]	prednisone + Budesonide	84	2 weeks/10 weeks	yes	yes	Ib
Hissaria, 2006 [576]	prednisolone	41	50mg/2 weeks	yes	yes	Ib

Table 7-7. Equivalence table of oral corticosteroids

Betamethasone	0.75 mg
Cortisone acetate	25 mg
Dexamethasone	0.75 mg
Hydrocortisone	20 mg
Methylprednisolone	4 mg
Prednisolone	5 mg
Prednisone	5 mg
Triamcinolone	4 mg

Virolainen and Puhakka [647] tested 400 g BDP in 22 patients and placebo in 18 in a randomized, double blind study. After one year of treatment 54% in BDP group were polyp free compared to 13% in the placebo group. No statistics were given. 86% in BDP group were free of nasal symptoms compared to 60% in placebo group.

Karlsson and Rundkrantz [648] treated 20 patients with BDP and 20 were followed with no treatment for NP (no placebo treatment) for 2.5 years. BDP was given 400 g daily for the first month and then 200 g daily. There was a statistically significant difference between the groups after 6 months in favour of BDP, which increased during the study period of 30 months.

Dingsor et al. [649] used flunisolide 2x25 g on both sides twice daily (200 g) after surgery in a placebo controlled study for 12 months (n=41). Flunisolide was significantly better than placebo at both 6 and 12 months both with respect to number and size of polyp recurrence.

Hartwig et al. [650] used budesonide 6 months after polypectomy in a double blind parallell-group on 73 patients. In the budesonide group, polyp scores were significantly lower than controls after 3 and 6 months. This difference was only significant for patients with recurrent polyposis and not for those operated on for the first time.

Dijkstra et al [651] performed a double-blind placebo-controlled randomized study in 162 patients with CRS with or without nasal polyps after FESS following failure of nasal steroid treatment. Patients were randomized and given FPANS 400 g b.i.d., FPANS 800 g b.i.d. or placebo b.i.d. for the duration of 1 year after FESS combined with peri-operative systemic corticosteroids. No differences in the number of patients withdrawn because of recurrent or persistent diseases were found between the patients treated with FPANS and patients treated with placebo. Also no positive effect was found for FPANS compared with placebo in several subgroups such as patients with nasal polyps, high score at FESS or no previous sinus surgery.

Rowe Jones et al [652] studied a similar group of one hundred nine patients studied prospectively for 5 years postoperatively. Seventy two patients attended the 5 year follow-up visit. The patients were entered into a randomised, stratified, prospective, double-blind placebo controlled study of fluticasone propionate aqueous nasal spray 200 g twice daily, commencing 6 weeks after FESS. The change in overall visual analogue score was significantly better in the FPANS group at 5 years. The changes in endoscopic oedema and polyp scores and in total nasal volumes were significantly better in the FPANS group at 4 years but not 5 years. Last value carried forward analysis demonstrated that changes in endoscopic polyp score and in total nasal volume was significantly better in the FPANS group at 5 years. Significantly more prednisolone rescue medication courses were prescribed in the placebo group.

Postoperative effect on recurrence rate of NP after polypectomy with intranasal steroids is well documented and the evidence level is Ib. Two studies describe the effect after FESS in a group of patients who underwent FESS after inadequate response to at least three months topical corticosteroid treatment. The studies show conflicting results though the reasons are not clear.

Table 7-8. Nasal corticosteroids in the post operative treatment of persistant rhinosinusitis to prevent recurrences of NP

study	drug	number	treatment time (weeks)	effect on nasal symptoms (*stat sig)	effect on polyp recurrence (method of test)	level of evidence
Virolainen, 1980 [647]	BDP	40	52	blockage	anterior rhinoscopy – yes	IV
Drettner , 1982 [646]	flunisolide	22	12	total nasal score (blockage,secretion sneezing)*	anterior rhinoscopy N.S.	Ib
Karlsson, 1982 [648]	BDP	40	120	not described	anterior rhinoscopy – yes	IIa
Dingsor, 1985 [649]	flunisolide	41	52	blockage* sneezing*	anterior rhinoscopy – yes	Ib
Hartwig, 1988 [650]	BUD	73	26	blockage N.S.	anterior rhinoscopy – yes	Ib
Dijkstra 2004 [651]	fluticasone propionate	162	52	not seen	nasal endoscopy not seen.	Ib
Rowe-Jones 2005 [652]	fluticasone propionate	109	5 years	overall visual analogue score	endoscopic polyp score and in total nasal volume	Ib

7-1-6 Side-effects of corticosteroids

The safety of nasal and oral corticosteroids has been the subject of concern in medical literature since many patients with chronic sinus disease are prescribed these drugs due to their good efficacy. Suppression of the hypothalamic-pituary-adrenal axis, osteoporosis or changes in bone mineral density, growth retardation in children, cataracts and glaucoma have been reported to be the main adverse effects of corticosteroid treatment [653]. In relation to adverse effects of corticosteroids, it is obvious that a clear distinction needs to be made between nasal and oral corticosteroids.

Nasal corticosteroid treatment represents one of the long-term treatment modalities in patients with chronic sinus disease. It is well established that absorption into the systemic circulation takes place after nasal administration of corticosteroids. However, several factors influence the systemic absorption, like the molecular characteristics of the corticosteroid, the prescribed dose, the mode of delivery and the severity of the underlying disease [653]. There is insufficient evidence from the literature to relate the use of nasal corticosteroids at licensed doses to changes in bone mineral biology, cataract and glaucoma. Adrenal suppression may occur with some nasal corticosteroids at licensed doses, but the clinical relevance remains uncertain. Overuse of nasal corticosteroids may be responsible for adrenal insufficiency and decrease in bone mineral density [654]. Of note, inhaled corticosteroids are the mainstay of treatment for children and adults with asthma and are more often associated with systemic side effects than the nasal route of treatment for rhinosinusitis [655].

Nasal corticosteroid-induced septal perforation is rarely described in literature [656]. Whether septal perforation relates to repeated traumas of the nasal mucosa and septal cartilage by the nasal device, to the underlying nasal disorder for which corticosteroids were prescribed or to a direct adverse effect of the steroid used, remains unclear.

Short treatment with oral corticosteroids is effective in chronic rhinosinusitis with nasal polyps. It is obvious that repeated or prolonged use of oral corticosteroids is associated with a significantly enhanced risk of the above mentioned side effects [657].

7-2 Treatment of rhinosinusitis with antibiotics

7-2-1 Acute community acquired rhinosinusitis

Although more than 2000 studies on the antibiotic treatment of ARS have already been published, only 49, involving 13660 participants, meet the Cochrane Board criteria for placebo control, statistical analysis, sufficient sample sizes, and the description of clinical improvements or success rates [40].

Primary outcomes were:
a. clinical cure;
b. clinical cure or improvement.

Secondary outcomes were:
a. radiographic improvement;
b. relapse rates;
c. dropouts due to adverse effects.

Major comparisons were antibiotic versus control (n=3) [658-660]; newer, non-penicillin antibiotic versus penicillin class (n=10); and amoxicillin-clavulanate versus other extended spectrum antibiotics (n=17), where n is the number of trials. Most trials were conducted in otolaryngology settings. Only 8 trials described adequate allocation and concealment procedures; 20 were double-blinded.

Compared to control, penicillin improved clinical cures [relative risk (RR) 1.72; 95% confidence interval (CI) 1.00 to 2.96]. For the outcome of cure or improvement, 77.2% of penicillin-treated participants and 61.5% of control participants were responders. Individuals treated with penicillin were more likely to be cured [RR 1.72; 95% CI 1.00 to 2.96] or cured/improved [RR 1.24; 95% CI 1.00 to 1.53]. Rates for cure or improvement were 82.3% for amoxicillin and 68.6% for placebo. Participants treated with amoxicillin were not more likely to be cured than with placebo [RR 2.06; 95% CI 0.65 to 6.53] or cured/improved [RR 1.26; 95% CI 0.91 to 7.94] but there was significant variability between studies. Radiographic outcomes were improved by antibiotic treatment. [40].

Comparisons between newer non-penicillins (cephalosporins, macrolides, minocycline), versus penicillins (amoxicillin, penicillin V) showed no significant differences [RR for cure 1.07; 95% CI 0.99 to 1.17]; Rates for cure or improvement were 84% for both antibiotic classes. Drop-outs due to adverse events were infrequent, and. these rates were not significantly different [RR 0.61; 95% CI 0.33 to 1.11]. Cumulative meta-analysis of studies ordered by year of publication (a proxy for prevalence of beta-lactamase-producing organisms) did not show a trend towards reduced efficacy of amoxicillin compared to newer non-penicillin antibiotics.

Because macrolides are bacteriostatic and cephalosporins bactericidal, subgroup analyses were performed to determine if one of these two classes were superior to penicillins. In the subgroup analyses, cephalosporins and macrolides showed similar response rates compared to penicillins.

Sixteen trials, involving 4818 participants, compared a newer non-penicillin antibiotic (macrolide or cephalosporin) to amoxicillin-clavulantate. Three studies were double-blind. Rates for cure or improvement were 72.7 % and 72.9 % for newer non-penicillins and amoxicillin-clavulanate respectively. Neither cure rates (RR 1.03; 95% CI 0.96 to 1.11) nor cured/improvement rates (RR 0.98; 95% CI 0.95 to 1.01), differed between the groups. Compared to amoxicillin-clavulanate, 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% and did not differ between the groups.

Six trials, of which 3 were double blind, involving 1067 participants, compared a tetracycline (doxycycline, tetracycline, minocycline) to a heterogeneous mix of antibiotics (folate inhibitor, cephalosporin, macrolide, amoxicillin). No relevant differences were found.

The reviewers conclude that in 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 [40].

It is interesting to see that in this review the local differences in susceptibility of micro-organisms to the antibiotics used is not acknowledged, although total cumulative meta-analysis of studies ordered by year of publication did not show a trend towards reduced efficacy of amoxicillin compared to newer non-penicillin antibiotics. Resistance patterns of predominant pathogens like *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*, vary considerably [47, 48]. The prevalence and degree of antibacterial resistance in common respiratory pathogens are increasing worldwide. The association between antibiotic consumption and the prevalence of resistance is widely assumed [50]. Thus the choice of agent may not be the same in all regions, as selection will depend on local resistance patterns and disease aetiology. [50, 661]. Moreover one might wonder whether the limited benefits of antibiotic treatment outweigh the considerable threat of antibiotic resistance. In 1995, upper respiratory tract infection was the most frequent reason for seeking ambulatory care in the United States, resulting in more than 37 million visits to physician practices and emergency departments [662].

Since the publication of the Cochrane review [40] a number of new studies have been published. Most are non-inferiority studies comparing two or three antibiotics [663-668]. These non-inferiority studies also show that a short short course of antibiotics is as good as a long course of antibiotics [665, 669-671].

Two studies comparing "real life" ARS treatment, with the diagnosis based on symptoms but not bacteriologically proven [607, 672] both showed no benefit treating patients with acute rhinosinusitis with antibiotics. Although more and more data point to a very limited effect of antibiotics in ARS, there are a limited group of patients, e.g. patients with immunodeficiencies that do benefit from antibiotics. We are in need of simple tests in the general practice that can discriminate the small group who would potentially benefit from antibiotics from the large group that has no benefit from the treatment but puts a burden on the resistance problems.

Relevant for the discussion about the efficacy of antibiotics in ARS is the recently published paper from the (mainly US) Rhinosinusitis Initiative: Rhinosinusitis: Developing guidance for clinical trials [6, 673]. This group of experts gave advice to determine the effect of a treatment intervention on the clinical course of ARS, as measured by time to resolution of symptoms. Because most antimicrobial trials have demonstrated clinical cure rates of 80% to 90% at 14 days, the Rhinosinusitis Initiative committee believed that it was important to demonstrate superiority to existing therapies by showing significant differences in time to symptom resolution or time to significant improvement based on total symptom score.

7-2-2 Antibiotics in chronic rhinosinusitis

7-2-2-1 Introduction
It is significantly more difficult to evaluate the efficacy of antibiotic treatment in CRS compared to ARS, because of the conflicts in terms of terminology and definition of the clinical picture of CRS in the literature. In most studies, no radiological diagnosis, such as CT, has been performed confirm the diagnosis of chronic rhinosinusitis. The data supporting the use of antibiotics in this condition, however, are limited and lacking in terms of randomized placebo controlled clinical trials.
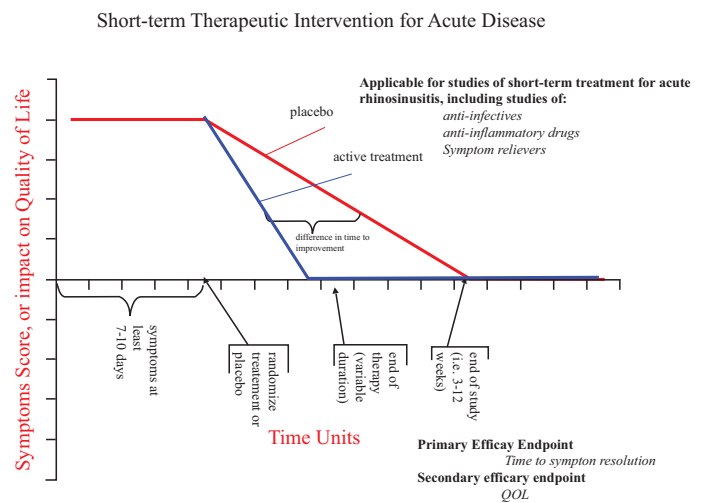
Figure 7-1. Adapted from Rhinosinusitis: Developing guidance for clinical trials [6, 673]. The rationale for the illustrated study design is to determine the effect of a treatment intervention on the clinical course of ARS, as measured by time to resolution of symptoms. Patient symptoms, QOL, or both are measured on the y-axis, and time is measured on the x-axis. The therapeutic intervention that is to be tested can be compared with either placebo or a comparator intervention. Success of the treatment intervention is based on a statistically significant difference in rate of symptom (or QOL) resolution between the comparator interventions. This graph is intended to convey the conceptual aspects of the type of study design. Therefore variables, such as timing of intervention, duration of treatment, type of intervention, and end of study, can be modified based on the specifics of the proposed study. Modified from Meltzer et al Rhinosinusitis:developing guidance for clinical trials

7-2-2-2 Short-term treatment with antibiotics in chronic rhinosinusitis

In a retrospective study, McNally et al [674] reported patient symptoms and physical examination findings in a cohort of 200 patients with CRS who were treated with a combination of 4 weeks of oral antibiotics, as well as topical corticosteroids and other adjunctive medications. All patients subjectively improved in response to therapy after 1 month.

Subramanian et al [675] retrospectively studied a group of 40 patients with CRS who were treated with a combination of 4 to 6 weeks of antibiotics and a 10-day course of systemic corticosteroids. Outcome measures, including comparison of pre- and post-treatment CT scan, as well as patient symptom scores, revealed improvement in both outcome parameters in 36 of 40 patients. In the latter study, 24 of 40 patients had sustained improvement for at least 8 weeks, which would seem to imply that whatever infection was present was fully eradicated in these patients.

In a prospective study by Legent et al. [676], 251 adult patients with CRS were treated in a double-blind manner with ciprofloxacin vs. amoxicillin/clavulanic acid for 9 days. Only 141 of the 251 patients had positive bacterial cultures from the middle meatus at the beginning of the study. At the end of the treatment period, nasal discharge disappeared in 60% of the patients in the ciprofloxacin group and 56% of those in the amoxicillin/clavulanic acid group. The clinical cure and bacteriological eradication rates were 59% and 89% for ciprofloxacin versus 51% and 91% for amoxicillin/clavulanic acid respectively. These differences were not significant. However, amongst patients who had a positive initial culture and who were evaluated 40 days after treatment, ciprofloxacin recipients had a significantly higher cure rate than those treated with amoxicillin/clavulanic acid (83.3% vs. 67.6%, $p = 0.043$). Clinical tolerance was significantly better with ciprofloxacin ($p = 0.012$), largely due to a large number of gastro-intestinal related side-effects in the amoxicillin/clavulanic acid group (n = 35). Ciprofloxacin proved to be at least as effective as amoxicillin/clavulanic acid.

The efficacy and safety of amoxicillin/clavulanic acid (AMX/CA) (875/125 mg b.i.d. for 14 days) were compared with that of cefuroxime axetil (500 mg b.i.d. for 14 days) in a multicentre, open, parallel-group, randomized clinical trial in 206 adults with chronic or acute exacerbation of CRS by a polish group. Clinical response was similar, with 95% of AMX/CA-, and 88% of cefuroxime-treated, clinically evaluable patients cured. In bacteriologically evaluable patients, cure rates, defined as eradication of the original pathogen with or without re-colonization with non-pathogenic flora, were also similar, with 65% of AMX/CA- and 68% of cefuroxime-treated patients cured. However, clinical relapse was significantly higher in the cefuroxime group: 8% (7/89) of clinically evaluable patients, compared with 0% (0/98) in the AMX/CA ($p = 0.0049$) group [677].

Table 7-9. "Short Term" Antibiotics in Chronic Rhinosinusitis

study	drug	number	time/dose	effect on symptoms	evidence
Huck et al, 1993 [678]	ceflaclor vs. amoxycillin	56 ARS 25 recurrent rhinosinusitis 15 chronic maxillary sinusitis	2x 500mg 3x500mg for 10 days	clinical improvement: ARS 86% recurrend 56% CRS. no statistics	Ib (-)
Legent et al, 1994 [676]	ciprofloxacin vs. amoxicillin clavulanate	251	9 days	nasal discharge disappeared: cipro – 60% amx/clav: 56% clinical cure: cipro 59% amx/clav 51% bacterological eradication: cipro 91% amx/ clav 89%	Ib (-)
McNally et al, 1997 [674]	oral antibiotics	200	4 weeks	yes, subjectively after 4 weeks	III
Subramanian et al; 2002 [675]	antibiotics 10 days corticosteroids	40	4 –6 weeks	yes, pre-/ posttreatment CT in 24 patients also improvement after 8 weeks	III
Namyslowski et al, 2002 [677]	amoxycillin clavulanate vs. cefuroxime axetil	206	875/125mg for 14 days 500mg for 14 days	clinical cured: amx/ca 95% cefurox 88% bacterial eradication: amx/ca 65% cefurox 68% clinical relapse: amx/ca 0/ 98 cefurox 7/89	Ib (-)

Huck et al. compared in a double-blind, randomized trial compared cefaclor with amoxicillin in the treatment of 56 acute, 25 recurrent, and 15 chronic maxillary sinusitis: Whether treated with cefaclor or amoxicillin, clinical improvement occurred in 86% of patients with ARS and 56% of patients with recurrent RS. Patients with CRS were too few to allow statistical analysis. The susceptibility of organisms isolated to the study drugs was unrelated to outcome [678].

To summarize, at the moment no placebo-controlled studies on the effect of antibiotic treatment are available. Studies comparing antibiotics have level II evidence and do not show significant differences between ciprofloxacin vs. amoxycillin/clavulanic acid, and cefuroxime axetil. The few available prospective studies show effect on symptoms in 56% to 95% of the patients. It is unclear which part of this effect is regression to the mean because placebo controlled studies are lacking. There is urgent need for randomized placebo controlled trials to study the effect of antibiotics in CRS and exacerbations of chronic rhinosinusitis.

7-2-2-3 Long-term treatment with antibiotics in chronic rhinosinusitis

The efficacy of long term treatment with antibiotics in diffuse panbronchiolitis, a disease of unclear aetiology, characterized by chronic progressive inflammation in the respiratory bronchioles inspired the Asians in the last decade to treat CRS in the same way [679, 680]. Subsequently a number of clinical reports have stated that long-term, low-dose macrolide antibiotics are

effective in treating CRS incurable by surgery or glucocorticosteroid treatment, with an improvement in symptoms varying between 60% and 80% in different studies [23, 679, 681, 682]. The macrolide therapy was shown to have a slow onset with ongoing improvement until 4 months after the start of the therapy. In animal studies macrolides have increased mucociliary transport, reduced goblet cell secretion and accelerated apoptosis of neutrophils, all factors that may reduce the symptoms of chronic inflammation. There is also increasing evidence in vitro of the anti-inflammatory effects of macrolides. Several studies have shown macrolides inhibit interleukin gene expression for IL-6 and IL-8, inhibit the expression of intercellular adhesion molecule essential for the recruitment of inflammatory cells. However, it remains to be established if this is a clinically relevant mechanism [683-689].

There is also evidence in vitro, as well as clinical experience, showing that macrolides reduce the virulence and tissue damage caused by chronic bacterial colonization without eradicating the bacteria. In addition long term treatment with antibiotics has been shown to increase ciliary beat frequency [690]. In a prospective RCT from the same group [536] ninety patients with polypoid and nonpolypoid CRS were randomised to medical treatment with 3 months of an oral macrolide (erythromycin) or endoscopic sinus surgery and followed over one year. Outcome assessments included symptoms (VAS), the SinoNasal Outcome Test (SNOT-22), Short Form 36 Health Survey (SF36), nitric oxide, acoustic rhinometry, saccharine clearance time and nasal endoscopy. Both the medical and sur-

Table 7-10. Long-term treatment with antibiotics in chronic rhinosinusitis

study	drug	number	time/dose	effect symptoms	level of evidence
Gahdhi et al, 1993 [682]	prophylatic antibiosis details not mentioned	26	not mentioned	19/26 decrease of acute exacerbation by 50% 7/26 decrease of acute exacerbation by less than 50%	III
Nishi et al, 1995 [681]	clarithromycin	32	400mg /d	pre- and post-therapy assesment of nasal clearence	III
Scadding et al 1995 [690]	oral antibiotic therapy	10	3 month	increased ciliary beating	III
Ichimura et al, 1996 [23]	roxithromycin roxithromycin and azelastine	20 20	150mg /d for at least 8 weeks 1mg /d	clinical improve-ment and polyp-shrinkage in 52% clinical improve-ment and polyp shrinkage in 68%	III
Hashiba et al, 1996 [679]	clarithromycin	45	400mg /d for 8 to 12 weeks	clinical improvement in 71%	III
Suzuki et al, 1997 [680]	roxithromycin	12	150mg /d	CT scan pre- and post-therapy: improvment in the aeration of nasal sinuses	III
Ragab et al, 2004 [536]	erythromycin v ESS	45 in each arm	3 months	improvement in upper & lower RT symptoms, SF36, SNOT-22, NO, Ac Rhin, SCT, nasal endoscopy at 6 & 12 mnths	Ib
Wallwork, 2006 [691]	roxithromycin	64	3 months	improvements in global rating of patients	Ib

RT: respiratory tract; SF 36: Short Form 36 QoL; SNOT-22: SinoNasal Outcome Test; NO:expired nitric oxide, Ac Rhin: acoustic rhinometry; SCT: saccharine clearance time.

gical treatment of CRS significantly improved almost all subjective and objective parameters, with no significant difference between the two groups nor between polypoid and nonpolypoid CRS except for total nasal volume which was greater after surgery and in the polypoid patients.

Wallwork et al [691] conducted a double-blind, randomized, placebo-controlled clinical trial on 64 patients with CRS. Subjects received either 150 mg roxithromycin daily for 3 months or placebo. The description of the patient populations is limited, but patients with NP were excluded (personal communication by author). They showed a significant improvement in global patient rating compared to placebo. The other comparisons were made between pre- and post-treatment situations. In this comparison a statistically significant improvement was found in SNOT-20 score, nasal endoscopy, saccharine transit time, and IL-8 levels in lavage fluid ($p < 0,05$) in the macrolide group. A correlation was noted between improved outcome measures and low IgE levels.

The benefit of long-term, low-dose macrolide treatment seems to be that it is, in selected cases, effective when topical steroids and short courses of antibiotics fail. The exact mechanism of action is not known, but it probably involves downregulation of the local host immune response as well as a downgrading of the virulence of the colonizing bacteria. Placebo-controlled studies should be performed to establish the efficacy of macrolides if this treatment is to be accepted as evidence-based medicine.

7-2-3 Exacerbations of chronic rhinosinusitis

7-2-3-1 Short-term treatment with oral antibiotics in acute exacerbations of chronic rhinosinusitis chronic rhinosinusitis
In open trials, oral antibiotics have an effect on the symptomatology of acute exacerbations of CRS [677, 692]. In some of these studies patients with ARS or CRS are combined with patients with acute exacerbations of CRS [693, 694]. No studies have shown efficacy of antibiotics in acute exacerbations of CRS in a double blind placebo controlled manner.

In conclusion data on the treatment of acute exacerbation of CRS are mostly level IV evidence and include oral and local antibiotics. Double-blind data show a positive effect of the addition of topical corticosteroid treatment to oral antibiotics in the treatment of acute exacerbation of CRS.

7-2-3-2 Short-term treatment with local antibiotics in acute exacerbations of chronic rhinosinusitis
Some studies have compared the effects of local antibiotics in CRS and acute exacerbation of CRS [620, 695-697].

Desrosiers studied in a randomized, double-blind trial of tobramycin-saline solution versus saline-only solution adminis-

tered thrice daily to the nasal passages by means of a large-particle nebulizer apparatus for 4 weeks in twenty patients with CRS refractory to medical and surgical therapy. He found no significant difference between the groups and concluded that large-particle nebulized aerosol therapy may offer a safe and effective management alternative for patients with refractory rhinosinusitis irrespective of the addition of gentamicin [698].

Sykes found no additional effect with the addition of neomycin to a spray containing dexamethasone and tramazoline four times daily to both nostrils for 2 weeks [621].

However, Mosges and Leonard did find differences between local antibiotics and placebo [695, 697]. Mosges showed a positive effect for fusafungine nasal spray as early as the first 24h of treatment which was not seen in the placebo group. The antimicrobiological effect of this preparation is unclear.

Schienberg et al. studied the effectiveness of aerosol delivery of antibiotics to the sinuses via a nebulizer in 41 patients who had chronic, recurrent rhinosinusitis that had persisted despite endoscopic sinus surgery (ESS) and that had not responded to multiple courses of oral antibiotics. Following 3 to 6 weeks of treatment, 34 patients (82.9%) experienced either an excellent or good response to treatment. Side effects were infrequent, mild, and transient. They concluded that nebulized antibiotics should be considered for all patients with CRS who have undergone ESS and who have failed to respond to oral antibiotics or who do not tolerate them [699].

Further studies with better characterized patient populations are needed.

7-2-4 Side-effects of antibiotics
Common side effects of antibiotics include sickness, diarrhoea, and, in women, vaginal yeast infections. Some side effects are more severe and, depending on the antibiotic, may influence kidney and liver function. Rarely the bone-marrow or other organs are affected. Blood tests are used to monitor such adverse reactions.
Some people who receive antibiotics develop colitis, an inflammation of the large intestine. The colitis results from a toxin produced by the bacterium, *Clostridium difficile*, which grows unchecked when other antibacteria are killed by the antibiotics.
Antibiotics can cause allergic reactions. Most are mild allergic reactions and consist of an itchy rash or slight wheezing. Patients claiming allergic reactions to antibiotics actually mean side-effects. This is important to realize because on one hand severe allergic reactions (anaphylaxis) can be life threatening, on the other hand some patients claim to be allergic to many different classes of antibiotics making treatment difficult. Most adverse events related to antimicrobials are reversible rapidly on cessation of the medication. Irreversible toxicities include

aminoglycoside-induced ototoxicity, Stevens-Johnson syndrome, and toxicity secondary to nitrofurantoin.

Another important consequence of the use of antibiotics is the development of resistance. Resistance to antibiotics is a major public-health problem and antibiotic use is being increasingly recognised as the main selective pressure driving this resistance. Prescription of antibiotics in Europe varies greatly: the highest rate was in France and the lowest was in the Netherlands [700]. A shift from the old narrow-spectrum antibiotics to the new broad-spectrum antibiotics is being seen. Higher rates of antibiotic resistance are found in high consuming countries, probably related to this higher consumption.

7-3 Other medical management for rhinosinusitis

Standard conservative treatment for ARS and CRS is based on short or long-term antibiotics and topical steroids with the addition of decongestants - mostly in a short term regimen and for the acute attack itself. Many other types of preparations have been investigated, but substantial evidence for their benefit is poor. These medications include antral washings, isotonic/hypertonic saline as nasal douche, antihistamines, antimycotics, mucolytic agents/phytomedical preparations, immunomodulators/immunostimulants and bacterial lysate preparations. For selected patients with CRS and gastroesophageal reflux, the impact of antireflux treatment on sinus symptom scores has been studied. Topical nasal application of furosemide and capsaicin have also been considered in the treatment of nasal polyposis and prevention of recurrence.

7-3-1 Decongestants

7-3-1-1 Acute rhinosinusitis
Nasal decongestants are applied in the treatment of ARS in order to decrease congestion and in the hope of improving better sinus ventilation and drainage and symptomatic relief of nasal congestion. Experimental trials on the effect of topical decongestants by CT [701] and MRI scans [702] on ostial and ostiomeatal complex patency have confirmed marked effect on congestion of inferior and middle turbinates and infundibular mucosa, but no effect on ethmoidal and maxillary sinus mucosa. Experimental studies suggested beneficial anti-inflammatory effect of xylometazoline and oxymetazoline by decreasing nitric oxide synthetase [703] and anti-oxidant action [704]. In contrast to previous in vitro trials on the effect of decongestants on mucociliary transport, a controlled clinical trial (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, and the clinical course of the disease between the groups was not significantly different.[705]. This is in concordance with previous randomized controlled trial in adult acute

maxillary sinusitis (Ib), which did not prove significant impact of decongestant when added to antibiotic treatment in terms of daily symptoms scores on headache and obstruction and sinus x-ray scores, although decongestant and placebo were applied through a bellow, which should have enabled better dispersion of the solution in the nasal cavity [706]. 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 (Ib) [707]. However, a double blind, randomized, placebo controlled trial demonstrated a significant protective effect of 14-day 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 [708]. 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 obseved in 8% and 20%, respectively [708].

Clinical experience, however, supports the use of topical application of decongestants to the middle meatus in ARS but not by spray or drops (evidence level IV).

7-3-1-2 Chronic rhinosinusitis without nasal polyps
The use of decongestants for adult CRS has not been evaluated in a randomized controlled trial. Decongestants and sinus drainge did not prove to be superior to saline in chronic paediatric maxillary sinusitis in terms of subjective or x-ray scores [709].

7-3-1-3 Chronic rhinosinusitis with nasal polyps
CT studies before and after decongestant application in patients with nasal polyposis did not show any densitometric changes in the sinuses or polyps, only decongestion of the inferior turbinates [710]. A randomized double blind placebo controlled trial did not show any difference between placebo, epinephrine and naphazoline on polyp size at endoscopy and lateral imaging [711].

7-3-1-4 Side effects of decongestants
The most frequent adverse event related to topical nasal decongestants is rebound nasal congestion in patients with prolonged treatment or overuse of vasoconstrictive topical medications. The effect occurs due to tachyphylaxis after 5 to 7 days of medication use. Shorter duration of decongestion and rebound effect results in increased daily dose and may lead to rhinitis medicamentosa [712]. Significantly greater nasal reactivity, compared to placebo, was demonstrated after few weeks of nasal decongestant.

Major adverse effects are more related to systemic decongestants, ranging in severity from tremor and headache to individual reports of stroke, myocardial infarction, chest pain, seizures, insomnia, nausea and vomiting, fatigue, and dizziness. There are even some case reports reporting on similar side effects of topical decongestants, especially in patients with increased cardiovascular risks [713-716].

7-3-2 Mucolytics

7-3-2-1 Acute rhinosinusitis
Mucolytics were used as adjuncts to antibiotic treatment and decongestant treatment in ARS in order to reduce the viscosity of sinus secretion. The benefit of such treatment has not been evaluated in many trials. In paediatric rhinosinusitis, a RCT (Ib) did not prove bromhexine superior to saline in inhalation for children with CRS [717]. A second RCT (Ib) suggested bromhexine was superior to placebo [718].

7-3-2-2 Chronic rhinosinusitis
A cohort study in a mixed group of 45 ARS and CRS patients suggested beneficial effect of adding mucolytic to standard rhinosinusitis treatment in terms of reducing treatment duration [719] (evidence level III).

7-3-2-3 Nasal polyps
No clinical trials have tested the effect of mucolytics in nasal polyp treatment.

7-3-3 Antihistamines, cromones

7-3-3-1 Acute rhinosinusitis
The beneficial effect of loratadine in terms of symptom reduction for the treatment of ARS in patients with allergic rhinitis was confirmed in a multicentre randomized double-blind, placebo controlled trial (Ib)[720]. Patients receiving loratadine as an adjunct to antibiotic treatment suffered significantly less sneezing and obstruction on daily VAS scores, and overall improvement was confirmed by their physicians. Cromolyn did not prove better than saline in a RCT (Ib) for treatment of acute hyperreactive sinusitis measured by subjective scores and ultrasound scans, leading to 50% improvement in both groups [721]. A RCT (Ib) for acute paediatric rhinosinusitis did not confirm any benefit of oral antihistamine-nasal decongestant drops [707].

7-3-3-2 Chronic rhinosinusitis
Although generally not recommended as rhinosinusitis treatment, an evaluation study of CRS treatment in the USA revealed antihistamines as rather often presribed medication in patients with CRS (an average of 2.7 antibiotic courses; nasal steroids and prescription antihistamines 18.3 and 16.3 weeks, respectively, in a 12-month period) [722]. However, no evidence of beneficial effects of antihistamine treatment for CRS is found, as there are no controlled trials evaluating such treatment.

7-3-3-3 Nasal polyps
Cetirizine in a dose of 20 mg/day for three months, significantly reduced sneezing, rhinorrhoea and obstruction compared to placebo in the postoperative treatment of recurrent polyposis but with no effect on polyp size (Ib) [723].

7-3-3-4 Antihistamines
Unlike first generation antihistamines, where central nervous system and peripheric muscarinic side effects are significant, frequency of side effects in newer second generation antihistamines is low. The most commonly reported events during treatment with second generation antihistamines were upper respiratory tract infection, wheezing, vulvitis, cough, headache, migraine, drowsiness, sedation and injury, most of them reported in 1 to 5% of the treated population, however, not necessarily related to medication. Although caution with cardiotoxicity and potential for interaction with drugs metabolised by the hepatic cytochrome P450 system, applied to older non-sedating antihistamines (like terfenadine or astemizole), this risk seems to be absent in newer compounds (desloratadine, levocetirizine, fexofenadine), at least in recommended treatment regimens.

7-3-4 Antimycotics
Antimycotics are used as topical and systemic treatment, as an adjunct to sinus surgery, in allergic fungal, and invasive fungal rhinosinusitis, especially in immunocompromized patients [724]. Surgery is considered the first line treatment for allergic fungal [725] and invasive fungal rhinosinusitis [726]. Although the use of antimycotics in the treatment of allergic fungal rhinosinusitis has not been tested in controlled trials, high dose postoperative itraconazole, combined with oral and topical steroids in a cohort of 139 patiens with AFS reduced the need for revision surgery rate to 20.5% [727]. The state-of-art treatment for invasive fungal sinusitis is based on small series of patients and case reports, which do not meet the criteria for meta-analysis and may be considered as level IV evidence.

7-3-4-1 Acute rhinosinusitis
No controlled trials for antimycotic treatment for ARS was found on the Medline search.

7-3-4-2 Chronic rhinosinusitis
The fungal hypothesis, based of the premise of an altered local immune (non-allergic) response to fungal presence in nasal/sinus secretions resulting in the generation of chronic eosinophilic rhinosinusitis and nasal polyposis [148], has led to idea of treating CRS with and without NPs with a topical antimycotic. Although the presence of fungus in sinus secretions was detected in a high proportion ($<$ 90%) of patients with CRS, as well as in a control disease-free population in a few study centres [148, 149], it cannot be taken as proof of aetiology. Until recently a few case studies (level IV) had been conducted [728, 729]. Ponikau et al, in a group of 51 patients with CRS, including polyposis patients, treated patients with topical amphotericin B as nasal/sinus washing, without placebo or other control treatment. The treatment resulted in 75% subjective improvement and 74% endoscopic improvement [728]. As the authors stated, antifungal treatment should be evaluated in a controlled trial to be justified.

In a recent small randomized, placebo-controlled, double-blind, trial using amphotericin B to treat 30 patients with CRS with or without NP Ponikau et al [730] were also not able to show significant effect on symptomatology although did show a reduced inflammatory mucosal thickening on both CT scan and nasal endoscopy and decreased levels of intranasal markers for eosinophilic inflammation in patients with CRS (a significant difference in the reduction of eosinophil derived neurotoxin (EDN), but not Il-5). The study by Weschta et al [731] did not reveal difference between amphotericin B and placebo treatments in the reduction of eosinophil cationic protein and tryptase, and no difference was found between cellular activation markers whether fungal elimination was achieved or not (for patients where fungal elements were detected), which supports the hypothesis that fungi are innocent bystanders and not the trigger for inflammatory (presumably eosinophil) cells activation [731]. Both trials used antimycotic solutions high above minimal inhibitory concentration for fungal elimination. However, the Ponikau trial used nasal lavage twice daily for 6 months (with significant endoscopic improvement after 3 and 6 months), while Weschta et al used nasal spray 4 times daily for 3 months. While difference in drug application and small sample size left the question of treatment success and different objective outcomes between the trials open, a multicentre randomized, placebo-controlled, double-blind, trial [156], in 120 patients (80% with polyps) using nasal lavage for 3 months and confirmed no benefit with amphotericin B added to nasal lavage compared with placebo lavage in the treatment of CRS with and without NPs. No difference between amphotericin B and placebo was found in terms of subjective and objective measures of improvement, i.e. mean VAS score , Sf-36, Rhinosinusitis Outcome Measure-31 (RSOM-31), endoscopy scores , SF-36, PNIF and polyp scores. Patients on placebo improved in total VAS, postnasal drip VAS, rhinorrhea VAS in non-asthma subgroup; PNIF deteriorated significantly on amphotericin B, though did not in those on placebo [156].

Oral antifungal treatment with high dose terbinafine for 6 weeks in a randomized, placebo-controlled, double-blind, multi-centre trial, also did not find any subjective or objective benefit after antifungal treatment, comparing outcomes in 53 adult patients with CRS [732]. No difference was found in CT scores improvement, sinus symptom scores and therapeutic evaluation, and confirmed the previous findings by Weschta et al that the presence of fungi in nasal mucus (fungus positive in 41/53 patients) made no difference to treatment outcomes [732].

7-3-4-3 Nasal polyposis
Another case study (as the previous trials also included patients with nasal polyposis) combined topical steroid treatment with amphotericin B in 74 patients with nasal polyposis for 4 weeks [733] and found 48% disappearance of the polyps at endoscopy in previously endoscopically operated patients.

In a double blind randomized placebo controlled trial in 60 patients with CRS with nasal polyps, topical treatment with amphotericin B was not superior to saline in CT scores (p 0,2) and subjective scores, which were (significantly) worse in active treatment group [731] .

A recent open randomized trial, comparing protective effects of lysine aspirin (LAS) and LAS combined with amphotericin B on nasal polyp recurrence in patients who underwent medical (depot i.m. steroid) or surgical polypectomy, suggested that adding amphotericin B to lysine aspirin in a long-term topical treatment may add benefit in terms of recurrence protection [734].Recurrence after 20 months was found in 13/25 patients treated with LAS after surgery, in 15/25 after medical polypectomy and LAS , while 5/16 after surgical polypectomy and 7/23 after medical polypectomy protected with LAS and amphotericin B, respectively. Fungi were detected in 8/39 patients in LAS+ampho B treated groups, and in none of 50 only LAS treated patients. Low fungal detection indicate that the presumed protective effect of amphotericin B, added to LAS treatment may not be due to antifungal effect but the complexities of this study make any conclusions difficult[734].

Table 7-11. Treatment with antimycotics in chronic rhinosinusitis

study	indication	treatment	number	duration	symptoms	objective	level of evidence
Weschta, 2004 [731]	NP	amphotericin B spray vs placebo 4 times daily	60	8 weeks	significantly worse on amphotericin B	no difference on CT, endoscopy, ECP and tryptase in lavage	Ib (-)
Ponikau, 2005 [730]	CRS + NP	amphotericin B lavage vs. placebo twice daily	30	6 months	no difference	CT less mucosal thickening and EDN, but not Il-5 in lavage for active treatment	Ib (+ only for CT)
Kennedy, 2005 [732]	CRS	625mg/ day oral terbinafine vs. placebo	53	6 weeks + 9 week follow up	no difference in symptoms and RSDI patient and physician	no difference in CT, MRI, endoscopy	Ib (-)
Ebbens, 2006 [156]	CRS + NP	amphotericin B lavage vs. placebo	116	3 months	no difference	no difference in polyp scores, PNIF, RSOM-31, SF-36 between groups	Ib (-)

7-3-4-4 Side effects of antimycotics

Adverse events reported after long-term oral antimycotic treatment most frequently are nausea, headache, skin rash, vomiting, abdominal pain and diarrhoea. Major adverse events, like serious liver disfunction is rare, and mostly seen in patients at risk and due to drug interactions.

Frequency of adverse events during 3 to 6 months topical amphotericin B treatment in 3 randomized placebo controlled trials was similar in the active and placebo groups. However, major adverse events were more common in the active treatment group (9% in active vs. 0% in placebo group respectively) although only 1 was judged to be drug-related (asthma attack). Oral treatment with terbinafine for 6 weeks did not induce more adverse events than placebo, none were drug-related, and no difference in liver function was observed between active and placebo group after 6 weeks.

The effect of amphotericin B on sinus mucosa may be explained by some other modes of action. In common with other polyene antibiotics and antimycotics, amphotericin B acts on cellular membrane permeability, which may reduce the size of nasal polyps by reducing oedema, leading to subjective improvement [735]. These studies were not placebo controlled and had short observation periods. Amphotericin B is a cytotoxic drug and long-term topical application may have systemic effect. On the other hand, nasal washings with hypertonic solution (without antifungal medication) offer up to 60% improvement (see under chapter 7-4-7 Nasal and antral irrigation - saline, hypertonic saline).

Another concern regarding the use of amphotericin B as topical treatment for CRS and nasal polyposis is the possibility that widespread use may lead to resistance. Amphotericin B remains a valuable antimycotic systemic treatment for potentially life-threatening invasive mycoses and increased selective pressure with topical treatment, may give rise to increase drug resistance in common fungal pathogens, like Candida. [736-738]. This is a real possibility due to different drug distribution pattern in the sinus cavities (some spaces have sub-therapeutic drug concentration), and, in time we may lose valuable antimycotic systemic drug, which still demonstrates low resistance.

7-3-5 Bacterial lysate preparations

Altered local (and systemic) immune response to bacterial infection (antigens) may be responsible for frequent recurrence of rhinosinusitis. The beneficial effect of antibiotic treatment is declining together with the increased microbial resistance after repeated treatments. Such patients are usually regarded as difficult-to-treat, and usually unresponsive in the long-term to medical and surgical treatment. As altered immune response is expected to be responsible for frequent recurrence, different immunomodulators or immunostimulants have been tested in such patients. The most common form of medications used are bacterial lysates. Efficacy of bacterial lysate preparations (*Enteroccocus faecalis* autolysate [739], ribosomal fractions of *Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae* and the membrane fraction of Kp [740], and mixed bacterial lysate [741] in terms of the reduction of the number of acute relapses in CRS, the period between the relapses and need for antibiotic treatment, have been tested in multicentre, placebo controlled RCTs (Ib) [739-741].

7-3-5-1 Acute rhinosinusitis

Bacterial lysates were tested in the treatment of acute recurrent rhinosinusitis and the outcomes measured were the reduced rate of acute episodes and antibiotic treatment. Enterococcus faecalis autolysate treatment for 6 months in 78 patients (3x30 drops daily) resulted in 50 relapses during 6 months treatment and 8 months follow-up compared to 79 placebo treated group with 90 recurrences. The time interval to the first relapse was clearly longer in the active arm (513 days) compared with placebo (311 days)[739]. A RCT of the effect of 6 months treatment with ribosomal fractions of *Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae* and the membrane fraction of Kp was compared to placebo in 327 adult patients (168 active and 159 placebo treatment) with recurrent acute infectious rhinitis (the criteria for recurrent rhinosinusitis was based on symptoms – 4.3 episodes per year) demonstrated 39% reduction of antibiotic courses and 32% of days with antibotics during the 6 months treatment period[740].

7-3-5-2 Chronic rhinosinusitis

Six months treatment with mixed bacterial lystate was tested in a multicentre randomized double-blind placebo-controlled trial in 284 patients with CRS (diagnosed by persistent nasal discharge, headache, and x-ray criteria). Reduction in symptom scores and over-all severity score, including cough and expectoration were significant during the treatment period [741].

Table 7-12. Treatment with bacterial lysates in chronic rhinosinusitis

study	indication	treatment	number	duration	symptoms	objective	level of evidence
Habermann, 2002 [739]	recurrent ARS	*Enterococcus faecalis*	157	6+8 months	reduced acute episodes	50 vs. 90 recurrences, 513 vs. 311 days to first relapse	Ib
Serrano, 1997 [740]	recurrent ARS	Ribomunyl	327	6 months	reduced acute episodes	39% reduction in antibiotic courses and 32% days on antibiotics	Ib
Heintz, 1989 [741]	CRS	Bronchovaxom	284	6 months	improved upper and lower airways	no of patients with total x-ray opacification drop 54 to 9 active vs. 46 to 25 on placebo	Ib

7-3-5-3 Nasal polyposis
No data could be found on treatment with bacterial lysates in nasal polyposis.

7-3-6 Immunomodulators/immunostimulants
Treatment with filgrastim, recombinant human granulocyte colony stimulating factor, was tested in a RCT (Ib) in a group of CRS patients refractory to conventional treatment, which did not confirm significantly improved outcomes after such expensive treatment [572]. A pilot study (III) with interferon gamma suggested this treatment may be beneficial in treating resistent CRS, but the number of patients was not adequate to provide evidence to justify such treatment [742]. Certain groups of antibiotics may be regarded as immunomodulators, like quinolones [743] and macrolides [744].

7-3-7 Nasal and antral irrigation (saline, hypertonic saline)
A number of randomized controlled trials have tested nasal and antral irrigation with isotonic or hypertonic saline in the treatment of acute and chronic rhinosinusitis. 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, endoscopic findings and HRQL improvement in patients with CRS. Hypertonic saline is preferred to isotonic treatment for rhinosinusitis by some authors in the USA, mostly based on a paper indicating it signifcantly improves nasal mucociliary clearance measured by saccharine test, in healty volunteers [745].

7-3-7-1 Acute rhinosinusitis
A randomized trial (Ib) by Adam et al [746] 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 (Ib) 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 [747].

7-3-7-2 Chronic rhinosinusitis
A randomised controlled trial (RCT) by Bachmann (Ib), comparing isotonic saline and EMS solution (balneotherapeutic

water) in the treatment of CRS in a double-blind fashion revealed improvement in both groups, with no difference between them [748]. In the 7-days follow-up, nasal air flow was not improved significantly. Subjective complaints, endonasal endoscopy, and radiology results revealed a significant improvement in both groups (p = 0.0001). A similar RCT by Taccariello et al (Ib),with a longer follow-up confirmed that nasal washing with sea water and alkaline nasal douche produced benefit over standard treatments. Douching per se improved endoscopic appearances (p = 0,009), and quality of life scores (p = 0,008) [749]. These measures did not change in a control group (n = 22) who received standard treatment for CRS, but no douche. There were significant differences between the two douching preparations - the alkaline nasal douche improved endoscopic appearances but did not enhance quality of life, whereas the opposite was true for the spray. Rabago et al. (Ib) tested benefit from daily hypertonic saline washings compared to standard CRS treatment (control) for 6 months in a RCT using subjective scores instruments: Medical Outcomes Survey Short Form (SF-12), the Rhinosinusitis Disability Index (RSDI), and a Single-Item Sinus-Symptom Severity Assessment (SIA). Experimental subjects reported fewer 2-week periods with sinus-related symptoms (p < 0,05), used less antibiotics (p < 0,05), and used less nasal spray (p = 0,06) [750]. On the exit questionnaire 93% of study subjects reported overall improvement of sinus-related quality of life, and none reported worsening (p < 0,001); on average, experimental subjects reported 57 -/+ 4.5% improvement measured by Medical Outcomes Survey Short Form (SF-12), the Rhinosinusitis Disability Index (RSDI), and a Single-Item Sinus-Symptom Severity Assessment (SIA). A double blind RCT (Ib) compared the effect of nasal wash with hypertonic saline (3.5%) versus normal saline (NS) (0.9%) for the 4 weeks in treatment of paediatric CRS using cough and nasal secretions/postnasal drip as subjective and a radiology score as objective outcome measures (751). Hypertonic saline demonstrated significant improvement for all the scores (13/15 for cough, 13/15 postnasal drip, 14/15 x-ray scores), while saline improved only postnasal drip.
A recent double blind randomized controlled trial in 57 patients with CRS , with minimum persistence of symptoms for 1 year and previously unsuccesfully treated with conventional medical treatment, demonstrated significantly better improvement after nasal lavage for 60 days with hypertonic Dead sea salt (DSS) solution compared to conventional hypertonic saline, in terms of rhinosinusitis symptoms scores and rhinoconjunctivitis quality-of-life scores which was attributed to the presence of magnesium and other oligominerals known to have an effect in nskin conditions [581]. Similar results were found in a recent case trial in 31 patients with resistant CRS. [752].
A randomized controlled clinical trial of nasal washing with normal saline, hypertonic buffered saline and no treatment in 60 patients after endoscopic sinus surgery did not prove any of the treatment superior. Hypertonic saline induced greater discharge during the first 5 postoperative days and increased pain

scores, compared to normal saline and no treatment, However, no objective evaluation was done in this trial [753].

Comparison of treatment with antral washouts in the treatment of chronic adult [754] and paediatric rhinosinusitis [755] did not prove benefit from such treatment. In a RCT by Pang et al. patients received either antral washouts followed by antibiotics and topical nasal steroids or antibiotics and topical nasal steroids alone. In each group 51.6 per cent and 50 per cent of patients respectively improved with treatment [754].

Instead of using saline or hypertonic solution, a few non-controlled pilot trials in a small number of patients analyzed the effect of active medication used intrasinusally. A trial in 12 patients was done using N-chlorotaurine, an endogenous oxidant with antimicrobial properties against bacteria and fungi. The intrasinusal application of N-chlorotaurine was done 3 times a week, during 4 weeks (12 applications) using a Yamik catether and improvement of symtpoms was found in 75 to 90% of patients, however, no improvement was found on the sinus CT scans, before and after the treament [756].

Although saline washes are frequently recommended post-operatively, level I evidence to support this is lacking.

7-3-7-3 Nasal polyps
Nasal saline has been used as a control treatment in trials on nasal polyposis with topical steroid, but there are no controlled trials on saline/hypertonic saline treatment alone in nasal polyposis.

7-3-7-4 Side effects
Side effects of saline, hypertonic saline nasal washings are not often reported. However, randomized controlled trial comparing isotonic and hypertonic saline for ARS or common cold reported significantly higher rate of nasal irritation for hypertonic saline (32% vs. 13% for saline, respectively), while dry nose was more common in patients using saline (36%), than in those using hypertonic saline (21%) [746].

Uncommon side effects were nausea caused by drainage, burning, cough, drowsiness and tearing. Interestingly, side effects of HS were less common in the treatment of CRS (6 months): nasal irritation, nasal burning, tearing, nosebleeds, headache, or nasal drainage were reported by 23% of the subjects, 80% of those who reported side effects, regarded them as not significant [750].

7-3-8 Capsaicin
Capsaicin, the active substance from red hot chilli pepppers, is a neurotoxin which depletes substance P with some other neurokinins and neuropeptides, leading to long lasting damage of unmyelinated axons and thinly myelinated axons when repeatedly applied to the respiratory mucosa. Substance P was found effective in reducing nasal symptoms after cumulative topical applications in the treatment of non-allergic hyperreactive rhinitis, probably acting as desenzitizer of nasal mucosa due to depletion of SP and neurokinins.The hypothesis that neurogenic inflammation may play a role in the pathogenesis of nasal polyps has led to trials on capsaicin treatment of nasal polyposis.

7-3-8-1 Acute and chronic rhinosinusitis without nasal polyps
No trials of treatment of acute or chronic rhinosinusitis with capsaicin could be found.

Table 7-13. Nasal irrigation (saline, hypertonic saline, Dead sea solution, balneotherapeutic water) randomized controlled trials

study	indication	solution	number	duration	symptoms	objective	level of evidence
Adam, 1998 [746]	ARS	saline vs. HS vs. NT	119	10 days	no difference	not done	Ib
Bachmann, 2000 [748]	CRS	saline vs. EMS	40	7 days	improved, no difference saline vs EMS	endoscopy, plain X-ray improved	Ib
Taccariello, 1999	CRS	sea water vs. Alkaline vs. NT	62	30 days	improved	endoscopy, HRQL improved	Ib
Rabago, 2002 [749]	CRS	HT vs. NT	76	6 months	improved	significantly less antibiotics, nasal sprays	Ib
Shoseyov, 1998 [751]	CRS in children	saline vs. HS	40	4 weeks	HS all symptoms improved, saline PND only	x-ray improved after HS	Ib
Friedman, 2006 [581]	CRS	HS vs. DSS	57	2 months	DSS significantly improved, better than HS	DSS - HRQL significantly improved	Ib
Pinto, 2006 [753]	CRS after ESS	saline vs. HS vs. NT	60	5 postop. days	higher discharge and pain in HS group	not done	Ib

Legend. HS: hypertonic saline; DSS: Dead Sea salt solution; NT: no treatment; ESS: endoscopic sinus surgery; HRQL: health related quality of life.

7-3-8-2 Nasal polyps

A case study (III) by Filiaci et al. has demonstrated significant reduction in the size of nasal polyps after five (weekly) topical applications of capsaicin (30 mmol/L) solution in patients with nasal polyposis [757]. The authors noted increased nasal eosinophilia after the treatment, which was not correlated to the polyp size. A case study by Baudoin et al. has demonstrated significant reduction of sinonasal polyposis after 5 consecutive days treatment with increasing doses (30-100 mmol/L) of topical capsaicin in massive polyposis measured by CT scans at entry and after 4 weeks (III) [758]. ECP in nasal lavage was not influenced by the treatment. Protection of polyp recurrence following endonasal surgery by 5 topical applications of capsaicin in 51 patient after surgery with a 9 months follow-up has confirmed significant recurrence protection and significantly better nasal patency in the active group in a randomized, double blind, placebo controlled trial (Ib) by Zheng et al [759]. The authors used 70% ethanol $3x10^{-6}$ ml capsaicin solution, which may explain the high rate of recurrence in the control group after ESS, which received only 70% ethanol. They noted 40% polyp stage 0 (Malm) and 45% stage 1 in the active treatment group, while controls demonstrated 45% stage 2 and 40% stage 3 polyposis following treatment at 9 months observation. The low cost of capsaicin treatment was noted as a certain advantage compared to other postoperative treatments. As capsaicin is NFκB antagonist in vitro, some other modes of action may be proposed [760].

7-3-8-3 Side effects

The most common side effect following nasal capsaicin application, if not previously topically anaesthetized, is severe burning sensation in the nose and lips, and lacrimation. However, previous topical nasal anaesthaesia with 10% xylocaine spray in placebo-controlled trial completely blinded the active treatment [761]. In the trials of nasal capsaicin treatment for idiopathic rhinitis, some other side effects were reported: dyspnoea, headache, cough, epistaxis, dryness of nasal mucosa and exanthema [762, 763].

7-3-9 Furosemide

The protection of the hyper-reactive response to different challenges (propranolol) [764]; metabisulphite [765]; and exercise [766] in asthmatics was demonstrated after inhalation of furosemide, suggesting bronchoprotective effects, similar to the effect of cromones.

7-3-9-1 Acute and chronic rhinosinusitis without nasal polyps

No trials of treatment of acute or chronic rhinosinusitis with furosemide have been found.

7-3-9-2 Nasal polyps

Protection against nasal polyp recurrence following surgery with 1-9 years follow-up, comparable to the effect of the topical steroid, was demonstrated after topical application of furosemide in 97 patients postoperatively versus mometasone furoate in 33 patients, in a prospective non-randomized controlled trial (IIa) by Passali et al [767], which had been previously reported by the same group in a case study. Relapses were recorded in 17.5% in the furosemide, 24.2% in the mometasone and 30% in the no treatment group, suggesting that furosemide, as a much cheaper medication than steroids, might be considered as a prophylaxis to polyp recurrence.

A recent randomized controlled trial compared the effect of short term pre-operative treatment with oral methylprednisolone (1mg/kg) versus inhalation of 10 ml of 6.6 mmol furosemide solution in 40 patients with nasal polyposis. Both were effective but no difference was found between the two treatment modalities after 7-day treatment, in terms of polyp size reduction on endoscopy, nasal symptom scores (except for olfaction, which was better in steroid group) and intraoperative bleeding. Histological analysis of the polyps at surgery suggested a strong anti-inflammatory effect of oral steroid (in terms of eosinophil count reduction), while furosemide treatment demonstrated only an effect on oedema [768].

Randomized placebo-controlled trials, especially long term treatment, are however lacking.

7-3-10 Proton pump inhibitors

Numerous trials during the past decade indicated an association between extraoesophageal reflux and airway disease, and beneficial effect of PPI treatment on upper airway symptoms, including some symptoms of CRS, was suggested., Postnasal drip, a relevant CRS symptom, was established as one of the symptoms responding to PPI treatment. However, sensation of postnasal drip (PND)was confirmed in groups of patients with idiopathic rhinitis, without evidence of rhinosinusitis, and in patients without rhinitis and sinusitis.[769], and greater exposure to gastric acid was demonstrated in patients with PND than in the controls. As PPI treatment reduces acidity, it is a dilemma if PPI acts on rhinitis, rhinosinusitis or sensation of PND. Most reviews on current evidence on the association between reflux and sinus disease advocate higher quality of controlled trials on both etiology and treatment, in pediatric and adult population. As PPI treatment of extraoesophageal reflux disease (like laryngitis) is based on long-term high-dose regimen, potential side effects should be considered.

7-3-10-1 Acute rhinosinusitis

There are no trials with proton pump inhibitors for ARS.

7-3-10-2 Chronic rhinosinusitis

There is no evidence for benefits in the general population suffering from rhinosinusitis following treatment with proton pump-inhibitors, although subjective improvement was noted in patients with laryngopharyngeal reflux (proved by pH-metry) and rhinosinusitis. Grade C evidence for a positive association between gastroesophageal reflux and rhinosinusitis was found in a meta analysis of the literature for this co-mor-

bidity (57 articles screened, 14 articles included) [770, 771]). A number of case trials of rhinosinusitis, especially paediatric [770], have tested the efficacy of anti-reflux treatment with proton pump inhibitors on the clinical course and symptoms of rhinosinusitis. Increased rates of reflux were detected in CRS in adults unresponsive to standard treatment [772, 773]. Further research is expected in this field, and such treatment should be justified by randomized controlled trials.

Non-controlled trials, especially in children, indicate the effect on some symptoms of rhinosinusitis, presumably postnasal drip and cough. However, a recent meta-analysis of randomized controlled trials of outcomes of the treatment of non-specific cough with proton pump inhibitors confirmed that it is insufficient evidence to definitely conclude that reflux treatment with PPI is universally beneficial for cough associated with reflux in adults. The beneficial effect was only seen in sub-analysis and its effect was small [774].

7-3-10-3 Nasal polyps
There are no data on proton-pump inhibitors in nasal polyposis.

7-3-11 Antileukotrienes
Leukotrienes are upregulated in asthma and nasal polyposis, especially in aspirin- sensitive disease.

7-3-11-1 Acute rhinosinusitis
No trials were done on the antileukotrienes treatment in ARS.

7-3-11-2 Chronic rhinosinusitis and nasal polyps
Open studies suggest that anti- leukotrienes might be of benefit in nasal polyposis [775-777].

Antileukotriene treatment in 36 patients with CRS with or without NP, added to standard treatment, resulted in statistically significant improvement in scores for headache, facial pain and pressure, ear discomfort, dental pain, purulent nasal discharge, postnasal drip, nasal congestion and obstruction, olfaction, and fever. Overall improvement was noted by 72% of the patients and side-effects occurred in 11% of the patients [778]. In a selected group of 15 ASA triad patients, addition of antileukotriene treatment resulted in 9/15 with sinusitis experiencing improvement and over-all benefit in 12/15 patients, which was confirmed by endoscopy [779]. In a group of patients with nasal polyposis, significant subjective improvement in nasal symptoms occurred in 64% aspirin tolerant patients and 50% aspirin sensitive patients Significant improvement in peak flow occurred only in aspirin tolerant patients, while acoustic rhinometry, nasal inspiratory peak flow and nitric oxide levels did not change [777]. A prospective double blind comparative study on 40 patients compared the effects of the leukotriene receptor antagonist, montelukast and beclomethasone nasal spray on the post-operative course of patients with sinonasal polyps. No significant differences were found between these two post-operative treatments in the year after surgery [780].

Results of these studies indicate that there is a need for (larger) controlled trials of antileukotriene treatment in CRS with or without NP.

7-3-12 Aspirin desensitization

7-3-12-1 Acute and chronic rhinosinusitis without nasal polyps
No controlled trials of aspirin desensitization treatment for acute and chronic rhinosinusitis were found.

7-3-12-2 Chronic rhinosinusitis and nasal polyps with aspirin intolerance
Systemic aspirin desensitisation or topical lysine-aspirin treatment (the only truly soluble form of aspirin) may be implicated in protection against chronic rhinosinusitis with nasal polyposis recurrence.

Sixty-five aspirin-sensitive patients with aspirin sensitive asthma underwent aspirin challenge, followed by aspirin desensitization and daily treatment with aspirin over 1 to 6 years (mean, 3.1 years). There were significant reductions in numbers of sinus infections per year and an improvement in olfaction. Numbers of sinus and polyp operations per year were significantly reduced and doses of nasal corticosteroids were significantly reduced. There were reductions in hospitalizations for treatment of asthma per year and reduction in use of systematic corticosteroids [781-783].

Nucera et al. have followed three groups of patients with nasal polyposis (about 50% aspirin sensitive), the first with 76 consecutive nasal polypectomy patients who had a topical lysine-acetylsalicylate-therapy afterwards, the second 49 patients with 40 mg triamcinolone retard ("medical polypectomy") and also further lysine-acetylsalicylate-therapy and the third with 191 control patients who underwent only polypectomy but received no placebo. The group treated with lysine-acetylsalicylate postoperatively had a recurrence rate of 6.9% after 1 year and 65% after six years postoperatively, while controls experienced recurrence in 51.3% at 1 year and 93.5% at six years after the operation, indicating a significant protection against recurrence from the lysine-acetylsalicylate treatment. Systemic corticoid therapy and nasal lysine-acetylsalicylate-therapy resulted in 33% with unchanged polyp size after three years compared to 15% in the operated-not treated group, but this was not statistically significant [784].

A case controlled trial of treament with lysine aspirin to one nostril and placebo to the other in 13 patients with bilateral nasal polyposis resulted in delayed polyp recurrence and 8 remained symptom free at 15 months observation period, which was significantly better than results of the patients previously treated with steroid for recurrence protection. Endoscopy and acoustic rhinometry indicated minor polyp size on the aspirin treated side [785].

Table 7-14. Other medical management for rhinosinusitis. Results from the treatment studies summarised

treatment	*acute*			*chronic without nasal polyps*			*chronic with nasal polyps*		
	study	*level of evidence*	*clinical importance*	*study*	*level of evidence*	*clinical importance*	*study*	*evidence*	*clinical importance*
decongestant	1 RCT, 1 CT	Ib (-)	no.	no trial	none	no	no trial	none	no
mucolytic	2 RCT	Ib (one +, one -)	no	1 cohort	III (-)	no	no trial	none	no
phytotherapy	1 RCT	Ib	no	1 CT	Ib	no	no trial	none	no
immuno-modu-lator	no trial	none	no	1 RCT	Ib (-)	no	no trial	none	no
antihistamine	1 RCT allergic	Ib	yes (in al-lergy only)	no trial	none	no	1 RCT al-lergic	Ib	yes (in al-lergy only
antileukotriene	no trial	none	no	1 cohort	III	no	3 cohort	III	no
proton pump inhibitor	no trial	none	no	3 cohort	III	no	no trial	none	no
lysine aspirin desensitisation	no trial	none	no	no trial	none	no	1 RCT 2 CT	Ib	yes
furosemide	no trial	none	no	no trial	none	no	1 RCT 1 CT	Ib (-)	yes
capsaicin	no trial	none	no	no trial	none	no	1 RCT	Ib	no
anti-IL-5	no trial	none	no	no trial	none	no	1 RCT	Ib (-)	no

A double blind, randomized, placebo controlled trial did not demonstrate any effect on nasal airway using 16mg of intranasal lysine aspirin every 48 hours, compared to placebo treatment, in aspirin sensitive patients, after 6 months treatment (786). Outcomes included subjective symptom scores, acoustic rhinometry, PNIF and PEF. However, final outcomes were analysed in only 11 available patients, and pathohistologic analysis revealed significant decrease of CylLT 1 receptor in the turbinate mucosa of the patients with active treatment, compared to placebo, so further trials were suggested.However, addition of intranasal lysine aspirin in doses up to 50mg daily to routine therapy reduced polyp size and did not adversely affect asthma (Ogata N, Darby Y, Scadding G. Intranasal lysine-acetylsalicylate (LAS) adminsitration decreases polyp volume in patients with aspirin intolerant asthma. J Laryngol Otol 2007 in press). The mechanisms of desensitisation probably involve reduction of leukotriene receptors [392].

7-3-13 Phytopreparations
Treatment of rhinosinusitis by alternative medicine, including herbal preparations is common in the general population. A study by interview in a random telephone sample population suffering from CRS and asthma revealed that 24% were taking herbal preparation [787]. Lack of randomized controlled trials comparing such treatment to standard medication in rhinosinusitis patients should be a concern to health care providers.

7-3-13-1 Acute rhinosinusitis
A standardized myrtol oil preparation was proven superior to other essential oils, and both were superior to placebo in a RCT for uncomplicated ARS. A need for antibiotic treatment after myrtol was 23%, compared to 40% for placebo [788].
With Andrographis paniculata in a fixed combination, Kan Jang showed significantly improved nasal symptoms and headache in ARS compared to placebo [789]

7-3-13-2 Chronic rhinosinusitis
Guaifenesin, a phytopreparation known for its mucolytic properties, was tested in a RCT on a selected population of HIV patients with CRS, demonstrating 20% higher improvement in subjective scores compared to placebo in this population [790].

7-3-13-3 Nasal polyps
No controlled trials on nasal polyp treatment with phytopreparations were found.

7-3-14 Anti-IL-5 antibodies
The first small study using humanized mouse anti-IL-5 antibodies in patients with nasal polyps [791] showed no significant treatment effect. However it indicated that local IL-5, but not IL-5 receptor concentrations, predicted the clinical response.

7-3-15 Conclusion
The results are summarized in the next table.

7-4 Evidence based surgery for rhinosinusitis

7-4-1 Introduction
In this chapter, systematic reviews on sinus surgery efficacy in CRS are first presented, followed by a description of comparative trials of sinus surgery with medical treatment. The role of various surgical modalities is then briefly reviewed, and reports on the

effects of concomitant diseases on sinus surgery outcomes are detailed. There is evidence that CRS with and without polyps are distinct subgroups of chronic inflammatory diseases of the upper airway mucosa (see chapters 2 to 4). Approximately 20% of patients with CRS develop nasal polyps [792], which may predispose to less favourable results of sinus surgery [793, 794]. Accordingly, reviewed articles are grouped into CRS without polyps and CRS with polyps, when the authors differentiated between these two subgroups. Except for a few reports on limited sinus surgery in recurrent ARS [795], sinus surgery is generally restricted to chronic rhinosinusitis (CRS). Therefore, currently available data do not suffice to judge the role of surgery in acute or acute recurrent rhinosinusitis. For surgical interventions in complications of ARS see chapter 8, for paediatric sinus surgery see chapter 9, for a detailed description of complications of sinus surgery refer to chapter 7, and for postoperative medical treatment please refer to chapter section 7-1-5.

It is difficult to generalise about sinus surgery studies because surgery is indicated in selected patients who are not sufficiently responsive to medical treatment. Moreover, only a few publications on sinus surgery qualify for evidence based evaluation [796] and frequently studies included in systematic reviews are assigned low evidence levels [797-799] This is in part due to specific problems in conducting surgical trials. In general, surgery is difficult to estimate or standardize, particularly in multi-centre trials, and the type of treatment is difficult to conceal (blinding). Randomization may pose ethical problems unless narrow inclusion criteria are set [514]. Low budget investigator initiated trials not monitored by professional clinical research organisations are the rule.

In addition, a variety of confounders make it difficult to obtain homogenous patient groups with comparable therapeutic procedures for unbiased evaluation of sinus surgery outcomes. Possible relevant surgical factors include whether an external or endonasal approach is chosen, whether a functional or conventional surgical procedure is selected, if the extent of the surgical intervention is limited, extended or radical, and what kind of instruments are employed. Patient dependent factors include age, extent and duration of disease, previous surgery, presence of polyps, concomitant diseases such as ASA-intolerance, asthma, or cystic fibrosis, and particular aetiologies including dental, autoimmune, immune, and fungal disease [800-803]. Moreover, mode and duration of pre- and post-operative drug therapy may alter the outcome.

7-4-2 Effectiveness of sinus surgery and comparison with medical treatment

7-4-2-1 Systematic reviews and outcomes research on sinus surgery effectiveness

Several reviews did not differentiate between CRS with and without polyps such as Terris and Davidson who analysed 10 case series. Patients' judgement of outcome using an unbalanced three item verbal rating scale was employed. [804]. A 'very good' result was defined as complete resolution of symptoms or less than 2 rhinosinusitis episodes per year, a 'good' result was improvement but without complete resolution of symptoms or 2-5 sinusitis episodes per year, and a 'poor' result was no improvement or deterioration. Articles reporting a total of 1,713 patients were evaluated. Subjectively, 63% of patients reported a very good result, 28% a good result, and 9% an unsatisfactory result. Twelve percent of patients required revision surgery and complications occurred in 1.6% of patients. With 1.5%, bleeding was most the most common complication (level IV).

In a systematic review, 12 case series of endoscopic sinus surgery were evaluated and compared with 6 case series of conventional techniques [797]. In patients with CRS with or without polyps, overall success rates ranging from approximately 70% to 90% after sinus surgery were reported. Revision surgery was reported in 7% to 10%. If reported, complications were below 1% (level IV).

In a recent meta-analysis, the impact of endoscopic sinus surgery on sinus symptoms and quality of life was evaluated in adults after failed medical treatment [803]. Articles dealing with both or not differentiating between CRS with and without polyps were included. Forty-five of 886 screened articles were included for full review. The reasons for exclusion were not detailed. Of the included articles, 1 article qualified for level II evidence, 42 for level IV evidence and 2 for level V evidence. The authors conclude that there is substantial level IV evidence with supporting level II evidence that endoscopic sinus surgery is effective in improving symptoms and QoL in adult patients with CRS.

In a recent Cochrane review, 3 randomized controlled sinus surgery studies were included [796]. The authors conclude that FESS, as practiced in the included trials, is not superior to medical treatment with or without sinus irrigation in patients with CRS.

7-4-2-1-1 CRS without polyps

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 [521]. 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. One third [952] of the 3128 patients participating in this study had CRS without nasal polyps and 2176 suffered from CRS with polyps. Outcomes are reported separately for the two rhinosinusitis subgroups. CRS-patients without polyps less frequently suffered from concomitant asthma and ASA-intolerance, had less previous sinonasal surgery, their mean CT score was lower and their mean SNOT-22 symptom score was slightly higher than that of CRS patients with polyps. All forms of sinus surgery

were considered 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 were demonstrated at 3, 12 and 36 months. Revision surgery was indicated in 4.1% at 12 months and 10.4% at 36 months (Level IIc).

In addition to this outcomes research study, 2 recent case series are also presented to supplement outcome data on CRS without polyps. In a retrospective analysis, 123 patients with CRS without nasal polyps who underwent primary FESS with a minimum 1-year follow-up period were evaluated [793]. Outcome parameters included the Sino-Nasal Outcome Test (SNOT-20) questionnaire, the Lund-Mackay CT-scoring system, and the need of revision surgery. SNOT-20 scores were 26.5 preoperatively with significant improvement to 5.1 at 6 months and 5.0 at 12 months postoperatively (85% improvement) (level IV). In a case series of 77 patients with CRS without polyps, symptom and endoscopy scores were followed between 3 and 9 years after FESS [805]. Saline douches and nasal steroids were postoperatively administered as required. After at least 3 years, more than 90% of the patients reported symptom improvement of 80% or more. Revision surgery was performed in 15%. At the end of the follow up period, 5 patients (7%) received nasal steroids.

7-4-2-1-2 CRS with polyps

Within the framework of the NHS R&D Health Technology Assessment Programme, the clinical effectiveness of functional endoscopic sinus surgery to treat CRS with polyps was reviewed. The authors screened 444 articles and evaluated 33 articles published between 1978 and 2001 [806]. Major reasons for exclusion were the narrative character of the publication or less than 50 patients with polyps. The authors reviewed 3 RCT comparing functional sinus surgery with Caldwell Luc or conventional endonasal procedures (n=240), 3 non-randomized studies also comparing different surgical modalities (n=2699) and 27 case series (n=8208). Consistently, patients judged their symptom 'improved' or 'greatly improved' in 75 to 95 percent (level IV). The percentage of overall complications was 1.4% for FESS compared to 0.8% for conventional procedures.

Two thirds (2176) of the 3128 patients participating in the National Comparative Audit had CRS with nasal polyps [521]. CRS patients with polyps had no longer duration of disease, no higher previous steroid treatment, nor ratings of their general health before surgery than CRS patients without polyps. Irrespective of extent of surgery, clinically significant improvement in the SNOT-22 scores were demonstrated at 3, 12 and 36 months. Polyp patients benefited more from surgery than the chronic rhinosinusitics without polyps. Revision surgery was indicated in 3.6% at 12 months and 11.8% at 36 months. Major complications were rare (Level IIc).

In this context, a case series study of CRS patients with particularly extensive polyposis is worth mentioning [807]. Of the 118 patients reviewed, 59 (50%) had asthma, and 93 (79%) had doc-

umented allergy. All patients received extensive bilateral nasal polypectomy, complete anterior and posterior ethmoidectomy, and maxillary sinusotomy. One hundred (85%) also had frontal or sphenoid sinusotomy. Follow-up ranged from 12 to 168 (median 40) months. Despite pre- and postoperative nasal and systemic steroid treatment in the majority of patients, 71 (60%) developed recurrent polyposis, 55 (47%) were advised to undergo revision surgery, and 32 (27%) underwent revision surgery. History of previous sinus surgery or asthma predicted higher recurrence and revision surgery rates. History of allergy also predicted recurrence and need for revision.

Conclusion: One major outcomes research study (level II) and more than a hundred reviewed case series (level IV) with highly consistent results suggest that patients with CRS with and without polyps benefit from sinus surgery. Major complications occur in less than 1%, and revision surgery is performed in approximately 10% within 3 years.

7-4-2-2 Combined surgical and medical treatment vs. sole medical treatment

CRS may be cured with medical treatment alone. Moreover, sinus surgery is almost always preceded and/or followed by various forms of medical treatment including nasal douches, nasal steroids, systemic steroids, and systemic antibiotics. Few studies compared sinus surgery, which was always combined with medical treatment, with medical treatment alone. In two studies, CRS patients with and without polyps were not differentiated.

In a prospective trial, 160 CRS patients with or without polyps were enrolled and treated with either medical therapy alone or medical therapy plus endonasal sinus surgery [486]. Group allocation was not randomized and the non-surgical cohort had less males, less concomitant diseases, less polyps, and less severe disease. Outcome parameters included the SF-36 and Chronic Rhinosinusitis Survey (CSS) questionnaire. At follow up after 3 months, the surgically treated group improved more than the non-surgically treated group, however, improvement was not adjusted for pre-treatment scores (level IV).

In a prospective observational study conducted by the Cooperative Outcomes Group for ENT of the American Academy of Otolaryngology – Head and Neck Surgery, 31 otolaryngologists enrolled 276 CRS patients with or without polyps [808]. Follow up was 207, 164 and 117 patients after 3, 6 and 12 months, respectively. Success was defined as 40% or more improvement in a subset of the CSS. Based on judgment of the participating physicians, 83 patients received functional endoscopic sinus surgery and 118 patients received medical treatment only. Surgically treated patients had a 3 times higher chance for success than patients treated only medically (p < 0.01), however, this disproportion disappeared when corrected for baseline CSS-scores in a logistic regression approach (level IV).

7-4-2-2-1 CRS without polyps

In a prospective, randomized, controlled trial, Ragab and coworkers enrolled 90 patients with CRS [536]. Of the 90 included patients, 55 suffered from CRS without polyps and are reported separately. During a run in phase, all patients received a 6-week regimen of dexamethasone-21-isonicotinate and tramazoline hydrochloride (DRS) spray and an alkaline nasal douche. Patients who remained symptomatic after this treatment were then randomized to a medically or a surgically treated arm. In the medically randomized group, all patients received a 12-week course of erythromycin, alkaline nasal douche, and intranasal corticosteroid preparations. In the surgically randomized group, FESS was performed tailored to the extent of disease. After endoscopic sinus surgery, all patients were prescribed a 2-week course of erythromycin, DRS spray, and alkaline nasal douche, followed by a 3-month course of fluticasone propionate intranasal spray. After that, topical corticosteroid spray was given as needed. Outcome parameters included the SNOT-20, SF-36, nasal NO and acoustic rhinometry measurements. At follow up visits after 6 months and at 1 year, significantly improved outcome parameters were observed in both treatment arms, with no significant difference being found between the medical and surgical groups (p > 0,05), except for the rhinometrically assessed total nasal volume, in which the surgical treatment demonstrated greater improvements (Level Ib).

7-4-2-2-2 CRS with polyps

In an open, randomized trial, Lildholdt and co-workers included 53 patients with nasal polyps [641]. All patients received nasal steroid spray during the 12 month study period. Snare polypectomy was additionally performed in 26 patients, whereas 27 patients received an intramuscular depot betamethasone injection. After 1 year, no relevant difference in the main outcome parameters including sense of smell, PNIF, and disease recurrence were observed (level Ib).

In a second open RCT, Lildholt and co-workers included 34 patients with nasal polyps who did not improve after participation in a preceding placebo controlled trial comparing two doses of intranasal budesonide[493]. Sixteen patients received a single depot injection of 14 mg betamethasone and 18 patients underwent intranasal snare polypectomy. Outcomes were assessed after 11 months additional nasal steroid treatment and again after 12 months without any treatment. Snare polypectomy and systemic betamethasone outcome 12 months after treatment were remarkably similar as measured by mean nasal improvement score, polyp score or mean score of sense of smell (p > 0,05). Within 1 year without nasal steroid treatment, 50% of the patients experienced further nasal polyps, however the authors did not differentiate polyp recurrence by medical or surgical treatment (level Ib).

In a study by Blomqvist and coauthors, 32 CRS patients with polyps were pretreated with systemic steroids (prednisolone for fourteen days) and budesonide for 4 weeks [809]. Thereafter, FESS was performed on one side while the other side remained untouched employing a randomized prospective matched samples design. Following surgery, intranasal steroids were given for an additional 12 months on both sides. The sense of smell was tested for each nostril separately. It improved after treatment with systemic and topical steroids without additional improvement on the operated side. Surgery had an additional beneficial effect on nasal obstruction and secretion that persisted over the study period. However, 25% percent of the patients required surgery also on the yet unoperated side. The authors conclude that surgical treatment is indicated after steroid treatment, if nasal obstruction persists but not if hyposmia is the primary symptom (Level Ib).

In the prospective, randomized, controlled trial by Ragab and co-authors already described [536], 35 CRS patients with polyps remained symptomatic after a 6-week intensive medical regimen and were randomized into the study. At follow up visits after 6 months and at 1 year, both treatment arms reported significantly improved outcome parameters, with no significant difference being found between the medical and surgical groups (p > 0,05), except for the total nasal volume, in which the surgical treatment demonstrated greater improvements (Level Ib).

In a recent RCT, 109 patients with CRS with extensive nasal polyps were included [587]. Fifty-three patients were randomly allocated to receive oral prednisone for 2 weeks (30 mg/day for 4 days followed by a two days reduction of 5 mg) and 56 to undergo endoscopic sinus surgery. All patients additionally received intranasal budesonide for 12 months. Patients were evaluated for nasal symptoms, polyp size, and QoL employing the SF-36 questionnaire. At 6 and 12 months, a significant improvement in all SF-36 domains, nasal symptoms and polyp size was observed after both medical and surgical treatment. A significant advantage for the surgically treated group was observed for nasal obstruction, loss of smell and polyp size 6 months after randomization and for polyp size also 12 months after randomization (level Ib).

Conclusion: In the majority of CRS patients, appropriate medical treatment is as effective as surgical treatment. Sinus surgery should be reserved for patients who do not satisfactorily respond to medical treatment.

7-4-3 Surgical modalities

7-4-3-1 Endonasal versus external approach

Endonasal approaches include surgical procedures performed through the nostril, irrespective of the extent of surgery and the kind of visualization of the surgical field. Today, endonasal procedures are predominantly performed employing endoscopes. The most commonly performed external surgical procedures include the sublabial transfacial Caldwell Luc approach with or without transantral ethmoidectomy and sphenoidectomy, and transfacial frontoethmoidectomy. In a few

studies, outcomes of external and transnasal procedures were compared though not differentiating between CRS patients with and without polyps.

Penttila and co-workers randomized 150 CRS patients after failed antimicrobial therapy and antral irrigations for chronic maxillary sinusitis to either endonasal endoscopic sinus surgery (n=75) or an external Caldwell Luc approach (n=75). The percent changes of symptom scores before and one year following surgery were evaluated (Level Ib). Functional endoscopic sinus surgery revealed significant advantages in the relief of nasal obstruction, hyposmia and rhinorrhea, but not facial pain. Patients overall judgement and rate of complication also significantly favoured the endonasal approach [810, 811]. The study population was re-evaluated 5 to 9 years later with 85% of the former study participants responding to a questionnaire. In both surgical groups, approximately 80% were asymptomatic or distinctly improved without relevant intergroup differences [812]. However, postoperative cheek pain and paraesthesia were noted in 23% of Caldwell Luc group, which is a frequent complication of this approach [813]. The histopathology of maxillary sinus specimens obtained before and 1 year after surgery from patients of the two treatment arms of the Penttila-studies were evaluated by Forsgren et al., indicating a greater reduction in inflammatory parameters in the mucosa of the maxillary sinus after the Caldwell-Luc approach [814].

In a retrospective evaluation, Unlu and coauthors randomly selected 37 Caldwell-Luc-operated and 40 endonasally operated patients. Outcome was assessed with nasal endoscopy and CT-scans [815]. CT was normal in 12% of Caldwell-Luc-operated patients in comparison to 75% of endosopically operated patients. Endoscopy revealed a patency rate of the antral window in 48% Caldwell-Luc-operated and 86.7% in endonasally operated patients. The authors conclude superiority of the endonasal approach. (Level IV).

Videler and co-authors treated 23 CRS patients refractory to repeated endonasal procedures, Caldwell Luc and intensive medical treatment via an Caldwell Luc approach with removal of the medial maxilarry wall [573]. Clinical improvement was observed the majority of patients (level IV).

7-4-3-1-1 CRS without polyps
No studies comparing endonasal surgery with external fontoethmoidectomy or Caldwell-Luc approach in patients with CRS without polyps were found.

7-4-3-1-2 CRS with polyps
No studies comparing endonasal surgery with external fontoethmoidectomy were identified. In several studies, endonasal sinus surgery was compared with the Caldwell-Luc approach in CRS patients with polyps. In the NHS R&D Health Technology Assessment Programme evaluation, an overall symptomatic improvement was reported in approximately 80% after endoscopic sinus surgery and in 43 to 84% after conventional surgery including Caldwell Luc. Disease

recurrence was 8% for FESS compared to 14% for Caldwell-Luc approach [806].

McFadden and co-workers evaluated the long term outcome (up to 11 years) in 25 patients with extensive nasal polyps and ASA-intolerance. Sixteen patients were operated via an extended endonasal approach and 9 via a Caldwell Luc approach with radical sphenoethmoidectomy. Of the endonasally operated patients, 6 underwent a revision surgery via a Caldwell Luc approach whereas none of the patients who had received a Caldwell Luc approach initially was reoperated [432].

Conclusion: Long term symptom relief in chronic sinusitis can be obtained by the endonasal endoscopic and the Caldwell-Luc approach, however, results favour the endonasal approach. The Caldwell-Luc approach carries a higher risk of early postoperative facial swelling and infraorbital nerve irritation. Comparative studies of endonasal versus external frontoethmoid approaches are currently not available.

7-4-3-2 Conventional endonasal surgery versus functional endonasal sinus surgery
Conventional sinus surgery is a collective term for surgical techniques already used before the devlopment of functional sinus surgery. They include external approaches, maxillary sinus irrigation, simple (snare) polypectomy, inferior meatal antrostomy, and radical transnasal spheno-ethmoidectomy with or without middle turbinate resection. Unlike functional techniques, conventional sinus procedures do not proceed along the natural pathways of sinus ventilation and mucociliary transport revealed by the fundamental work of Messerklinger [816]. Restoring ventilation and mucociliary transport by functional surgery along the natural ostia allows recovery of the diseased sinus mucosa, which is not resected [817, 818]. Concurrently with the development of the functional approach, rigid endoscopes became available, which improved visualization during endonasal surgery. The evolving concept of functional endoscopic sinus surgery (FESS) spread worldwide by the efforts of Stammberger and Kennedy [819, 820]. In two studies, a conventional approach was compared with functional sinus surgery in CRS patients with or without polyps.

In a prospective controlled trial, Arnes and coauthors performed an inferior meatal antrostomy on one side and a middle meatal antrostomy in the opposite nasal cavity in 38 patients with recurrent acute or chronic maxillary sinusitis [821]. The laterality was randomized. After an observation period ranging between 1 and 5 years, no significant side differences in symptom scores or radiological findings were observed (level Ib).

In a randomized controlled trial, 25 patients after functional endoscopic sinus surgery were compared with 25 after conventional surgery. Conventional surgery included antral puncture, intranasal ethmoidectomy, and Caldwell-Luc procedures. Follow up ranged from 15-33 months with a mean of 19 months, at the end of which 76% of the functional group had

complete relief of symptoms, 16% partial relief and 8% no relief as compared to 60%, 16%, 24% in the conventionally treated group [822]. However, this study is flawed by an elusive method of randomization, lack of information on homogeneity of patients groups, and high variability of procedures performed. (no level applied).

7-4-3-2-1 CRS without polyps
Eighty-nine patients with chronic sinusitis confined to the maxillary sinus without nasal polyps were enrolled in a prospective randomized controlled trial [823]. After antibiotic therapy for at least 4 weeks prior to inclusion, 45 patients received sinus irrigation only and 44 patient sinus irrigation followed by FESS. Patients were followed in regular intervals up to one year. The per protocol analysis included 36 'irrigation only' and 41 'irrigation and FESS' patients. In 13 'irrigation only' patients and 2 'irrigation and FESS' patients, second surgery was performed due to lack of efficacy (p < 0.001). Moreover, outcomes for purulent discharge and loss of smell showed significant improvement in 'irrigation and FESS' group as compared with those obtained by sinus irrigation alone after one year's observation. Scores for other sinusitis symptoms did not differ significantly between the groups (Level Ib).

7-4-3-2-2 CRS with polyps
In the NHS R&D Health Technology Assessment Programme evaluation (806), polyp recurrence was 28% following functional endoscopic ethmoidectomy compared to 35% following intranasal polypectomy. The percentage of overall complications was 1.4% for FESS compared to 0.8% for conventional procedures.

Hopkins and co-workers analyzed 1848 patients with nasal polyps, a subgroup of 3128 patients who participated in the National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis [824]. The authors compared the SNOT-20 supplemented with two additional items (SNOT-22) after simple polypectomy and after more extensive surgery both largely performed endoscopically in addition to medical treatment. The SNOT-scores did not differ significantly between the two treatment arms after 12 and 36 months, if adjusted for relevant confounders. Revision surgery was carried out more frequently in the polypectomy only group in the first 12 months after surgery (p = 0.04), but this difference was not significant at 36 months. Complication rates did not differ significantly.

Conclusion: Functional endoscopic surgery is superior to minimal conventional procedures including polypectomy and antral irrigations, but superiority to inferior meatal antrostomy or conventional sphenoethmoidectomy is not yet proven.

7-4-3-3 Extent of surgery
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 (infundibulectomy) 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 [825]. Recall rates were below 60%. Outcome parameters revealed no relevant differences after 3, 6 and 12 months (level Ib).

Based on the concept that diseased sinus prechambers, not small sinus ostia, are the cause for chronic sinus inflammation, minimal invasive sinus surgery (MIST) is advocated by some authors [826]. Basically, sinus ostia are exposed during MIST, but not enlarged. In a prospective, uncontrolled trial, Catalano and Roffman followed 85 patients with CRS for a mean 24 months. Changes in the CSS score served as outcome parameter and revealed significant improvements similar to FESS studies (level IV).

Some authors advocate partial resection of the middle turbinate to expand the surgical approach [827], while others modify it only in case of abnormalities and leave as much as possible of the middle turbinate intact as a landmark in case revision surgery is needed [817]. In a retrospective evaluation including 100 FESS patients, Giacchi and coauthors preserved the middle turbinate on one side and partially resected it on the other side [828]. The authors observed no side differences in the outcome parameters studied (level Ib).

In a randomized trial, 1106 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 [829]. Partial middle turbinate resection was associated with less synechia formation (p < 0.05) and less revision surgeries (p < 0.05) than middle turbinate preservation. Complications particularly caused by partial middle turbinate resection were not observed (level Ib).

In a prospective, randomized trial, uncinectomy was performed in 295 patients with chronic maxillary sinusitis. In 140 patients, a large middle meatal window (diameter > 16 mm) was either unilaterally or bilaterally created, whereas in 140 patients small middle meatal antral windows (diameter < 6 mm) were produced. In 170 patients, no preoperative CT was available. Follow up visits were attended by 133 (45%) patients 12 to 38 months after surgery. Outcome parameters included patients judgment of symptom change (absent, improved, unchanged, worsened) and various endoscopic findings. Symptom relief, endoscopy findings and antral window size did not depend on the surgically created antral window diameter [830].

7-4-3-3-1 CRS without polyps
No reports comparing less or more extensive surgical procedures explicitly in CRS patients without polyps could be identified.

7-4-3-3-2 CRS with polyps

The patency rate after large middle meatal antrostomy and undisturbed maxillary ostium in endoscopic sinus surgery for nasal Polyposis was compared in 60 patients with bilateral nasal polyps and chronic maxillary sinusitis [831]. 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 sides were chosen randomly. The patency rates of a large middle meatal antrostomy were significantly higher 3 months after surgery when compared with undisturbed maxillary ostium. This difference became insignificant after 12 months (level Ib).

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 [832]. 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 endoscopy scores at the follow up visit (level IV).

Conclusion: In CRS patients not previously operated, extended surgery does not yield better results than limited surgical procedures. Although not evidence based, the extent of surgery is frequently tailored to the extent of disease, which appears to be a reasonable approach. In primary paranasal surgery, surgical conservatism is recommended.

7-4-3-4 Revision surgery

Approximately 10% operated patients respond insufficiently to sinus surgery with concomitant medical therapy and eventually require a secondary surgical procedure [833]. Middle turbinate lateralisation, synechiae and scar formation in the middle meatus, an incompletely resected uncinate process, and retained ethmoid cells are frequent findings in patients undergoing revision surgery [834-836]. Previous revision surgery, extensive polyps, bronchial asthma, ASA-intolerance and cystic fibrosis are predictors for revision surgery [793, 801, 837-840]. Inflammatory involvement of underlying bone may also be of significance [159]. Technical issues of sinus revision surgery have recently be reported by Cohen and Kennedy [841]. A more extensive surgical procedure and also external approaches may be indicated [573, 832, 842]. Success rates of revision endoscopic sinus surgery has been reported to range between 50 and 70% [514, 838] (level IV). Complication rates of revision surgery are higher when compared with initial surgery and approximate 1%, but may be as high as 7% [833, 840].

7-4-3-4-1 CRS without polyps

In a case series of CRS patients without polyps, 15% were surgical revisions [805]. These patients had higher CT scores before their initial surgery and also before the revision surgery than patients undergoing primary surgery (level IV). McMains and Kountakis reported a series of 125 patients with a follow up of at least 2 years after revision endonasal sinus surgery [839]. Outcome parameters included the SNOT-20 and an endoscopy score. Of these patients, 66 suffered from CRS without nasal polyps. These patients experienced a significant improvement of their outcome parameters comparable with the results after primary surgery reported in other trials (level IV).

7-4-3-4-2 CRS with polyps

McMains and Kountakis also reported the results of 59 CRS patients with nasal polyps after revision surgery [839]. Consistent with the results of the National Comparative Audit [824] and the comparative study by Deal and co-workers [793], CRS patients with polyps had lower SNOT scores preoperatively (less severe symptoms), more previous surgeries, and a higher CT score preoperatively than CRS patients without polyps. However, the improvement of outcome parameters after revision surgery was significant and comparable with the improvement in CRS patients without polyps.

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 is 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 hypersclerotic bony margins in an extensively operated sinus system. As a rule, revision surgery is not indicated in these patients.

7-4-3-5 Instruments

In recent years, numerous instruments have been developed for sinus surgery. Cutting forceps may improve controlled mucosal resection and help to avoid mucosal tearing. Powered instruments may facilitate controlled resection, particularly of large nasal polyps. Continuous suction/irrigation of microdebriders improve visualisation of the surgical field. Moreover, lasers have been employed for mucosal excisions and bone ablation. Given the number of devices available, only a few comparative studies have been published. In these reports, CRS patients with and without polyps were not differentiated.

7-4-3-6 Cutting instruments

In a prospective double blind trial, 100 consecutive patients were followed after endoscopic sinus surgery [843]. Cutting forceps had been randomly used on one side and non-cutting forceps on the other side. Lateralised symptoms (headache, maxillary pressure, nasal obstruction and secretions) and endoscopic findings (secretion, pus, blood, crusts, oedema, polyps and

adhesions) were evaluated on both sides 1 year postoperatively. Both types of instruments gave satisfactory healing situations. No significant difference in the global symptom and endoscopic score between the 2 types of instruments was found (level Ib).

7-4-3-7 Powered instruments

Microdebriders were initially developed for arthroscopic surgery. They consist of a suction based powered instrument with a blunt end and guarded inner 90° oscillating or rotating blade, frequently supplemented with a device for irrigation. Cutting and removing only tissue suctioned into the instrument opening while blood and tissue debris are removed by suction/irrigation, they provide excellent control and precision of soft tissue resection [844].

In a retrospective case series study, a group of 250 patients undergoing surgery with a microdebrider was compared with a group of 225 patients undergoing endoscopic sinus surgery with conventional instruments [845]. The assignment of patients to each group was arbitrary and non-random, with the majority of the standard technique patients being treated earlier in the study. The use of the microdebrider demonstrated faster healing with less crusting than standard techniques, as well as decreased bleeding, synechia formation, lateralization of the middle turbinate, and ostial reocclusion (level IV).

In a prospective randomized trial, 24 CRS patients were treated with microdebriders on one side and with conventional instruments on the other side [846]. The authors were unable to demonstrate an advantage of mechanical debriders over conventional instrumentation (level Ib).

Hackman and Ferguson reviewed both, positive and negative tissue effects secondary to powered instrumentation [844]. The authors conclude that microdebriders will continue to advance the field of endoscopic surgery, providing clearer operative fields and causing less tissue trauma in experienced hands. However, their literature review also illustrates the potential severity of complications, when orbital and cerebral contents are rapidly aspirated by the powered instrument (no level applied).

7-4-3-8 Laser

In a randomized controlled trial, outcomes for holmium-YAG assisted sinus surgery were evaluated in 32 patients with CRS undergoing ESS [847]. Following a randomization plan, one side was operated with conventional instruments and the contralateral side with laser. The use of holmium-YAG laser in ESS resulted in significantly lower blood loss during surgery and less post-operative crust formation than conventional ESS, but long term subjective outcomes did not show significant differences between the methods (level Ib).

In a similar experimental setup, the application of KTP lasers in endoscopic sinus surgery was investigated in 24 patients [848]. Laser-assisted FESS was performed on one side and FESS with conventional instruments on the other side. Patient symptoms were recorded using a self-administered questionnaire preoperatively, and postoperatively on weeks 1, 4, 12 and 24. Of the parameters assessed in the course of healing, oedema prevailed on the laser-assisted side, while crusting was characteristic in the traditional operation site. Overall, KTP-laser-assisted FESS was as effective as endonasal sinus surgery with conventional instruments. Disadvantages of the laser-assisted procedure included the investment for the instrument and the additional time needed for laser surgery (level Ib).

Conclusion: Laser assisted endonasal surgery, powered instruments or sharp forceps offer some advantages over conventional instruments but may be associated with some particular risks. Currently, there is no evidence that they improve sinus surgery outcomes.

7-5 Influence of age concomitant diseases on sinus surgery outcome

7-5-1 Sinus surgery in the elderly

Previous survey data ranks rhinosinusitis the sixth most common chronic condition of elderly persons, occurring more frequently than cataracts, diabetes and general visual impairment [849]. In a case series study, 56 CRS patients between 61 and 80 years old were followed after functional endoscopic sinus surgery with nasal endoscopy and the SNOT-20 [849]. Outcomes were comparable to reports from younger patient populations, no severe complication occurred (level IV). In a retrospective case control study, functional endonasal sinus surgery outcome in 46 CRS patients > 65 years were compared with 522 CRS patients who were 18-64 years old [850]. In the elder patient group, complications occurred significantly more frequently than in the younger patients group. In particular orbital complication were frequently observed in the elder patient group (level III). Jiang and Su retrospectively compared complication rates of 171 CRS patients elder 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 [851].

Conclusion: CRS is a common condition in the elderly. Reported sinus surgery outcomes do not differ from a younger patient population. 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.

7-5-1-1 Asthma

Bronchial asthma is frequently associated with CRS with and without polyps and may have influence on sinus surgery outcomes. A trend for more severe sinus disease in CRS patients with concomitant asthma without aspirin intolerance has been reported by Kennedy [514]. Clinically, CRS patients with polyps and asthma have higher CT-scores, more severe nasal obstruc-

tion and hyposmia, and more severe asthma, while CRS patients without polyps and asthma experience more severe headache and postnasal discharge [852]. Investigations of concomitant asthma on sinus surgery outcomes in CRS patients with or without nasal polyps yielded inconsistent results [853]. Concomitant asthma was associated with worse postoperative endoscopy findings in two retrospective analyses [801, 803], 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 outcomes in 21 asthmatic compared with 77 non-asthmatic. No difference was found in other outcome parameters between the two groups [854] (level IV)

In 3 other studies on various predictors of treatment success of sinus surgery, asthma had no independent influence on outcome parameters [514, 802, 855].

7-5-1-1-1 CRS without polyps

Concomitant asthma is frequent in patients with sinusitis without polyps. In a retrospective evaluation, 13 of 73 CRS patients without polyps had also asthma. However, concomitant asthma did not influence sinus surgery outcomes in this study [805]. In a case series studies, Dunlop and coworkers followed the course of 50 CRS patients with bronchial asthma after sinus surgery [852]. In this group, 16 CRS patients without polyps had concomitant asthma. Their sinusitis symptoms improved significantly following sinus surgery (level IV).

7-5-1-1-2 CRS with polyps

In a prospective outcome analysis, 79 patients underwent endoscopic sinus surgery for CRS with polyps [853]. In a subgroup of 22 CRS patients with concomitant asthma, more recurrences and less symptom score improvement was observed (level IV). In the study by Dunlop and coworkers described above [852], 34 CRS patients with polyps and concomitant asthma revealed improved sinus symptoms 1 year after sinus surgery (level IV).

Conclusion: Currently there is no evidence that CRS patients with asthma benefit less from sinus surgery than patients without asthma concerning their CRS symptoms.

7-5-2 Effect of sinus surgery on bronchial asthma

The incidence of self reported rhinosinusitis in asthma patients was recently evaluated employing the data of two major asthma trials [856]. 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. The question, how sinus surgery and medical CRS treatment may alter the course of bronchial asthma, was reviewed by Lund [857] and Scadding [858]. 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. However, once again, authors did not differentiate between CRS with and without polyps.

In a follow up analysis of long term results of functional endonasal sinus surgery, 72 of 120 patients answered a questionnaire. A subgroup of 30 patients with CRS and asthma were analysed [859]. On average 6.5 years post surgery, asthma symptom improvement, less asthma attacks, less inhaler and less oral steroid use were reported by the majority of patients (level IV).

Park and co-authors retrospectively evaluated the data of a subgroup of 79 of 134 sinus surgery patients with asthma (860) with a questionnaire. Improved asthma was noted by 80% of the patients (level IV)

In a controlled study, 15 patients with CRS and asthma underwent endoscopic sinus surgery and 6 patients, who rejected surgery, were treated with nasal steroids only [861]. The authors compared peak expiatory flow (PEF) and oral steroid consumption 6 months before and after treatment. In the surgically treated patients, mean PEF improved 98±45 l/min (p<0.005) whereas no change was observed in the medically treated group. Oral steroid consumption was reduced in 7 surgically treated patients, remained unchanged in 2 and increased in 2 and was not nedded before and after surgery in 4 patients (level IV).

In a retrospective medical record analysis 13 patients with chronic bronchial asthma who underwent FESS and received comprehensive asthma care before and after FESS (mean, 19.3 and 33.1 months, respectively) were included. Outcomes comprised pre- and post-FESS individual and group mean asthma symptom scores, medication use scores, pulmonary function test results, and emergency department visits or hospital admissions for asthma [862]. Following FESS, there was no statistically significant change in group mean asthma symptom scores, asthma medication use scores, pulmonary function test results, and the number of emergency department visits or hospital admissions (level IV).

In a case series study, 50 CRS patients with concomitant asthma were included [852]. Twelve months after endoscopic sinus surgery, 40% noted asthma improvement, 54% stated that there was no difference and 6% thought their asthma control was worse. Inhalant steroids could be reduced by 20%, and were taken at the same dose as preoperatively by 64%. However, oral steroid consumption was reduced significantly (p<0.001) and hospital admissions for asthma were less frequent in the year after surgery than in the year before (p < 0.025, level IV).

Dhong and co-authors followed the clinical course of 19 patients with CRS and asthma who underwent ESS for rhinosinusitis [863]. They observed a significant improvement in diurnal and nocturnal asthma symptoms and asthma medication scores. Pulmonary function tests did not change (level IV).

Ragab and co-workers report a prospective evaluation of a subgroup of 43 asthma patients [864] joining a randomised trial com-

paring the effects of sinus surgery and medical treatment in CRS patients with and without polyps [865]. 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 post-operatively. Treatment of chronic rhinosinusitis, medical or surgical, benefits concomitant asthma; that associated with nasal polyposis benefits more from medical therapy (level Ib).

Although asthma may accompany chronic rhinosinusitis with and without polyps, several studies particularly addressed lower airway effects of sinus surgery in CRS patients with polyps. In a prospective outcome analysis, 79 patients underwent endoscopic sinus surgery for CRS [853]. Twenty-eight patients with asthma symptoms were assessed before and after surgery, using peak flow (liter/second) and medication scores Patients showed improvement in terms of their asthma symptoms, peak flow and medication score. (level IV).

Palmer and co-workers 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 [866]. 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 (preoperative 84 versus postoperative 63 days (p < 0.0001). Postoperatively, patients required an average of 1300 mg less oral prednisone (p < 0.033). Antibiotic use also decreased (p < 0.045), with an average use of antibiotic nine weeks preoperatively versus seven weeks postoperatively (level IV).

In a prospective trial, Lamblin and co-workers included 46 CRS patients with polyps and concomitant bronchial asthma (n=16) or non-symptomatic bronchial hyperresponsiveness (n=30). Outcome parameters measured at baseline (T0), after 1 year (T1) and after 4 years (T2) included nasal symptom scores, various spirometry values and a bronchial carbachol challenge [867]. All patients were treated first with nasal steroids for 6 weeks (beclomethasone 600 g/d). Eighteen patients were successfully treated with nasal steroids (nasal steroids responders) and medical CRS treatment was continued without sinus surgery. In 28 patients who did not improve with nasal steroids (nasal steroids non-responders), intranasal shenoethmoidectomy was performed in addition to continued nasal steroid treatment. At baseline, clinical characteristics of nasal steroid responders and non-responders -including the frequency of Samter's triad- did not reveal significant differ-

ences. Despite combined surgical and medical CRS-treatment, nasal steroid non-responders demonstrated a significant decrease of their spirometry values at T1 (p < 0.05) and at T2 (p < 0.0005), whereas no significant change was observed in nasal steroid responders. BHR did not significantly change over the 4-yr follow-up period in the two groups. No change in pulmonary symptoms and/or asthma severity occurred.

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.

7-5-2-1 ASA intolerance
Intolerance to acetylsalicylic acid derived compounds such as aspirin or other acid NSAIDs frequently manifests as Samter's triad characterized by bronchial asthma, aspirin sensitivity, and CRS with polyps. The majority of CRS patients with aspirin intolerance have diffuse, extensive rhinosinusitis [514]. In an early report, poorer outcome in 11 patients with ASA-intolerance out of 120 prospectively followed patients treated with sinus surgery was observed [514]. However, when stratified for extent of disease, ASA-intolerance did not adversely affect outcome (Level IV). In more recent trials, ASA-intolerance was rather consistently found to adversely affect sinus surgery outcomes.

In a case series study, 80 patients with ASA-intolerance and mostly extensive polyps were followed after sinus surgery [868]. Sinus symptoms and asthma severity improved in more than 80% of the patients. Before surgery, more than 30% were steroid dependent due to asthma severity and less than 10% after surgery. However, a significant incidence of revision surgery was observed in this patient group (level IV).

A higher number of repeat operations was also observed in a retrospective case control trial [869] including 18 patients with and 22 patients without ASA-intolerance (level IV).

In a retrospective chart review, 17 patients who underwent ESS with nasal polyps and steroid-dependent asthma with or without aspirin sensitivity and a minimum of 1 year postoperative follow-up were evaluated [870]. Nine patients were ASA sensitive, and eight patients were ASA tolerant. The postoperative Lund-Mackay scores (p < 0,001), the forced expiratory volume at 1 second (FEV1, p < 0,05), and systemic steroid consumption (p < 0,05) improved significantly in the 17 patients. Unlike ASA tolerant patients, the 9 ASA sensitive patients did not have a significant improvement in postoperative FEV1 and sinonasal symptoms (level IV).

In a multivariate analysis of various outcome predictors, 119 adult patients with CRS were prospectively followed-up for 1.4 +/- 0.35 years after sinus surgery. ASA intolerance was the only concomitant condition significantly worsening the outcome [519].

Conclusion: CRS patients with ASA-intolerance tend to suffer from more extensive sinus disease. They benefit from sinus surgery, but to a lesser extent than patients without ASA-intolerance. They are more prone to disease recurrence and more frequently undergo revision surgery than ASA-tolerant CRS patients.

7-5-2-2 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 [871]. Walker and co-authors matched a cohort of 19186 individuals without ENT disease registered in 1988 in the U.S: Navy Aviation Medical Data retrieval System with 678 persons with AR as the only ENT disease [872]. During the period from 1990 to 1995, physicals were identified of 465 AR cases and 12,628 controls. The incidence of chronic sinusitis in the AR group was 5/465 compared to 30/12628 in the control group (risk ratio = 4.5, 95% CI 1.7 to 11.6). Consistently, the reported incidence of atopy in CRS patients ranges between 50 and 80% which is higher than in the general population. CRS in atopic patients appears to be more severe [60, 873-878]. Atopy was equally frequently associated with CRS with and without polyps [879]. Conversely, in patients with positive skin prick tests to house dust mites, pathologic CT findings were significantly more frequent than in prick test negative controls [880].

In several trials not differentiating between CRS with and without polyps, atopy interfered with sinus surgery outcome. It was associated with less symptom improvement in one retrospective evaluation of several sinus surgery outcome predictors [801], but had no relevant influence on pre- or postoperative CT or endoscopy findings nor on QoL scores in an other evaluation [803].

However, antiallergic treatment appears to compensate for the possible shortcomings of sinus surgery in allergic patients. Nishioka and co-authors compared postoperative middle meatal antrostomy patency, middle meatal synechia formation and polyp recurrence in 211 non-allergic CRS patients and 72 CRS patients considered allergic based on clinical history, skin prick tests and serum specific IgE [879]. Of the 72 allergic patients, 66 received an allergen specific immunotherapy either before or after surgery. Allergic patients had a significantly higher incidence of recurrent sinusitis, which could be reduced by allergen specific immunotherapy. The authors conclude that allergic patients treated with surgery and concomitant immunotherapy do as well as non-allergic patients, whereas allergic patients treated with surgery alone do substantially worse (level IV).

Similarly, immunotherapy and medical allergy treatment before surgery improved the surgical success rate at a 1 year follow up in children with CRS from 64% to 84% (p = 0,022) [881]. The latter figure was identical to the success rate in children without allergy (level IV).

A consistent finding was reported earlier by Schlenter and Mann, who surgically treated 31 allergic and 34 non-allergic CRS patients [882]. Of the 31 allergic patients, 15 underwent concomitant allergen specific immunotherapy. Surgical outcome was comparable in non-allergic and allergic patients after concomitant immunotherapy, but significantly worse in allergic patients without immunotherapy, despite antiallergic medical treatment (level IV).

7-5-2-2-1 CRS without polyps

In a prospective study, 24 CRS patients without polyps allergic to perennial allergens and 82 patients with CRS without polyps without allergy underwent endoscopic endonasal ethmoidectomy after medical pre-treatment [883]. Comparing both groups, symptom scores did not differ significantly before and 6 to 18 months after surgery.

Consistently, in a case series of 77 CRS patients without polyps, concomitant allergy had no influence on surgical outcome [805].

In a double-blind placebo-controlled trial, 26 CRS-patients without polyps with positive skin prick tests to house dustmite and persistent symptoms after sinus surgery received 256 microg budesonide daily or placebo through an intubation device into one of the maxillary sinuses for 3 weeks before clinical assessment and a second biopsy [619]. The authors found an improvement in the symptom scores in 11 of the 13 patients who received budesonide and a decrease in CD3 positive cells (p = 0,02) and eosinophils (p = 0,002), and a decrease in the density of cells expressing interleukin 4 (p = 0,0001) and interleukin 5 messenger RNA (p = 0,006) after treatment.

7-5-2-2-2 CRS with polyps

In patients with extensive polyposis [807], allergy diagnosis predicted a worse outcome and increased recurrence rate (level IV)

Conclusion: Allergic rhinitis may predispose to and aggravate CRS. In several studies, positive skin prick tests and/or serum specific IgE to inhalant allergens were associated with poorer sinus surgery outcome, particularly in CRS with polyps. This shortcoming can be compensated for with antiallergic treatment. After confirmation of allergy by allergic history or appropriate clinical tests, allergen specific immunotherapy apparently improves sinus surgery results in atopic or allergic CRS patients.

7-5-2-3 Cystic fibrosis

This autosomal recessive genetic disease is characterized by epithelial secretory dysfunction and frequently associated with CRS. In cystic fibrosis, CRS with and without nasal polyps is observed [884]. Immunologically, CRS in cystic fibrosis (CF) patients differs from CRS in patients without CF [425, 884]. Persistent colonisation with Pseudomonas aeruginosa is a

common finding. Vitamin K deficiency related coagulopathies are also common [885]. Reports concentrating on CRS in CF patients have mainly concerned the paediatric population, which is in part due to reduced life expectancy.

Due to underlying medical issues such as acquired coagulopathies and advanced pulmonary disease, perioperative morbidity is assumed to be higher in this group [886]. In 41 patients with CF undergoing 52 sinus surgeries performed by a single surgeon over a 34-month period, complication occurred in 11.5%, including 2 cases of epistaxis, 1 case of periorbital ecchymosis, and 1 case of pulmonary hemorrhage. Delayed complications included 1 case of epistaxis and 1 case of intranasal scarring (level IV). No increased perioperative risk was found by others [887] (level IV).

The paranasal sinuses may act as a reservoir from where bacteria spread to the lower respiratory tract. After lung transplantation, sinus derived graft infection with Pseudomonas aeruginosa may induce a frequently lethal bronchiolitis obliterans syndrome. In 37 patients with cystic fibrosis after lung transplantation, sinus surgery was performed and repeated sinus aspirates and bronchoalveolar lavages were obtained for microbiological examniations. 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 [888]. A significant correlation of bacterial growth in sinus aspirates and bronchoalveolar 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 (Level IV).

Functional endoscopic sinus surgery with subsequent monthly antimicrobial antral lavages (n=32) were compared with a historic control group receiving conventional sinus surgery without postoperative lavages (n=19). CF-patients with CRS with and without nasal polyps were included. For repeated antral lavages, modified 19 gauge butterfly intravenous catheters were fixed in the maxillary sinus. Conventionally operated patients underwent one or more of the following procedures: polypectomy, ethmoidectomy, antrostomy, or Caldwell-Luc operation [889]. The group treated with functional sinus surgery 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%) (level IV).

<u>7-5-2-3-1 CRS with polyps</u>
Several reports explicitly describe CRS with polyps in CF patients. From a cohort of 650 patients undergoing endoscopic sinus surgery for CRS, 28 patients suffered from cystic fibrosis [800]. Overall subjective improvement rate in the cohort as a whole was 91% improved, whereas 54% of the cystic fibrosis patients derived significant benefit at six month follow-up. (Level IV).

In a retrospective report, 8 CRS patients with polyps out of 16 adults with cystic fibrosis underwent sinus surgery [890]. The

mean number of previous surgery in the surgically treated group was 2.7. The authors report improved pulmonary function, sinus symptoms, and exercise tolerance 3 months post surgery, however, polyps recurred in all patients within 18 months (Level IV).

Rowe-Jones and Mackay performed endoscopic sinus surgery on 46 cystic fibrosis patients with chronic, polypoid rhinosinusitis [891]. Their mean age at first surgery was 23 ± 7.5 years. Follow-up ranged from 1 month to 6 years (mean, 28.2 months). Overall, 50% of the patients suffered either recurrence of preoperative severity or had to undergo second endoscopic sinus procedure (level IV).

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.

7-5-2-4 Sinus surgery in the immune compromised patient
Immune deficiency states are frequently associated with CRS include HIV-infection, bone marrow transplantation and humoral immmondeficiencies.

<u>7-5-2-4-1 HIV</u>
Rhinosinusitis in the HIV-infected is an increasingly common problem. The gradual depression of humoral and cellular immunity, delayed mucociliary transport, nasopharyngeal lymphoid tissue hyperplasia and a tendency towards increased IgE levels may contribute to sinusitis development. Particularly at CD4-counts below 50 cells per mm3, Pseudomonas aeruginosa is a common pathogen [892]. Cytomegalovirus may cause sinusitis in HIV-infected patients and they have an increased risk to develop invasive fungal sinusitis. Thus CT scans, and sinus lavages with special stains, cytologies and cultures are required in refractory sinusitis or patients with low CD4 counts [893]. 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 [117]. At an average follow-up time of 16 months, 14 of the endoscopic sinus surgery patients reported improvement from their preoperative condition (level IV).

In a retrospective case series study, 106 HIV+ patients who underwent sinus surgery between 1987 and 1998 were evaluated [894]. 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 (level IV).

In two case series, Murphy and co-workers observed the clinical outcome of 30 HIV-positive CRS patients refractory to medical treatment [895]. 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 (level IV).

Patients with AIDS may develop acute invasive fungal sinusitis. If detected early, combined surgical and antifungal treatment may be beneficial [896, 897].

7-5-2-4-2 Bone marrow transplant

Bone marrow transplantation (BMT) is a frequent cause of acquired immune deficiency. Both, cellular and humoral immunity are impaired. Particularly allogeneic BMT requires intense immunosuppression to allow initial engraftment and to prevent graft versus host disease. Allogeneic BMT is associated with acute and chronic CRS in approximately 40% [898]. Sinus micobiology was investigated in 18 BMT patients who developed sinusitis evaluating 41 microbiolgcal specimens obtained by antral puncture and nasal swabs from the middle meatus [899]. 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. Micorbiological 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 1692 bone marrow transplants performed). All patients received medical management, such as amphotericin, rifampin, and colony-stimulating factors, in addition to surgical intervention [900]. 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 (level IV).

Sinus surgery was performed in 28 of 311 bone marrow transplant patients retrospectively evaluated [901]. No fungal sinusitis was observed. An aggressive surgical approach yielded a high mortality rate whereas limited surgical approaches with intensive postoperative care proved appropriate (level IV).

7-5-2-4-3 Non-acquired immunodeficiencies

Patients with humoral immunodeficiencies including common variable immunodeficiency, ataxia telangiextasia, or X-linked agammaglobulinaemia are at increased risk to develop CRS [902-

[905]. In patients with CRS refractory to medical and surgical treatment, non-acquired immune deficiencies may affect humoral, cellular, and frequently both immune response pathways. 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 [114]. 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 [906, 907]. However, in unselected patients with sinus fungus ball, CRS with and without polyps, humoral deficiencies were not more frequent than in the general population [908]. 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 [909-912]. One publication reporting on sinus surgery results in 11 patients with humoral deficiencies was identified [913], and resolution of sinus symptoms was observed in 5 of 9 evaluable patients under concomitant IV immunoglobulin therapy (level IV).

Conclusion: IN HIV-positive patients, three case series suggest beneficial effects of sinus surgery refractory to medical treatment. In patients sinusitis before or after bone marrow transplantation and in non-acquired immunodeficiency syndromes, current data to judge the role of sinus surgery are insufficient.

7-6 Complications of surgical treatment

7-6-1 Introduction

After the introduction of endoscopic sinus surgery, the indication for operations in this region expanded, the number of operators increased together with an increase in the numbers of operations, but also increasing the absolute number of iatrogenic complications. As a consequence, for a period of time in the United States, paranasal sinus surgery was the most frequent source of medicolegal claims [914].

7-6-2 Complications of sinus surgery

Factors responsible for complications are the variability of the anatomy of this region, the proximity of the brain and orbita and last but not least the ability of the operator to maintain orientation especially in revision surgery.

The typical complications are listed in Table 7-15.

7-6-3 Epidemiology of complications of sinus surgery using non-endoscopic techniques

The following table presents the number of complications in several studies using non-endoscopic sinus surgery.

Table 7-15. Complications following paranasal sinus surgery

location	minor complications	major complications
orbital	orbital emphysema ecchymosis of the eyelid	orbital hematoma loss of visual acuity/blindness diplopia enophthalmia nasolacrimal duct damage
intracranial	CSF leak - uncomplicated	CSF leak pneumcephalus (Tension) encephalocoele brain abcess meningitis intracranial (subarachnoid) bleeding direct brain trauma
bleeding	small amount of bleeding stopped with packing no need for blood transfusion	damage to anterior ethmoidal artery damage to sphenopalatine artery damage to internal carotid artery bleeding which requires transfusion
other	synechiae slight exacerbation of pre-existent asthma hyposmia local infection (osteitis) post-FESS MRSA infection atrophic rhinitis myospherulosis temporary irritation of infraorbital nerve hyperaesthesia of lip or teeth	toxic-shock syndrome anosmia severe exacerbation of pre-exsitent asthma or broncospasm death

7-6-4 Epidemiology of complications of sinus surgery using endoscopic techniques

The following Table 7-16 presents the number of complications in studies using endoscopic sinus surgery and which included a minimum of 100 patients. Meta-analysis of these data suggests major complications occur in about 0.5% and minor complications in about 4% of cases. In a recent prospective multicentre study of 3128 patients undergoing endoscopic sinus surgery, major complications occured in 0.4% of patients. Of note, the complication rate was linked to the extent of the disease in terms of symptom severity and health-related quality of life, the extent of nasal polyps, levels of opacity of the sinuses on CT scans and the presence of comorbidity, but not to surgical characteristics [521].

7-6-5 Comparison of various techniques

Comparison of non-endoscopic and endoscopic techniques

shows similar frequencies of complications. Differences in minor complication rates, with for example more synechiae being seen in endoscopic surgery, could be a result of the more precise follow-up using an endoscope, as compared to follow-up with anterior rhinoscopy. On the other hand ecchymosis was not always considered a complication in the pre-endoscopic period.

In a study by Kennedy et. al [944], a survey regarding complications of sinus surgery was mailed to 6969 otolaryngologists; 3933 responses (56.44%) were obtained, and 3043 of these physicians (77.37%) reported that they performed ethmoidectomy. Completed questionnaires were available for review from 42.21% of all Academy fellows (2942 physicians). The survey confirmed that there has been a marked rise in the frequency of ethmoidectomy and in the amount of training in ethmoidectomy since 1985. At the same time the frequency of microscopic, external or transantral ethmoidectomy seemed to decrease. In 86% a preoperative CT-scan was routinely done.

The study did not demonstrate a clear and consistent statistical relationship between the incidence of complications, the type of surgery performed, and the quality of training. Moreover, physicians who provided data from record review tended to report higher rates than those who estimated responses. The majority of physicians discussed specific potential complications with their patients before surgery and routinely performed preoperative computed tomography. The study demonstrated that physicians who experienced complications at higher rates were more likely to discuss these complications

Table 7-16. Epidemiology of complications following paranasal surgery, using non-endoscopic techniques

author, year	N	orbita	intracranial	bleeding	others	minor
Freedman and Kern, 1979 [915]	565	4	2	2	1	16
Taylor et al, 1982 [916]	284	1	3	-	-	8
Stevens and Blair, 1988 [917]	87	3	-	3	-	8
Eichel, 1982 [918]	123	1	2	1	-	no numbers
Sogg, 1989 [919]	146	-	-	-	-	4
Friedman and Katsantonis, 1990 [920]	1163	-	4	3	-	25
Lawson, 1991 [921]	600	2	3	-	2	5
Sogg and Eichel, 1991 [922]	3000	-	5	2	-	288

Table 7-17. Epidemiology of complications following paranasal surgery, using endoscopic techniques (adapted from (923))

author, year	N	orbital	intracranial*	bleeding	others	minor
Schaefer et al, 1989 [924]	100	-	-	-	-	14
Toffel et al, 1989 [925]	170	-	-	1	-	6
Rice, 1989 [926]	100	-	-	-	-	10
Stammberger and Posawetz, 1990 [927]	500	-	-	1	-	22
Salman, 1991 [928]	118	-	-	-	-	28
Wigand and Hoseman, 1991 [929]	500	-	10	-	-	no numbers
Lazar et al, 1992 [930]	210	-	-	-	3	16
Vleming et al, 1992 [931]	593	2	2	2	1	38
Weber and Draf, 1992 [932]	589	20	15	1	-	no numbers
Kennedy, 1992 [514]	120	-	-	-	-	1
May et al, 1993 [1105]	1165	-	4	3	-	94
Smith and Brindley, 1993 [933]	200	1	-	-	-	16
Dessi et al, 1994 [934]	386	3	2	-	-	no numbers
Cumberworth et al, 1994 [935]	551	1	2	-	-	no numbers
Lund and Mackay, 1994 [800]	650	1	1	-	-	no numbers
Ramadan and Allen, 1995 [936]	337	1	3	-	-	34
Danielson and Olafson, 1996 [937]	230	-	-	-	10	6
Castillo et al, 1996 [938]	553	2	2	8	-	36
Weber et al, 1997 [939]	325	4	3	30		no numbers
Rudert et al, 1997 [940]	1172	3	10	10	-	no numbers
Dursum et al, 1998 [941]	415	12	1	12	-	56
Keerl et al, 1999 [942]	1500	2	5	9	-	no numbers
Marks, 1999 [943]	393	1	3	5	-	22
Hopkins et al, 2006 (944)	3128	7	2	2	-	207
total amount	14005	60 (0,40%)	65 (0,50%)	84 (0,60%)	14 (0,01%)	506 (3,60%)

* includes CSF leaks

with patients before surgery (76% discussed CSF leak, 63% meningitis, 54% permanent diplopia, 66% intraorbital hematoma, 87% lost of vision, 46% intracranial lesions, 40% death in relation with the operation).

Between 1985 and 1990 the following complication rates were seen:

The complication rate in this study was significantly lower in the hands of experienced operators with 11 to 20 years experience.

Table 7-18. Complications comparison of non-endoscopic and endoscopic techniques

technique	major complications	no of deaths
endoscopic ethmoidectomy	0.41%	3
intranasal ethmoidectomy with headlamp	0.36%	23
external ethmoidectomy	0.52%	9
transantral ethmoidecthomy	0.18%	3

In Australia Kane [945] did an similar review, presenting an overall major complication rate of 0.03% (12 major orbital complications and 22 intracranial complications in 10000 FESS operations).

7-6-6 Risk factors for complications in sinus surgery

The risk of complications in sinus surgery depends on several factors:

α extent of the pathology (ie requiring infundibulotomy or complete pansinus operation);
α first or revision surgery (loss of landmarks, dehiscent lamina papyracea);
α right- or left sided pathology (right side most often affected);
α operation under local or systemic anaesthesia (feedback from patient!);
α amount of bleeding during the operation;
α expertise of the operator (learning curves).

With respect to the last point, a structured training program for beginners in sinus surgery is recommended, including cadaver dissection, hands-on training and supervision during the first operations.

Table 7-19. Predicitve factors of sinus surgery outcomes

	Outcome parameter	*RP*	*FP*	*An*	*A*	*S*	*PO*	*E*	*Al*	*As*	*NP*	*AI*	*PS*
Chambers 1997 [855]	questionnaire, endoscopy	182	12	u[1]	-	-		-	no	no	no		-
Gliklich [486]	SF-36, CSS, endoscopy	108	6	m[2]	no	no		no[3]	-	no	no		-
Kennedy [514]	verbal rating, endoscopy	120		u[4]	-	-		yes	no	no	-	no	no
Kim [946]	endoscopy score	98	12	m	no	no	-	no	no	yes	-	-	no
Marks [801]	improvement score	93	12	u	no	yes[5]	-	no	no	no	-	-	no
Marks [801]	endoscopy score	93	12	m	no	no	-	yes	no	no	-	-	no
Marks [801]	revision needed	93	12	m	yes	no	-	no	no	no	-	-	yes
Smith [803]	endoscopy score	119	12	m	-	no	yes[6]	0.09	no	no	no	yes[7]	no
Smith [803]	RSDI	119	12	m	-	no	yes[8]	no	no	no	no	yes[9]	no
Smith [803]	CSS	119	12	m	-		yes[10]	0.09	no	no	no	0.09	no
Wang [802]	CSS	230	6	m	-	-	yes	yes	-	-	-	-	yes
Wang [802]	endoscopy score	230	6	m			-	yes	-	-	-	-	-

RP: Recall/participants; FP: Minimum follow up; An: Analysis; A: Age; S: Sex; PO: Pre-operative score; E: Extent; Al: Allergy; As: Asthma; NP: Polyps; AI: Aspirin intolerance; PS: Previous surgery

1: univariate, 2: multivariate, 3: high preoperative CSS score was associated with worse outcome, 4: stratified for disease severity, 5: less symptomatic improvement in females (p=0.008), 6: worse scores associated with more improvement, 7: associated with less improvement, 8: worse scores associated with more improvement, 9: ssociated with less improvement, 10: worse scores associated with more improvement

7-6-7 Conclusion

Sinus surgery is well established and there are several techniques used to adequately treat the pathology. Nevertheless, the risk of minor or major complications exists and has to be balanced with the expected result of operative or conservative treatment. The learning curve of less-experienced operators has to be considered, as well as the complexity of the individual case.

A preoperative CT-scan is nowadays standard in the preoperative assessment and especially important in revision surgery where image guidance may have a role.
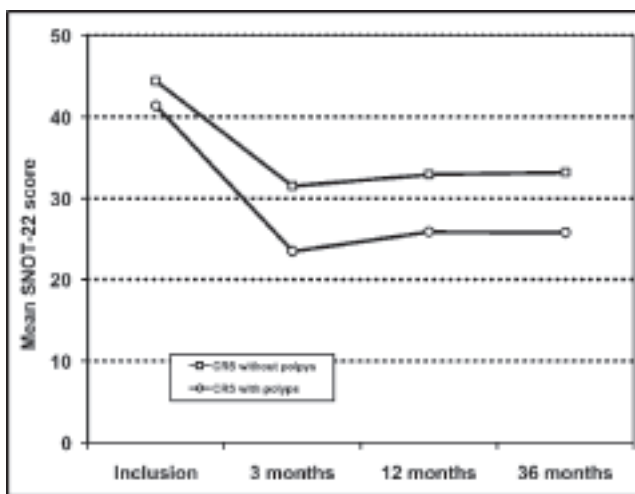

Figure 7-2. SNOT-22 scores in the National Comparative Audit in CRS patients with and without nasal polyps (adapted from (521).
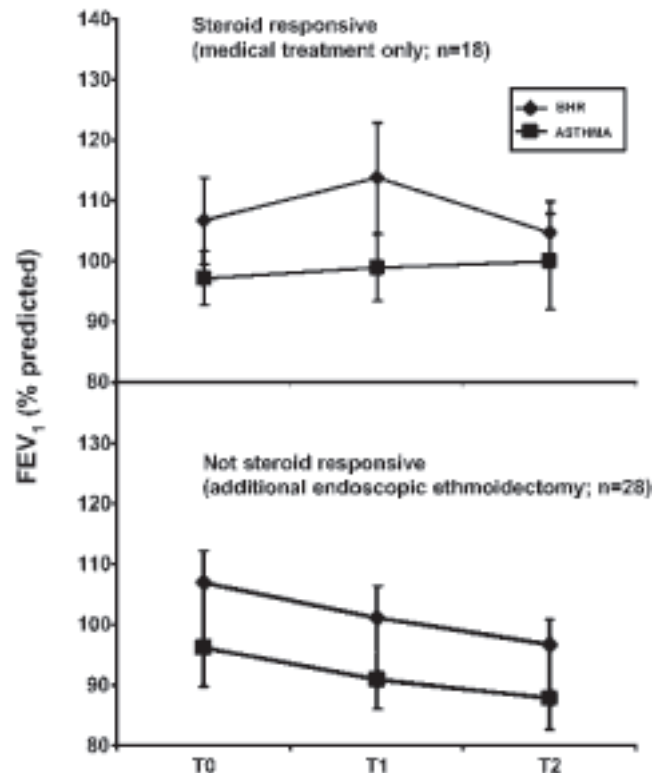

Figure 7-3. Forced expiratory volume in one second (FEV1) in percent of the predicted value (y-axis) in CRS-patients with polyps and concomitant asthma (n=16) and concomitant non-symptomatic bronchial hyperreactivity (BHR, n = 30) following CRS treatment. In 18 patients CRS was sufficiently controlled by medical treatment only (Steroid responsive) and 28 patients required additional endonasal surgery for sufficient CRS control (Not steroid responsive, adapted from (867).

8. Complications of rhinosinusitis and nasal polyps

8-1 Introduction

In the pre-antibiotic era, complications of rhinosinusitis represented extremely common and dangerous clinical events. Today, thanks to more reliable diagnostic methods (CT, MRI) and to 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 [947]. In patients affected by acute bacterial rhinosinusitis with intracranial spread despite antibiotic therapy, there still is a high incidence of morbidity and mortality rate, estimated at between 5% and 10% [948].

Complications of rhinosinusitis are classically defined as orbital, osseous and endocranial [948] though rarely some unusual complications can develop (Table 8-1) [949-953].

An extremely useful test, although not specific, is the white cell count which, if elevated in ARS unresponsive to treatment, is highly suggestive of a complication.

8-2 Epidemiology of complications

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 acute or chronic rhinosinusitis and the various complications is not clearly defined in the literature. This is probably related to the different number and methods of sampling patients in the various studies and no account is taken of local demographics. For these reasons, as Table 8-1 clearly shows, an attempt to make a comparison of the different epidemiological data available is difficult.

For example, whilst the percentage is similar in two studies that compared two different groups of selected patients affected with pansinusitis (72.4% and 75% respectively) [472,473], the percentage in another [955] is smaller (37%); this is probably due to the fact that in this sample, both acute and chronic disease were studied, whereas the other two authors focused their attention on acute cases.

In another mixed (acute and chronic) sample, Clayman highlighted the frequency of intracranial complications in patient with complicated rhinosinusitis as about 3.7 %, but no data concerning the global prevalence of complications were given. [959].

8-3 Orbital complications

8-3-1 Systemic

If there is a complication in rhinosinusitis, the eye is often involved [956, 1111] especaialy in ethmoiditis, whereas this is rare in sphenoidal infection [961]. The spread of infection directly via the thin and often dehiscent lamina papyracea [961]; or by veins [962] occurs with relative ease.

According to Chandler's classification orbital complications may progress in the following steps [963]:

periorbital cellulitis (preseptal edema),
orbital cellulitis,
subperiosteal abscess,
orbital abscess or phlegmon and
cavernous sinus thrombosis [947, 964].

Moreover orbital complications especially in children, often occur without pain [965, 1106]. Orbital involvement is manifested by

Table 8-1. Epidemiological data of complications in rhinosinusitis

author	country	age	pathology	pts	total % of complications	orbital	intracranial	osseous	soft tissue
Mortimore, 1999 [954]	South Africa	adults	acute pansinusitis	87	72.4% (63/87)				
Ogunleye, 2001 [955]	Nigeria	adults	acute/chronic pansinusitis	90	37% (33/90)	41%	5%	32%	18%
Eufinger, 2001 [956]	Germany	adults/ children	acute pansinusitis	36	75% (27/36)	58% (20+1/36)	11% (3+1/36)		8.4% (3/36)
Kuranov, 2001 [957]	Russia	adults	rhinosinusitis			0.8%	0.01%		
Gallagher, 1998 [958]	USA	adults	rhinosinusitis	176			8.5% (15/176)		
Clayman, 1991 [959]	USA	adults	acute/chronic rhinosinusitis	649			3.7% (24/649)		
Lerner, 1995 [960]	USA	children	rhinosinusitis	443			3% (14/443)		

swelling, exophthalmos, and impaired extra-ocular eye movements [966]. 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 [964].

8-3-2 Periorbital cellulitis
Periorbital cellulitis (inflammation of the eyelid and conjunctiva) [953] involves the tissue anterior to the orbital septum and is readily seen on CT scan as soft tissue swelling. It is the most common complication of rhinosinusitis in children [967] and it manifests itself as orbital pain, blepharal oedema and high fever [968]. Periorbital cellulitis usually responds to an oral antibiotic appropriate to common sinus organisms but if not aggressively treated, may spread beyond the orbital septum [967].

8-3-3 Orbital cellulitis
As the inflammatory changes spread beyond the orbital septum, proptosis develops together with some limitation of ocular motion, indicating orbital cellulitis. Further signs are conjunctival oedema (chemosis), a protruding eyeball (proptosis), ocular pain and tenderness, and decreased movement of the extraocular muscles [953, 969].

This complication requires aggressive treatment with intravenous antibiotics.

Any children with rhinosinusitis and proptosis, ophthalmoplegia, or decreased visual acuity should have a CT scan of the sinuses with orbital detail to distinguish between an orbital and periorbital (subperiosteal) abscess. Both conditions cause proptosis and limited ocular movement. Evidence of an abcess on the CT scan or progressive orbital findings after initial i.v. antibiotic therapy are indications for orbital exploration and drainage. Repeated ophthalmologic examination 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 if the ophthalmological symptoms and signs are resolving [967].

8-3-4 Subperiosteal or orbital abscess
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.

An orbital abcess generally results from diagnostic delay or to immunosuppression of the patient [968] with a frequency of 9% and 8.3% [351, 970] in paediatric studies.

A CT scan of the sinuses with orbital sequences to distinguish between orbital and periorbital (subperiosteal) abscess should be performed. 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. An ophthalmologist should check visual acuity from the early stages of the illness and i.v. therapy should cover aerobic and anaerobic pathogens. It can be converted to an oral preparation when the patient has been afebrile for 48 hours [967].

Blindness may result from central retinal artery occlusion, optic neuritis, corneal ulceration, or pan-ophthalmitis. In such a case 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 abscess, in which there is sometimes air due to anaerobic bacteria. Sepsis not infrequently can spread intracranially as well as anteriorly into the orbit [971].

8-4 Endocranial complications

These include epidural or subdural abscesses, brain abscess, meningitis (most commonly), cerebritis, and cavernous sinus thrombosis [967, 972, 973].

The clinical presentation of all these complication is non-specific, being characterized by high fever, frontal or retro-orbital migraine, generic signs of meningeal irritation and by various degrees of altered mental state [958] while intracranial abscesses are often heralded by signs of increased intracranial pressure, meningeal irritation, and focal neurologic deficits [966]. Although an intracranial abscess is relatively asymptomatic, subtle affective and behavioral changes often occur showing altered neurologic function, altered consciousness, gait instability, and severe, progressive headache [953, 967].

Endocranial complications are most often associated with ethmoidal or frontal rhinosinusitis. Infections can proceed from the paranasal cavities to the endocranial structures by two different routes: pathogens, starting from the frontal sinus most commonly or ethmoid sinus, can pass through the diploic veins to reach the brain; alternatively, they can reach the intracranial structures by eroding the sinus bones [958].

All endocranial complications start as cerebritis, 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.

A CT scan is essential for diagnosis as it allows an extremely accurate definition of bone involvement, whereas MRI is

Table 8-2. Endocranial complications in rhinosinusitis

author	number	complications	mortality/further defects
Gallagher, 1998 [958]	176 patients	meningitis represented 18% cerebral abscess 14% epidural abscess 23%	mortality 7% morbidity 13%
Albu, 2001 [974]	16 patients	6 meningitis 6 frontal lobe abscess 5 epidural abscess 4 subdural abscess 2 cavernous sinus thrombophlebitis	
Dunham, 1994 [967]		subdural empyema in 18%	mortality 40% surviving patients often have neurological disability
Eufinger, 2001 [956]		together meningitis, empyema and brain abscess constitute 12% of all the intracranial complications	
Oxford, LE 2005 [1106]	18 patients (mean age 12 y)	7 epidural abscess 6 subdural abscess 2 intracerebral abscess 2 meningitis 1 cavernous sinus thrombophlebitis	
Germiller, 2006 [1107]	25 patients (mean age 13 y)	13 epidural abscess 9 subdural abscess 6 meningitis 2 encephalitis 2 intracerebral abscess 2 cavernous sinus trhomboplebitis	mortality 4 %
Quraishi, 2006 [1108]	12 patients (mean age 14 y)	2 frontal lobe abscess 8 subdural abscess 1 subdural abscess 2 cavernous sinus thrombophlebitis	mortality 8% morbidity 16 %
Hakim, 2006 [1109]	8 patients (mean age 12 y)	1 cerebral abscess 1 cerebral infarct 3 frontal bone osteomyelitis 4 subdural abscess 4 subdural abscess	no mortality

essential when there are some degrees of soft tissues involvement such as in cavernous sinus thrombosis [958]. Moreover, if meningitis is suspected, a lumbar puncture could be useful [958] once an abscess has been excluded.

High dose long term i.v. antibiotic therapy followed by craniotomy and surgical drainage are usually required for successful treatment [351]. Pathogens most commonly involved in the pathogenesis of endocranial complications are *Streptococcus* and *Staphylococcus* species and anaerobes [973].

8-5 Cavernous sinus thrombosis

When the veins surrounding the paranasal sinuses are affected, further spread can lead to cavernous sinus thrombophebitis causing sepsis and multiple cranial nerve involvement [967]. Such a complication has been estimated at 9% of intracranial complications [958, 974] and is a fortunately rare and dramatic complication of ethmoidal or sphenoidal sinusitis. [968].

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. [964].

The cornerstone of diagnosis is high-resolution CT scan with orbit sequences [975] which show low enhancement compared to normal [976]. 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% [977]. The use of anticoagulants in these patients is still controversial [964] but is probably indicated if imaging shows no evidence of any intracerebral haemorrhagic changes [978].

8-6 Osseous 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 [964]. The most common osseous complications are osteomyelitis of the maxillary (typically in infancy) or frontal bones [976].

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 tumor) whereas from the posterior wall spread occurs directly or via thrombophlebitis of the valveless diploic veins leading to meningitis, peridural abscess or brain abscess [964].

In this context, Gallagher [958] reviewing the files of 125 patients with complicated rhinosinusitis, found that osteomyelitis developed in about 9% of cases. The sinus walls were affected in 32% of patients in Ogunleye's data [955]. Lang in 2001 recorded 10 cases of subdural empyema in adults and children secondary to frontal sinus infection: among them 4 had Pott's puffy tumor and 1 had periorbital abscess [948].

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, papilloedema, coma and focal neurological signs.

Ocular signs can appear controlaterally. 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 [964].

8-7 Unusual complications of rhinosinusitis

Table 8-3. Unusual complications of rhinosinusitis

complication	*author, year*
lacrimal gland abscess	Mirza, 2001 [949] Patel, 2003 [950]
nasal septal perforation	Sibbery, 1997 [979]
visual field loss	Gouws, 2003 [952]
mucocoele or mucopyocoele	Low, 1997 [972]
displacement of the globe	Low, 1997 [972]
septicaemia	Rimal, 2006 [1110]

9. Special considerations: Rhinosinusitis in children special

9-1 Introduction

Rhinosinusitis is a common problem in children that is often overlooked. It is a multifactorial disease in which the importance of several predisposing factors changes with age and is different from the adult form of the disease in many respects (Table 9-1). The management of rhinosinusitis in children is a controversial and rapidly evolving issue.

Table 9-1. Differences between paediatric and adult chronic rhinosinusitis

	young children	*adults*
Commensal microflora		
Coagulase negative staphylococci	30%	35%
Staphylococcus aureus	20%	8%
Haemophilus influenzae	40%	0%
Moraxella catarrhalis	24%	0%
Streptococcus pneumoniae	50%	26%
Corynebacterium species	52%	23%
Streptococcus viridans	30%	4%
Immunity	immature: defective response to polysaccharide antigens (IgG2, IgA)	mature, except in a subset
History	self-limited in time (improves after the age of 6-8 years)	no history of spontaneous improvement after certain age
Histology	mainly neutrophilic disease, less basement membrane thickening and mucus gland hyperplasia, more mast cells (Sobo, 2003)	mainly eosinophils
Endoscopy	polyps are rare, except in CF	polyps frequently present
CT-scan	younger child more diffuse sinusitis, involving all sinus	sphenoid and posterior sinus less often involved

9-2 Anatomy

In the newborn, the maxillary sinus extends to a depth of about 7 mm, is 3 mm wide and 7 mm high [980]. In the newborn, two to three ethmoid cells are found bilaterally, and by the age of four the ethmoid labyrinth has formed. The sphenoid sinuses are also present in the neonate. Each sphenoid sinus is 4 mm wide and 2 mm high. At birth the frontal sinuses are not present, but they gradually develop from the anterior ethmoid cells into the cranium. When the upper edge of the aircell (cupola) reaches the same level as the roof of the orbit, it can be termed a frontal sinus, a situation that appears around the age of five. When a child reaches the age of 7-8 years the floor of the maxillary sinus already occupies the same level as the nasal floor.

9-3 Epidemiology and pathophysiology

Since the introduction of CT-scanning, it has become clear that a runny nose in a child is not only due to limited rhinitis or adenoid hypertrophy, but that in the majority of the cases the sinuses are involved as well. Van der Veken [220] in a CT scan study showed that in children with a history of chronic purulent rhinorrhea and nasal obstruction, 64 % showed involvement of the sinuses. In a MRI study of a non-ENT paediatric population [981] it was shown that the overall prevalence of sinusitis signs in children is 45 %. This prevalence increases in the presence of a history of nasal obstruction to 50 %, to 80 % when bilateral mucosal swelling is present on rhinoscopy, to 81 % after a recent upper respiratory tract infection (URTI), and to 100 % in the presence of purulent secretions. Also Kristo et al [982] found a similar overall percentage (50 %) of abnormalities on MRI in 24 school children. They included, however, a follow-up after 6 to 7 months, and found that about half of the abnormal sinuses on MRI findings had resolved or improved without any intervention.

Epidemiologic studies on rhinosinusitis in children are limited but reveal the following information on the pathophysiology and clinically relevant factors influencing the prevalence of rhinosinusitis in children:

1. There is a clear-cut decrease in the prevalence of rhinosinusitis after 6 to 8 years of age. This is the natural history of the disease in children and is probably related to an immature immune system in the younger child [222, 223]

2. In temperate climates there is a definite increase in the occurrence of CRS in children during the autumn and in the wintertime, so that the season seems to be another important factor [222].

3. Younger children staying in day care centres show a dramatic increase in the prevalence of chronic or recurrent rhinosinusitis compared to children staying at home. See also section 1-1.

Although viruses are uncommonly recovered from sinus aspirates [983], most authors agree [984, 985] that viral infections are the trigger to rhinosinusitis. Although CT scan abnormalites can be seen up to several weeks after the onset of a URTI, one can assume that only 5 to 10 % of the URTIs in early childhood are

complicated by ARS [986]. The time course (i.e. clinical symptoms) of viral to bacterial rhinosinusitis is the same as in adults.

The most common bacterial species isolated from the maxillary sinuses of patients with ARS are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*, the latter being more common in children [45, 46].

Antral punctures are now rarely performed in children but it is interesting to know from studies in the past there is a good correlation of bacteriology between the maxillary sinus and the middle meatal specimen (83 %), and a poor correlation between those of the nasopharynx and the maxillary sinus (45 %) [987].

9-4 Symptoms and signs

Table 9-2. Presenting symptoms of rhinosinusitis in children. [223, 988, 989].

rhinorrhoea (71 to 80 %)	all forms
cough (50 to 80 %)	all forms
fever (50 to 60 %)	acute
pain (29 to 33 %)	acute
nasal obstruction (70 to 100 %)	chronic
mouth breathing (70 to 100 %)	chronic
ear complaints (recurrent purulent otitis media or OME in 40 to 68 %)	chronic

Wald stresses that 3 common clinical developments should alert a clinician to the possibility of rhinosinusitis [990]:
1. signs and symptoms of a cold that are persisting beyond 10 days (any nasal discharge, daytime cough worsening at night)
2. a cold that seems more severe then usual (high fever, copious purulent discharge, peri-orbital oedema and pain)
3. a cold that after several days of improvement worsen (with or without fever) .

The neutrophil content of nasal brushings if > or = 5% predicts maxillary sinusitis as judged from x-rays with a sensitivity of 91% and a predictive value of 84%, but only in non-allergic children [991].

9-5 Clinical examination

Physical examination of a child's nose is often difficult, and only limited rhinoscopy is tolerated. The examination may be simply accomplished by lifting the tip of the nose upwards (young children have wide noses with round nostrils, allowing easy examination of the condition of the inferior turbinates). Another convenient method is the use of an otoscope [992, 993]. Usually the nasal and pharyngeal mucosa appears erythematous with yellow to greenish purulent rhinorrhoea of varying viscosity. A post nasal drip was seen in 60%, pus in the middle

meatus in 50% in one study [989]. Turbinate swelling was present in 29% in another [988]. Lymphoid hyperplasia of the tonsils, adenoids and parapharyngeal wall may also be observed. The cervical lymph nodes may be moderately enlarged and slightly tender [992, 994].

Anterior rhinoscopy remains the first step but is inadequate by itself.
Endoscopy with a 2.7 mm rigid endoscope in the younger child (when possible a 4 mm in the older child) is more useful then flexible nasendoscopy, not only for the diagnosis but also for the exclusion of other conditions such as: presence of polyps, foreign bodies, tumours and septal deviations. In the younger child total anaesthesia is necessary to perform a thorough nasal endoscopy. Moreover it allows direct sampling of middle meatus flora.

9-6 Investigations

9-6-1 Microbiology
Microbiological assessment is usually not necessary in children with uncomplicated acute or chronic rhinosinusitis.
Indication for microbiology are: [995]
1. severe illness or toxic child;
2. acute illness in a child not improving with medical therapy within 48-72 hours;
3. an immuocompromised host;
4. the presence of suppurative (intra-orbital, intracranial) complications (orbital cellulitis excepted).
Quantification of bacterial growth can also help in distinguishing contamination from real infection, and isolates should be considered positive when a type of bacteria is present in a quantity of at least 10000 colonies/ml [990].

9-6-2 Imaging
Imaging is not necessary to confirm the diagnosis of rhinosinusitis in children. The increase in thickness of both the soft tissue and the bony vault of the palate in children under 10 years of age limits the usefulness of transillumination and ultrasonography in the younger age group [505].
Plain x-rays are insensitive with limited usefulness for diagnosis or to guide surgery and correlate very poorly with CT scans. The marginal benefits are insufficient to justify the exposure to radiation [220].
CT scanning remains the imaging methodology of choice, because of its ability to resolve both bone and soft tissue, with good visualisation of the ostiomeatal complex. The indications for CT scanning in a child are the same as those given previously for a microbiology specimen with one extra indication which is if surgery is being considered after failure of medical therapy. The high incidence of asymptomatic children with CT scan abnormalities [996] must be remembered plus the fact that such children do not require treatment [997].

A number of studies suggest that the growth of the maxillary sinus is not impaired by extensive or chronic disease, unlike the temporal bone and it seems that the presence of a hypoplastic maxillary sinus per se is not an indication for surgery [998]

9-6-3 Additional investigations

In the presence of recalcitrant rhinosinusitis, underlying conditions must be considered, preferably before undertaking any surgical procedure.

9-6-3-1 Allergy

The role of atopy in chronic rhinosinusitis is unclear. Many authors attribute a great deal of importance to allergy [101, 988, 993] although others [61, 220, 999] did not find an increased prevalence of rhinosinusitis in allergic children.

In a CT scan study Iwens et al. (1994) found signs of mucosal inflammation in 61 % of atopic children [61]. Ramadan (1999) showed that allergic patients had a higher CT scan score than non-allergic patients [875]. Allergic children have more URT problems and more time off school than their non-allergic peers [1000]. Therefore in children with CRS and with a suggestive history (asthma, eczema), and/or physical examination findings (allergic salute, watery rhinorrhea, nasal blockage, sneezing, boggy turbinate), allergic assessment (skin prick, RAST) should be performed.

9-6-3-2 Immune deficiency

All young children have a physiologic primary immune deficiency [993, 1001]. Defence against polysaccharide encapsulated bacteria via immunoglobulin G subclasses 2 and 4 may not reach adult levels until the age of 10 years [1002]. IgG subclass deficiency can lead to protracted or chronic rhinosinusitis [1003-1005]. According to Polmar [1004] recurrent and chronic rhinosinusitis is the most common clinical presentation of common variable immunodeficiencies. Although not all patients who lack secretory IgA antibodies have an increased number of more severe respiratory infections, the subject who has IgA deficiency and chronic rhinosinusitis is a difficult management problem, especially if an IgG subclass deficiency is also present. Replacement therapy cannot be provided [1005]. Patients with primary or acquired immune deficiencies (e.g. treatment for malignancies, organ transplants, maternally transmitted AIDS or blood-transmitted AIDS in haemophilics, drug induced conditions) are at risk for developing a difficult-to-treat rhinosinusitis with resistant or uncommon micro-organisms and fungi. Also the initial signs and symptoms may be non-specific, such as thin rhinorrhea, mild congestion, and chronic cough [993].

9-6-3-3 Cystic fibrosis

Cystic fibrosis is caused by a mutation of the gene FES1 encoding the cystic fibrosis transmembrane conductance regulator (CFTR). This gene contains 27 exons encompassing approximately 252 kb of DNA on chromosone 7q31.2. The most common mutation, deletion of phenylalanine at position 508 (F508) accounts for nearly 70 % of mutuations in European-derived Caucasian population [1006].

In children with cystic fibrosis, sinusitis is a common problem. Although the prevalence of nasal disease was previously estimated to be between 6 and 20% [1007], Yung et al [1008] found it to be over 50 % and Brihaye et al. [1009] reported that performing rigid endoscopy in 84 patients with cystic fibrosis, revealed inflammatory polyps in 45 % (mean age 15 years) and medial bulging of the lateral nasal wall in 12 % (mean age 5 years). In patients with cystic fibrosis and chronic rhinosinusitis, CT showed in 100 % [1009] opacification of the anterior complex (anterior ethmoid, maxillary and -if developed- frontal sinus) and 57 % showed clouding of the posterior complex (posterior ethmoid and sphenoid). In all children with a medial displacement of the lateral nasal wall, there was a soft tissue mass in the maxillary antrum (large quantity of secretions surrounded by polyposal mucosa, representing a mucopurulent rhinosinusitus). In 80 % of these children the displacement was so extreme that the lateral nasal wall touched the septum, resulting in total nasal blockage. In a study by Brihaye et al [1009] massive polyposis was never found before the age of 5 years. Mucopurulence in the maxillary sinus occurs at a younger age (3 months to 8 years) and the maxillary sinus seems to be the first sinus affected by the disease. Recent data suggest that CF heterozygotes are over-represented in the paediatric CRS population [1010].

9-6-3-4 Primary ciliary dyslcinesia

Primary ciliary dyskinesia (PCD) [1011], an autosomal recessive disorder involving dysfunction of cilia is present in 1 of 15000 of the population and should always be considered in any neonate with respiratory or ENT problems of unknown origin. At least half of the PCD patients have symptoms when first born and especially in a term baby with no risk factor for congenital infection showing signs of rhinitis at birth, PCD should be excluded. The same applies to an infant or older child with atypical asthma, unresponsive to treatment, chronic wet cough and sputum production, very severe gastro-oesophageal reflux, bronchiectasis, rhinosinusitis (rarely with polyposis), chronic and severe secretory otitis media, particularly with continuous, long lasting and diffuse discharge from the ears after grommet insertion. Roughly half the children with PCD have situs inversus and bronchiectasis in addition to rhinosinusitis (Kartagener's syndrome).

There are two ways to screen for PCD: saccharine test and nasal nitric oxide. The saccharine test is a cheap and easy procedure to screen older children and adults, but is relatively unreliable Nasal nitric oxide (nNO) measurements can be made in children over 5years old. Recent data suggests that PCD epithelia have a common defect – a lack of inducible nitric oxide synthase. In PCD values of nNO are usually less than 100; values exceeding 250ppb have a sensitivity of 95 % for excluding the diagnosis of PCD [1012]. Since very low nNO

values can occur with severe nasal congestion the procedure should be repeated after decongestion or a brief course of oral plus topical corticosteroids.

If the child is too young for the tests, if there is any doubt about the validity of the saccharine test, or the results are positive (transport time longer than 60 minutes, nNO less than 250ppb) or there exists a strong clinical suspicion, the ciliary beat frequency should be tested from a nasal epithelial biopsy.

If direct inspection of the ciliary beat frequency is abnormal (less than 11-16 Hz) an ultrastructure study of cilia is needed. The most common ciliary abnormalities in PCD are: dynein arm defects (absence or reduced number of inner, outer or both dynein arms), tubular defects (transposition and extra microtubules), radial spokes defects or absence, ciliary dysorientation (suspected if mean standard deviation of angle is larger than 20°), abnormal basal apparatus, ciliary aplasia, abnormally long cilia [1013]. Many of these abnormalities on TEM (transmission electron microscopy), however, can be transient or occur secondarily after infection. Secondary ciliary dyskinesia, the acquired form (infections, inflammatory or toxic) is mostly correlated with other anomalies, such as microtubular abnormalities and composed cilia. However, there exists a great overlap of ultrastructural abnormalities between the two [534]. Therefore the study of cilia after sequential monolayer-suspension culture technique excludes the acquired form [1014].

9-6-3-5 Gastro-oesophageal reflux

The parallel existence of upper airway inflammation with ensuing problems of intractable rhinosinusitis, otitis, and gastro-oesophageal reflux (GER) has been observed and suggests a causal relationship. Barbero found in a group of patients with upper airway disease and GER, that anti-reflux measures may permit a greater well-being and that GER maybe among the variables leading to refractory chronic upper airway disease [1015]. The otolaryngologist should be suspicious of GER in children complaining of chronic nasal discharge and obstruction combined with chronic cough, hoarseness and stridulous respiration. The endoscopic appearance of the laryngeal and tracheal areas are of considerable importance in conjunction with oesophageal examination, in determining the potential relationship between GER and otolaryngologic abnormalities. The diagnosis needs to be confirmed by oesophageal 24 hours pH monitoring: in 30 children with chronic sinus disease 63 % had oesophageal reflux and 32 % had nasopharyngeal reflux [772].

9-7 Management

9-7-1 Management of acute rhinosinusitis in children

Just as in adults acute rhinosinusitis in children usually only needs symptomatic treatment.

9-7-1-1 Antibiotics in ARS in children

A Cochrane meta-analysis [1016] of antibiotics for persistent nasal discharge concluded that antibiotics given for 10 days reduced the probability of persistence in the short to medium term. The benefits were modest and for 8 children treated one additional child would be cured (NNT 8, 95% CI 5 to 29). No long term benefits were documented. This meta-analysis is a combination of studies in rhinosinusitis in children with symptoms for as little as 10 days [1017] to more than 3 months [1018]. Two more recent RCT comparing antibiotics to placebo or another therapy do not alter the conclusions of the meta – analysis [1019, 1020]. According to the members of the consensus meeting in Brussels, 1996: Management of rhinosinusitis in children: [1021] antibiotics should be reserved largely for severe disease e.g.:

1. a severe illness or toxic condition in a child with suspected or proven suppurative complication. Intravenous administration of an appropriate agent is recommended. The antibiotic selected should be effective against the penicillin-resistant *Streptococcus pneumonia, beta-lactamase producing H. influenzae* and *Moraxella catarrhalis*
2. severe acute rhinosinusitis: in ambulatory patients for whom oral therapy is appropriate, an agent should be selected that is resistant to the action of beta-lactamase enzymes (amoxicillin-potassium clavunate or a second generation cephalosporin such as cefuroxime axetil)
3. non-severe acute rhinosinusitis: only in a child with protracted symptoms to whom antibiotics can be given on an individual basis (presence of asthma, chronic bronchitis, acute otitis media, etc.)

In those children for whom antibiotic therapy is preferred, amoxicillin (45 mg/kg/day, doubled if under 2 or with risk factors for resistance) is appropriate. If the patient's condition has not improved within 72 hours, a change of antibiotic to an agent effective against the resistant organism prevalent in the community should be considered.

Patients with a penicillin allergy should receive a suitable alternative antibiotic such as azithromycin or clarithromycin as first-line therapy.

9-7-1-2 Topical corticosteroids in ARS

Topical corticosteroids may be a useful ancillary treatment to antibiotics in childhood rhinosinusitis, effective in reducing the cough and nasal discharge earlier in the course of ARS [610, 1022]. There are a large number of studies showing that local corticosteroids are effective and safe in children with rhinitis [1023-1027].

9-7-1-3 Topical or oral decongestants

Most authors prefer topical α2 agonists (xylo- and oxymetazoline) in appropriate concentrations. Careful dosage is important when treating infants and young children, to prevent toxic manifestations.

A double blind, randomised controlled trial (RCT) by Michel [1028] (III, no power), compared isotonic EMS solution (balneotherapeutic water) with xylometazoline 0.05% solution in the treat-

ment of acute rhinosinusitis with middle ear involvement during 14 days in 66 children, aged 2-6 years, and revealed no difference in improvement in both groups, in terms of mucosal inflammation, nasal patency, middle ear function and general state of health, as outcome measures [1028]. A double blind, randomised controlled trial (RCT) by McCormick [707] showed no additive effect of adding decongestant-antihistamine (nasal oxymetazolone and oral syrup containing brompheniramine and phenylpropanolamine) to amoxicillin (III, no power).

9-7-1-4 Nasal douching

Saline nose drops or sprays are popular with paediatricians [993, 994, 1005]. As long as the saline is isotonic and at body temperature, it can help in eliminating nasal secretions and it can decrease nasal oedema.

9-7-2 Management of chronic rhinosinusitis in children

Chronic rhinosinusitis in the young child does not have to be treated, as spontaneous resolution is the norm [1029]. Van Buchem et al. followed 169 children with a runny nose for 6 months, treating them only with decongestants or saline nose drops. They did not find a single child who developed a clinically serious disease with general symptoms such as marked pain, pressure on sinuses, local swelling, or empyema, showing that complications of rhinosinusitis in a child are uncommon [223].

9-7-2-1 Treatment of chronic rhinosinusitis

The data on specific treatment of CRS in children very are limited. A quality of life tool for children SN-5 is now available [584].

9-7-2-2 Antibiotics

As described under 9-7-1-1 Antibiotic in ARS in children a Cochrane meta-analysis [1016] of antibiotics for persistent nasal discharge concluded that antibiotics given for 10 days reduced the probability of persistence in the short to medium term. The benefits were modest and for 8 children treated one additional child would be cured (NNT 8, 95% CI 5 to 29). No long term benefits were documented. The only study really treating CRS [1018] was negative.

9-7-2-3 Topical corticosteroids

There are no data describing the efficacy of topical corticosteroids in paediatric CRS. There are a large number of studies showing that local corticosteroids are effective and safe in children with rhinitis [1023-1027] and one may assume that the same is true for CRS (level IV).

9-7-2-4 Nasal douching

In one double-blind RCT twenty children aged 3 to 14 years with a history of bronchial asthma complicated by chronic sinusitis were studied in a double-blind study. Patients received, at random, over a period of 2 weeks, either 2 ml saline or 2 ml bromhexine (2 mg/ml) t.i.d. by means of a home nebulizer. Both types of nebulization were equally efficient in

reducing the symptom score (level III, no power) [717]. A second randomized study in thirty children with CRS aged 3 to 16 years compared the effect of 4 weeks of douching with hypertonic saline (HS) (3.5%) versus normal saline (NS) (0.9%). Both treatments were effective although the HS seemed to be a little more effective than the NS [751]. No data on side effects were given (level III).

9-7-2-5 GER therapy

In children with chronic rhinosinusitis and gastro-oesophageal reflux (GER) proven by 24 hours of pH monitoring Phipps et al. [772] found that most children showed improvement of sinus disease. Bothwell et al. [1030] suggested that in 89 % of the children (25 out of 28) surgery could be avoided. These studies indicate that GER should be evaluated and treated in children with chronic sinus disease before sinus surgical intervention (level III).

9-7-2-6 Effect on asthma

In a study of eighteen children with sinusitis and asthma, medical treatment of sinusitis with topical corticosteroids, antibiotics and 2 days of oral steroid improved asthma and increased the interferon-γ / IL4 ratio in nasal lavage [1031]. Tsao noted that nasal douching improved bronchial hyperreactivity in asthmatic children [1032] level III.

9-7-2-7 Surgical treatment of rhinosinusitis

In chronic rhinosinusitis surgery should follow thorough investigation of underlying factors and a prolonged trial of medical therapy.

The following procedures are ineffective and therefore not recommended: antral lavage [992, 1033], inferior meatal antrostomy [992, 1034], except possibly in PCD. The Caldwell – Luc operation is contra-indicated because it can damage unerupted teeth [993, 1005].

Most of the controversies seem to centre on the indications for functional endoscopic sinus surgery in children. (FESS or paediatric FESS=PESS). The "functional" in FESS stands for the restoration of the function of the ostiomeatal complex i.e. ventilation and drainage. In 1998 an international consensus was reached concerning the indications of FESS in children [1021]:

a. absolute indications:
  1. complete nasal obstruction in cystic fibrosis due to massive polyposis or due to medialization of the lateral nasal wall;
  2. orbital abscess;
  3. intracranial complications;
  4. antrochoanal polyp;
  5. mucocoeles or mucopyocoeles;
  6. fungal rhinosinusitis;
b. possible indications:
  in chronic rhinosinusitis with frequent exacerbations that persist despite optimal medical management and after exclusion of any systemic disease, endoscopic sinus surgery

is a reasonable alternative to continuous medical treatment. Optimal management includes a 2-6 weeks of adequate antibiotics (IV or oral) with treatment of concomitant disease.

Surgery for chronic rhinosinusitis with frequent exacerbation is mostly limited to a partial ethmoidectomy: removal of the uncinate process, with or without a maxillary antrostomy in the middle meatus, and opening of the bulla is often sufficient. In other cases such as in cystic fibrosis with massive polyposis, extensive ethmosphenoidectomy may be necessary.

Most results are judged on symptomatic relief and do not include endoscopic examination or CT scan.

A meta-analysis performed by Hebert et al. [1035] showed in 8 published articles (832 patients) positive outcome rates going from 88 to 92 %. The average combined follow-up was 3.7 years. They concluded that FESS is a safe and effective treatment for chronic rhinosinusitis that is refractory to medical treatment. Further, similar results have been published [1036-1038]. Lieu and Piccirrillo [1039] retrospectively analysed the results of ESS in 133 children unresponsive to medical therapy using a 4 stage classification and suggested that operation was particularly effective for those in the intermediate stages.

Chan (1999) reported on 14 children with post FESS refractory rhinosinusitis and noted that 10 of them who were operated when under 4.8 years needed a disproportionately higher rate of further surgical intervention compared to the remaining clinical population. Ostiomeatal scarring was the most difficult complication [1040]. They recommended judicious use of FESS in the very young. ESS is unlikely to be successful in under three year olds [1041] and its efficacy is reduced if the child is exposed to tobacco smoke. [1042]. Disease duration prior to surgery does not affect outcome [1043]. Intravenous dexamethasone per-operatively reduced swelling and scarring and was particularly useful in children with asthma, lower CT grades, no tobacco smoke exposure and in those over 6 years [1044].

Similar results were published by Jiang et al. [1036] and Fakhri et al. [1037] showing a postoperative improvement in 84 % of the FESS patients (n=121). For this indication Bothwell et al. [1038] found no statistically significant difference in the outcome of facial growth between a retrospective age-matched cohort outcome study between 46 children who underwent FESS surgery and 21 children who did not, using qualitative antropomorphic analysis of 12 standard facial measurements after a 13.2 years follow-up.

Duplechain [1045] reported for the first time the results of this kind of surgery in cystic fibrosis children followed by many other authors [891, 1008, 1046, 1047]. Co-ordinated care by paediatricians, pulmonologists anaesthetists, surgeons and physiotherapists is

required, complication rates are around 11% in a recent study [886]. The results are less good than in non-CF children with around 50% of children reporting improvement at 2 years. However, sinus surgery post-lung transplantation is associated with a lower incidence of tracheobronchitis and pneumonia [888].

The effectiveness of adenoidectomy in the management of paediatric rhinosinusitis is still a controversial issue. It is difficult to differentiate between the symptoms typical for chronic rhinosinusitis and those of adenoid hypertrophy. Hibert [1048] showed that nasal obstruction, snoring and speech defects occur more frequently in children with adenoid hypertrophy while symptoms of rhinorrhoea, cough, headache, signs of mouth breathing, and abnormalities on anterior rhinoscopy occur as frequently in children with chronic rhinosinusitis as in children with adenoid hypertrophy.

Antibiotic-resistant bacteria were found on adenoid tissue culture in 56% of children undergoing adenoidectomy for hypertrophy plus OME and CRS compared to 22% undergoing adenoidectomy for hypertrophy without those complications [1049]. Wang et al. e.g. found no significant correlation between the size of the adenoid and the presence of purulent secretions in the middle meatus on fibreoptic examination in 420 children between the age of 1 and 7 years, while there was a very significant correlation between the size of the adenoid and the complaints of mouth breathing ($p < 0.001$) and snoring ($p < 0.001$) [1050]. The size of the adenoid and associated diseases seem to be factors for consideration.

Adenoidectomy was included in the stepwise protocol for the treatment of paediatric rhinosinusitis proposed by Don et al. [1051]. Recently, Ungkanont et al. proved adenoidectomy to be effective in the management of paediatric rhinosinusitis. They suggest performing an adenoidectomy as a surgical option before endoscopic sinus surgery (ESS), especially in younger children with obstructive symptoms [1052].

Ramadan (1999) has undertaken a prospective non- randomized study comparing ESS to adenoidectomy in the treatment of rhinosinusitis in 66 children with improvement in 77% of 31 children in the ESS group compared to 47% of 30 in the adenoidectomy group, (OR 3.9, $p = 0.01$) [1053]. Multivariate analysis demonstrated that ESS was significantly better after age, sex, allergy, asthma, day care and CT stage were adjusted for (OR 5.2, $p = 0.03$). Asthma was an independent predictor of success (OR 4.3, $p = 0.03$).

10. Chronic rhinosinusitis with or without nasal polyps in relation to the lower airways

10-1 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 lower airways [1054] 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 defense 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 [1055] 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 naso-bronchial 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 [1056]. Recently, the systemic nature of the interaction between nose and bronchi has been proposed. Indeed, many inflammatory diseases of the upper airways show a systemic immunologic component involving the blood stream and bone marrow [1057]. In addition, genetic factors may also play a role in the manifestation of nasal and/or bronchial disease [1058]. 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 [1059].

10-2 Asthma and Chronic Rhinosinusitis without NP

Bronchial asthma is considered a comorbid condition of CRS. In some centres, around 50% of patients with CRS have clinical asthma [1060, 1061] Interestingly, most patients with CRS who do not report having asthma show bronchial hyperreactivity when given a metacholine challenge test [1061]. Others report that 60 % of patients with CRS have lower airway involvement, assessed by history, pulmonary function and histamine provocation tests [865]. Alternatively, sinonasal symptoms are frequently reported in asthmatic patients, ranging up to 80 % in some studies. Radiologic imaging of the sinuses has demonstrated mucosal thickening of the sinus mucosa in up to 84 % of patients with severe asthma [1062]. However, these epidemiologic and radiologic data should be interpreted with caution as they may reflect a large referral bias.

CRS is currently thought to have a multifactorial etiology, in which host factors like anatomical, local defense and immunologic factors, act in synergy with microbial and environmental factors in the development and chronicity of the disorder. Histopathologic features of CRS and asthma largely overlap. Heterogeneous eosinophilic inflammation and features of airway remodeling like epithelial shedding and basement membrane thickening are found in the mucosa of CRS and asthma patients [1061]. Cytokine patterns in sinus tissue of CRS highly resemble those of bronchial tissue in asthma [30], 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 [266]. Beside the similarities in pathophysiology, sinusitis has been aetiologically 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 [422]. Here, mucosal contact with enterotoxin B induced the systemic release of the typical T helper 2 cytokines IL-4, IL-5 and IL-13, leading to aggravation of experimental asthma. However, the interaction between both rhinosinusitis and asthma in not always clinically present, as Ragab et al. [266] found no correlation between rhinosinusitis and asthma severity. However, patients with asthma showed more CT scan abnormalities than non-asthmatic patients [1063], and CT scan abnormalities in severe asthmatic patients correlated with sputum eosinophilia and pulmonary function [1062].

Endoscopic sinus surgery (ESS) for CRS aims at alleviating sinonasal symptoms but also improves bronchial symptoms and reduces medication use for bronchial asthma [861, 863, 1064, 1065]. 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 [1060]. 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 [1066]. Lung function in asthma patients with CRS was reported to benefit from ESS by some authors [853, 861], but denied by others [863, 1064, 1066]. Of note, not all studies show beneficial effects of ESS on asthma [862]. 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 [853, 1065]. Poor outcomes after ESS have also been reported in patients with aspirin-intolerant asthma [869, 1067, 1068]. On the other hand, other authors report that asthma does not represent a predictor of poor symptomatic outcome after primary [855, 1069] or revision ESS [1063]. In a series of 120 patients undergoing ESS, Kennedy [514] 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.

Until recently, no well-conducted clinical trials have been performed showing beneficial effects of medical therapy for CRS on bronchial asthma. Ragab et al. [864] 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.

10-3 Asthma and Chronic Rhinosinusitis with NP

Seven percent of asthma patients have nasal polyps [174] and in non-atopic asthma and late onset asthma, polyps are diagnosed more frequently (10-15%). Aspirin-induced asthma is a distinct clinical syndrome characterized by the triad aspirin sensitivity, asthma and nasal polyposis and has an estimated prevalence of 1% in the general population and 10% among asthmatics [556].

Increased nasal colonization by *Staphylococcus aureus* and presence of specific IgE directed against *Staphylococcus aureus* enterotoxins was found in NP patients [415]. 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 superantigenic activity, enterotoxins may activate inflammatory cells in an antigen-non-specific way. Indeed, nasal application of *Staphylococcus aureus* enterotoxin B is capable of aggravating experimental allergic asthma [422]. Besides bacterial enterotoxins, Ponikau et al. report on the potentially important role of fungi, especially *Alternaria*, in the generation of chronic sinus disease with NP [1070]. By their capacity to induce eosinophil degranulation [1071], *Alternaria* may contribute to the inflammatory spectrum of CRS with/without NP and asthma.

No well-conducted trials on the effects of medical therapy for NP on asthma have been conducted so far. Therefore, well-designed trials on nasal corticosteroids, oral antibiotics, vaccination therapy or anti-leukotriene treatment in patients with NP and asthma are warranted. 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 [1068]. In a small series of patients with NP, endoscopic sinus surgery did not affect the asthma state [589]. However, nasal breathing and quality of life improved in most patients.

10-4 COPD and rhinosinusitis

Up to 88 % of patients with COPD presenting at an academic unit of respiratory disease may experience nasal symptoms, most commonly rhinorrhoea [1072]. Nasal symptoms in COPD patients correspond well with an overall impairment of the quality of life [1072]. So far, no further information is available on the nasobronchial interaction in COPD patients.

11. Socio-economic cost of chronic rhinosinusitis and nasal polyps

11-1 Direct Costs

Chronic rhinosinusitis, can be debilitating for patients and imposes a major economic cost on society in terms of both direct costs as well as decreased productivity. To better evaluate the socioeconomic impact of chronic rhinosinusitis, the current English literature has been reviewed. Data from outside the USA are very limited. In a 1999 publication, Ray et al [3] estimated the total direct (medical and surgical) costs of sinusitis to be a staggering $5.78 billion in the US. This figure was extrapolated from governmental surveys such as the national health care survey and medical expenditure data. The cost of physician visits resulting in a primary diagnosis of sinusitis was $3.39 billion, which does not reflect the complete cost of radiographic studies, medication, or productivity losses.

Acknowledging that other airway disorders are closely tied to rhinosinusitis, Ray et al [3] used the Delphi method to quantify how often rhinosinusitis is a secondary diagnosis contributing to the primary diagnosis assigned by physicians. An expert panel examined the co-incidence of rhinosinusitis in diseases such as asthma, otitis media, and allergic rhinitis, and determined that 10-15% of the cost of these other diseases was attributable to rhinosinusitis, increasing the economic burden of rhinosinusitis to the often quoted $5.78 billion sum. Ray's paper relied on data collected by the National Centre for Health Statistics and did not attempt to distinguish ARS from the chronic form of this disease. Addressing the cost analysis in the diagnosis of chronic rhinosinusitis, Stankiewicz and Chow concluded that, at the present moment, subjective diagnostic paradigm for chronic rhinosinusitis is most cost-effective, although less accurate [1073]. Franzese and Stringer made an economic analysis comparing a normal CT scan to limited coronal CT scan [1074]. In this study limited CT scan was found to be less cost-effective than the full CT scan, costing $217,13 more per correct diagnosis

In 2002, Murphy et al [1075] examined a single health maintenance organization to evaluate the cost of CRS. The authors compared the costs of healthcare for members with a diagnosis of CRS to the cost of those without the diagnosis during 1994 and were able to determine the direct medical costs of the disease based on reimbursements paid rather than charges submitted. According to Murphy's study, patients with a diagnosis of CRS made 43% more outpatient and 25% more urgent care visits than the general population (p = 0.001). CRS patients filed 43% more prescriptions, yet had fewer hospital stays than the general HMO adult population. In total, the cost of treating patients with CRS was $2609 per year, 6% more than the average adult in the HMO. Because patients received all healthcare services in one integrated system, this figure includes the costs

of radiography, hospitalization, and medication. CRS care specifically cost $206 per patient per year, thus contributing to a calculated nationwide direct cost of $4.3 billion annually based on the 1994 statistic of 20.9 million individuals seeking care for CRS. Using the more recent value of 32 million affected, [80] the overall cost would increase to $6.39 billion annually.

Addressing the cost of pharmacologic management of CRS, Gliklich and Metson's [1076] 1998 study reported an annual expenditure of $1220. This figure is the sum of OTC medications ($198), nasal sprays ($250), and antibiotics ($772). In an ARS pharmacoeconomic review article on antibacterial use, Wasserfallen et al suggest that, of the different treatment strategies, symptomatic treatment (patients being treated with antibacterials only if they fail to improve after 7 days) was the most cost-effective approach, compared with treating patients on the basis of specific clinical criteria, empirical treatment with antibiotics, or radiology-guided treatment [1077].

Only one study in Europe has been found which considers the costs of CRS. This study was done in patients with severe chronic rhinosinusitis visiting a university hospital in the Netherlands [1078]. The direct cost of the CRS of these severe patients was $ 1861/year.
No data are available distinguishing costs of nasal polyps from CRS.

In conclusion we can deduce from these limited data that the average direct costs of CRS per patient per year is between $ 200,- and $ 2000,- depending on the severity of the disease.

11-2 Indirect Costs

The studies of direct medical costs demonstrate the social economic burden of the disorder. However, the total costs of CRS are greater. With 85% of patients with CRS of working age (between 18-65 years old) indirect costs such as missed workdays and decreased productivity at work significantly add to the economic burden of disease [80].

Goetzel et al [2] 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 (375000), total healthcare payments per

employee per year for rhinosinusitis (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.

In his 2003 study, Bhattacharyya [722] used patient-completed surveys to determine the direct and indirect costs of CRS. Patients completed a survey assessing symptoms of disease, detailing medication use, and quantifying missed worked days attributable to CRS. According to Bhattacharyya, the cost of treating CRS per patient totalled $1539 per year. Forty percent of these costs were 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). Bhattacharyya's study attempts to analyze both the direct and indirect costs of CRS and the final figures are enormous. Assuming a cost of $1500 per patient per year, and assuming CRS affects 32 million americans, the overall cost of the disease would be $47 billion if the severity of disease was similar to that assessed in the study for all patients with the disorder. However, this would appear to be an unlikely assumption.

It should be noted that in this last study, the patient population evaluated were generated through visits to an otorhinolaryngologist. Therefore, this patient population had already failed initial therapy by primary care givers and possibly by other otolaryngologists. The therapeutic interventions by the specialist are therefore likely to be biased toward more aggressive and thus more expensive therapy.

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 [588]. 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 rhinosinusitis was 12.5 million and restricted activity days was 58.7 million days [3]. Economic loss due to presenteeism cannot be easily quantified, but surely increases the cost burden of the disease.

12. Outcomes measurements in research

Trial design has largely focussed on medical therapy. The FDA recommends three components [1079]

1. the objective of the study must be clearly stated, coupled with a summary of the methods used for analysis of the results
2. the design must permit quantitative assessment of drug (ie therapeutic) effectiveness by a valid comparison with a control group
3. the study protocol should accurately define the design and duration of the study, sample size issues and whether treatments are parallel or sequential.

A single primary outcome measure is preferred to minimise the possibility of a Type I error (incorrectly assuming that a drug is effective). However, the FDA recognises that 2 may be appropriate.

Trials may be conducted in acute and chronic rhinosinusitis with or without polyps and may consider single, short-term or longer term interventions. Studies may be conducted in primary or secondary care and the criteria for diagnosis, inclusion and exclusion together with outcome measures will depend upon the setting.

Table 12-1 Criteria for studies conducted in primary and secondary care

criteria	*primary care*	*secondary care*
symptom profile & severity using VAS	+	+
endoscopy (scoring eg 0-3)	-	+
imaging plain x-ray CT (scoring eg Lund-Mackay 0-24)	+ -	- +
medication use	+	+
co-morbidity (eg allergy, asthma, aspirin sensitivity)	+	+
smoking history	+	+
additional tests (eg micro-biology, smell, mediators, cytology, mucociliary function, haematology, airway	±	±

Table 12-2. Data for all studies to include:

Title
rationale for study
objectives
design
study population: inclusion & exclusion criteria
outcomes:
primary & secondary
subjective & objective
safety assessments
statistical methodology/power analysis
ethics approval
drop-out analysis

13. Evidence based schemes for diagnostic and treatment

13-1 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. 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.

Table 13-1. Treatment evidence and recommendations for adults with acute rhinosinusitis

therapy	level	grade of recommen-dation	relevance
oral antibiotic	Ia	A	yes: after 5 days, or in severe cases
topical corticosteroid	Ib	A	yes
topical steroid and oral antibiotic combined	Ib	A	yes
oral corticosteroid	Ib	A	yes reduces pain in severe disease
oral antihistamine	Ib	B	yes, only in allergic patients
nasal douche	Ib (-)#	D	no
decongestant	Ib (-)#	D	yes, as symtomatic relief
mucolytics	none	no	no
phytotherapy	Ib	D	no

Table 13-2. Treatment evidence and recommendations for children with acute rhinosinusitis

therapy	level	grade of recom-mendation	relevance
oral antibiotic	Ia	A	yes: after 5 days, or in severe cases
topical corticosteroid	IV	D	yes
topical steroid on top of oral antibiotic	Ib	A	yes
topical decongestant	III (-)	C	no
saline douching	IV	D	yes

\# : Ib (-) study with a negative outcome

Table 13-3 Treatment evidence and recommendations for adults with chronic rhinosinusitis without nasal polyps *

therapy	level	grade of recommendation	relevance
oral antibiotic therapy short term < 2 weeks	Ib (-)	C	no
oral antibiotic therapy long term > 12 weeks	Ib	A	yes
Antibiotics – topical	III	D	no
steroid – topical	Ib (-)	A	yes
steroid – oral	no data	D	no
nasal saline douche	Ib (-)	A	yes
decongestant oral / topical	no data	D	no
mucolytics	III	C	no
antimycotics – systemic	Ib (-)#	D	no
antimycotics – topical	Ib (-)#	D	no
oral antihistamine in allergic patients	no data	D	no
proton pump inhibitors	no data	D	no
bacterial lysates	Ib (-)	A	no
immunomodulators	Ib (-)#	D	no
phytotherapy	Ib (-)#	D	no
anti-leukotrienes	III	C	no

* Some of these studies also included patients with CRS with nasal polyps
* Acute exacerbations of CRS should be treated like acute rhinosinusitis
\# : Ib (-) study with a negative outcome

Table 13-4 Treatment evidence and recommendations postoperative care in adults with chronic rhinosinusitis without NP*

therapy	level	grade of recommendation	relevance
oral antibiotic short term < 2 weeks	no data	D	yes, immediately postoperative, if pus was seen during operation
oral antibiotic long term ~ 12 weeks	no data	D	yes
topical antibiotics	no data	D	no
topical steroid	Ib (one +, one -)	B	yes
oral steroid	no data	D	short term yes long term no
nasal douche	no data available	D	yes

* Some of these studies also included patients with CRS with nasal polyps

Table 13-7 Treatment evidence and recommendations for children with chronic rhinosinusitis

Therapy	level	grade of recommendation	relevance
oral antibiotic	Ia	A	yes, small effect
topical corticosteroid	IV	D	yes
saline douching	III	C	yes
Therapy for gastro-oesophageal reflux	III	C	yes

Table 13-5. Treatment evidence and recommendations for adults with chronic rhinosinusitis with nasal polyps *

therapy	level	grade of recommendation	relevance
oral antibiotics short term < 2 weeks	no data	D	no
oral antibiotic long term > 12 weeks	Ib	A	yes, for late relapse
topical antibiotics	no data	D	no
topical steroids	Ib	A	yes
oral steroids	Ib	A	yes
nasal douche	Ib no data in single use	A	yes for symptomatic relief
decongestant topical / oral	no data in single use	D	no
mucolytics	no data	D	no
antimycotics – systemic	Ib (-)#	D	no
antimycotics – topical	Ib (-)#	A	no
oral antihistamine in allergic patients	Ib (1)#	A	no, in allergy
capsaicin	II	B	no
proton pump inhibitors	II	C	no
immunomodulators	no data	D	no
phytotherapy	no data	D	no
anti leukotrienes	III	C	no

* Some of these studies also included patients with CRS without nasal polyps
# : Ib (-) study with a negative outcome

Table 13-6. Treatment evidence and recommendations postoperative treatment in adults with chronic rhinosinusitis with nasal polyps*

Therapy	Level	Grade of recommendation	Relevance
oral antibiotics short term < 2 weeks	no data	D	immediately post-operative, if pus was seen during operation
oral antibiotics long term > 12 weeks	Ib	A	yes
topical steroids after FESS	Ib (2 studies one + one -)	B	yes
topical steroids after polypectomy	Ib	A	yes
oral steroids	no data	D	yes
nasal douche	no data	D	yes

* Some of these studies also included patients with CRS without nasal polyps .

13-2 Introduction

Since the preparation of the first EP3OS document an increasing amount of evidence on the pathophysiology, diagnosis and treatment has been published (Figure1-1).

However, in compiling the tables on the various forms of therapy, it may be that despite well powered level Ib trials, no 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.

13-3 Evidence based management scheme for adults with acute rhinosinusitis

13-3-1 Evidence based management scheme for adults with acute rhinosinusitis for primary care

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;

Treatment
Treatment evidence and recommendations for acute rhinosinusitis see Table 13-1.
Initial treatment depending on the severity of the disease:
See Figure 13-1.
- mild: start with symptomatic relief (decongestants, saline, analgesics);
- moderate: additional topical steroids
- severe: additional antbibiotics and topical steroids

Figure 13-1. Treatment scheme for primary care for adults with acute rhinosinusitis

13-3-2 Evidence based management scheme for adults with acute rhinosinusitis for ENT specialists

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.
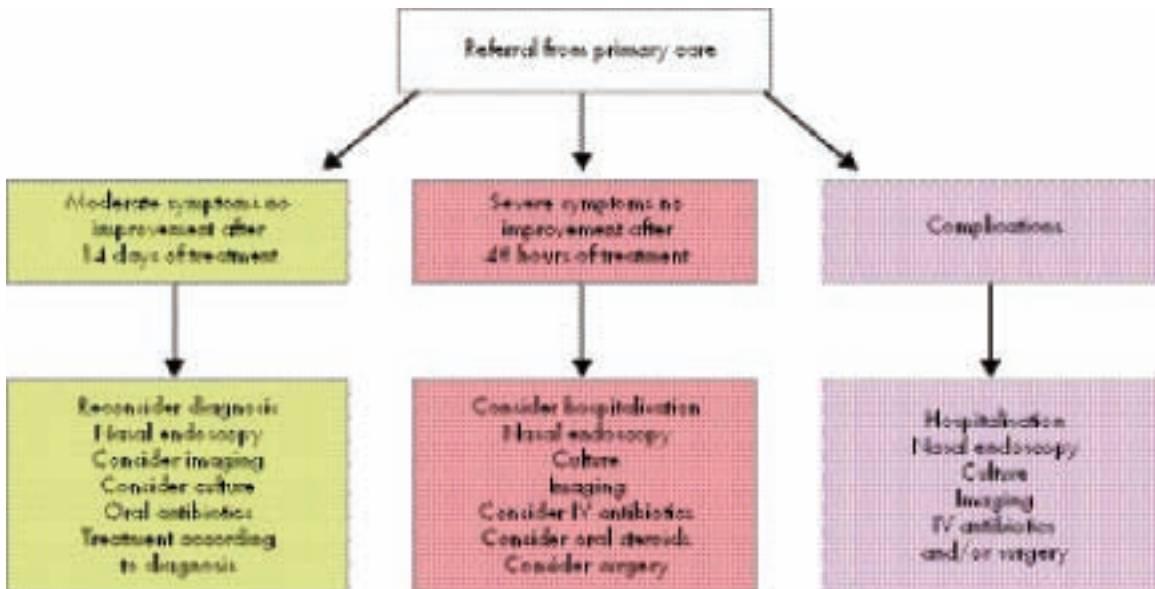
Figure 13-2. Treatment scheme for ENT specialists for adults with acute rhinosinusitis

13-4 Evidence based management scheme for adults with chronic rhinosinusitis without nasal polyps

13-4-1 Evidence based management scheme for adults with CRS with or without NP for primary care and non-ENT specialists

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;

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

Acute exacerbations of CRS should be treated like acute rhinosinusitis [1080].
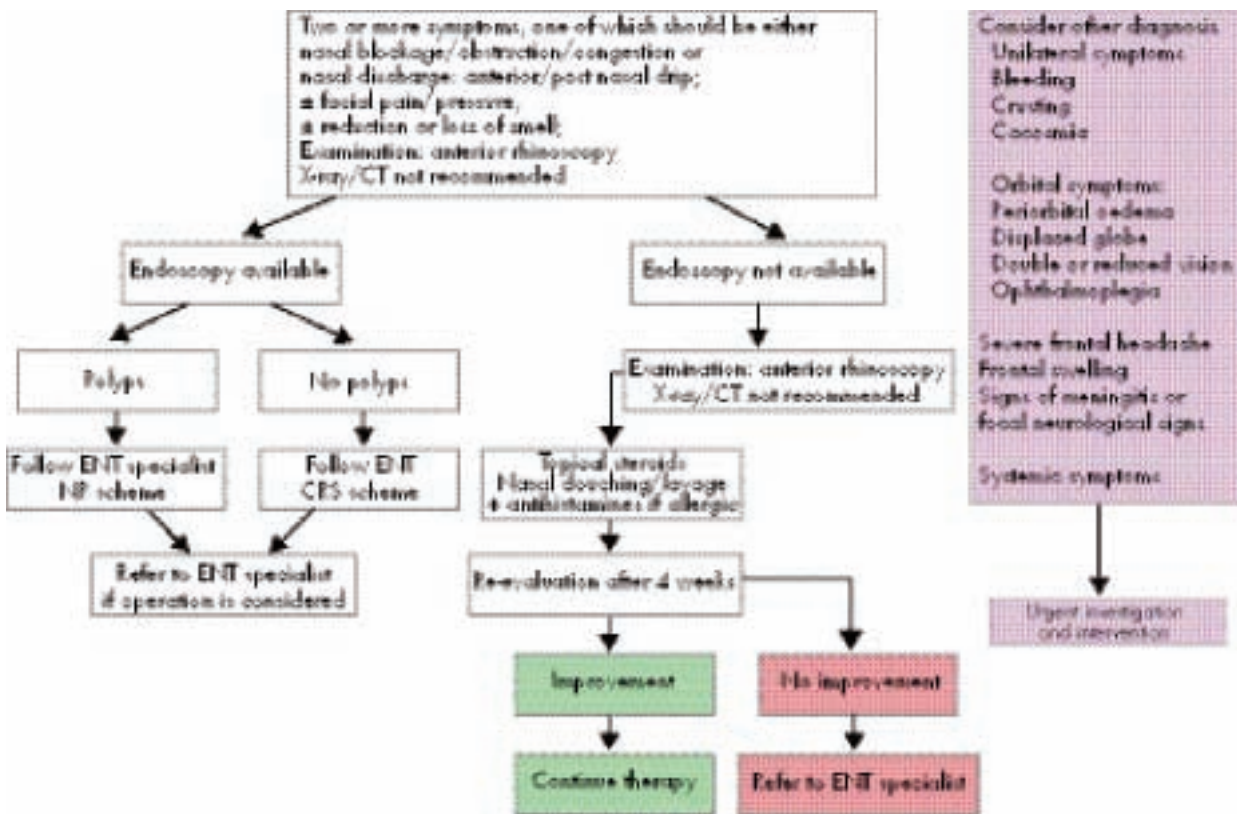
Figure 13-3 Treatment scheme for Chronic Rhinosinusitis with or without nasal polyps for primary care and non-ENT specialists

13-4-2 Scheme for adults with CRS without NP for ENT-Specialists

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.

Treatment should be based on severity of symptoms
- Decide on severity of symptomatology using VAS
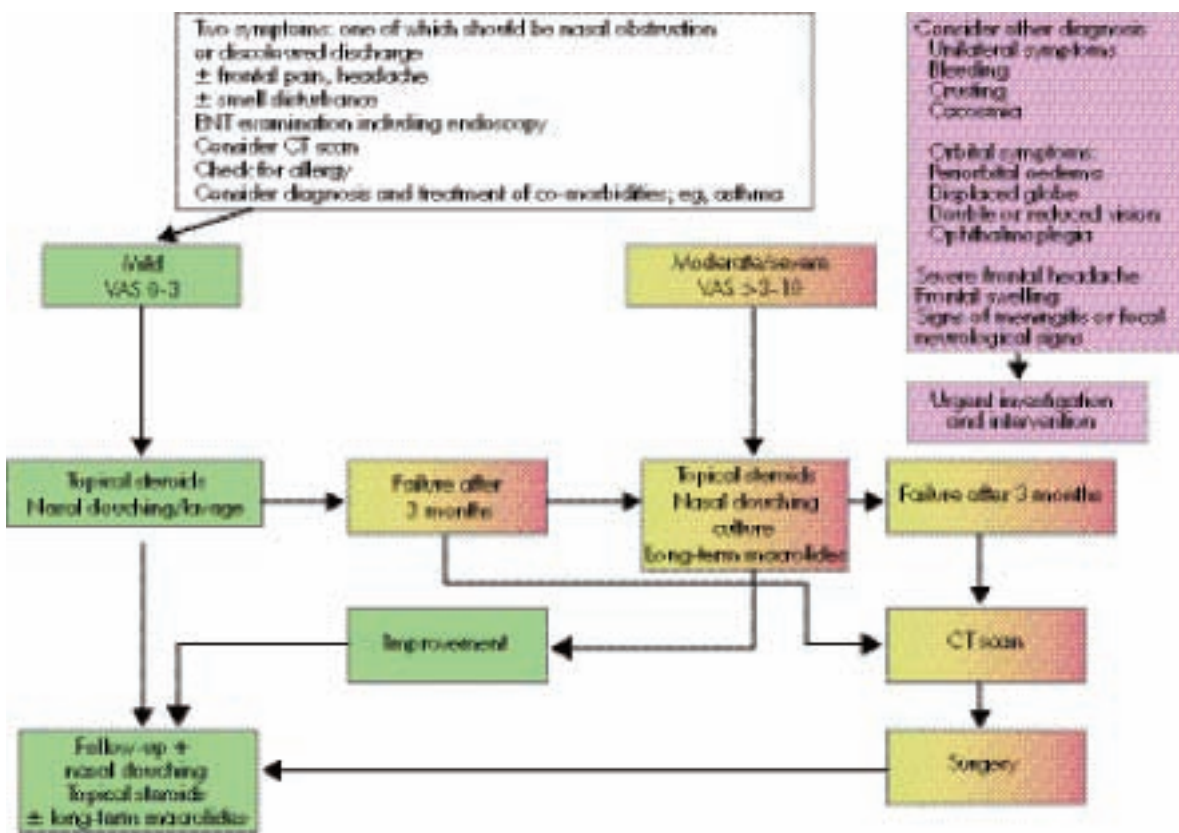
Figure 13-4. Treatment scheme for ENT-Specialists for adults with CRS without nasal polyps

13-4-3 Scheme for adults with NP for ENT-Specialists

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 not already done.

Severity of the symptoms
- (following the VAS score for the total severity) mild/moderate/severe.
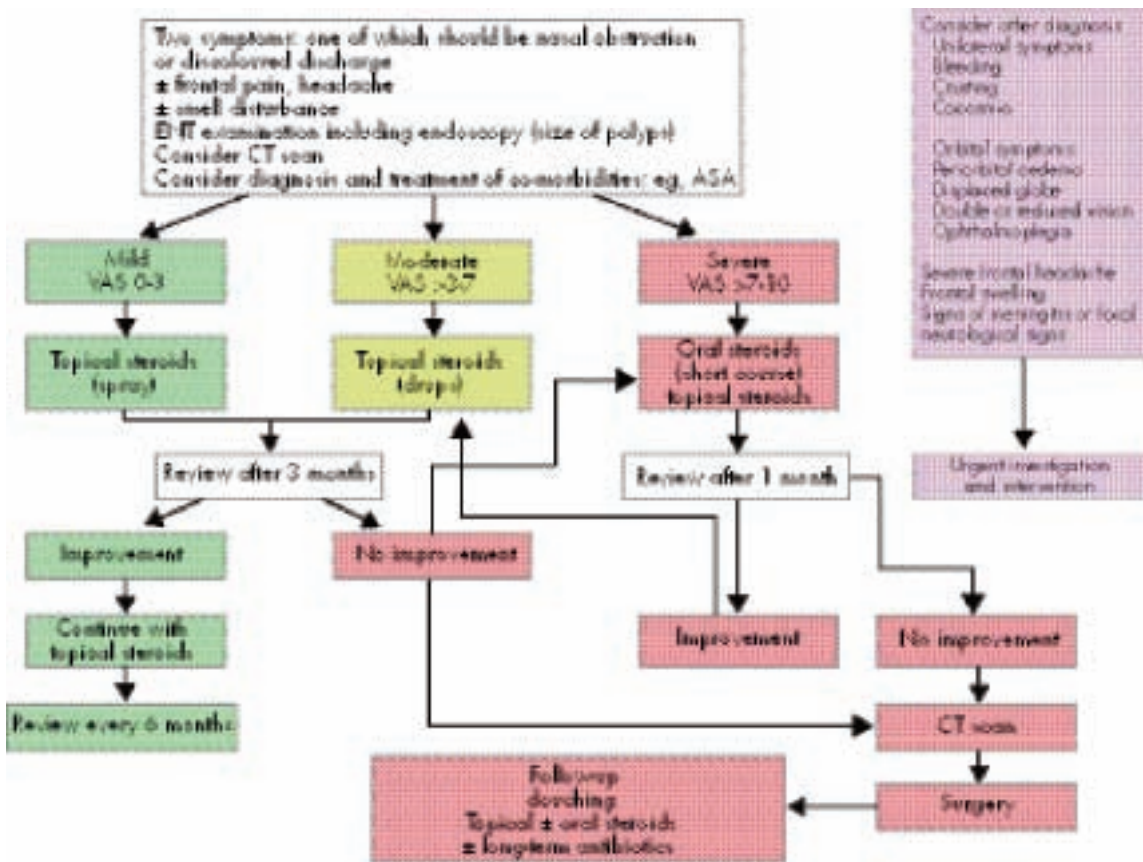
Figure 13-5. Treatment scheme for ENT-Specialists for adults with CRS with nasal polyps

13-5 Evidence based schemes for therapy in children

The following scheme should help different disciplines in the treatment of rhinosinusitis in children. The recommendations are based on the available evidence, but the choices need to be made depending on the circumstances of the individual case.

13-5-1 Evidence based management scheme for children with acute rhinosinusitis

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 (if applicable)
- 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.

Treatment
Treatment evidence and recommendations for acute rhinosinusitis see Table 13-2.
Initial treatment depending on the severity of the disease:
See Figure 13-6.
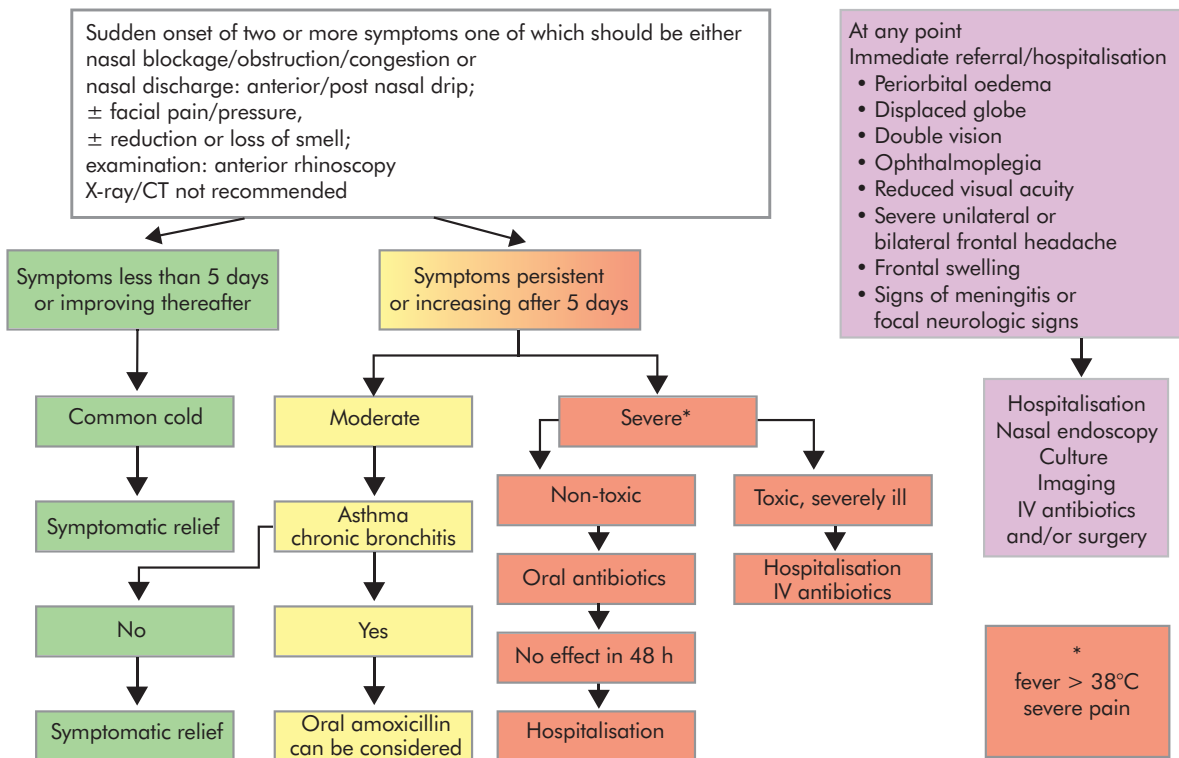
Figure 13-6. Treatment scheme for children with acute rhinosinusitis

13-5-2 Evidence based management scheme for children with chronic rhinosinusitis

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;

Additional diagnostic information
• questions on allergy should be added and, if positive, allergy testing should be performed.
• other predisposing fsctors should be considered: immune deficiency (innate , acquired, GERD)

Signs (if applicable)
• 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.
• ENT examination, endoscopy if available.

Treatment should be based on severity of symptoms

Figure 13-7 Treatment scheme for Chronic Rhinosinusitis in children

14. Research needs and priorities

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.

14-1 Epidemiology: Identifying the risk factors for development of CRS and NP

Our understanding of factors predisposing to CRS and NP remain embryonic with few studies to date. Epidemiologic studies aimed at identification of personal risk factors and environmental modifiers are required to increase our understanding of the disease process, select appropriate populations for clinical trials and interpret information from genetic studies.

Addressing this need will require detailed assessment and long-term follow up of a well-characterised patient populations to identify risk factors associated with development of CRS. A prospective population study of age- and sex-matched controlled atopic and non-atopic individuals might allow better characterization of the incidence of all upper respiratory tract symptoms including acute and chronic rhinosinusitis over a 5-year period. Similarly, a long-term follow-up of a cohort of patients with nasal polyposis would allow study of the natural history of the condition.

Identification of environmental modifiers will require prospective assessment of a very large cohort of patients to monitor for development of disease. While probably impractical for CRS alone, the trend to development of databases of medical and genetic information on large populations such as the UK BioBank initiative may eventually offer populations for this research.

14-2 Beyond infection: New roles for bacteria

It is increasingly recognised that bacteria may play a role in the chronic inflammation of CRS. Among others, *Staphylococcus aureus* has been specifically implicated, with possible persistence favoured by bacterial biofilms. In the light of this evidence, the role of bacteria in CRS needs to further explored in at least three areas.

1. Host factors favouring persistence of bacterial colonisation need to be better characterised.
2. The relative importance of biofilms and intracellular *S. aureus* in the development and persistence of CRS must be assessed
3. The role of *S. aureus* in development or persistence of CRS via postulated staphylococcal enterotoxins stimulating T-cells directly via a superantigenic mechanism needs to be validated.

14-3 Host response

Further studies into the mechanisms leading to the development of CTRS need to be identified. Events occurring at the level of the epithelium including non-specific defences such as innate immunity need better description and offer potential targets for therapy.

14-4 Genetics

Finally, pathogenesis of CRS may be better explored with research techniques taken from the growing field of genetics. Population association studies may allow detection of polymorphisms in genes in individuals suffering from CRS. Studies of candidate genes in currently known pathways may allow identification of specific genetic polymorphisms in the different steps of the pathways, while whole genome scans probing the entire genome offer the hope of identification of novel genes not suspected of being implicated.

Studies of gene expression in biopsy samples will help identify differential gene activation in different disease states and following different courses of therapy. Both of these offer the hope for development of tests allowing better differentiation of disease states and targeted therapy, with the tantalizing promise of identification of new drug targets not presently exploited.

These studies will require a cohort of investigators trained in these new techniques and development of multidisciplinary groups to collect and exploit the large populations required for these studies. Multinational collaborative initiatives will have to be initiated to collect the large sample sizes of affected individuals required for this work.

14-5 Clinical trials

Although much work has been recently been done on chronic rhinosinusitis and nasal polyps this work needs to be validated in terms of its clinical impact. Our understanding needs to translate into therapy for disease and experimental hypotheses need to verify by appropriate clinical trials. The following suggestions should highlight some areas of interest for further investigation.

1. Areas that have been identified need to be targeted with specific therapies. In particular, means of targeting biofilms, reducing *S. aureus* colonisation and of modulating response to *S. aureus* enterotoxins need to be developed and assessed by means of well-designed clinical trials.
2. Emerging therapies need to be assessed critically in order to determine which ones are effective and in which settings. There is an urgent need for randomized placebo controlled trials to study the effect of antibiotics in acute rhinosinusitis, chronic rhinosinusitis and exacerbations of chronic rhinosinusitis. These

should be compared with nasal steroids as a single modality of treatment for these conditions.

3. A well-powered prospective study of the effectiveness of macrolides in CRS and NP would allow validation of the positive effects suggested by some studies. The role of topical antibiotic therapy in exacerbations of CRS needs to be performed with well-characterized patients to identify optimal situations for use.

4. In the same fashion, novel therapies introduced over the coming years should be scrutinised closely prior to widespread adoption. Specifically, it is hoped that in the future clinicians will remain vigilant to claims made without the support of prospective, adequately powered clinical trials.

5. Surgical management for CRS and NP will probably continue to play a role in the management of CRS. In the future, rather than attempting to demonstrate superiority of one therapy over another, studies should target selected patient populations or situations so as to guide the clinician to a rational use of medical and/or surgical therapy as part of a comprehensive treatment plan individualised to stage of disease and patient needs.

6. Most QoL and symptom-specific questionnaires have been designed for a North American population and need to be validated for European patients.

7. The relationship between the upper and lower respiratory tract needs further investigation and will offer further insight into pathophysiology of inflammation and therapeutic possibilities.

15. Glosarry terms

Acute non-viral rhinosinusitis (ARS): an episode of sudden onset with an increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration.

Acute viral rhinosinusitis: an episode of sudden onset with duration of symptoms for less than 10 days

Common cold: Acute viral rhinosinusitis

Chronic rhinosinusitis (CRS): a condition lasting for >12 weeks, comprising 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;
May occur with or without polyps

Cacosmia: awareness of an unpleasant smell, often rotten or faeculent

Cobblestoned: an irregular bumpy mucosal surface usually post-surgery for polyps

Conventional surgery: a range of operations which predated endoscopic sinus surgery eg polypectomy, inferior meatal antrostomy, Caldwell-Luc operation, Denker's procedure, external fronto-ethmoidectomy

Endonasal surgery: any surgery performed through the nose

Functional surgery: an operation which aims to restore function eg restitution of mucocilary clearance, improvement in olfaction

Iatrogenic: a condition induced unintentionally by a physician, usually by a therapeutic action

Local corticosteroid: topical intranasal instillation of a corticosteroid preparation

Middle meatus: that area of the lateral wall of the nose lying lateral to the middle turbinate

Middle meatal antrostomy: an opening into the maxillary sinus thourgh the lateral wall of the middle meatus

Mucopurulent secretion: a mixture of opaque and discoloured mucus which is not frank pus

Orbital complications:
Ecchymosis: an area of discoloration beneath the skin secondary to bleeding
Enophthalmos: abnormal retraction of the eyeball into the socket
Myospherulosis: granulomatous foreign body reaction in soft tissues due to extravasation of paraffin or oil
Orbital emphysema: the presence of air within the soft tissues of the eye
Periorbital cellulitis: inflammation of the eyelid and conjunctiva

Ostiomeatal complex: that area of the middle meatus into which the maxillary, anterior ethmoid and frontal sinuses drain

Pansinustis: involvement of all paranasal sinuses, usually demonstrated radiologically

Pathogen: any organism capable of producing disease

Rhinitis medicamentosa: a condition associated with use of intranasal decongestants in which the nasal mucosa undergoes atrophy

Rhinorrhoea: any discharge from the nose. May run from the front of the nose (anterior) or into the back (posterior or post-nasal discharge)

Rhinosinusitis: inflammation of the nose and paranasal sinuses

Simple polypectomy: surgical removal of polyps from the nasal cavity without additional surgery on the paranasal sinuses

Treatment:
  short term treatment: usually 2 weeks or less
  long-term treatment: usually 12 weeks or longer

16. Information on QOL instruments:

16-1 General health status instruments:

- SF-36: www.sf-36.org
- Euro-QOL: www.euroqol.org
- SF-12: derived from the SF-36: www.sf-36.org
- Quality of Well-Being Scale: jharvey@ucsd.edu
- Glasgow Benefit Inventory: www.ihr.mrc.ac.uk/scottish/products/ghsq.php
- Mc-Gill pain questionnaire: Ronald Melzack: Department of Psychology, McGill University, 1205 Dr. Penfield Avenue, Montreal, Que. H3A 1B1, , Canada

16-2 Disease specific health status instruments:

- RSOM-31: Jay Piccirillo: piccirij@msnotes.wustl.edu
- SNOT-20: derived from the RSOM-31: Jay Piccirillo: piccirij@msnotes.wustl.edu
- SNOT-16: derived from the SNOT-20: Eric Anderson, Department of Otolaryngology-Head and Neck Surgery, University of Washington School of Medicine, Box 356515, Seattle, WA 98195-6515, USA
- RSDI: Michael Benninger, Department of Otolaryngology-Head and Neck Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202, USA
- RQLQ: www.qoltech.co.uk
- RSUI: D.A. Revicki: revicki@medtap.com
- SN-5: David Kay: davidkay@pol.net
- RhinoQol: Steven Atlas: satlas@partners.org

17. Survey of published olfactory tests

Author(s)	Year	Test name	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Cain [1081-1083]	1983 1988 1989	CCCRC	35 min	USA	>700		Age, gender, diseases, olfactory disorders.	1/ Threshold. N-butanol. 2AFC 4-correct-in-a-row method. Separate nostrils. Odours in squeeze bottles 2/Identification. 10 odours (score on &+1). Forced choice from 20 (or 16) descriptors. Odours in jars. Separate nostrils. Feedback.
Doty et al [1084]	1984 (a,b) 1985	UPSIT	15 min	USA	>3000	r=0.981	Age, gender, culture, smoker, disease, olfactory disorder, malingering.	Identification of 40 encapsuated odours. 4AFC. Scratch-and-sniff- technique
Wright [1085]	1987	Odourant Confusion	15 min	USA	480		Disease.	Identification of 10 odours each presented once (100 stimuli or 121 if a blank is added). Forced choice from list of 10 names. Pattern of odorant identification and misidentification.
Kurtz et al [1086]	2001	Matrix (OCM)						
Hendriks [1087]	1988	GITU		Netherlands	221		Age, gender, olfactory disorders.	Identification of 18 or 36 odours. Forced choice either from 4 alternatives or from a list of 24 for 18 odours to identify. "Everyday life" odours. Odours in jars.
Corwin [1088]	1989 1992	YN-OIT		USA			Age, disease	Based on 20 UPSIT odours. Yes or no matching of a descriptor to a proposed odour.
Takagi [1089]	1989	T&T Olfacto-meter		Japan	>1000		Olfactory disorders.	Thresholds of detection and recognition for 5 odorants. Odours on slips of filter papers. Separate nostrils.
Anderson et al	1992	SDOIT		USA	Young children		Age.	Identification of 10 odours. Forced choice using an array of 20 visual stimuli. Odours in jars.
Eloit and Trotier [1090]	1994			France	84		Olfactory disorder, disease.	Odours in bottles. 1/Threshold to 5 odorants. 2/Identification of 6 odorants. Odours in bottles.
Doty et al [1091, 1092]	1995 1996	CC-SIT MOD-SIT	5 min	USA Europe Asia	>3000	r=0.71	Age, gender, olfactory disorders.	Identification of 12 encapsulated odours. 4AFC. Scratch and sniff technique.

Author(s)	Year	Test name	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Kobal et al [1093]	1996		5 min	Germany	152	r=0.73	Gender, olfactory disorder, age.	Identification of 7 odours in pens. Forced choice from 4 alternatives.
Robson et al [1094]	1996	Combined olfactory test		UK and New Zealand	227		Olfactory disorder.	1/Threshold for n-butanol. Odours in plastic containers. 2/Identification of 9 odours. 4AFCE. Odours in jars.
Hummel et al [1095] Kobal et al [1096]	1997 2000	Sniffin'-Sticks		Germany, Switzerland, Austria, Australia, Italy, USA	>1000	r=0.72	Age, olfactory disorder.	Odours in pens. 1/Threshold for n-butanol. Triple forced choice paradigm. Single staircase method. 2/Discrimination: 16 odorant triplets. Identify the pen with the different smell. Forced choice. 3/Identification: 16 odours. 4AFC
Davidson and Murphy [1097]	1997	AST	5 min	USA	100		Olfactory disorder.	Detection of isopropanol. Measure as distance from nose.
Ahlskog et al [1098]	1998	CA-UPSIT		Guamanian Chamorro	57		Neuro-degenerative disease. Educational level.	Identification of 20 encapsulated odours. 4AFC. Scratch-and-sniff technique.
Nordin [1099]	1998	SOIT	15 min	Sweden Finland	>600	r=0.79	Age, gender, olfactory disorder.	Identification of 16 odours in bottles. 4AFC
Kremer et al [1100]	1998		4 min	Germany Netherlands	>200		Hyposmia.	6 aromas sprayed into open mouth. Odours in nasal sprays.
McCaffrey et al [1101]	2000	PST		USA	40		Discrimination between Alzheimer's dementia and major depression.	Identification of 3 encapsulated odours. 4AFC. Scratch-and-sniff technique.
Kobal et al [1102]	2001	"Random" test	10 min	Germany	273	r=0.71	Gender, olfactory disorder.	Labelling of 16 concentrations of two odorants randomly presented.
Hummel et al [1103]	2001	"Four-minute odour identification test"	4 min	Germany	1,012	r=0.78	Age, olfactory disorder.	Identification of 12 odours. 4AFC. Odours in pens.
Cardesin et al., [1104]	2006	Barcelona Smell Test - 24 (BAST-24)		Spanish	120			24 odours scoring smell detection, identification, and forced choice

18. References

1. Durr DG, Desrosiers MY, Dassa C. Impact of rhinosinusitis in health care delivery: the Quebec experience. J Otolaryngol. 2001;30(2):93-7.

2. 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;45(1):5-14.

3. Ray NF, Baraniuk JN, Thamer M, Rinehart CS, Gergen PJ, Kaliner M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol. 1999;103(3 Pt 1):408-14.

4. Anon JB, Jacobs MR, Poole MD, Ambrose PG, Benninger MS, Hadley JA, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg. 2004 Jan;130(1 Suppl):1-45.

5. Report of the Rhinosinusitis Task Force Committee Meeting. Alexandria, Virginia, August 17, 1996. Otolaryngol Head Neck Surg. 1997 Sep;117(3 Pt 2):S1-68.

6. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: Developing guidance for clinical trials. J Allergy Clin Immunol. 2006 Nov;118(5 Suppl):S17-61.

7. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: Establishing definitions for clinical research and patient care. Otolaryngology - Head & Neck Surgery. 2004;131(6 SUPPL.):S1-S62.

8. Fokkens W, Lund V, al. e. European position paper on rhinosinusitis and nasal polyps. Rhinol Suppl. 2005(18):1-87.

9. 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;60(5):583-601.

10. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. Bmj. 1996 Jan 13;312(7023):71-2.

11. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. Bmj. 1999 Feb 27;318(7183):593-6.

12. New guidelines for sinusitis target prescribing practices. Dis Manag Advis. 2004 Mar;10(3):27-30.

13. 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;58(3):176-91.

14. Lim M, Lew-Gor S, Darby Y, Brookes N, Scadding GK, VJ L. The relationship between subjective assessment instruments in chronic rhinosinusitis. . Rhinology. 2007;in press.

15. Winstead W. Rhinosinusitis. Prim Care. 2003;30(1):137-54.

16. Slavin RG. Nasal polyps and sinusitis. Jama. 1997;278(22):1849-54.

17. Sturgess JM, Chao J, Wong J, Aspin N, Turner JA. Cilia with defective radial spokes: a cause of human respiratory disease. N Engl J Med. 1979;300(2):53-6.

18. Bhattacharyya Nl. The role of infection in chronic rhinosinusitis. Curr Allergy Asthma Rep. 2002;2(6):500-6.

19. Zacharek MA, Krouse JH. The role of allergy in chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2003;11(3):196-200.

20. Jones NS. CT of the paranasal sinuses: a review of the correlation with clinical, surgical and histopathological findings. Clin Otolaryngol. 2002;27(1):11-7.

21. Jones NS, Strobl A, Holland I. A study of the CT findings in 100 patients with rhinosinusitis and 100 controls. Clin Otolaryngol. 1997;22(1):47-51.

22. 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. J Allergy Clin Immunol. 2003;111(2):342-9.

23. 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.

24. Dykewicz MS. 7. Rhinitis and sinusitis. J Allergy Clin Immunol. 2003;111(2 Suppl):S520-9.

25. Vento SI, Ertama LO, Hytonen ML, Wolff CH, Malmberg CH. Nasal polyposis: clinical course during 20 years. Ann Allergy Asthma Immunol. 2000;85(3):209-14.

26. Bachert C, Van Cauwenberge PBl. Inflammatory mechanisms in chronic sinusitis. Acta Otorhinolaryngol Belg. 1997;51(4):209-17.

27. Berger G, Kattan A, Bernheim J, Ophir Dl. Polypoid mucosa with eosinophilia and glandular hyperplasia in chronic sinusitis: a histopathological and immunohistochemical study. Laryngoscope. 2002;112(4):738-45.

28. Rudack C, Stoll W, Bachert C. Cytokines in nasal polyposis, acute and chronic sinusitis. Am J Rhinol. 1998;12(6):383-8.

29. 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;15(4):443-50.

30. 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. J Allergy Clin Immunol. 1995;96(4):537-44.

31. Bachert C, Wagenmann M, Hauser U, Rudack Cl. IL-5 synthesis is upregulated in human nasal polyp tissue. J Allergy Clin Immunol. 1997;99(6 Pt 1):837-42.

32. 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;28(4):717-22.

33. Larsen K. The clinical relationship of nasal polyps to asthma. Allergy Asthma Proc. 1996;17(5):243-9.

34. Settipane GA, Chafee FH. Nasal polyps in asthma and rhinitis. A review of 6,037 patients. J Allergy Clin Immunol. 1977;59(1):17-21.

35. Caplin I, Haynes JT, Spahn J. Are nasal polyps an allergic phenomenon? Ann Allergy. 1971;29(12):631-4.

36. 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. Clin Infect Dis. 2005 Aug 15;41(4):490-7.

37. Gwaltney JM, Jr., Jones JG, Kennedy DW. Medical management of sinusitis: educational goals and management guidelines. The International Conference on sinus Disease. Ann Otol Rhinol Laryngol Suppl. 1995;167:22-30.

38. Leggett JE. Acute sinusitis. When--and when not--to prescribe antibiotics. Postgrad Med. 2004 Jan;115(1):13-9.

39. Lindbaek M. Acute sinusitis: guide to selection of antibacterial therapy. Drugs. 2004;64(8):805-19.

40. Williams Jr JW, Aguilar C, Cornell J, Chiquette E. Dolor RJ, Makela M, Holleman DR, et al. Antibiotics for acute maxillary sinusitis (Cochrane Review). Cochrane Database Syst Rev. 2003(4).

41. 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.

42. Engels EA, Terrin N, Barza M, Lau J. Meta-analysis of diagnostic tests for acute sinusitis. J Clin Epidemiol. 2000 Aug;53(8):852-62.

43. Giesbers HrNo-IVTV, Nationale Atlas Volksgezondheid. Bilthoven: RIVM, < Gezondheid\Ziekten en aandoeningen\Ziekten van de ademhalingswegen, 27 september 2002. Neusbijholte ontsteking 1995-1999. 2002 [cited; Available from: http://www.zorgatlas.nl

44. Gijsen R, Poos M. Nationaal Kompas. 2003 [cited; Available from:

45. Gwaltney JM, Jr. Acute community-acquired sinusitis. Clin Infect Dis. 1996;23(6):1209-23; quiz 24-5.

46. 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.

47. Felmingham D, Feldman C, Hryniewicz W, Klugman K, Kohno S, Low DE, et al. Surveillance of resistance in bacteria causing community-acquired respiratory tract infections. Clin Microbiol Infect. 2002;8(Suppl 2):12-42.

48. Hoban D, Felmingham D. The PROTEKT surveillance study: antimicrobial susceptibility of Haemophilus influenzae and Moraxella catarrhalis from community-acquired respiratory tract infections. J Antimicrob Chemother. 2002;50(Suppl S1):49-59.

49. Klossek JM, Chidiac C, Serrano E. Current position of the management of community-acquired acute maxillary sinusitis or rhinosinusitis in France and literature review. Rhinology. 2005;43(SUPPL. 19):1-33.

50. Cars O, Molstad S, Melander A. Variation in antibiotic use in the European Union. Lancet. 2001;357(9271):1851-3.

51. Benninger M, Brook I, Farrell DJ. Disease severity in acute bacterial rhinosinusitis is greater in patients infected with Streptococcus pneumoniae than in those infected with Haemophilus influenzae. Otolaryngol Head Neck Surg. 2006 Oct;135(4):523-8.

52. 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.

53. Hinni ML, McCaffrey TV, Kasperbauer JL. Early mucosal changes in experimental sinusitis. Otolaryngol Head Neck Surg. 1992 Oct;107(4):537-48.

54. Kaliner M. Treatment of sinusitis in the next millennium. Allergy Asthma Proc. 1998;19(4):181-4.

55. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg. 1997;117(3 Pt 2):S1-7.

56. Savolainen S. Allergy in patients with acute maxillary sinusitis. Allergy. 1989;44(2):116-22.

57. 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.

58. Hinriksdottir I, Melen I. Allergic rhinitis and upper respiratory tract infections. Acta Otolaryngol Suppl. 1994;515:30-2.

59. Newman LJ, Platts-Mills TA, Phillips CD, Hazen KC, Gross CW. Chronic sinusitis. Relationship of computed tomographic findings to allergy, asthma, and eosinophilia. Jama. 1994;271(5):363-7.

60. Emanuel IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. Otolaryngol Head Neck Surg. 2000;123(6):687-91.

61. Iwens P, Clement PA. Sinusitis in allergic patients. Rhinology. 1994;32(2):65-7.

62. Naclerio RM, deTineo ML, Baroody FM. Ragweed allergic rhinitis and the paranasal sinuses. A computed tomographic study. Arch Otolaryngol Head Neck Surg. 1997;123(2):193-6.

63. Moser FG, Panush D, Rubin JS, Honigsberg RM, Sprayregen S, Eisig SB. Incidental paranasal sinus abnormalities on MRI of the brain. Clin Radiol. 1991 Apr;43(4):252-4.

64. Lloyd GA. CT of the paranasal sinuses: study of a control series in relation to endoscopic sinus surgery. J Laryngol Otol. 1990;104(6):477-81.

65. Havas TE, Motbey JA, Gullane PJ. Prevalence of incidental abnormalities on computed tomographic scans of the paranasal sinuses. Arch Otolaryngol Head Neck Surg. 1988;114(8):856-9.

66. Patel K, Chavda SV, Violaris N, Pahor AL. Incidental paranasal sinus inflammatory changes in a British population. J Laryngol Otol. 1996 Jul;110(7):649-51.

67. Zinreich SJ, Kennedy DW, Kumar AJ, Rosenbaum AE, Arrington JA, Johns ME. MR imaging of normal nasal cycle: comparison with sinus pathology. J Comput Assist Tomogr. 1988 Nov-Dec;12(6):1014-9.

68. Holzmann D, Willi U, Nadal D. Allergic rhinitis as a risk factor for orbital complication of acute rhinosinusitis in children. Am J Rhinol. 2001;15(6):387-90.

69. Chen CF, Wu KG, Hsu MC, Tang RB. Prevalence and relationship between allergic diseases and infectious diseases. J Microbiol Immunol Infect. 2001 Mar;34(1):57-62.

70. Karlsson G, Holmberg K. Does allergic rhinitis predispose to sinusitis? Acta Otolaryngol Suppl. 1994;515:26-8; discussion 9.

71. Wise SK, Wise JC, DelGaudio JM. Association of nasopharyngeal and laryngopharyngeal reflux with postnasal drip symptomatology in patients with and without rhinosinusitis. American Journal of Rhinology. 2006;20(3):283-9.

72. Dinis PB, Martins ML, Subtil J. Does Helicobacter pylori play a role in upper respiratory tract inflammation? A case report. Ear Nose Throat J. 2005 Apr;84(4):238-40.

73. Skoulas IG, Helidonis E, Kountakis SE. Evaluation of sinusitis in the intensive care unit patient. Otolaryngol Head Neck Surg. 2003 Apr;128(4):503-9.

74. Rouby JJ, Poete P, Martin de Lassale E, Nicolas MH, Bodin L, Jarlier V, et al. Prevention of gram negative nosocomial bronchopneumonia by intratracheal colistin in critically ill patients. Histologic and bacteriologic study. Intensive Care Med. 1994;20(3):187-92.

75. Holzapfel L. Nasal vs oral intubation. Minerva Anestesiol. 2003 May;69(5):348-52.

76. van Zanten AR, Dixon JM, Nipshagen MD, de Bree R, Girbes AR, Polderman KH. Hospital-acquired sinusitis is a common cause of fever of unknown origin in orotracheally intubated critically ill patients. Crit Care. 2005 Oct 5;9(5):R583-90.

77. Le Moal G, Lemerre D, Grollier G, Desmont C, Klossek JM, Robert R. Nosocomial sinusitis with isolation of anaerobic bacteria in ICU patients. Intensive Care Med. 1999 Oct;25(10):1066-71.

78. Degano B, Genestal M, Serrano E, Rami J, Arnal JF. Effect of treatment on maxillary sinus and nasal nitric oxide concentrations in patients with nosocomial maxillary sinusitis. Chest. 2005 Sep;128(3):1699-705.

79. Collins JG. Prevalence of selected chronic conditions: United States, 1990-1992. Vital Health Stat 10. 1997(194):1-89.

80. Blackwell DCJ, Coles R. Summary health statistics for US adults: National Health Interview Survey 1997. National Center for Health Statistics. Vital Health Stat. 2002;10(205):15.

81. Shashy RG, Moore EJ, Weaver A. Prevalence of the chronic sinusitis diagnosis in Olmsted County, Minnesota. Arch Otolaryngol Head Neck Surg. 2004 Mar;130(3):320-3.

82. Hughes RG, Jones NS. The role of nasal endoscopy in outpatient management. Clin Otolaryngol. 1998;23(3):224-6.

83. Bhattacharyya N. Clinical and symptom criteria for the accurate diagnosis of chronic rhinosinusitis. Laryngoscope. 2006 Jul;116(7 Pt 2 Suppl 110):1-22.

84. 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.

85. Chen Y, Dales R, Lin M. The epidemiology of chronic rhinosinusitis in Canadians. Laryngoscope. 2003;113(7):1199-205.

86. Greisner WA, 3rd, Settipane GA. Hereditary factor for nasal polyps. Allergy Asthma Proc. 1996;17(5):283-6.

87. Gordts F, Clement, P.A.R., Buisseret, T. Prevalence of sinusitis signs in a non-ENT population. Otorhinolaryngology. 1996;58:315-9.

88. 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.

89. Al-Rawi MM, Edelstein DR, Erlandson RAl. Changes in nasal epithelium in patients with severe chronic sinusitis: a clinicopathologic and electron microscopic study. Laryngoscope. 1998;108(12):1816-23.

90. Hadfield PJ, Rowe-Jones JM, Mackay IS. The prevalence of nasal polyps in adults with cystic fibrosis. Clin Otolaryngol. 2000;25(1):19-22.

91. Rowe-Jones JM, Shembekar M, Trendell-Smith N, Mackay IS. Polypoidal rhinosinusitis in cystic fibrosis: a clinical and histopathological study. Clin Otolaryngol. 1997;22(2):167-71.

92. Rowe-Jones JM, Trendell-Smith N, Shembekar M, Mackay IS. Polypoid rhinosinusitis in patients with host defence deficiencies: cellular infiltration and disease severity. Rhinology. 1997;35(3):113-7.

93. Wojtczak HA, Kerby GS, Wagener JS, Copenhaver SC, Gotlin RW, Riches DW, et al. Beclomethasone diproprionate reduced airway inflammation without adrenal suppression in young children with cystic fibrosis: a pilot study. Pediatr Pulmonol. 2001 Oct;32(4):293-302.

94. Krause HF. Allergy and chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2003;128(1):14-6.

95. Jones NS, Carney AS, Davis A. The prevalence of allergic rhinosinusitis: a review. J Laryngol Otol. 1998 Nov;112(11):1019-30.

96. Bailey B. The impact of pollution on the upper alimentary and respiratory tracts. Otolaryngol Head Neck Surg. 1992;106:736-40.

97. Stammberger H. Functional endoscopic sinus surgery. Philadelphia: B.C. Decker; 1991.

98. Slavin RG. Sinusitis in adults and its relation to allergic rhinitis, asthma, and nasal polyps. J Allergy Clin Immunol. 1988;82(5 Pt 2):950-6.

99. 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. J Allergy Clin Immunol. 1993;92(1 Pt 1):39-48.

100. Rachelefsky GS, Goldberg M, Katz RM, Boris G, Gyepes MT, Shapiro MJ, et al. Sinus disease in children with respiratory allergy. J Allergy Clin Immunol. 1978;61(5):310-4.

101. Shapiro GG. Role of allergy in sinusitis. Pediatr Infect Dis. 1985;4(6 Suppl):S55-9.

102. Shapiro GG, Virant FS, Furukawa CT, Pierson WE, Bierman CW. Immunologic defects in patients with refractory sinusitis. Pediatrics. 1991;87(3):311-6.

103. Beninger M. Rhinitis, sinusitis and their relationship to allergies. Am J Rhinol. 1992;6:37-43.

104. Grove R, Farrior, J. Chronic hyperplastic sinusitis in allergic patients: a bacteriologic study of 200 operative cases. J Allergy Clin Immunol. 1990;11:271-6.

105. Friedman WH. Surgery for chronic hyperplastic rhinosinusitis. Laryngoscope. 1975;85(12 pt 1):1999-2011.

106. Lane AP, Pine HS, Pillsbury HC, 3rd. Allergy testing and immunotherapy in an academic otolaryngology practice: a 20-year review. Otolaryngol Head Neck Surg. 2001 Jan;124(1):9-15.

107. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001 Nov;108(5 Suppl):S147-334.

108. Slavin RG. Relationship of nasal disease and sinusitis to bronchial asthma. Ann Allergy. 1982;49(2):76-9.

109. Juntunen K, Tarkkanen J, Makinen J. Caldwell-Luc operation in the treatment of childhood bronchial asthma. Laryngoscope. 1984;94(2 Pt 1):249-51.

110. Nisioka GJ, Cook, P.R., Davis, W.E., McKinsey, J.P. Functional endoscopic sinus surgery in patients with chronic sinusitis and asthma. Otolaryngol Head Neck Surg. 1994;110(6):494-500.

111. Salvin RG, Cannon RE, Friedman WH, Palitang E, Sundaram M. Sinusitis and bronchial asthma. J Allergy Clin Immunol. 1980 Sep;66(3):250-7.

112. Schwartz HJ, Thompson JS, Sher TH, Ross RJ. Occult sinus abnormalities in the asthmatic patient. Arch Intern Med. 1987;147(12):2194-6.

113. Bresciani M, Paradis L, Des Roches A, Vernhet H, Vachier I, Godard P, et al. Rhinosinusitis in severe asthma. J Allergy Clin Immunol. 2001;107(1):73-80.

114. Chee L, Graham SM, Carothers DG, Ballas ZK. Immune dysfunction in refractory sinusitis in a tertiary care setting. Laryngoscope. 2001;111(2):233-5.

115. Porter JP, Patel AA, Dewey CM, Stewart MG. Prevalence of sinonasal symptoms in patients with HIV infection. Am J Rhinol. 1999 May-Jun;13(3):203-8.

116. Garcia-Rodriguez JF, Corominas M, Fernandez-Viladrich P, Monfort JL, Dicenta M. Rhinosinusitis and atopy in patients infected with HIV. Laryngoscope. 1999 Jun;109(6):939-44.

117. 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;19(6):351-6.

118. 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. 1989 Sep 8;245(4922):1066-73.

119. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. Science. 1989 Sep 8;245(4922):1073-80.

120. 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.

121. 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;34(4):194-7.

122. Kerrebijn JD, Poublon RM, Overbeek SE. Nasal and paranasal disease in adult cystic fibrosis patients. Eur Respir J. 1992;5(10):1239-42.

123. Stern RC, Boat TF, Wood RE, Matthews LW, Doershuk CF. Treatment and prognosis of nasal polyps in cystic fibrosis. Am J Dis Child. 1982;136(12):1067-70.

124. Davidson TM, Stearns G. Extended indications for endoscopic sinus surgery. Ear Nose Throat J. 1994 Jul;73(7):467-8, 73-4.

125. Jorissen MB, De Boeck K, Cuppens H. Genotype-phenotype correlations for the paranasal sinuses in cystic fibrosis. Am J Respir Crit Care Med. 1999;159(5 Pt 1):1412-6.

126. 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;284(14):1814-9.

127. Ellegard EK. The etiology and management of pregnancy rhinitis. Am J Respir Med. 2003;2(6):469-75.

128. 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.

129. Sorri M, Hartikainen-Sorri AL, Karja J. Rhinitis during pregnancy. Rhinology. 1980 Jun;18(2):83-6.

130. Zinreich SJ, Mattox, D.E., Kennedy, D.W., Chisholm, H.L., Diffley, D.M., Rosenbaum, A.E. Concha bullosa: CT evaluation. J Comput Assist Tomogr. 1988;12:788-4.

131. Caughey RJ, Jameson MJ, Gross CW, Han JK. Anatomic risk factors for sinus disease: fact or fiction? Am J Rhinol. 2005 Jul-Aug;19(4):334-9.

132. Bolger WE, Butzin CA, Parsons DS. Paranasal sinus bony anatomic variations and mucosal abnormalities: CT analysis for endoscopic sinus surgery. Laryngoscope. 1991;101(1 Pt 1):56-64.

133. 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.

134. Wagenmann M, Naclerio RM. Complications of sinusitis. J Allergy Clin Immunol. 1992;90(3 Pt 2):552-4.

135. Willner A, Choi SS, Vezina LG, Lazar RH. Intranasal anatomic variations in pediatric sinusitis. Am J Rhinol. 1997;11(5):355-60.

136. Min YG, Jung HW, Kim HS, Park SK, Yoo KY. Prevalence and risk factors of chronic sinusitis in Korea: results of a nationwide survey. Eur Arch Otorhinolaryngol. 1996;253(7):435-9.

137. 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.

138. Calhoun KH, Waggenspack GA, Simpson CB, Hokanson JA, Bailey BJ. CT evaluation of the paranasal sinuses in symptomatic and asymptomatic populations. Otolaryngol Head Neck Surg. 1991;104(4):480-3.

139. Kayalioglu G, Oyar O, Govsa F. Nasal cavity and paranasal sinus bony variations: a computed tomographic study. Rhinology. 2000;38(3):108-13.

140. 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;197(Pt 2):221-7.

141. Bhattacharyya N. Bacterial infection in chronic rhinosinusitis: A controlled paired analysis. American Journal of Rhinology. 2005;19(6):544-8.

142. Araujo E, Palombini BC, Cantarelli V, Pereira A, Mariante Al. Microbiology of middle meatus in chronic rhinosinusitis. Am J Rhinol. 2003;17(1):9-15.

143. Brook I. Microbiology and management of sinusitis. J Otolaryngol. 1996;25(4):249-56.

144. Brook I. Bacteriology of chronic maxillary sinusitis in adults. Ann Otol Rhinol Laryngol. 1989;98(6):426-8.

145. 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 Dec;44(4):249-54.

146. Schubert MS. Fungal rhinosinusitis: diagnosis and therapy. Curr Allergy Asthma Rep. 2001;1(3):268-76.

147. Schubert MS. Allergic fungal sinusitis. Otolaryngol Clin North Am. 2004 Apr;37(2):301-26.

148. Ponikau JU, Sherris DA, Kern EB, Homburger HA, Frigas E, Gaffey TA, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc. 1999;74(9):877-84.

149. Braun H, Buzina W, Freudenschuss K, Beham A, Stammberger H. 'Eosinophilic fungal rhinosinusitis': a common disorder in Europe? Laryngoscope. 2003;113(2):264-9.

150. Pant H, Kette FE, Smith WB, Wormald PJ, Macardle PJ. Fungal-specific humoral response in eosinophilic mucus chronic rhinosinusitis. Laryngoscope. 2005;115(4):601-6.

151. 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 & Neck Surgery. 2005;13(1):2-8.

152. 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.

153. Ragab A, Clement P, Vincken W, Nolard N, Simones F. Fungal cultures of different parts of the upper and lower airways in chronic rhinosinusitis. Rhinology. 2006 Mar;44(1):19-25.

154. Murr AH, Goldberg AN, Vesper S. Fungal speciation using quantitative polymerase chain reaction (QPCR) in patients with and without chronic rhinosinusitis. Laryngoscope. 2006;116(8):1342-8.

155. Weschta M, Rimek D, Formanek M, Podbielski A, Riechelmann H. Effect of nasal antifungal therapy on nasal cell activation markers in chronic rhinosinusitis. Archives of Otolaryngology -- Head & Neck Surgery. 2006;132(7):743-7.

156. 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. J Allergy Clin Immunol. 2006 Nov;118(5):1149-56.

157. 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;20(3):278-82.

158. Kennedy DW, Senior BA, Gannon FH, Montone KT, Hwang P, Lanza DC. Histology and histomorphometry of ethmoid bone in chronic rhinosinusitis. Laryngoscope. 1998;108(4 Pt 1):502-7.

159. Khalid AN, Hunt J, Perloff JR, Kennedy DW. The role of bone in chronic rhinosinusitis. Laryngoscope. 2002;112(11):1951-7.

160. Perloff JR, Gannon FH, Bolger WE, Montone KT, Orlandi R, Kennedy DW. Bone involvement in sinusitis: an apparent pathway for the spread of disease. Laryngoscope. 2000;110(12):2095-9.

161. 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.

162. Gutman M, Houser S. Iatrogenic maxillary sinus recirculation and beyond. Ear Nose Throat J. 2003 Jan;82(1):61-3.

163. Morinaka S, Ichimiya M, Nakamura H. Detection of Helicobacter pylori in nasal and maxillary sinus specimens from patients with chronic sinusitis. Laryngoscope. 2003;113(9):1557-63.

164. Ozdek A, Cirak MY, Samim E, Bayiz U, Safak MA, Turet S. A possible role of Helicobacter pylori in chronic rhinosinusitis: a preliminary report. Laryngoscope. 2003;113(4):679-82.

165. Johansson L, Akerlund A, Holmberg K, Melen I, Bende M. Prevalence of nasal polyps in adults: the Skovde population-based study. Ann Otol Rhinol Laryngol. 2003;112(7):625-9.

166. 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.

167. 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.

168. 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.

169. Larsen PL, Tos M. Origin of nasal polyps. Laryngoscope. 1991;101(3):305-12.

170. 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;33(4):185-8.

171. Larsen P, Tos M. Anatomic site of origin of nasal polyps: endoscopic nasal and paranasal sinus surgery as a screening method for nasal polyps in autopsy material. Am J Rhinol. 1996;10:211=6.

172. Drake-Lee A. Nasal polyps. In: Mygind N, Naclerio RM, editor. Allergic and non-allergic rhinitis. Copenhagen: Munksgaard; 1993.

173. Larsen K, Tos M. The estimated incidence of symptomatic nasal polyps. Acta Otolaryngol. 2002;122(2):179-82.

174. Settipane GA, Chafee, F.H. Nasal polyps in asthma and rhinitis. J Allergy Clin Immunol. 1977;59:17-21.

175. Larsen K. The clinical relationship of nasal polyps to asthma. In: Settipane G, Lund VJ, Bernstein JM, Tos M, editor. Nasal polyps: epidemiology, pathogenesis and treatment. Rhode Island: Oceanside Publications; 1997. p. 97-104.

176. Larsen K, Tos M. A long-term follow-up study of nasal polyp patients after simple polypectomies. Eur Arch Otorhinolaryngol. 1997;254(Suppl 1):S85-8.

177. 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;40(2):75-9.

178. Collins MM, Pang YT, Loughran S, Wilson JA. Environmental risk factors and gender in nasal polyposis. Clin Otolaryngol. 2002;27(5):314-7.

179. Drake-Lee AB, Lowe D, Swanston A, Grace A. Clinical profile and recurrence of nasal polyps. J Laryngol Otol. 1984;98(8):783-93.

180. Moloney JR. Nasal polyps, nasal polypectomy, asthma, and aspirin sensitivity. Their association in 445 cases of nasal polyps. J Laryngol Otol. 1977;91(10):837-46.

181. Larsen K, Tos M. Clinical course of patients with primary nasal polyps. Acta Otolaryngol. 1994;114(5):556-9.

182. Settipane G. Epidemiology of nasal polyps. In: Settipane G, Lund VJ, Bernstein JM, Tos M., editor. Nasal polyps: epidemiology, pathogenesis and treatment. Rhode Island: Oceanside Publications; 1997. p. 17-24.

183. Hosemann W, Gode U, Wagner W. Epidemiology, pathophysiology of nasal polyposis, and spectrum of endonasal sinus surgery. Am J Otolaryngol. 1994;15(2):85-98.

184. Bunnag C, Pacharee P, Vipulakom P, Siriyananda C. A study of allergic factor in nasal polyp patients. Ann Allergy. 1983;50(2):126-32.

185. Kern R, Schenck H-P. Allergy: a constant factor in the etiology of so-called mucous nasal polyps. J Allergy. 1993;4:483.

186. Delaney JC. Aspirin idiosyncrasy in patients admitted for nasal polypectomy. Clin Otolaryngol. 1976;1(1):27-30.

187. Blumstein GI, Tuft Ll. Allergy treatment in recurrent nasal polyposis: its importance and value. Am J Med Sci. 1957;234(3):269-80.
188. English G. Nasal polyposis. In: GM E, editor. Otolaryngology. Philadelphia: Harper and Row; 1985. p. 1-30.
189. Pepys J, Duveen GE. Negative skin tests in allergic rhinitis and nasal polyposis. Int Arch Allergy Immunol. 1951;2:147-60.
190. Drake-Lee AB. Histamine and its release from nasal polyps: preliminary communication. J R Soc Med. 1984;77(2):120-4.
191. Liu CM, Shun CT, Hsu MM. Lymphocyte subsets and antigen-specific IgE antibody in nasal polyps. Ann Allergy. 1994;72(1):19-24.
192. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge Pl. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol. 2001;107(4):607-14.
193. Collins MM, Loughran S, Davidson P, Wilson JA. Nasal polyposis: prevalence of positive food and inhalant skin tests. Otolaryngol Head Neck Surg. 2006 Nov;135(5):680-3.
194. Pang YT, Eskici O, Wilson JA. Nasal polyposis: role of subclinical delayed food hypersensitivity. Otolaryngol Head Neck Surg. 2000;122(2):298-301.
195. Downing E, Braman S, Settipane GA. Bronchial reactivity in patients with nasal polyposis before and after polypectomy. J Allergy Clin Immunol. 1982;69(2):102.
196. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. Eur Respir J. 2000;16(3):432-6.
197. Settipane GA, Chafee FH, Klein DE. Aspirin intolerance. II. A prospective study in an atopic and normal population. J Allergy Clin Immunol. 1974;53(4):200-4.
198. Chafee F, Settipane GA. Aspirin intolerance. I. Frequency in an allergic population. J Allergy Clin Immunol. 1974;53:193-9.
199. 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. J Allergy Clin Immunol. 1979;64(1):32-7.
200. Szczeklik A, Gryglewski RJ, Czerniawska-Mysik G. Clinical patterns of hypersensitivity to nonsteroidal anti-inflammatory drugs and their pathogenesis. J Allergy Clin Immunol. 1977;60(5):276-84.
201. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. J Allergy Clin Immunol. 1979;64(6 Pt 1):500-6.
202. Ogino S, Harada T, Okawachi I, Irifune M, Matsunaga T, Nagano T. Aspirin-induced asthma and nasal polyps. Acta Otolaryngol Suppl. 1986;430:21-7.
203. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis and management. J Allergy Clin Immunol. 1999;104(1):5-13.
204. May A, Wagner D, Langenbeck U, Weber A. [Family study of patients with aspirin intolerance and rhinosinusitis]. Hno. 2000;48(9):650-4.
205. Moloney JR, Oliver RT. HLA antigens, nasal polyps and asthma. Clin Otolaryngol. 1980;5(3):183-9.
206. 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;43(3):162-8.
207. Lockey RF, Rucknagel DL, Vanselow NA. Familial occurrence of asthma, nasal polyps and aspirin intolerance. Ann Intern Med. 1973;78(1):57-63.
208. Settipane GA. Benefit/risk ratio of aspirin. NES Allergy Proceedings. 1981;2:96-102.
209. Drake-Lee A. Nasal polyps in identical twins. J Laryngol Otol. 1992;106(12):1084-5.
210. 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.
211. 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. Am J Rhinol. 2006 Sep-Oct;20(5):550-3.
212. Luxenberger W, Posch U, Berghold A, Hofmann T, Lang-Loidolt D. HLA patterns in patients with nasal polyposis. Eur Arch Otorhinolaryngol. 2000;257(3):137-9.
213. Molnar-Gabor E, Endreffy E, Rozsasi A. HLA-DRB1, -DQA1, and -DQB1 genotypes in patients with nasal polyposis. Laryngoscope. 2000;110(3 Pt 1):422-5.
214. 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.
215. 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.
216. 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.
217. 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.
218. Kim J, Hanley JA. The role of woodstoves in the etiology of nasal polyposis. Arch Otolaryngol Head Neck Surg. 2002;128(6):682-6.
219. Maresh MM Washburn A. Paranasal sinuses from birth to late adolescence. Clinical and roentgengraphic evidence of infection. Am J Dis Child. 1940(60):841-61.
220. van der Veken PJ, Clement PA, Buisseret T, Desprechins B, Kaufman L, Derde MP. CT-scan study of the incidence of sinus involvement and nasal anatomic variations in 196 children. Rhinology. 1990;28(3):177-84.
221. 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.
222. Bagatsch K DK, Parthenheimer F, Ritter B. 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.
223. Van Buchem FL, Peeters MF, Knottnerus JA. Maxillary sinusitis in children. Clin Otolaryngol. 1992;17(1):49-53.
224. Kakish KS, Mahafza T, Batieha A, Ekteish F, Daoud A. Clinical sinusitis in children attending primary care centers. Pediatr Infect Dis J. 2000 Nov;19(11):1071-4.
225. 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.
226. Chen Y, Li WX, Yu SZ, Qian WH. Chang-Ning epidemiological study of children's health: I: Passive smoking and children's respiratory diseases. Int J Epidemiol. 1988;17(2):348-55.
227. Samet JM. Adverse effects of smoke exposure on the upper airway. Tob Control. 2004 Mar;13 Suppl 1:i57-60.
228. Baier G, Stopper H, Kopp C, Winkler U, Zwirner-Baier Il. [Respiratory diseases and genotoxicity in tobacco smoke exposed children]. Laryngorhinootologie. 2002;81(3):217-25.
229. Incaudo GA. Diagnosis and treatment of allergic rhinitis and sinusitis during pregnancy and lactation. Clinical Reviews in Allergy & Immunology. 2004;27(2):159-77.
230. Jain SK, Tunkel DE, Bishai WR. Management of acute rhinosinusitis, bronchitis syndromes, and acute otitis media. Advanced Studies in Medicine. 2005;5(7):344-50.
231. Sih T. Correlation between respiratory alterations and respiratory diseases due to urban pollution. Int J Pediatr Otorhinolaryngol. 1999;49(Suppl 1):S261-7.
232. Kvaerner KJ, Tambs K, Harris JR, Mair IW, Magnus P. Otitis media: relationship to tonsillitis, sinusitis and atopic diseases. Int J Pediatr Otorhinolaryngol. 1996 Apr;35(2):127-41.
233. Krzeski A, Kapiszewska-Dzedzej D, Gorski NP, Jakubczyk I. Cystic fibrosis in rhinologic practice. Am J Rhinol. 2002;16(3):155-60.

234. 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;109(1):E13.

235. 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;24(6):400-5.

236. Yu X, Sperling A, Blair C, Thompson K, Naclerio R. Antigen stimulation of TH2 cells augments acute bacterial sinusitis in mice. J Allergy Clin Immunol. 2004 Aug;114(2):328-34.

237. Ramadan HH, Meek RB, Dawson GS, Spirou GA, Cuff CF, Berrebi AS. Histologic and immunologic observations of viral-induced rhinosinusitis in the mouse. Am J Rhinol. 2002;16(1):61-7.

238. Khoury P, Baroody FM, Klemens JJ, Thompson K, Naclerio RM. Effect of montelukast on bacterial sinusitis in allergic mice. Ann Allergy Asthma Immunol. 2006 Sep;97(3):329-35.

239. 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.

240. Rudack C, Hauser U, Wagenmann M, Bachert C, Ganzer U. [Cytokine pattern in various forms of sinusitis]. Laryngorhinootologie. 1998;77(1):34-7.

241. Perloff JR, Palmer JN. Evidence of bacterial biofilms in a rabbit model of sinusitis. Am J Rhinol. 2005 Jan-Feb;19(1):1-6.

242. Min YG, Lee KS. The role of cytokines in rhinosinusitis. J Korean Med Sci. 2000;15(3):255-9.

243. Whiteman SC, Bianco A, Knight RA, Spiteri MA. Human rhinovirus selectively modulates membranous and soluble forms of its intercellular adhesion molecule-1 (ICAM-1) receptor to promote epithelial cell infectivity. J Biol Chem. 2003 Apr 4;278(14):11954-61.

244. Engquist S, Lundberg C, Venge P. Granulocyte proteases in human maxillary sinus secretions. Scand J Infect Dis. 1983;15(1):119-23.

245. Westrin KM, Stierna P, Soderlund K. Microorganisms and leukocytes in purulent sinusitis: a symbiotic relationship in metabolism. Acta Otolaryngol Suppl. 1994;515:18-21.

246. Repka-Ramirez S, Naranch K, Park YJ, Clauw D, Baraniuk JN. Cytokines in nasal lavage fluids from acute sinusitis, allergic rhinitis, and chronic fatigue syndrome subjects. Allergy Asthma Proc. 2002;23(3):185-90.

247. Bachert C, Wagenmann M, Hauser U. Proinflammatory cytokines: measurement in nasal secretion and induction of adhesion receptor expression. Int Arch Allergy Immunol. 1995 May-Jun;107(1-3):106-8.

248. Riechelmann H, Deutschle T, Rozsasi A, Keck T, Polzehl D, Burner H. Nasal biomarker profiles in acute and chronic rhinosinusitis. Clinical & Experimental Allergy. 2005;35(9):1186-91.

249. Roseler S, Holtappels G, Wagenmann M, Bachert C. Elevated levels of interleukins IL-1 beta, IL-6 and IL-8 in naturally acquired viral rhinitis. Eur Arch Otorhinolaryngol. 1995;252 Suppl 1:S61-3.

250. 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.

251. Papi A, Johnston SL. Respiratory epithelial cell expression of vascular cell adhesion molecule-1 and its up-regulation by rhinovirus infection via NF-kappaB and GATA transcription factors. J Biol Chem. 1999 Oct 15;274(42):30041-51.

252. Sarin S, Undem B, Sanico A, Togias A. The role of the nervous system in rhinitis. J Allergy Clin Immunol. 2006 Nov;118(5):999-1016.

253. Tai CF, Baraniuk JN. Upper airway neurogenic mechanisms. Curr Opin Allergy Clin Immunol. 2002;2(1):11-9.

254. Stierna P, Carlsoo B. Histopathological observations in chronic maxillary sinusitis. Acta Otolaryngol. 1990;110(5-6):450-8.

255. Georgitis JW, Matthews BL, Stone B. Chronic sinusitis: characterization of cellular influx and inflammatory mediators in sinus lavage fluid. Int Arch Allergy Immunol. 1995;106(4):416-21.

256. Jankowski R, Bouchoua F, Coffinet L, Vignaud JM. Clinical factors influencing the eosinophil infiltration of nasal polyps. Rhinology. 2002;40(4):173-8.

257. Muluk NB, Koc C, Atasoy P. Localization of T cells and subtypes in the paranasal sinus and turbinate mucosa in patients with chronic sinusitis. Journal of Otolaryngology. 2004;33(4):235-42.

258. 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.

259. Bhattacharyya N, Vyas DK, Fechner FP, Gliklich RE, Metson Rl. Tissue eosinophilia in chronic sinusitis: quantification techniques. Arch Otolaryngol Head Neck Surg. 2001;127(9):1102-5.

260. 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. Am J Rhinol. 2002;16(3):131-4.

261. Zadeh MH, Banthia V, Anand VK, Huang C. Significance of eosinophilia in chronic rhinosinusitis. Am J Rhinol. 2002;16(6):313-7.

262. 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.

263. Citardi MJ, Song W, Batra PS, Lanza DC, Hazen SL. Characterization of oxidative pathways in chronic rhinosinusitis and sinonasal polyposis. American Journal of Rhinology. 2006;20(3):353-9.

264. 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.

265. Hafidh M, Harney M, Kane R, Donnelly M, Landers R, Smyth D. The role of fungi in the etiology of chronic rhinosinusitis: A prospective study. Auris Nasus Larynx. 2006 Oct 26.

266. Ragab A, Clement P, Vincken W. Correlation between the cytology of the nasal middle meatus and BAL in chronic rhinosinusitis. Rhinology. 2005;43(1):11-7.

267. Lindsay R, Slaughter T, Britton-Webb J, Mog SR, Conran R, Tadros M, et al. Development of a murine model of chronic rhinosinusitis. Otolaryngology - Head & Neck Surgery. 2006;134(5):724-30.

268. 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. Laryngoscope. 2005;115(9):1580-5.

269. 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.

270. Polzehl D, Weschta M, Podbielski A, Riechelmann H, Rimek D. Fungus culture and PCR in nasal lavage samples of patients with chronic rhinosinusitis. Journal of Medical Microbiology. 2005;54(1):31-7.

271. Claeys S, De Belder T, Holtappels G, Gevaert P, Verhasselt B, Van Cauwenberge P, et al. Macrophage mannose receptor in chronic sinus disease. Allergy. 2004 Jun;59(6):606-12.

272. Kramer MF, Burow G, Pfrogner E, Rasp G. In vitro diagnosis of chronic nasal inflammation. Clin Exp Allergy. 2004 Jul;34(7):1086-92.

273. 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.

274. Rudack C, Sachse F, Alberty J. Chronic rhinosinusitis--need for further classification? Inflamm Res. 2004 Mar;53(3):111-7.

275. 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.

276. Rudack C, Sachse F, Alberty J. Chronic rhinosinusitis - Need for further classification? Inflammation Research. 2004;53(3):111-7.

277. Seiberling KA, Grammer L, Kern RC. Chronic rhinosinusitis and superantigens. Otolaryngologic Clinics of North America. 2005;38(6):1215-36.

278. 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;53(1):2-13.

279. Rhyoo C, Sanders SP, Leopold DA, Proud D. Sinus mucosal IL-8 gene expression in chronic rhinosinusitis. J Allergy Clin Immunol. 1999;103(3 Pt 1):395-400.

280. Nonoyama T, Harada T, Shinogi J, Yoshimura E, Sakakura Y. Immunohistochemical localization of cytokines and cell adhesion molecules in maxillary sinus mucosa in chronic sinusitis. Auris Nasus Larynx. 2000;27(1):51-8.

281. Demoly P, Crampette L, Mondain M, Enander I, Jones I, Bousquet J. Myeloperoxidase and interleukin-8 levels in chronic sinusitis. Clin Exp Allergy. 1997;27(6):672-5.

282. Takeuchi K, Yuta A, Sakakura Y. Interleukin-8 gene expression in chronic sinusitis. Am J Otolaryngol. 1995;16(2):98-102.

283. Suzuki H, Takahashi Y, Wataya H, Ikeda K, Nakabayashi S, Shimomura A, et al. Mechanism of neutrophil recruitment induced by IL-8 in chronic sinusitis. J Allergy Clin Immunol. 1996;98(3):659-70.

284. Persson CGA EJ, Andersson M, et al. Epithelium, microcirculation and eosinophils - new aspects of the allergic airway in vivo. Allergy. 1997;52:241.

285. Xu R, Xu G, Shi J, Wen W. A correlative study of NF-kappaB activity and cytokines expression in human chronic nasal sinusitis. J Laryngol Otol. 2006 Oct 11:1-6.

286. Rudack C, Sachse F, Alberty J. Primary role of growth-related oncogene-a and granulocyte chemotactic protein-2 as neutrophil chemoattractants in chronic rhinosinusitis. Clinical & Experimental Allergy. 2006;36(6):748-59.

287. Bradley DT, Kountakis SE. Role of interleukins and transforming growth factor-beta in chronic rhinosinusitis and nasal polyposis. Laryngoscope. 2005;115(4):684-6.

288. 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. Journal of Allergy & Clinical Immunology. 2005;115(6):1189-96.

289. 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.

290. Liu T, Wang BQ, Yang PC. A possible link between sinusitis and lower airway hypersensitivity: the role of Staphylococcal enterotoxin B. Clin Mol Allergy. 2006;4:7.

291. Damm M, Quante G, Rosenbohm J, Rieckmann R. Proinflammatory effects of Staphylococcus aureus exotoxin B on nasal epithelial cells. Otolaryngol Head Neck Surg. 2006 Feb;134(2):245-9.

292. 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. Arch Otolaryngol Head Neck Surg. 2004 Dec;130(12):1374-80.

293. 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.

294. Elhini A, Abdelwahab S, Ikeda K. Th1 and Th2 cell population in chronic ethmoidal rhinosinusitis: A chemokine receptor assay. Laryngoscope. 2005;115(7):1272-7.

295. Lee JH, Kang HJ, Woo JS, Chae SW, Lee SH, Hwang SJ, et al. Up-regulation of chemokine ligand 20 in chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2006 May;132(5):537-41.

296. 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.

297. 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.

298. Watelet JB CC, Perez-Novo C, Gevaert P, van Cauwenberge P, Bachert C. TGF-beta 1 in remodeling of nasal tissue: differences between chronic rhinosinusitis and nasal polyposis. Am J Rhinol. 2003;in press.

299. Watelet JB BC, Claeys C, van Cauwenberge P. Matrix Metalloproteinases MMP-7, MMP-9 and their tissue inhibitor TIM-1: expression in chronic sinusitis versus nasal polyposis. Allergy. 2003;in press.

300. Watelet JB, Demetter P, Claeys C, Van Cauwenberge P, Cuvelier C, Bachert C. Neutrophil-derived metalloproteinase-9 predicts healing quality after sinus surgery. Laryngoscope. 2005;115(1 I):56-61.

301. Watelet JB, Claeys C, Perez-Novo C, Gevaert P, Van Cauwenberge P, Bachert C. Transforming growth factor beta1 in nasal remodeling: Differences between chronic rhinosinusitis and nasal polyposis. American Journal of Rhinology. 2004;18(5):267-72.

302. Lu X, Liu Z, Cui Y. [The protein expression difference of transforming growth factor beta1, matrix metalloproteinases 1,7,9 and tissue inhibitors of matrix metalloproteinases-1 between chronic rhinosinusitis, nasal polyps and normal mucosa tissues]. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2005 Jul;19(14):633-5.

303. Watelet JB, Claeys C, Van Cauwenberge P, Bachert C. Predictive and monitoring value of matrix metalloproteinase-9 for healing quality after sinus surgery. Wound Repair Regen. 2004 Jul-Aug;12(4):412-8.

304. Wallwork B, Coman W, Mackay-Sim A, Cervin A. Effect of clarithromycin on nuclear factor-kappa B and transforming growth factor-beta in chronic rhinosinusitis. Laryngoscope. 2004 Feb;114(2):286-90.

305. Lin A, Busaba NY. Staphylococcus aureus and endoscopic sinus surgery. Current Opinion in Otolaryngology & Head & Neck Surgery. 2006;14(1):19-22.

306. Watelet JB, Demetter P, Claeys C, Van Cauwenberge P, Cuvelier C, Bachert C. Wound healing after paranasal sinus surgery: Neutrophilic inflammation influences the outcome. Histopathology. 2006;48(2):174-81.

307. 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. J Allergy Clin Immunol. 2004 Oct;114(4):981-3.

308. Lal D, Baroody FM, Weitzel EK, DeTineo M, Naclerio RM. Total IgE levels do not change 1 year after endoscopic sinus surgery in patients with chronic rhinosinusitis. International Archives of Allergy & Immunology. 2006;139(2):146-8.

309. Wang C, Dong Z, Guan G, Yang Z. [Expression of inducible nitric oxide synthase mRNA in epithelial cell of nasal mucosa is upregulated through Toll-like receptor-4]. Lin Chuang Er Bi Yan Hou Ke Za Zhi. 2004 May;18(5):268-9.

310. Ragab SM, Lund VJ, Saleh HA, Scadding G. Nasal nitric oxide in objective evaluation of chronic rhinosinusitis therapy. Allergy. 2006;61(6):717-24.

311. Struben VM, Wieringa MH, Feenstra L, de Jongste JC. Nasal nitric oxide and nasal allergy. Allergy. 2006 Jun;61(6):665-70.

312. Baraniuk JNl. Neurogenic mechanisms in rhinosinusitis. Curr Allergy Asthma Rep. 2001;1(3):252-61.

313. Bellamy JL, Cady RK, Durham PL. Salivary levels of CGRP and VIP in rhinosinusitis and migraine patients. Headache. 2006;46(1):24-33.

314. Kim DH, Chu HS, Lee JY, Hwang SJ, Lee SH, Lee HM. Up-regulation of MUC5AC and MUC5B mucin genes in chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2004 Jun;130(6):747-52.

315. Viswanathan H, Brownlee IA, Pearson JP, Carrie S. MUC5B secretion is up-regulated in sinusitis compared with controls. Am J Rhinol. 2006 Sep-Oct;20(5):554-7.

316. Ali MS, Hutton DA, Wilson JA, Pearson JP. Major secretory mucin expression in chronic sinusitis. Otolaryngology - Head & Neck Surgery. 2005;133(3):423-8.

317. Lee HM, Kim DH, Kim JM, Lee SH, Hwang SJ. MUC8 mucin gene up-regulation in chronic rhinosinusitis. Ann Otol Rhinol Laryngol. 2004 Aug;113(8):662-6.

318. Martinez-Anton A, Debolos 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. Clin Exp Allergy. 2006 Apr;36(4):448-57.

319. Martinez-Anton A, Roca-Ferrer J, Mullol J. Mucin gene expression in rhinitis syndromes. Current Allergy & Asthma Reports. 2006;6(3):189-97.

320. Pena A. [A medical history of Bernardo O'Higgins (1778-1842)]. Rev Med Chil. 1999;127(7):862-8.

321. Sun D, Matsune S, Ohori J, Fukuiwa T, Ushikai M, Kurono Y. TNF-a and endotoxin increase hypoxia-induced VEGF production by cultured human nasal fibroblasts in synergistic fashion. Auris, Nasus, Larynx. 2005;32(3):243-9.

322. 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.

323. Lee HM, Kang HJ, Woo JS, Chae SW, Lee SH, Hwang SJ. Upregulation of surfactant protein A in chronic rhinosinusitis. Laryngoscope. 2006 Feb;116(2):328-30.

324. Maniscalco M, Sofia M, Weitzberg E, De Laurentiis G, Stanziola A, Rossillo V, et al. Humming-induced release of nasal nitric oxide for assessment of sinus obstruction in allergic rhinitis: pilot study. Eur J Clin Invest. 2004 Aug;34(8):555-60.

325. Hall-Stoodley L, Stoodley P. Biofilm formation and dispersal and the transmission of human pathogens. Trends Microbiol. 2005 Jan;13(1):7-10.

326. Stoodley P, Sauer K, Davies DG, Costerton JW. Biofilms as complex differentiated communities. Annu Rev Microbiol. 2002;56:187-209.

327. Post JC, Stoodley P, Hall-Stoodley L, Ehrlich GD. The role of biofilms in otolaryngologic infections. Curr Opin Otolaryngol Head Neck Surg. 2004 Jun;12(3):185-90.

328. Harvey R, Lund V. Biofilms and chronic rhinosinusitis: systematic review of evidence, current concepts and directions for research. Rhinology. 45(1):3-13 2007.

329. Cryer J, Schipor I, Perloff JR, Palmer JN. Evidence of bacterial biofilms in human chronic sinusitis. ORL J Otorhinolaryngol Relat Spec. 2004;66(3):155-8.

330. 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.

331. Ferguson BJ, Stolz DB. Demonstration of biofilm in human bacterial chronic rhinosinusitis. American Journal of Rhinology. 2005;19(5):452-7.

332. Palmer JN. Bacterial biofilms: Do they play a role in chronic sinusitis? Otolaryngologic Clinics of North America. 2005;38(6):1193-201.

333. Ramadan HH, Sanclement JA, Thomas JG. Chronic rhinosinusitis and biofilms. Otolaryngology - Head & Neck Surgery. 2005;132(3):414-7.

334. Sanclement JA, Webster P, Thomas J, Ramadan HH. Bacterial biofilms in surgical specimens of patients with chronic rhinosinusitis. Laryngoscope. 2005;115(4):578-82.

335. 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.

336. Bendouah Z, Barbeau J, Hamad WA, Desrosiers M. Use of an in vitro assay for determination of biofilm-forming capacity of bacteria in chronic rhinosinusitis. Am J Rhinol. 2006 Sep-Oct;20(5):434-8.

337. Sanderson AR, Leid JG, Hunsaker D. Bacterial biofilms on the sinus mucosa of human subjects with chronic rhinosinusitis. Laryngoscope. 2006;116(7):1121-6.

338. 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.

339. Taylor M. Histochemical studies on nasal polypi. J Laryngol Otol. 1963;77:326-41.

340. Kakoi H, Hiraide F. A histological study of formation and growth of nasal polyps. Acta Otolaryngol. 1987;103(1-2):137-44.

341. Mygind N LT. Nasal Polyposis: an inflammatory disease and its treatment. Copenhagen: Munksgaard; 1997.

342. Stoop AE, van der Heijden HA, Biewenga J, van der Baan S. Eosinophils in nasal polyps and nasal mucosa: an immunohistochemical study. J Allergy Clin Immunol. 1993;91(2):616-22.

343. Bachert C, Gevaert P, Holtappels G, Cuvelier C, van Cauwenberge Pl. Nasal polyposis: from cytokines to growth. Am J Rhinol. 2000;14(5):279-90.

344. 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.

345. 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.

346. 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. Am J Rhinol. 2006 Jul-Aug;20(4):445-50.

347. 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. Am J Rhinol. 2006 Sep-Oct;20(5):534-9.

348. Conley DB, Tripathi A, Ditto AM, Reid K, Grammer LC, Kern RC. Chronic sinusitis with nasal polyps: Staphylococcal exotoxin immunoglobulin E and cellular inflammation. American Journal of Rhinology. 2004;18(5):273-8.

349. 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. J Allergy Clin Immunol. 2003;111(5):1131-2.

350. Jankowski R. Eosinophils in the pathophysiology of nasal polyposis. Acta Otolaryngol. 1996;116(2):160-3.

351. Sobol SE, Christodoulopoulos P, Manoukian JJ, Hauber HP, Frenkiel S, Desrosiers M, et al. Cytokine profile of chronic sinusitis in patients with cystic fibrosis. Arch Otolaryngol Head Neck Surg. 2002;128(11):1295-8.

352. 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;52(4):436-9.

353. Loesel LS. Immunopathologic study of chronic sinusitis: a proposal for atopic and non-atopic IgE-activated mast cell allergic inflammation. Ann Otol Rhinol Laryngol. 2001;110(5 Pt 1):447-52.

354. Drake-Lee A, Price J. Mast cell ultrastructure in the inferior turbinate and stroma of nasal polyps. J Laryngol Otol. 1997;111(4):340-5.

355. 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.

356. Shin SH, Lee SH, Jeong HS, Kita H. The effect of nasal polyp epithelial cells on eosinophil activation. Laryngoscope. 2003;113(8):1374-7.

357. 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.

358. Watanabe K, Shirasaki H, Kanaizumi E, Himi T. Effects of glucocorticoids on infiltrating cells and epithelial cells of nasal polyps. Ann Otol Rhinol Laryngol. 2004 Jun;113(6):465-73.

359. Seong JK, Koo JS, Lee WJ, Kim HN, Park JY, Song KS, et al. Upregulation of MUC8 and downregulation of MUC5AC by inflammatory mediators in human nasal polyps and cultured nasal epithelium. Acta Otolaryngol. 2002;122(4):401-7.

360. Chen PH, Fang SY. The expression of human antimicrobial peptide LL-37 in the human nasal mucosa. Am J Rhinol. 2004 Nov-Dec;18(6):381-5.

361. Jahnsen FL, Brandtzaeg P, Haye R, Haraldsen G. Expression of functional VCAM-1 by cultured nasal polyp-derived microvascular endothelium. Am J Pathol. 1997;150(6):2113-23.

362. 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. Eur Arch Otorhinolaryngol. 2002;259(6):294-8.

363. Gosepath J, Brieger J, Lehr HA, Mann WJ. Expression, localization, and significance of vascular permeability/vascular endothelial growth factor in nasal polyps. American Journal of Rhinology. 2005;19(1):7-13.

364. Chen PH, Fang SY. Expression of human beta-defensin 2 in human nasal mucosa. Eur Arch Otorhinolaryngol. 2004 May;261(5):238-41.

365. 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. Am J Rhinol. 2006 Jul-Aug;20(4):451-5.

366. 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. Am J Rhinol. 2007 Jan-Feb;21(1):110-6.

367. 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.

368. 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. Clin Exp Allergy. 1995;25(7):607-15.

369. Ohno I, Lea R, Finotto S, Marshall J, Denburg J, Dolovich J, et al. Granulocyte/macrophage colony-stimulating factor (GM-CSF) gene expression by eosinophils in nasal polyposis. Am J Respir Cell Mol Biol. 1991;5(6):505-10.

370. 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. Clin Exp Allergy. 1994;24(4):307-17.

371. 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;158(8):3902-8.

372. Ming YG LC, Rhee CS, et al. Inflammatory cytokine expression on nasal polyps developed in allergic and infectious rhinitis. Acta Otolaryngol Suppl. 1997;117:302.

373. Lee CH, Rhee CS, Min YG. Cytokine gene expression in nasal polyps. Ann Otol Rhinol Laryngol. 1998;107(8):665-70.

374. Wagenmann M G-AM, Helmig P. Increased production of type-2 and type-1 cytokines in nasal polyps. J Allergy Clin Immunol. 2000;105(Supplement):S210.

375. Gevaert P, Bachert C, Holtappels G, Novo CP, Van Der Heyden J, Fransen L, et al. Enhanced soluble interleukin-5 receptor alpha expression in nasal polyposis. Allergy. 2003;58(5):371-9.

376. 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;35(4):171-4.

377. 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;163(3):1545-51.

378. 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.

379. 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. Clin Exp Allergy. 2006 Jan;36(1):52-8.

380. 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. Laryngoscope. 2000;110(8):1353-7.

381. Symon FA, Walsh GM, Watson SR, Wardlaw AJ. Eosinophil adhesion to nasal polyp endothelium is P-selectin-dependent. J Exp Med. 1994;180(1):371-6.

382. 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;12(6):624-32.

383. Tingsgaard PK, Bock T, Larsen PL, Tos M. Topical budesonide treatment reduces endothelial expression of intercellular adhesion molecules (vascular cell adhesion molecule-1 and P-selectin) and eosinophil infiltration in nasal polyps. Acta Otolaryngol. 1999;119(3):362-8.

384. Palframan RT, Collins PD, Severs NJ, Rothery S, Williams TJ, Rankin SM. Mechanisms of acute eosinophil mobilization from the bone marrow stimulated by interleukin 5: the role of specific adhesion molecules and phosphatidylinositol 3-kinase. J Exp Med. 1998;188(9):1621-32.

385. Baenkler HW, Schafer D, Hosemann Wl. Eicosanoids from biopsy of normal and polypous nasal mucosa. Rhinology. 1996;34(3):166-70.

386. Klapan I, Culo F, Culig J, Bukovec Z, Simovic S, Viseslav C, et al. Arachidonic acid metabolites and sinonasal polyposis. I. Possible prognostic value. Am J Otolaryngol. 1995;16(6):396-402.

387. Szczeklik A, Sladek K, Dworski R, Nizankowska E, Soja J, Sheller J, et al. Bronchial aspirin challenge causes specific eicosanoid response in aspirin-sensitive asthmatics. Am J Respir Crit Care Med. 1996;154(6 Pt 1):1608-14.

388. Kowalski ML, Sliwinska-Kowalska M, Igarashi Y, White MV, Wojciechowska B, Brayton P, et al. Nasal secretions in response to acetylsalicylic acid. J Allergy Clin Immunol. 1993;91(2):580-98.

389. 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.

390. Kedda MA, Shi J, Duffy D, Phelps S, Yang I, O'Hara K, et al. Characterization of two polymorphisms in the leukotriene C4 synthase gene in an Australian population of subjects with mild, moderate, and severe asthma. J Allergy Clin Immunol. 2004 May;113(5):889-95.

391. Chao SS, Graham SM, Brown CL, Kline JN, Hussain I. Cysteinyl leukotriene 1 receptor expression in nasal polyps. Annals of Otology, Rhinology & Laryngology. 2006;115(5):394-7.

392. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH. Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl J Med. 2002;347(19):1493-9.

393. Figueroa DJ, Borish L, Baramki D, Philip G, Austin CP, Evans JF. Expression of cysteinyl leukotriene synthetic and signalling proteins in inflammatory cells in active seasonal allergic rhinitis. Clin Exp Allergy. 2003 Oct;33(10):1380-8.

394. Maclouf JA, Murphy RC. Transcellular metabolism of neutrophil-derived leukotriene A4 by human platelets. A potential cellular source of leukotriene C4. J Biol Chem. 1988 Jan 5;263(1):174-81.

395. 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. J Allergy Clin Immunol. 2002;109(5):824-30.

396. Gosepath J, Brieger J, Gletsou E, Mann WJ. Expression and localization of cyclooxigenases (Cox-1 and Cox-2) in nasal respiratory mucosa. Does Cox-2 play a key role in the immunology of nasal polyps? J Investig Allergol Clin Immunol. 2004;14(2):114-8.

397. Smith WL, Dewitt DL. Prostaglandin endoperoxide H synthases-1 and -2. Adv Immunol. 1996;62:167-215.

398. 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. Am J Respir Crit Care Med. 1999;160(1):291-6.

399. Pinto S, Gallo O, Polli G, Boccuzzi S, Paniccia R, Brunelli T, et al. Cyclooxygenase and lipoxygenase metabolite generation in nasal polyps. Prostaglandins Leukot Essent Fatty Acids. 1997;57(6):533-7.

400. 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.

401. 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.

402. 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.

403. McMahon B, Godson C. Lipoxins: endogenous regulators of inflammation. Am J Physiol Renal Physiol. 2004 Feb;286(2):F189-201.

404. Maddox JF, Serhan CN. Lipoxin A4 and B4 are potent stimuli for human monocyte migration and adhesion: selective inactivation by dehydrogenation and reduction. J Exp Med. 1996 Jan 1;183(1):137-46.

405. Edenius C, Kumlin M, Bjork T, Anggard A, Lindgren JA. Lipoxin formation in human nasal polyps and bronchial tissue. FEBS Lett. 1990;272(1-2):25-8.

406. Chu HW, Balzar S, Westcott JY, Trudeau JB, Sun Y, Conrad DJ, et al. Expression and activation of 15-lipoxygenase pathway in severe asthma: relationship to eosinophilic phenotype and collagen deposition. Clin Exp Allergy. 2002 Nov;32(11):1558-65.

407. Sanak M, Levy BD, Clish CB, Chiang N, Gronert K, Mastalerz L, et al. Aspirin-tolerant asthmatics generate more lipoxins than aspirin-intolerant asthmatics. Eur Respir J. 2000 Jul;16(1):44-9.

408. 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.

409. Kanai K, Asano K, Hisamitsu T, Suzaki H. Suppression of matrix metalloproteinase production from nasal fibroblasts by macrolide antibiotics in vitro. Eur Respir J. 2004 May;23(5):671-8.

410. Parikh A, Scadding GK, Gray P, Belvisi MG, Mitchell JA. High levels of nitric oxide synthase activity are associated with nasal polyp tissue from aspirin-sensitive asthmatics. Acta Otolaryngol. 2002;122(3):302-5.

411. Donovan R, Johansson SG, Bennich H, Soothill JF. Immunoglobulins in nasal polyp fluid. Int Arch Allergy Appl Immunol. 1970;37(2):154-66.

412. 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.

413. 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. Laryngoscope. 2004 Oct;114(10):1822-6.

414. 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. Clin Exp Allergy. 2004 Aug;34(8):1270-5.

415. 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 [6]. Journal of Allergy & Clinical Immunology. 2004;114(4):981-3.

416. 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.

417. Hofer MF, Harbeck RJ, Schlievert PM, Leung DY. Staphylococcal toxins augment specific IgE responses by atopic patients exposed to allergen. J Invest Dermatol. 1999;112(2):171-6.

418. Jabara HH, Geha RS. The superantigen toxic shock syndrome toxin-1 induces CD40 ligand expression and modulates IgE isotype switching. Int Immunol. 1996;8(10):1503-10.

419. Roben PW, Salem AN, Silverman GJ. VH3 family antibodies bind domain D of staphylococcal protein A. J Immunol. 1995;154(12):6437-45.

420. Bachert C, Gevaert P, van Cauwenberge P. Staphylococcus aureus enterotoxins: a key in airway disease? Allergy. 2002;57(6):480-7.

421. Herz U, Ruckert R, Wollenhaupt K, Tschernig T, Neuhaus-Steinmetz U, Pabst R, et al. Airway exposure to bacterial super-antigen (SEB) induces lymphocyte-dependent airway inflammation associated with increased airway responsiveness--a model for non-allergic asthma. Eur J Immunol. 1999 Mar;29(3):1021-31.

422. 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. Clin Exp Allergy. 2006 Aug;36(8):1063-71.

423. Rohde G, Gevaert P, Holtappels G, Borg I, Wiethege A, Arinir U, et al. Increased IgE-antibodies to Staphylococcus aureus enterotoxins in patients with COPD. Respir Med. 2004 Sep;98(9):858-64.

424. Carrabino S, Carpani D, Livraghi A, Di Cicco M, Costantini D, Copreni E, et al. Dysregulated interleukin-8 secretion and NF-kappaB activity in human cystic fibrosis nasal epithelial cells. Journal of Cystic Fibrosis. 2006;5(2):113-9.

425. 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.

426. Hauber HP, Manoukian JJ, Nguyen LH, Sobol SE, Levitt RC, Holroyd KJ, et al. Increased expression of interleukin-9, interleukin-9 receptor, and the calcium-activated chloride channel hCLCA1 in the upper airways of patients with cystic fibrosis. Laryngoscope. 2003;113(6):1037-42.

427. 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. 1995;50(3):270-4.

428. Bachert C, Gevaert P, Holtappels G, Johansson SG, van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol. 2001 Apr;107(4):607-14.

429. 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.

430. Samter M, Beers RF, Jr. Intolerance to aspirin. Clinical studies and consideration of its pathogenesis. Ann Intern Med. 1968;68(5):975-83.

431. Jantti-Alanko S, Holopainen E, Malmberg H. Recurrence of nasal polyps after surgical treatment. Rhinol Suppl. 1989;8:59-64.

432. McFadden EA, Kany RJ, Fink JN, Toohill RJ. Surgery for sinusitis and aspirin triad. Laryngoscope. 1990;100(10 Pt 1):1043-6.

433. Kowalski ML. Rhinosinusitis and nasal polyposis in aspirin sensitive and aspirin tolerant patients: are they different? Thorax. 2000;55(Suppl 2):S84-6.

434. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. J Allergy Clin Immunol. 2006 Oct;118(4):773-86; quiz 87-8.

435. 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;1(5949):67-9.

436. 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. Clin Exp Allergy. 1996;26(7):807-14.

437. 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.

438. 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. J Allergy Clin Immunol. 1994 Dec;94(6 Pt 1):1046-56.

439. 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;145(1):65-9.

440. Pawliczak R, Lewandowska-Polak A, Kowalski ML. Pathogenesis of nasal polyps: An update. Current Allergy & Asthma Reports. 2005;5(6):463-71.

441. 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.

442. 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). Clin Exp Allergy. 1998;28(9):1145-52.

443. 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. Eur Respir J. 1999;14(3):610-5.

444. 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.

445. 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;57(6):493-500.

446. Pawankar R. Nasal polyposis: an update: editorial review. Curr Opin Allergy Clin Immunol. 2003;3(1):1-6.

447. 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;9(5):415-25.

448. 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. Am J Respir Crit Care Med. 2000;161(2 Pt 1):391-8.

449. 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. J Allergy Clin Immunol. 2004 10;114(4):814-9.

450. 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;58(2):122-6.

451. 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.

452. Jung TT, Juhn SK, Hwang D, Stewart R. Prostaglandins, leukotrienes, and other arachidonic acid metabolites in nasal polyps and nasal mucosa. Laryngoscope. 1987;97(2):184-9.

453. Gray PA, Warner TD, Vojnovic I, Del Soldato P, Parikh A, Scadding GK, et al. Effects of non-steroidal anti-inflammatory drugs on cyclo-oxygenase and lipoxygenase activity in whole blood from aspirin-sensitive asthmatics vs healthy donors. Br J Pharmacol. 2002 Dec;137(7):1031-8.

454. 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.

455. 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.

456. 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.

457. Lund VJ, Kennedy DW. Quantification for staging sinusitis. The Staging and Therapy Group. Ann Otol Rhinol Laryngol Suppl. 1995;167:17-21.

458. Spector SL, Bernstein IL, Li JT, Berger WE, Kaliner MA, Schuller DE, et al. Parameters for the diagnosis and management of sinusitis. J Allergy Clin Immunol. 1998 Dec;102(6 Pt 2):S107-44.

459. Damm M, Quante G, Jungehuelsing M, Stennert E. Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. Laryngoscope. 2002;112(2):310-5.

460. O'Hara J, Jones NS. "Post-nasal drip syndrome": most patients with purulent nasal secretions do not complain of chronic cough. Rhinology. 2006 Dec;44(4):270-3.

461. Benninger MS, Senior BA. The development of the Rhinosinusitis Disability Index. Arch Otolaryngol Head Neck Surg. 1997;123(11):1175-9.

462. Metson RB, Gliklich RE. Clinical outcomes in patients with chronic sinusitis. Laryngoscope. 2000;110(3 Pt 3):24-8.

463. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.

464. Anderson RT, Aaronson NK, Wilkin D. Critical review of the international assessments of health-related quality of life. Qual Life Res. 1993;2(6):369-95.

465. Piccirillo JF, Merritt MG, Jr., Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). Otolaryngol Head Neck Surg. 2002;126(1):41-7.

466. Fairley JW, Durham LH, Ell SR. Correlation of subjective sensation of nasal patency with nasal inspiratory peak flow rate. Clin Otolaryngol. 1993;18(1):19-22.

467. 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.

468. Simola M, Malmberg H. Sensation of nasal airflow compared with nasal airway resistance in patients with rhinitis. Clin Otolaryngol. 1997;22(3):260-2.

469. Hirschberg A, Rezek O. Correlation between objective and subjective assessments of nasal patency. ORL J Otorhinolaryngol Relat Spec. 1998;60(4):206-11.

470. Numminen J, Ahtinen M, Huhtala H, Rautiainen M. Comparison of rhinometric measurements methods in intranasal pathology. Rhinology. 2003;41(2):65-8.

471. Jones AS, Willatt DJ, Durham LM. Nasal airflow: resistance and sensation. J Laryngol Otol. 1989;103(10):909-11.

472. Eccles R, Jones AS. The effect of menthol on nasal resistance to air flow. J Laryngol Otol. 1983 Aug;97(8):705-9.

473. 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.

474. Szucs E, Clement PA. Acoustic rhinometry and rhinomanometry in the evaluation of nasal patency of patients with nasal septal deviation. Am J Rhinol. 1998;12(5):345-52.

475. 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.

476. 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.

477. Amoore JE, Ollman BG. Practical test kits for quantitatively evaluating the sense of smell. Rhinology. 1983;21(1):49-54.

478. Cain WS. Testing olfaction in a clinical setting. Ear Nose Throat J. 1989;68(4):316, 22-8.

479. Simola M. Allergic and non-allergic rhinitis: a long-term clinical follow-up study. Helsinki: Helsinki University; 2001.

480. 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.

481. 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.

482. Jones NS, Cooney TR. Facial pain and sinonasal surgery. Rhinology. 2003 Dec;41(4):193-200.

483. Mudgil SP, Wise SW, Hopper KD, Kasales CJ, Mauger D, Fornadley JA. Correlation between presumed sinusitis-induced pain and paranasal sinus computed tomographic findings. Ann Allergy Asthma Immunol. 2002 Feb;88(2):223-6.

484. Linder A. Symptom scores as measures of the severity of rhinitis. Clin Allergy. 1988 Jan;18(1):29-37.

485. Gliklich RE, Metson R. Techniques for outcomes research in chronic sinusitis. Laryngoscope. 1995;105(4 Pt 1):387-90.

486. Gliklich RE, Metson R. Effect of sinus surgery on quality of life. Otolaryngol Head Neck Surg. 1997;117(1):12-7.

487. Metson R, Gliklich RE. Clinical outcome of endoscopic surgery for frontal sinusitis. Arch Otolaryngol Head Neck Surg. 1998;124(10):1090-6.

488. Hoffman SR, Mahoney MC, Chmiel JF, Stinziano GD, Hoffman KN. Symptom relief after endoscopic sinus surgery: an outcomes-based study. Ear Nose Throat J. 1993;72(6):413-4, 9-20.

489. Annamalai S, Kumar NA, Madkour MB, Sivakumar S, Kubba H. An association between acquired epiphora and the signs and symptoms of chronic rhinosinusitis: A prospective case-control study. American Journal of Rhinology. 2003;17(2):111-4.

490. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology. 1993;31(4):183-4.

491. Lildholdt T, Rundcrantz H, Lindqvist N. Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. Clin Otolaryngol. 1995;20(1):26-30.

492. Johansson L, Akerlund A, Holmberg K, Melen I, Stierna P, Bende M. Evaluation of methods for endoscopic staging of nasal polyposis. Acta Otolaryngol. 2000;120(1):72-6.

493. Lildholdt T, Rundcrantz H, Bende M, Larsen K. Glucocorticoid treatment for nasal polyps. The use of topical budesonide powder, intramuscular betamethasone, and surgical treatment. Arch Otolaryngol Head Neck Surg. 1997;123(6):595-600.

494. Klossek JM, Dubreuil L, Richet H, Richet B, Sedallian A, Beutter P. Bacteriology of the adult middle meatus. J Laryngol Otol. 1996;110(9):847-9.

495. Gold SM, Tami TA. Role of middle meatus aspiration culture in the diagnosis of chronic sinusitis. Laryngoscope. 1997;107(12 Pt 1):1586-9.

496. Vogan JC, Bolger WE, Keyes AS. Endoscopically guided sinonasal cultures: a direct comparison with maxillary sinus aspirate cultures. Otolaryngol Head Neck Surg. 2000 Mar;122(3):370-3.

497. Casiano RR, Cohn S, Villasuso E, 3rd, Brown M, Memari F, Barquist E, et al. Comparison of antral tap with endoscopically directed nasal culture. Laryngoscope. 2001;111(8):1333-7.

498. 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.

499. 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 & Neck Surgery. 2006;134(1):3-9.

500. Talbot GH, Kennedy DW, Scheld WM, Granito K. Rigid nasal endoscopy versus sinus puncture and aspiration for microbiologic documentation of acute bacterial maxillary sinusitis. Clin Infect Dis. 2001 Nov 15;33(10):1668-75.

501. Jonas I, Mann W. [Misleading x-ray diagnosis due to maxillary sinus asymmetries (author's transl)]. Laryngol Rhinol Otol (Stuttg). 1976;55(11):905-13.

502. 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;153(6):1259-64.

503. Iinuma T, Hirota Y, Kase Y. Radio-opacity of the paranasal sinuses. Conventional views and CT. Rhinology. 1994;32(3):134-6.

504. Landman MD. Ultrasound screening for sinus disease. Otolaryngol Head Neck Surg. 1986;94(2):157-64.

505. Otten FW, Grote JJ. The diagnostic value of transillumination for maxillary sinusitis in children. Int J Pediatr Otorhinolaryngol. 1989;18(1):9-11.

506. 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.

507. 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.

508. Kazkayasi M, Karadeniz Y, Arikan OK. Anatomic variations of the sphenoid sinus on computed tomography. Rhinology. 2005;43(2):109-14.

509. 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.

510. 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.

511. Badia L, Lund VJ, Wei W, Ho WK. Ethnic variation in sinonasal anatomy on CT-scanning. Rhinology. 2005 Sep;43(3):210-4.

512. 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.

513. Friedman WH, Katsantonis GP, Sivore M, Kay S. Computed tomography staging of the paranasal sinuses in chronic hyperplastic rhinosinusitis. Laryngoscope. 1990;100(11):1161-5.

514. Kennedy DW. Prognostic factors, outcomes and staging in ethmoid sinus surgery. Laryngoscope. 1992;102(12 Pt 2 Suppl 57):1-18.

515. Glicklich R, Metson R. A comparison of sinus computed tomography (CT) staging system for outcomes research. Am J Rhinol. 1994;8:291-7.

516. Jorgensen RA. Endoscopic and computed tomographic findings in ostiomeatal sinus disease. Arch Otolaryngol Head Neck Surg. 1991;117(3):279-87.

517. Gaskins RE. A surgical staging system for chronic sinusitis. Am J Rhinol. 1992;6:5-12.

518. 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.

519. Smith TL, Batra PS, Seiden AM, Hanley M. Evidence supporting endoscopic sinus surgery in the management of adult chronic rhinosinusitis: A systematic review. American Journal of Rhinology. 2005;19(6):537-43.

520. Browne JP, Hopkins C, Slack R, Topham J, Reeves B, Lund V, et al. Health-related quality of life after polypectomy with and without additional surgery. Laryngoscope. 2006 Feb;116(2):297-302.

521. 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. Laryngoscope. 2006;116(8):1494-9.

522. 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.

523. Bhattacharyya N. A comparison of symptom scores and radiographic staging systems in chronic rhinosinusitis. American Journal of Rhinology. 2005;19(2):175-9.

524. Ashraf N, Bhattacharyya Nl. Determination of the "incidental" Lund score for the staging of chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2001;125(5):483-6.

525. Hill M, Bhattacharyya N, Hall TR, Lufkin R, Shapiro NL. Incidental paranasal sinus imaging abnormalities and the normal Lund score in children. Otolaryngol Head Neck Surg. 2004 Feb;130(2):171-5.

526. Andersen I, Camner P, Jensen PL, Philipson K, Proctor DF. Nasal clearance in monozygotic twins. Am Rev Respir Dis. 1974;110(3):301-5.

527. 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.

528. 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.

529. 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. Eur Arch Otorhinolaryngol. 1999;256(7):335-7.

530. Rutland J, Dewar A, Cox T, Cole P. Nasal brushing for the study of ciliary ultrastructure. J Clin Pathol. 1982;35(3):357-9.

531. 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 May;112(5):845-51.

532. 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.

533. Abdel-Hak B, Gunkel A, Kanonier G, Schrott-Fischer A, Ulmer H, Thumfart Wl. Ciliary beat frequency, olfaction and endoscopic sinus surgery. ORL J Otorhinolaryngol Relat Spec. 1998;60(4):202-5.

534. 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. Eur Respir J. 1991 Feb;4(2):210-7.

535. Colantonio D, Brouillette L, Parikh A, Scadding GK. Paradoxical low nasal nitric oxide in nasal polyposis. Clin Exp Allergy. 2002;32(5):698-701.

536. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. Laryngoscope. 2004 May;114(5):923-30.

537. 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.

538. Lund VJ, Flood J, Sykes AP, Richards DH. Effect of fluticasone in severe polyposis. Arch Otolaryngol Head Neck Surg. 1998;124(5):513-8.

539. Ottaviano G, Scadding GK, Coles S, Lund VJ. Peak nasal inspiratory flow; normal range in adult population. Rhinology. 2006 Mar;44(1):32-5.

540. Braat JP, Fokkens WJ, Mulder PG, Kianmaneshrad N, Rijntjes E, Gerth van Wijk R. Forced expiration through the nose is a stimulus for NANIPER but not for controls. Rhinology. 2000 Dec;38(4):172-6.

541. 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.

542. Numminen J, Dastidar P, Heinonen T, Karhuketo T, Rautiainen M. Reliability of acoustic rhinometry. Respir Med. 2003;97(4):421-7.

543. 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.

544. Grudemo H, Juto JE. Intranasal histamine challenge in normal subjects and allergic rhinitis before and after intranasal budesonide studied with rhinostereometry and micromanipulator-guided laser Doppler flowmetry. ORL J Otorhinolaryngol Relat Spec. 2000 Jan-Feb;62(1):33-8.

545. Amoore JE. Odor standards in squeeze bottlekits for matching quality and intensity. Wat Sci Tech. 1992;25:1-9.

546. 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.

547. Delank KW, Stoll W. Olfactory function after functional endoscopic sinus surgery for chronic sinusitis. Rhinology. 1998;36(1):15-9.

548. 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;32(3):489-502.

549. Simmen D. Screeningtest des Geruchssinnes mit Riechdisketten. Laryngorhinootologie. 1998;77:1-6.

550. Briner HR, Simmen D, Jones N. Impaired sense of smell in patients with nasal surgery. Clin Otolaryngol. 2003 Oct;28(5):417-9.

551. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin' sticks": screening of olfactory performance. Rhinology. 1996;34(4):222-6.

552. 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.

553. Gerth van Wijk R, Dieges PH. Nasal hyper-responsiveness to histamine, methacholine and phentolamine in patients with perennial non-allergic rhinitis and in patients with infectious rhinitis. Clin Otolaryngol. 1991 Apr;16(2):133-7.

554. Simola M, Malmberg H. Sense of smell in allergic and nonallergic rhinitis. Allergy. 1998;53(2):190-4.

555. Stevenson DD. Diagnosis, prevention, and treatment of adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs. J Allergy Clin Immunol. 1984;74(4 Pt 2):617-22.

556. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. J Allergy Clin Immunol. 2003 May;111(5):913-21; quiz 22.

557. Nizankowska E, Bestynska-Krypel A, Cmiel A, Szczeklik A. Oral and bronchial provocation tests with aspirin for diagnosis of aspirin-induced asthma. Eur Respir J. 2000 May;15(5):863-9.

558. Dahlen B, Zetterstrom O. Comparison of bronchial and per oral provocation with aspirin in aspirin-sensitive asthmatics. Eur Respir J. 1990 May;3(5):527-34.

559. Schmitz-Schumann M, Schaub E, Virchow C. [Inhalation provocation test with lysine-acetylsalicylic acid in patients with analgetics-induced asthma (author's transl)]. Prax Klin Pneumol. 1982 Jan;36(1):17-21.

560. Phillips GD, Foord R, Holgate ST. Inhaled lysine-aspirin as a bronchoprovocation procedure in aspirin-sensitive asthma: its repeatability, absence of a late-phase reaction, and the role of histamine. J Allergy Clin Immunol. 1989 Aug;84(2):232-41.

561. Melillo G, Balzano G, Bianco S, Dahlen B, Godard P, Kowalsky ML, et al. Report of the INTERASMA Working Group on Standardization of Inhalation Provocation Tests in Aspirin-induced Asthma. Oral and inhalation provocation tests for the diagnosis of aspirin-induced asthma. Allergy. 2001 Sep;56(9):899-911.

562. Ortolani C, Mirone C, Fontana A, Folco GC, Miadonna A, Montalbetti N, et al. Study of mediators of anaphylaxis in nasal wash fluids after aspirin and sodium metabisulfite nasal provocation in intolerant rhinitic patients. Ann Allergy. 1987 Nov;59 (5 Pt 2):106-12.

563. Patriarca G, Nucera E, DiRienzo V, Schiavino D, Pellegrino S, Fais G. Nasal provocation test with lysine acetylsalicylate in aspirin-sensitive patients. Ann Allergy. 1991 Jul;67(1):60-2.

564. Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Dahlén B, Dahlén S-E, Picado C, et al. EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. . J Allergy. Allergy 2007; june in press.

565. Cambau E. [C-reactive protein: general review and role in the study of infections]. Pathol Biol (Paris). 1988 Dec;36(10):1232-6.

566. Ahlers AA, Schonheyder HC. [C-reactive protein in patients with infection]. Ugeskr Laeger. 1990 Dec 31;153(1):13-6.

567. Hansen JG, Dahler-Eriksen BS. [C-reactive protein and infections in general practice]. Ugeskr Laeger. 2000 Apr 24;162(17):2457-60.

568. Radenne F, Lamblin C, Vandezande LM, Tillie-Leblond I, Darras J, Tonnel AB, et al. Quality of life in nasal polyposis. J Allergy Clin Immunol. 1999;104(1):79-84.

569. Winstead W, Barnett SN. Impact of endoscopic sinus surgery on global health perception: an outcomes study. Otolaryngol Head Neck Surg. 1998;119(5):486-91.

570. Linder JA, Singer DE, Ancker M, Atlas SJ. Measures of health-

related quality of life for adults with acute sinusitis. J Gen Intern Med. 2003;18(5):390-401.

571. Salhab M, Matai V, Salam MA. The impact of functional endoscopic sinus surgery on health status. Rhinology. 2004 Jun;42(2):98-102.

572. van Agthoven M, Fokkens WJ, van de Merwe JP, Marijke van Bolhuis E, Uyl-de Groot CA, Busschbach JJ. Quality of life of patients with refractory chronic rhinosinusitis: effects of filgrastim treatment. Am J Rhinol. 2001;15(4):231-7.

573. Videler WJM, Wreesmann VB, Van Der Meulen FW, Knegt PP, Fokkens WJ. Repetitive endoscopic sinus surgery failure: A role for radical surgery? Otolaryngology - Head & Neck Surgery. 2006;134(4):586-91.

574. Piccirillo JF ED, Haiduk A et al. Psychometric and clinimetric validity of the 3-item rhinosinusitis outcome measure (RSOM-31). Am J Rhinol. 1995;9:297-306.

575. Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - Which is best? Clinical Otolaryngology. 2006;31(2):103-9.

576. 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.

577. Browne J, Hopkins J, Hopkins C, Slack R, van der Meulen J, Lund V, et al. The National Comparative Audit of Surgery for Nasal Polyposis and Chronic Rhinosinusitis. Royal College of Surgeons of England 2003. 2003.

578. Anderson ER, Murphy MP, Weymuller EA, Jr. Clinimetric evaluation of the Sinonasal Outcome Test-16. Student Research Award 1998. Otolaryngol Head Neck Surg. 1999;121(6):702-7.

579. Senior BA, Glaze C, Benninger MS. Use of the Rhinosinusitis Disability Index (RSDI) in rhinologic disease. Am J Rhinol. 2001;15(1):15-20.

580. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy. 1991;21(1):77-83.

581. Friedman M, Vidyasagar R, Joseph N. A randomized, prospective, double-blind study on the efficacy of Dead Sea salt nasal irrigations. Laryngoscope. 2006;116(6):878-82.

582. 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. 2005;14(5):1375-86.

583. Revicki DA, Leidy NK, Brennan-Diemer F, Thompson C, Togias A. Development and preliminary validation of the multiattribute Rhinitis Symptom Utility Index. Qual Life Res. 1998;7(8):693-702.

584. Kay DJ, Rosenfeld RM. Quality of life for children with persistent sinonasal symptoms. Otolaryngol Head Neck Surg. 2003;128(1):17-26.

585. Rudnick EF, Mitchell RB. Improvements in quality of life in children after surgical therapy for sinonasal disease. Otolaryngology - Head & Neck Surgery. 2006;134(5):737-40.

586. Durr DG, Desrosiers MY, Dassa C. Quality of life in patients with rhinosinusitis. J Otolaryngol. 1999;28(2):108-11.

587. 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.

588. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg. 1995;113(1):104-9.

589. 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;116(3):185-9.

590. Mendolia-Loffredo S, Laud PW, Sparapani R, Loehrl TA, Smith TL. Sex differences in outcomes of sinus surgery. Laryngoscope. 2006;116(7):1199-203.

591. Gliklich RE, Hilinski JM. Longitudinal sensitivity of generic and specific health measures in chronic sinusitis. Qual Life Res. 1995;4(1):27-32.

592. Wang PC, Tai CJ, Lin MS, Chu CC, Liang SC. Quality of life in Taiwanese adults with chronic rhino-sinusitis. Qual Life Res. 2003;12(4):443-8.

593. Aukema AA, Fokkens WJ. Chronic rhinosinusitis: management for optimal outcomes. Treat Respir Med. 2004;3(2):97-105.

594. Khalid AN, Quraishi SA, Kennedy DW. Long-term quality of life measures after functional endoscopic sinus surgery. Am J Rhinol. 2004 May-Jun;18(3):131-6.

595. 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;109(1):6-11.

596. 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. Clin Exp Allergy. 1997;27(12):1432-41.

597. 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. Respir Med. 2000;94(5):428-31.

598. 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. Eur Respir J. 1997;10(7):1489-95.

599. 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. Respir Med. 2001;95(5):408-14.

600. Leung DY, Bloom JW. Update on glucocorticoid action and resistance. J Allergy Clin Immunol. 2003;111(1):3-22; quiz 3.

601. 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. 2002;283(4):C1324-31.

602. Oakley RH, Sar M, Cidlowski JA. The human glucocorticoid receptor beta isoform. Expression, biochemical properties, and putative function. J Biol Chem. 1996;271(16):9550-9.

603. 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. Respir Med. 2003;97(1):90-6.

604. 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. J Allergy Clin Immunol. 2001;108(1):59-68.

605. Knutsson PU, Bronnegard M, Marcus C, Stierna P. Regulation of glucocorticoid receptor mRNA in nasal mucosa by local administration of fluticasone and budesonide. J Allergy Clin Immunol. 1996;97(2):655-61.

606. 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;24(1):49-57.

607. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: Comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. Journal of Allergy & Clinical Immunology. 2005;116(6):1289-95.

608. Qvarnberg Y, Kantola O, Salo J, Toivanen M, Valtonen H, Vuori E. Influence of topical steroid treatment on maxillary sinusitis. Rhinology. 1992;30(2):103-12.

609. 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. J Allergy Clin Immunol. 1993;92(6):812-23.

610. 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. Ann Allergy Asthma Immunol. 1997;78(6):598-601.

611. 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. J Allergy Clin Immunol. 2000;106(4):630-7.

612. Dolor RJ, Witsell DL, Hellkamp AS, Williams JW, Jr., Califf RM, Simel DL. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. Jama. 2001;286(24):3097-105.

613. Nayak AS, Settipane GA, Pedinoff A, Charous BL, Meltzer EO, Busse WW, et al. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. Ann Allergy Asthma Immunol. 2002;89(3):271-8.

614. 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.

615. 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]. Presse Med. 2004 Mar 13;33(5):303-9.

616. Puhakka T, Makela MJ, Malmstrom K, Uhari M, Savolainen J, Terho EO, et al. The common cold: effects of intranasal fluticasone propionate treatment. J Allergy Clin Immunol. 1998 Jun;101(6 Pt 1):726-31.

617. Cook PR. J Allergy Clin Immunol 2002 Feb(1):39-56.

618. 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;39(2):75-9.

619. 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. Laryngoscope. 2002;112(5):858-64.

620. 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.

621. 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;2(8503):359-60.

622. 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.

623. Mygind N, Pedersen CB, Prytz S, Sorensen H. Treatment of nasal polyps with intranasal beclomethasone dipropionate aerosol. Clin Allergy. 1975;5(2):159-64.

624. Deuschl H, Drettner B. Nasal polyps treated by beclomethasone nasal aerosol. Rhinology. 1977;15(1):17-23.

625. Holopainen E, Grahne B, Malmberg H, Makinien J, Lindqvist N. Budesonide in the treatment of nasal polyposis. Eur J Respir Dis Suppl. 1982;122:221-8.

626. 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. Am J Rhinol. 1998;12(3):183-9.

627. Vendelo Johansen L, Illum P, Kristensen S, Winther L, Vang Petersen S, Synnerstad B. The effect of budesonide (Rhinocort) in the treatment of small and medium-sized nasal polyps. Clin Otolaryngol. 1993;18(6):524-7.

628. Holmberg K, Juliusson S, Balder B, Smith DL, Richards DH, Karlsson G. Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. Ann Allergy Asthma Immunol. 1997;78(3):270-6.

629. Keith P, Nieminen J, Hollingworth K, Dolovich J. Efficacy and tolerability of fluticasone propionate nasal drops 400 microgram once daily compared with placebo for the treatment of bilateral polyposis in adults. Clin Exp Allergy. 2000;30(10):1460-8.

630. Penttila M, Poulsen P, Hollingworth K, Holmstrom M. Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 microg once daily and twice daily in the treatment of bilateral nasal polyposis: a placebo-controlled randomized study in adult patients. Clin Exp Allergy. 2000;30(1):94-102.

631. Hadfield PJ, Rowe-Jones JM, Mackay IS. A prospective treatment trial of nasal polyps in adults with cystic fibrosis. Rhinology. 2000;38(2):63-5.

632. 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. Journal of Allergy & Clinical Immunology. 2005;116(6):1275-81.

633. 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;132(2):179-85.

634. 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.

635. Aukema AAC, Mulder PGH, Fokkens WJ. Treatment of nasal polyposis and chronic rhinosinusitis with fluticasone propionate nasal drops reduces need for sinus surgery. Journal of Allergy & Clinical Immunology. 2005;115(5):1017-23.

636. 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.

637. 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. 2006 Mar;44(1):26-31.

638. 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. Clin Otolaryngol. 1998;23(1):69-73.

639. 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. Ann Allergy Asthma Immunol. 2006 Apr;96(4):514-25.

640. Skoner D. Update of growth effects of inhaled and intranasal corticosteroids. Curr Opin Allergy Clin Immunol. 2002 Feb;2(1):7-10.

641. Lildholdt T, Fogstrup J, Gammelgaard N, Kortholm B, Ulsoe C. Surgical versus medical treatment of nasal polyps. Acta Otolaryngol. 1988;105(1-2):140-3.

642. van Camp C, Clement PA. Results of oral steroid treatment in nasal polyposis. Rhinology. 1994;32(1):5-9.

643. Damm M, Jungehulsing M, Eckel HE, Schmidt M, Theissen P. Effects of systemic steroid treatment in chronic polypoid rhinosinusitis evaluated with magnetic resonance imaging. Otolaryngol Head Neck Surg. 1999;120(4):517-23.

644. 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. Laryngoscope. 2006;116(5):770-5.

645. Sean C. Sweetman, Paul S. Blake, Julie M. McGlashan, C. G. Martindale: the complete Drug reference. London: Pharmaceutical Press.

646. Drettner B, Ebbesen A, Nilsson M. Prophylactive treatment with flunisolide after polypectomy. Rhinology. 1982;20(3):149-58.

647. Virolainen E, Puhakka H. The effect of intranasal beclomethasone dipropionate on the recurrence of nasal polyps after ethmoidectomy. Rhinology. 1980;18(1):9-18.

648. Karlsson G, Rundcrantz H. A randomized trial of intranasal

beclomethasone dipropionate after polypectomy. Rhinology. 1982;20(3):144-8.

649. Dingsor G, Kramer J, Olsholt R, Soderstrom 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):49-58.

650. Hartwig S, Linden M, Laurent C, Vargo AK, Lindqvist N. Budesonide nasal spray as prophylactic treatment after polypectomy (a double blind clinical trial). J Laryngol Otol. 1988;102(2):148-51.

651. 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. Clin Exp Allergy. 2004 Sep;34(9):1395-400.

652. 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.

653. Cave A, Arlett P, Lee E. Inhaled and nasal corticosteroids: factors affecting the risks of systemic adverse effects. Pharmacol Ther. 1999 Sep;83(3):153-79.

654. Licata AA. Systemic effects of fluticasone nasal spray: report of 2 cases. Endocr Pract. 2005 May-Jun;11(3):194-6.

655. Allen DB. Effects of inhaled steroids on growth, bone metabolism, and adrenal function. Adv Pediatr. 2006;53:101-10.

656. Cervin A, Andersson M. Intranasal steroids and septum perforation--an overlooked complication? A description of the course of events and a discussion of the causes. Rhinology. 1998 Sep;36(3):128-32.

657. Walsh LJ, Lewis SA, Wong CA, Cooper S, Oborne J, Cawte SA, et al. The impact of oral corticosteroid use on bone mineral density and vertebral fracture. Am J Respir Crit Care Med. 2002 Sep 1;166(5):691-5.

658. 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. 1996;313(7053):325-9.

659. van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet. 1997;349(9053):683-7.

660. Axelsson A, Chidekel N, Grebelius N, Jensen C. Treatment of acute maxillary sinusitis. A comparison of four different methods. Acta Otolaryngol. 1970;70(1):71-6.

661. hCars O. The hidden impact of antibacterial resistance in respiratory tract infection. Steering an appropriate course: principles to guide antibiotic choice. Respir Med. 2001;95(Suppl A):S20-5; discussion S6-7.

662. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. Jama. 1995;273(3):214-9.

663. 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 & Neck Surgery. 2005;133(2):194-200.

664. Polonovski JM, El Mellah M. Treatment of acute maxillary sinusitis in adults: Comparison of cefpodoxime-proxetil and amoxicillin-clavulanic acid. [French]. Presse Medicale. 2006;35(1 I):33-8.

665. 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 & Neck Surgery. 2006;134(1):10-7.

666. 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.

667. 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. Clinical Therapeutics. 2004;26(12):2026-33.

668. Riffer E, Spiller J, Palmer R, Shortridge V, Busman TA, Valdes J. Once daily clarithromycin extended-release vs twice-daily amoxicillin/clavulanate in patients with acute bacterial sinusitis: A randomized, investigator-blinded study. Current Medical Research & Opinion. 2005;21(1):61-70.

669. Keating KN, Friedman HS, Perfetto EM. Moxifloxacin versus levofloxacin for treatment of acute rhinosinusitis: A retrospective database analysis of treatment duration, outcomes, and charges. Current Medical Research & Opinion. 2006;22(2):327-33.

670. Jareoncharsri P, Bunnag C, Fooanant S, Tunsuriyawong P, Voraprayoon S, Srifuengfung S, et al. An open label, randomized comparative study of levofloxacin and amoxicillin/clavulanic acid in the treatment of purulent sinusitis in adult Thai patients. Rhinology. 2004 Mar;42(1):23-9.

671. Murray JJ, Emparanza P, Lesinskas E, Tawdrous M, Breenz JD, Marple BF. Editorial commentary: Dilemma in trial design: Do current study designs adequately evaluate effectiveness antibiotic in ABRS? Otolaryngology - Head & Neck Surgery. 2005;133(2):200-1.

672. Merenstein D, Whittaker C, Chadwell T, Wegner B, D'Amico F. Are antibiotics beneficial for patients with sinusitis complaints? A randomized double-blind clinical trial. Journal of Family Practice. 2005;54(2):144-51.

673. Meltzer EO, Hamilos DL, Hadley JA, Lanza DC, Marple BF, Nicklas RA, et al. Rhinosinusitis: Developing guidance for clinical trials. Otolaryngol Head Neck Surg. 2006 Nov;135(5 Suppl):S31-80.

674. McNally PA, White MV, Kaliner MA. Sinusitis in an allergist's office: analysis of 200 consecutive cases. Allergy Asthma Proc. 1997;18(3):169-75.

675. Subramanian HN, Schechtman KB, Hamilos DL. A retrospective analysis of treatment outcomes and time to relapse after intensive medical treatment for chronic sinusitis. Am J Rhinol. 2002;16(6):303-12.

676. 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.

677. 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;14(5):508-17.

678. 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;2(5):497-503.

679. Hashiba M, Baba S. Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. Acta Otolaryngol Suppl. 1996;525:73-8.

680. 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.

681. 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]. Nihon Kyobu Shikkan Gakkai Zasshi. 1995;33(12):1392-400.

682. Gandhi A, Brodsky L, Ballow M. Benefits of antibiotic prophylaxis in children with chronic sinusitis: assessment of outcome predictors. Allergy Proc. 1993;14(1):37-43.

683. Kohyama T, Takizawa H, Kawasaki S, Akiyama N, Sato M, Ito K. Fourteen-member macrolides inhibit interleukin-8 release by human eosinophils from atopic donors. Antimicrob Agents Chemother. 1999;43(4):907-11.

684. Khair OA, Andrews JM, Honeybourne D, Jevons G, Vacheron F, Wise R, et al. Lung concentrations of telithromycin after oral dosing Bacterial-induced release of inflammatory mediators by bronchial epithelial cells

Effect of erythromycin on Haemophilus influenzae endotoxin-induced

release of IL-6, IL-8 and sICAM-1 by cultured human bronchial epithelial cells. J Antimicrob Chemother. 2001;47(6):837-40.

685. Khair OA, Devalia JL, Abdelaziz MM, Sapsford RJ, Davies RJ. Effect of erythromycin on Haemophilus influenzae endotoxin-induced release of IL-6, IL-8 and sICAM-1 by cultured human bronchial epithelial cells. Eur Respir J. 1995 Sep;8(9):1451-7.

686. Suzuki H, Shimomura A, Ikeda K, Furukawa M, Oshima T, Takasaka T. Inhibitory effect of macrolides on interleukin-8 secretion from cultured human nasal epithelial cells. Laryngoscope. 1997;107(12 Pt 1):1661-6.

687. Miyanohara T, Ushikai M, Matsune S, Ueno K, Katahira S, Kurono Y. Effects of clarithromycin on cultured human nasal epithelial cells and fibroblasts. Laryngoscope. 2000;110(1):126-31.

688. Nonaka M, Pawankar R, Saji F, Yagi T. Effect of roxithromycin on IL-8 synthesis and proliferation of nasal polyp fibroblasts. Acta Otolaryngol Suppl. 1998;539:71-5.

689. Cervin A. The anti-inflammatory effect of erythromycin and its derivatives, with special reference to nasal polyposis and chronic sinusitis. Acta Otolaryngol. 2001;121(1):83-92.

690. Scadding GK, Lund VJ, Darby YC. The effect of long-term antibiotic therapy upon ciliary beat frequency in chronic rhinosinusitis. J Laryngol Otol. 1995;109(1):24-6.

691. 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. Laryngoscope. 2006 Feb;116(2):189-93.

692. Fombeur JP, Barrault S, Koubbi G, Laurier JN, Ebbo D, Lecomte F, et al. Study of the efficacy and safety of ciprofloxacin in the treatment of chronic sinusitis. Chemotherapy. 1994;40(Suppl 1):24-8.

693. Matthews BL, Kohut RI, Edelstein DR, Rybak LP, Rapp M, McCaffrey TV, et al. Evaluation of cefixime in the treatment of bacterial maxillary sinusitis. South Med J. 1993;86(3):329-33.

694. Pakes GE, Graham JA, Rauch AM, Collins JJ. Cefuroxime axetil in the treatment of sinusitis. A review. Arch Fam Med. 1994;3(2):165-75.

695. Mosges R, Spaeth J, Berger K, Dubois F. Topical treatment of rhinosinusitis with fusafungine nasal spray. A double-blind, placebo-controlled, parallel-group study in 20 patients. Arzneimittelforschung. 2002;52(12):877-83.

696. Wahl KJ, Otsuji A. New medical management techniques for acute exacerbations of chronic rhinosinusitis. Curr Opin Otolaryngol Head Neck Surg. 2003;11(1):27-32.

697. Leonard DW, Bolger WE. Topical antibiotic therapy for recalcitrant sinusitis. Laryngoscope. 1999;109(4):668-70.

698. 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. Otolaryngol Head Neck Surg. 2001;125(3):265-9.

699. Scheinberg PA, Otsuji A. Nebulized antibiotics for the treatment of acute exacerbations of chronic rhinosinusitis. Ear Nose Throat J. 2002;81(9):648-52.

700. 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 Feb 12-18;365(9459):579-87.

701. Stringer SP, Mancuso AA, Avino AJ. Effect of a topical vasoconstrictor on computed tomography of paranasal sinus disease. Laryngoscope. 1993;103(1 Pt 1):6-9.

702. Benammar-Englmaier M, Hallermeier JK, Englmaier B. [Alpha-mimetic effects on nasal mucosa in magnetic resonance tomography]. Digitale Bilddiagn. 1990;10(2):46-50.

703. 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. Eur Respir J. 2000;16(3):437-44.

704. 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.

705. Inanli S, Ozturk O, Korkmaz M, Tutkun A, Batman C. The

706. 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.

707. McCormick DP, John SD, Swischuk LE, Uchida T. A double-blind, placebo-controlled trial of decongestant-antihistamine for the treatment of sinusitis in children. Clin Pediatr (Phila). 1996;35(9):457-60.

708. 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. 2006;32(9):1452-3.

709. Otten FW. Conservative treatment of chronic maxillary sinusitis in children. Long-term follow-up. Acta Otorhinolaryngol Belg. 1997;51(3):173-5.

710. Elbez M, De Pressigny M, Halimi P, Aidan D, Bonfils P, Trotoux J. [Does the use of nasal vasoconstrictor agents change tomodensitometric images of nasosinusal polyposis?]. Ann Otolaryngol Chir Cervicofac. 1993;110(5):277-80.

711. Johansson L, Oberg D, Melen I, Bende M. Do topical nasal decongestants affect polyps? Acta Oto-Laryngologica. 2006;126(3):288-90.

712. Graf P, Enerdal J, Hallen H. Ten days' use of oxymetazoline nasal spray with or without benzalkonium chloride in patients with vasomotor rhinitis. Arch Otolaryngol Head Neck Surg. 1999 Oct;125(10):1128-32.

713. Glazener F, Blake K, Gradman M. Bradycardia, hypotension, and near-syncope associated with Afrin (oxymetazoline) nasal spray. N Engl J Med. 1983 Sep 22;309(12):731.

714. Montalban J, Ibanez L, Rodriguez C, Lopez M, Sumalla J, Codina A. Cerebral infarction after excessive use of nasal decongestants. J Neurol Neurosurg Psychiatry. 1989 Apr;52(4):541-3.

715. Loewen AH, Hudon ME, Hill MD. Thunderclap headache and reversible segmental cerebral vasoconstriction associated with use of oxymetazoline nasal spray. Cmaj. 2004 Sep 14;171(6):593-4.

716. Zavala JA, Pereira ER, Zetola VH, Teive HA, Novak EM, Werneck LC. Hemorrhagic stroke after naphazoline exposition: case report. Arq Neuropsiquiatr. 2004 Sep;62(3B):889-91.

717. Van Bever HP, Bosmans J, Stevens WJ. Nebulization treatment with saline compared to bromhexine in treating chronic sinusitis in asthmatic children. Allergy. 1987;42(1):33-6.

718. Tarantino V, Stura M, Marenco G, 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.

719. Szmeja Z, Golusinski W, Mielcarek-Kuchta D, Laczkowska-Przybylska J. [Use of mucolytic preparations (Mucosolvan) in selected diseases of the upper respiratory tract. Part II]. Otolaryngol Pol. 1997;51(5):480-6.

720. 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;52(6):650-5.

721. Sederberg-Olsen JF, Sederberg-Olsen AE. Intranasal sodium cromoglycate in post-catarrhal hyperreactive rhinosinusitis: a double-blind placebo controlled trial. Rhinology. 1989;27(4):251-5.

722. Bhattacharyya Nl. The economic burden and symptom manifestations of chronic rhinosinusitis. Am J Rhinol. 2003;17(1):27-32.

723. 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;112(11):1042-6.

724. Kuhn FA, Javer AR. Allergic fungal rhinosinusitis: perioperative management, prevention of recurrence, and role of steroids and antifungal agents. Otolaryngol Clin North Am. 2000;33(2):419-33.

725. Schubert MS. Medical treatment of allergic fungal sinusitis. Ann Allergy Asthma Immunol. 2000;85(2):90-7; quiz 7-101.

726. Rizk SS, Kraus DH, Gerresheim G, Mudan S. Aggressive combi-

nation treatment for invasive fungal sinusitis in immunocompromised patients. Ear Nose Throat J. 2000 Apr;79(4):278-80, 82, 84-5.

727. Rains BM, 3rd, Mineck CW. Treatment of allergic fungal sinusitis with high-dose itraconazole. Am J Rhinol. 2003;17(1):1-8.

728. Ponikau JU, Sherris DA, Kita H, Kern EB. Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2002;110(6):862-6.

729. 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.

730. Ponikau JU, Sherris DA, Weaver A, Kita H. Treatment of chronic rhinosinusitis with intranasal amphotericin B: A randomized, placebo-controlled, double-blind pilot trial. Journal of Allergy & Clinical Immunology. 2005;115(1):125-31.

731. 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. J Allergy Clin Immunol. 2004 Jun;113(6):1122-8.

732. 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. Laryngoscope. 2005;115(10 I):1793-9.

733. Ricchetti A, Landis BN, Maffioli A, Giger R, Zeng C, Lacroix JS. Effect of anti-fungal nasal lavage with amphotericin B on nasal polyposis. J Laryngol Otol. 2002;116(4):261-3.

734. Corradini C, Del Ninno M, Buonomo A, Nucera E, Paludetti G, Alonzi C, et al. Amphotericin B and lysine acetylsalicylate in the combined treatment of nasal polyposis associated with mycotic infection. Journal of Investigational Allergology & Clinical Immunology. 2006;16(3):188-93.

735. Hartsel SC, Benz SK, Ayenew W, Bolard J. Na+, K+ and Cl-selectivity of the permeability pathways induced through sterol-containing membrane vesicles by amphotericin B and other polyene antibiotics. Eur Biophys J. 1994;23(2):125-32.

736. Yang YL, Li SY, Cheng HH, Lo HJ. The trend of susceptibilities to amphotericin B and fluconazole of Candida species from 1999 to 2002 in Taiwan. BMC Infect Dis. 2005;5:99.

737. Barker KS, Crisp S, Wiederhold N, Lewis RE, Bareither B, Eckstein J, et al. Genome-wide expression profiling reveals genes associated with amphotericin B and fluconazole resistance in experimentally induced antifungal resistant isolates of Candida albicans. J Antimicrob Chemother. 2004 Aug;54(2):376-85.

738. Rogers TR. Antifungal drug resistance: limited data, dramatic impact? Int J Antimicrob Agents. 2006 Jun;27 Suppl 1:7-11.

739. Habermann W, Zimmermann K, Skarabis H, Kunze R, Rusch V. [Reduction of acute recurrence in patients with chronic recurrent hypertrophic sinusitis by treatment with a bacterial immunostimulant (Enterococcus faecalis Bacteriae of human origin]. Arzneimittelforschung. 2002;52(8):622-7.

740. Serrano E, Demanez JP, Morgon A, Chastang C, Van Cauwenberge P. Effectiveness of ribosomal fractions of Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae and the membrane fraction of Kp (Ribomunyl) in the prevention of clinical recurrences of infectious rhinitis. Results of a multicenter double-blind placebo-controlled study. Eur Arch Otorhinolaryngol. 1997;254(8):372-5.

741. 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;27(11):530-4.

742. Jyonouchi H, Sun S, Kelly A, Rimell FL. Effects of exogenous interferon gamma on patients with treatment-resistant chronic rhinosinusitis and dysregulated interferon gamma production: a pilot study. Arch Otolaryngol Head Neck Surg. 2003;129(5):563-9.

743. Dalhoff A, Shalit I. Immunomodulatory effects of quinolones. Lancet Infect Dis. 2003;3(6):359-71.

744. Davidson R, Peloquin L. Anti-inflammatory effects of the macrolides. J Otolaryngol. 2002;31(Suppl 1):S38-40.

745. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered hypertonic saline solution. Laryngoscope. 1997;107(4):500-3.

746. Adam P, Stiffman M, Blake RL, Jr. A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis. Arch Fam Med. 1998;7(1):39-43.

747. 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.

748. Bachmann G, Hommel G, Michel Ol. Effect of irrigation of the nose with isotonic salt solution on adult patients with chronic paranasal sinus disease. Eur Arch Otorhinolaryngol. 2000;257(10):537-41.

749. Taccariello M, Parikh A, Darby Y, Scadding G. Nasal douching as a valuable adjunct in the management of chronic rhinosinusitis. Rhinology. 1999;37(1):29-32.

750. Rabago D, Zgierska A, Mundt M, Barrett B, Bobula J, Maberry R. Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial. J Fam Pract. 2002;51(12):1049-55.

751. Shoseyov D, Bibi H, Shai P, Shoseyov N, Shazberg G, Hurvitz H. Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. J Allergy Clin Immunol. 1998;101(5):602-5.

752. Levine HL, Cordray S, Miner LA. Use of Dead Sea salt solution for chronic rhinitis and rhinosinusitis. Operative Techniques in Otolaryngology-Head & Neck Surgery. 2006;17(2):147-50.

753. 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.

754. Pang YT, Willatt DJ. Do antral washouts have a place in the current management of chronic sinusitis? J Laryngol Otol. 1996;110(10):926-8.

755. Maes JJ, Clement PA. The usefulness of irrigation of the maxillary sinus in children with maxillary sinusitis on the basis of the Water's X-ray. Rhinology. 1987;25(4):259-64.

756. Neher A, Fischer H, Appenroth E, Lass-Florl C, Mayr A, Gschwendtner A, et al. Tolerability of N-chlorotaurine in chronic rhinosinusitis applied via yamik catheter. Auris, Nasus, Larynx. 2005;32(4):359-64.

757. Filiaci F, Zambetti G, Luce M, Ciofalo A. Local treatment of nasal polyposis with capsaicin: preliminary findings. Allergol Immunopathol (Madr). 1996;24(1):13-8.

758. Baudoin T, Kalogjera L, Hat Jl. Capsaicin significantly reduces sinonasal polyps. Acta Otolaryngol. 2000;120(2):307-11.

759. Zheng C, Wang Z, Lacroix JS. Effect of intranasal treatment with capsaicin on the recurrence of polyps after polypectomy and ethmoidectomy. Acta Otolaryngol. 2000;120(1):62-6.

760. Sancho R, Lucena C, Macho A, Calzado MA, Blanco-Molina M, Minassi A, et al. Immunosuppressive activity of capsaicinoids: capsiate derived from sweet peppers inhibits NF-kappaB activation and is a potent antiinflammatory compound in vivo. Eur J Immunol. 2002;32(6):1753-63.

761. Van Rijswijk JB, Boeke EL, Keizer JM, Mulder PG, Blom HM, Fokkens WJ. Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study. Allergy. 2003 Aug;58(8):754-61.

762. Lacroix JS, Buvelot JM, Polla BS, Lundberg JM. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clin Exp Allergy. 1991 Sep;21(5):595-600.

763. Riechelmann H, Davris S, Bader D. [Treatment of perennial non-allergic rhinopathy with capsaicin]. Hno. 1993 Oct;41(10):475-9.

764. Myers JD, Higham MA, Shakur BH, Wickremasinghe M, Ind PW. Attenuation of propranolol-induced bronchoconstriction by frusemide. Thorax. 1997 Oct;52(10):861-5.

765. Yates DH, O'Connor BJ, Yilmaz G, Aikman S, Worsdell M, Barnes PJ, et al. Effect of acute and chronic inhaled furosemide on bronchial hyperresponsiveness in mild asthma. Am J Respir Crit Care Med. 1995 Dec;152(6 Pt 1):2173-5.

766. Munyard P, Chung KF, Bush A. Inhaled frusemide and exercise-

induced bronchoconstriction in children with asthma. Thorax. 1995 Jun;50(6):677-9.

767. Passali D, Bernstein JM, Passali FM, Damiani V, Passali GC, Bellussi L. Treatment of recurrent chronic hyperplastic sinusitis with nasal polyposis. Arch Otolaryngol Head Neck Surg. 2003;129(6):656-9.

768. 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.

769. Loehrl TA, Smith TL, Merati A, Torrico-Brusky L, Hoffman RG, Toohill RJ. Pharyngeal pH probe findings in patients with post-nasal drainage. Am J Rhinol. 2005 Jul-Aug;19(4):340-3.

770. Weaver EM. Association between gastroesophageal reflux and sinusitis, otitis media, and laryngeal malignancy: a systematic review of the evidence. Am J Med. 2003;115(Suppl 3A):81S-9S.

771. Yuengsrigul A, Chin TW, Nussbaum E. Immunosuppressive and cytotoxic effects of furosemide on human peripheral blood mononuclear cells. Ann Allergy Asthma Immunol. 1999;83(6 Pt 1):559-66.

772. Phipps CD, Wood WE, Gibson WS, Cochran WJ. Gastroesophageal reflux contributing to chronic sinus disease in children: a prospective analysis. Arch Otolaryngol Head Neck Surg. 2000;126(7):831-6.

773. Ulualp SO, Toohill RJ, Hoffmann R, Shaker R. Possible relationship of gastroesophagopharyngeal acid reflux with pathogenesis of chronic sinusitis. Am J Rhinol. 1999;13(3):197-202.

774. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev. 2006(4):CD004823.

775. Dahlen B, Nizankowska E, Szczeklik A, Zetterstrom O, Bochenek G, Kumlin M, et al. Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. Am J Respir Crit Care Med. 1998 Apr;157(4 Pt 1):1187-94.

776. Kieff DA, Busaba NY. Efficacy of montelukast in the treatment of nasal polyposis. Annals of Otology, Rhinology & Laryngology. 2005;114(12 I):941-5.

777. Ragab S, Parikh A, Darby YC, Scadding GK. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. Clin Exp Allergy. 2001;31(9):1385-91.

778. Parnes SM, Chuma AV. Acute effects of antileukotrienes on sinonasal polyposis and sinusitis. Ear Nose Throat J. 2000;79(1):18-20, 4-5.

779. Ulualp SO, Sterman BM, Toohill RJ. Antileukotriene therapy for the relief of sinus symptoms in aspirin triad disease. Ear Nose Throat J. 1999;78(8):604-6, 8, 13, passim.

780. Mostafa BE, Abdel HH, Mohammed HE, Yamani M. Role of leukotriene inhibitors in the postoperative management of nasal polyps. ORL J OtorhinolaryngolRelat Spec. 2005;67(3):148.

781. Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA. Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. J Allergy Clin Immunol. 1996 Oct;98(4):751-8.

782. Stevenson DD. Aspirin desensitization in patients with AERD. Clin Rev Allergy Immunol. 2003;24(2):159-68.

783. Mardiney M, Borish L. Aspirin desensitization for chronic hyperplastic sinusitis, nasal polyposis, and asthma triad. Arch Otolaryngol Head Neck Surg. 2001;127(10):1287.

784. Nucera E, Schiavino D, Milani A, Del Ninno M, Misuraca C, Buonomo A, et al. Effects of lysine-acetylsalicylate (LAS) treatment in nasal polyposis: two controlled long term prospective follow up studies. Thorax. 2000;55(Suppl 2):S75-8.

785. Scadding GK, Hassab M, Darby YC, Lund VJ, Freedman A. Intranasal lysine aspirin in recurrent nasal polyposis. Clin Otolaryngol. 1995;20(6):561-3.

786. Parikh AA, Scadding GK. Intranasal lysine-aspirin in aspirin-sensitive nasal polyposis: A controlled trial. Laryngoscope. 2005;115(8):1385-90.

787. Blanc PD, Trupin L, Earnest G, Katz PP, Yelin EH, Eisner MDl.

Alternative therapies among adults with a reported diagnosis of asthma or rhinosinusitis : data from a population-based survey. Chest. 2001;120(5):1461-7.

788. 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;76(1):23-7.

789. 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;9(7):589-97.

790. Wawrose SF, Tami TA, Amoils CP. The role of guaifenesin in the treatment of sinonasal disease in patients infected with the human immunodeficiency virus (HIV). Laryngoscope. 1992;102(11):1225-8.

791. 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. J Allergy Clin Immunol. 2006 Nov;118(5):1133-41.

792. Settipane GA. Epidemiology of nasal polyps. Allergy Asthma Proc. 1996;17(5):231-6.

793. Deal RT, Kountakis SE. Significance of nasal polyps in chronic rhinosinusitis: Symptoms and surgical outcomes. Laryngoscope. 2004;114(11 I):1932-5.

794. Eichel BS. A proposal for a staging system for hyperplastic rhinosinusitis based on the presence or absence of intranasal polyposis. Ear Nose Throat J. 1999;78(4):262-5, 8.

795. Cook PR, Nishioka GJ, Davis WE, McKinsey JP. Functional endoscopic sinus surgery in patients with normal computed tomography scans. OtolaryngolHead Neck Surg. 1994;110(6):505.

796. Khalil HS, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. CochraneDatabaseSystRev. 2006;3:CD004458.

797. Lund VJ. Evidence-based surgery in chronic rhinosinusitis. Acta Otolaryngol. 2001;121(1):5-9.

798. Wasserman JM, Wynn R, Bash TS, Rosenfeld RM. Levels of evidence in otolaryngology journals. Otolaryngol Head Neck Surg. 2006 May;134(5):717-23.

799. McLeod RS. Issues in surgical randomized controlled trials. World J Surg. 1999 Dec;23(12):1210-4.

800. Lund VJ, MacKay IS. Outcome assessment of endoscopic sinus surgery. J R Soc Med. 1994;87(2):70-2.

801. Marks SC, Shamsa F. Evaluation of prognostic factors in endoscopic sinus surgery. Am J Rhinol. 1997;11(3):187-91.

802. Wang PC, Chu CC, Liang SC, Tai CJ. Outcome predictors for endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2002;126(2):154-9.

803. Smith TL, Mendolia-Loffredo S, Loehrl TA, Sparapani R, Laud PW, Nattinger AB. Predictive factors and outcomes in endoscopic sinus surgery for chronic rhinosinusitis. Laryngoscope. 2005;115(12):2199.

804. Terris MH, Davidson TM. Review of published results for endoscopic sinus surgery. Ear Nose Throat J. 1994;73(8):574-80.

805. 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. Otolaryngol Head Neck Surg. 2004 Oct;131(4):534-41.

806. 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.

807. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. Laryngoscope. 2004 May;114(5):811-3.

808. Witsell DL, Stewart MG, Monsell EM, Hadley JA, Terrell JE, Hannley MT, et al. The Cooperative Outcomes Group for ENT: A multicenter prospective cohort study on the effectiveness of medical and surgical treatment for patients with chronic rhinosinusitis. Otolaryngology - Head & Neck Surgery. 2005;132(2):171-9.

809. Blomqvist EH, Lundblad L, Anggard A, Haraldsson PO, Stjarne

Pl. A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis. J Allergy Clin Immunol. 2001;107(2):224-8.

810. Penttil„ MA. Endoscopic findings after functional and radical sinus surgery: A prospective randomized study. Am J Rhinology. 1994;8:71.

811. Penttila 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.

812. Penttila M, Rautiainen M, Pukander J, Kataja M. Functional vs. radical maxillary surgery. Failures after functional endoscopic sinus surgery. Acta Otolaryngol Suppl. 1997;529:173-6.

813. DeFreitas J, Lucente FE. The Caldwell-Luc procedure: institutional review of 670 cases: 1975-1985. Laryngoscope. 1988;98(12):1297-300.

814. Forsgren K, Fukami M, Penttila M, Kumlien J, Stierna P. Endoscopic and Caldwell-Luc approaches in chronic maxillary sinusitis: a comparative histopathologic study on preoperative and postoperative mucosal morphology. Ann Otol Rhinol Laryngol. 1995;104(5):350-7.

815. Unlu HH, Akyar S, Caylan R, Nalca Y. Concha bullosa. J Otolaryngol. 1994;23(1):23-7.

816. Messerklinger W. [On the drainage of the human paranasal sinuses under normal and pathological conditions. 1]. Monatsschr Ohrenheilkd Laryngorhinol. 1966;100(1-2):56-68.

817. Stammberger H. An endoscopic study of tubal function and the diseased ethmoid sinus. Arch Otorhinolaryngol. 1986;243(4):254-9.

818. Guevara N, Hofman V, Hofman P, Santini J, Castillo L. A comparison between functional and radical sinus surgery in an experimental model of maxillary sinusitis. Rhinology. 2006 Dec;44(4):255-8.

819. Stammberger H. Endoscopic endonasal surgery--concepts in treatment of recurring rhinosinusitis. Part II. Surgical technique. Otolaryngol Head Neck Surg. 1986;94(2):147-56.

820. Kennedy DW, Zinreich SJ, Shaalan H, Kuhn F, Naclerio R, Loch E. Endoscopic middle meatal antrostomy: theory, technique, and patency. Laryngoscope. 1987;97(8 Pt 3 Suppl 43):1-9.

821. Arnes E, Anke IM, Mair IWl. A comparison between middle and inferior meatal antrostomy in the treatment of chronic maxillary sinus infection. Rhinology. 1985;23(1):65-9.

822. Venkatachalam VP, Jain A. Comparative evaluation of functional endoscopic sinus surgery and conventional surgery in the management of chronic sinusitis. J Indian Med Assoc. 2002;100(2):78-9, 82-3.

823. Hartog B, van Benthem PP, Prins LC, Hordijk GJ. Efficacy of sinus irrigation versus sinus irrigation followed by functional endoscopic sinus surgery. Ann Otol Rhinol Laryngol. 1997;106(9):759-66.

824. 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;31(5):390.

825. Kuehnemund M, Lopatin A, Amedee RG, Mann WJ. Endonasal sinus surgery: extended versus limited approach. Am J Rhinol. 2002;16(4):187-92.

826. Catalano PJ, Roffman EJ. Evaluation of middle meatal stenting after minimally invasive sinus techniques (MIST). Otolaryngol Head Neck Surg. 2003;128(6):875-81.

827. Toffel PH. Secure endoscopic sinus surgery with partial middle turbinate modification: a 16-year long-term outcome report and literature review. Curr Opin Otolaryngol Head Neck Surg. 2003;11(1):13-8.

828. Giacchi RJ, Lebowitz RA, Jacobs JB. Middle turbinate resection: issues and controversies. Am J Rhinol. 2000;14(3):193-7.

829. Havas TE, Lowinger DS. Comparison of functional endonasal sinus surgery with and without partial middle turbinate resection. Ann Otol Rhinol Laryngol. 2000;109(7):634-40.

830. Albu S, Tomescu E. Small and large middle meatus antrostomies in the treatment of chronic maxillary sinusitis. Otolaryngol Head Neck Surg. 2004 Oct;131(4):542-7.

831. Wadwongtham W, Aeumjaturapat S. Large middle meatal antrostomy vs undisturbed maxillary ostium in the endoscopic sinus surgery of nasal polyposis. J Med Assoc Thai. 2003;86(Suppl 2):S373-8.

832. 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.

833. Bhattacharyya N. Clinical outcomes after revision endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg. 2004 Aug;130(8):975-8.

834. Musy PY, Kountakis SE. Anatomic findings in patients undergoing revision endoscopic sinus surgery. American Journal of Otolaryngology - Head & Neck Medicine & Surgery. 2004;25(6):418-22.

835. Ramadan HH. Surgical causes of failure in endoscopic sinus surgery. Laryngoscope. 1999;109(1):27.

836. Richtsmeier WJ. Top 10 reasons for endoscopic maxillary sinus surgery failure. Laryngoscope. 2001;111(11 Pt 1):1952-6.

837. Marks SC, Kissner D. Endoscopic sinus surgery in patients with cystic fibrosis. Otolaryngol Head Neck Surg. 1996 Jun;114(6):840-1.

838. King JM, Caldarelli DD, Pigato JB. A review of revision functional endoscopic sinus surgery. Laryngoscope. 1994 Apr;104(4):404-8.

839. McMains KC, Kountakis SE. Revision functional endoscopic sinus surgery: Objective and subjective surgical outcomes. American Journal of Rhinology. 2005;19(4):344-7.

840. Chu CT, Lebowitz RA, Jacobs JB. An analysis of sites of disease in revision endoscopic sinus surgery. Am J Rhinol. 1997 Jul-Aug;11(4):287-91.

841. Cohen NA, Kennedy DW. Revision Endoscopic Sinus Surgery. Otolaryngologic Clinics of North America. 2006;39(3):417-35.

842. Cutler JL, Duncavage JA, Matheny K, Cross JL, Miman MC, Oh CK. Results of Caldwell-Luc after failed endoscopic middle meatus antrostomy in patients with chronic sinusitis. Laryngoscope. 2003;113(12):2148.

843. Vauterin T, Vander Poorten V, Jorissen M. Long term effects of cutting forceps in endoscopic sinus surgery. Rhinology. 2006 Jun;44(2):123-7.

844. Hackman TG, Ferguson BJ. Powered instrumentation and tissue effects in the nose and paranasal sinuses. Curr Opin Otolaryngol Head Neck Surg. 2005 Feb;13(1):22-6.

845. Krouse JH, Christmas DA, Jr. Powered instrumentation in functional endoscopic sinus surgery. II: A comparative study. Ear Nose Throat J. 1996;75(1):42.

846. Selivanova O, Kuehnemund M, Mann WJ, Amedee RG. Comparison of conventional instruments and mechanical debriders for surgery of patients with chronic sinusitis. Am J Rhinol. 2003;17(4):197-202.

847. Metson R. Holmium:YAG laser endoscopic sinus surgery: a randomized, controlled study. Laryngoscope. 1996;106(1 Pt 2 Suppl 77):1-18.

848. Gerlinger I, Lujber L, Jarai T, Pytel J. KTP-532 laser-assisted endoscopic nasal sinus surgery. Clin Otolaryngol. 2003;28(2):67-71.

849. Colclasure JC, Gross CW, Kountakis SE. Endoscopic sinus surgery in patients older than sixty. Otolaryngology - Head & Neck Surgery. 2004;131(6):946-9.

850. Ramadan HH, VanMetre R. Endoscopic sinus surgery in geriatric population. Am J Rhinol. 2004 Mar-Apr;18(2):125-7.

851. Jiang RS, Hsu CY. Endoscopic sinus surgery for the treatment of chronic sinusitis in geriatric patients. Ear Nose Throat J. 2001;80(4):230-2.

852. Dunlop G, Scadding GK, Lund VJ. The effect of endoscopic sinus surgery on asthma: management of patients with chronic rhinosinusitis, nasal polyposis, and asthma. Am J Rhinol. 1999;13(4):261-5.

853. 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 & Immunology. 2005;138(2):97-104.

854. Kim HY, Dhong HJ, Chung SK, Chung YJ, Kim MG. Clinical

characteristics of chronic rhinosinusitis with asthma. Auris Nasus Larynx. 2006;33(4):403.

855. 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. Laryngoscope. 1997;107(4):504-10.

856. 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.

857. Lund VJ. The effect of sinonasal surgery on asthma. Allergy. 1999;54(Suppl 57):141-5.

858. Scadding G. The effect of medical treatment of sinusitis upon concomitant asthma. Allergy. 1999;54(Suppl 57):136-40.

859. Senior BA, Kennedy DW. Management of sinusitis in the asthmatic patient. Ann Allergy Asthma Immunol. 1996;77(1):6-15; quiz -9.

860. Park AH, Lau J, Stankiewicz J, Chow J. The role of functional endoscopic sinus surgery in asthmatic patients. J Otolaryngol. 1998;27(5):275.

861. 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. Ann Otol Rhinol Laryngol. 1999;108(4):355-9.

862. Goldstein MF, Grundfast SK, Dunsky EH, Dvorin DJ, Lesser R. Effect of functional endoscopic sinus surgery on bronchial asthma outcomes. Arch Otolaryngol Head Neck Surg. 1999;125(3):314-9.

863. Dhong HJ, Jung YS, Chung SK, Choi DC. Effect of endoscopic sinus surgery on asthmatic patients with chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2001;124(1):99-104.

864. Ragab S, Scadding GK, Lund VJ, Saleh H. Treatment of chronic rhinosinusitis and its effects on asthma. Eur Respir J. 2006 Jul;28(1):68-74.

865. Ragab A, Clement P, Vincken W. Objective assessment of lower airway involvement in chronic rhinosinusitis. Am J Rhinol. 2004 Jan-Feb;18(1):15-21.

866. 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. Am J Rhinol. 2001;15(1):49-53.

867. Lamblin C, Brichet A, Perez T, Darras J, Tonnel AB, Wallaert B. Long-term follow-up of pulmonary function in patients with nasal polyposis. Am J Respir Crit Care Med. 2000;161(2 Pt 1):406-13.

868. McFadden EA, Woodson BT, Fink JN, Toohill RJ. Surgical treatment of aspirin triad sinusitis. Am J Rhinol. 1997;11(4):263-70.

869. Amar YG, Frenkiel S, Sobol SEl. Outcome analysis of endoscopic sinus surgery for chronic sinusitis in patients having Samter's triad. J Otolaryngol. 2000;29(1):7-12.

870. Batra PS, Kern RC, Tripathi A, Conley DB, Ditto AM, Haines GK, III, et al. Outcome analysis of endoscopic sinus surgery in patients with nasal polyps and asthma. Laryngoscope. 2003;113(10):1703.

871. 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. Ann Allergy Asthma Immunol. 2002;88(6):624.

872. 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.

873. Ferguson BJ, Johnson JT. Allergic rhinitis and rhinosinusitis. Is there a connection between allergy and infection? PostgradMed. 1999;105(4):55.

874. Pinto JM, Baroody FM. Chronic sinusitis and allergic rhinitis: at the nexus of sinonasal inflammatory disease. J Otolaryngol. 2002;31(Suppl 1):S10-7.

875. Ramadan HH, Fornelli R, Ortiz AO, Rodman S. Correlation of allergy and severity of sinus disease. Am J Rhinol. 1999;13(5):345-7.

876. Smart BA. The impact of allergic and nonallergic rhinitis on pedi-

atric sinusitis. Current Allergy & Asthma Reports. 2006;6(3):221-7.

877. Gutman M, Torres A, Keen KJ, Houser SM. Prevalence of allergy in patients with chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2004 May;130(5):545-52.

878. 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.

879. Nishioka GJ, Cook PR, Davis WE, McKinsey JP. Immunotherapy in patients undergoing functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 1994;110(4):406-12.

880. Berrettini S, Carabelli A, Sellari-Franceschini S, Bruschini L, Abruzzese A, Quartieri F, et al. Perennial allergic rhinitis and chronic sinusitis: correlation with rhinologic risk factors. Allergy. 1999;54(3):242.

881. Ramadan HH, Hinerman RA. Outcome of endoscopic sinus surgery in children with allergic rhinitis. Am J Rhinol. 2006;20(4):438.

882. Schlenter WW, Mann WJ. [Operative therapy in chronic sinusitis - results in allergic and nonallergic patients]. Laryngol Rhinol Otol (Stuttg). 1983;62(6):284-8.

883. Bertrand B, Eloy P, Rombeaux Pl. Allergy and sinusitis. Acta Otorhinolaryngol Belg. 1997;51(4):227-37.

884. 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.

885. Conway SP. Vitamin K in cystic fibrosis. J R Soc Med. 2004;97 Suppl 44:48.

886. Albritton FD, Kingdom TTl. Endoscopic sinus surgery in patients with cystic fibrosis: an analysis of complications. Am J Rhinol. 2000;14(6):379-85.

887. Schulte DL, Kasperbauer JL. Safety of paranasal sinus surgery in patients with cystic fibrosis. Laryngoscope. 1998;108(12):1813-5.

888. 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.

889. Moss RB, King VV. Management of sinusitis in cystic fibrosis by endoscopic surgery and serial antimicrobial lavage. Reduction in recurrence requiring surgery. Arch Otolaryngol Head Neck Surg. 1995;121(5):566-72.

890. Halvorson DJ, Dupree JR, Porubsky ES. Management of chronic sinusitis in the adult cystic fibrosis patient. Ann Otol Rhinol Laryngol. 1998;107(11 Pt 1):946-52.

891. Rowe-Jones JM, Mackay IS. Endoscopic sinus surgery in the treatment of cystic fibrosis with nasal polyposis. Laryngoscope. 1996;106(12 Pt 1):1540-4.

892. Shah AR, Hairston JA, Tami TA. Sinusitis in HIV: Microbiology and therapy. Current Allergy & Asthma Reports. 2005;5(6):495-9.

893. Belafsky P, Kissinger P, Davidowitz SB, Amedee RG. HIV sinusitis: rationale for a treatment algorithm. J La State Med Soc. 1999 Jan;151(1):11-8.

894. Friedman M, Landsberg R, Tanyeri H, Schults RA, Kelanic S, Caldarelli DD. Endoscopic sinus surgery in patients infected with HIV. Laryngoscope. 2000;110(10 Pt 1):1613.

895. 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. Laryngoscope. 2000;110(10 Pt 1):1707-10.

896. Hunt SM, Miyamoto RC, Cornelius RS, Tami TA. Invasive fungal sinusitis in the acquired immunodeficiency syndrome. OtolaryngolClin North Am. 2000;33(2):335.

897. Anselmo-Lima WT, Lopes RP, Valera FCP, Demarco RC. Invasive fungal rhinosinusitis in immunocompromised patients. Rhinology. 2004;42(3):141-4.

898. Savage DG, Taylor P, Blackwell J, Chen F, Szydlo RM, Rule SA, et al. Paranasal sinusitis following allogeneic bone marrow transplant. Bone Marrow Transplant. 1997;19(1):55-9.

899. 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.

900. Kennedy CA, Adams GL, Neglia JP, Giebink GS. Impact of surgi-

cal treatment on paranasal fungal infections in bone marrow transplant patients. Otolaryngol Head Neck Surg. 1997;116(6 Pt 1):610-6.

901. Sterman BM. Sinus surgery in bone marrow transplantation patients. Am J Rhinol. 1999;13(4):315.

902. 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.

903. Rose MA, Schubert R, Schmitt-Grohe S, Reichenbach J, Zielen S. Immunoglobulins and inflammatory cytokines in nasal secretions in humoral immunodeficiencies. Laryngoscope. 2006;116(2):239.

904. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34.

905. Sneller MC. Common variable immunodeficiency. Am J Med Sci. 2001;321(1):42.

906. 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.

907. Sethi DS, Winkelstein JA, Lederman H, Loury MC. Immunologic defects in patients with chronic recurrent sinusitis: diagnosis and management. Otolaryngol Head Neck Surg. 1995;112(2):242-7.

908. Jiang RS, Hsu CY. Serum immunoglobulins and IgG subclass levels in sinus mycetoma. Otolaryngol Head Neck Surg. 2004 May;130(5):563-6.

909. Buckley RH. Immunoglobulin G subclass deficiency: fact or fancy? Curr Allergy Asthma Rep. 2002;2(5):356.

910. Maguire GA, Kumararatne DS, Joyce HJ. Are there any clinical indications for measuring IgG subclasses? Ann Clin Biochem. 2002;39(Pt 4):374.

911. 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.

912. 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. Ann Otol Rhinol Laryngol. 2001;110(7 Pt 1):675-81.

913. Lusk RP, Polmar SH, Muntz HR. Endoscopic ethmoidectomy and maxillary antrostomy in immunodeficient patients. Arch Otolaryngol Head Neck Surg. 1991;117(1):60-3.

914. Rice DH. Endoscopic sinus surgery. Otolaryngol Clin North Am. 1993 Aug;26(4):613-8.

915. Freedman HM, Kern EB. Complications of intranasal ethmoidectomy: a review of 1,000 consecutive operations. Laryngoscope. 1979;89(3):421-34.

916. Taylor JS, Crocker PV, Keebler JS. Intranasal ethmoidectomy and concurrent procedures. Laryngoscope. 1982;92(7 Pt 1):739-43.

917. Stevens HE, Blair NJ. Intranasal sphenoethmoidectomy: 10-year experience and literature review. J Otolaryngol. 1988;17(5):254-9.

918. Eichel BS. The intranasal ethmoidectomy: a 12-year perspective. Otolaryngol Head Neck Surg. 1982;90(5):540-3.

919. Sogg A. Long-term results of ethmoid surgery. Ann Otol Rhinol Laryngol. 1989 Sep;98(9):699-701.

920. Friedman WH, Katsantonis GP. Intranasal and transantral ethmoidectomy: a 20-year experience. Laryngoscope. 1990;100(4):343-8.

921. Lawson W. The intranasal ethmoidectomy: an experience with 1,077 procedures. Laryngoscope. 1991 Apr;101(4 Pt 1):367-71.

922. Sogg A, Eichel B. Ethmoid surgery complications and their avoidance. Ann Otol Rhinol Laryngol. 1991 Sep;100(9 Pt 1):722-4.

923. Brenkman CJ, Vries de N e. Neusbijholte chirurgie, goedaardige aandoeningen. Den Haag: Kugler; 2002.

924. Schaefer SD, Manning S, Close LG. Endoscopic paranasal sinus surgery: indications and considerations. Laryngoscope. 1989 Jan;99(1):1-5.

925. Toffel PH, Aroesty DJ, Weinmann RHt. Secure endoscopic sinus surgery as an adjunct to functional nasal surgery. Arch Otolaryngol Head Neck Surg. 1989;115(7):822-5.

926. Rice DH. Endoscopic sinus surgery: results at 2-year followup.

Otolaryngol Head Neck Surg. 1989 Oct;101(4):476-9.

927. Stammberger H, Posawetz W. Functional endoscopic sinus surgery. Concept, indications and results of the Messerklinger technique. Eur Arch Otorhinolaryngol. 1990;247(2):63-76.

928. Salman SD. Complications of endoscopic sinus surgery. Am J Otolaryngol. 1991 Nov-Dec;12(6):326-8.

929. Wigand ME, Hosemann WG. Results of endoscopic surgery of the paranasal sinuses and anterior skull base. J Otolaryngol. 1991;20(6):385-90.

930. Lazar RH, Younis RT, Gross CW. Pediatric functional endonasal sinus surgery: review of 210 cases. Head Neck. 1992;14(2):92-8.

931. Vleming M, Middelweerd RJ, de Vries N. Complications of endoscopic sinus surgery. Arch Otolaryngol Head Neck Surg. 1992 Jun;118(6):617-23.

932. Weber R, Draf W. [Complications of endonasal micro-endoscopic ethmoid bone operation]. Hno. 1992;40(5):170-5.

933. Smith LF, Brindley PC. Indications, evaluation, complications, and results of functional endoscopic sinus surgery in 200 patients. Otolaryngol Head Neck Surg. 1993 Jun;108(6):688-96.

934. Dessi P, Castro F, Triglia JM, Zanaret M, Cannoni M. Major complications of sinus surgery: a review of 1192 procedures. J Laryngol Otol. 1994;108(3):212-5.

935. Cumberworth VL, Sudderick RM, Mackay IS. Major complications of functional endoscopic sinus surgery. Clin Otolaryngol. 1994;19(3):248-53.

936. Ramadan HH, Allen GC. Complications of endoscopic sinus surgery in a residency training program. Laryngoscope. 1995;105(4 Pt 1):376-9.

937. Danielsen A, Olofsson J. Endoscopic endonasal sinus surgery. A long-term follow-up study. Acta Otolaryngol. 1996;116(4):611-9.

938. Castillo L, Verschuur HP, Poissonnet G, Vaille G, Santini J. Complications of endoscopically guided sinus surgery. Rhinology. 1996 Dec;34(4):215-8.

939. Weber R, Draf W, Keerl R, Schick B, Saha A. Endonasal microendoscopic pansinusoperation in chronic sinusitis. II. Results and complications. Am J Otolaryngol. 1997;18(4):247-53.

940. Rudert H, Maune S, Mahnke CG. [Complications of endonasal surgery of the paranasal sinuses. Incidence and strategies for prevention]. Laryngorhinootologie. 1997;76(4):200-15.

941. Dursun E, Bayiz U, Korkmaz H, Akmansu H, Uygur K. Follow-up results of 415 patients after endoscopic sinus surgery. Eur Arch Otorhinolaryngol. 1998;255(10):504-10.

942. Keerl R, Stankiewicz J, Weber R, Hosemann W, Draf W. Surgical experience and complications during endonasal sinus surgery. Laryngoscope. 1999 Apr;109(4):546-50.

943. Marks SC. Learning curve in endoscopic sinus surgery. Otolaryngol Head Neck Surg. 1999 Feb;120(2):215-8.

944. Kennedy DW, Shaman P, Han W, Selman H, Deems DA, Lanza DC. Complications of ethmoidectomy: a survey of fellows of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg. 1994 Nov;111(5):589-99.

945. Kane K. Australian experience with functional endoscopic sinus surgery and its complications. Ann Otol Rhinol Laryngol. 1993 Aug;102(8 Pt 1):613-5.

946. Kim HY, Dhong HJ, Chung SK, Chung YJ, Min JY. Prognostic factors of pediatric endoscopic sinus surgery. Int J Pediatr Otorhinolaryngol. 2005;69(11):1535.

947. Healy GB. Chandler et al.: "The pathogenesis of orbital complications in acute sinusitis." (Laryngoscope 1970;80:1414-1428). Laryngoscope. 1997;107(4):441-6.

948. Lang EE, Curran AJ, Patil N, Walsh RM, Rawluk D, Walsh MA. Intracranial complications of acute frontal sinusitis. Clin Otolaryngol. 2001;26(6):452-7.

949. Mirza S, Lobo CJ, Counter P, Farrington WT. Lacrimal gland abscess: an unusual complication of rhinosinusitis. ORL J Otorhinolaryngol Relat Spec. 2001;63(6):379-81.

950. Patel N, Khalil HM, Amirfeyz R, Kaddour HS. Lacrimal gland abscess complicating acute sinusitis. Int J Pediatr Otorhinolaryngol. 2003;67(8):917-9.

951. Kuo WT, Lee TJ, Chen YL, Huang CC. Nasal septal perforation

caused by invasive fungal sinusitis. Chang Gung Med J. 2002;25(11):769-73.

952. Gouws P. Visual-field loss caused by sinusitis: a case report. Ear Nose Throat J. 2003;82(1):42-5.

953. Gungor A, Corey JP. Pediatric sinusitis: a literature review with emphasis on the role of allergy. Otolaryngol Head Neck Surg. 1997;116(1):4-15.

954. Mortimore S, Wormald PJ. Management of acute complicated sinusitis: a 5-year review. Otolaryngol Head Neck Surg. 1999;121(5):639-42.

955. Ogunleye AO, Nwaorgu OG, Lasisi AO. Complications of sinusitis in Ibadan, Nigeria. West Afr J Med. 2001;20(2):98-101.

956. Eufinger H, Machtens E. Purulent pansinusitis, orbital cellulitis and rhinogenic intracranial complications. J Craniomaxillofac Surg. 2001;29(2):111-7.

957. Kuranov NI. [Orbital and intracranial complications of rhinosinusitis]. Vestn Otorinolaringol. 2001(4):46-7.

958. Gallagher RM, Gross CW, Phillips CD. Suppurative intracranial complications of sinusitis. Laryngoscope. 1998;108(11 Pt 1):1635-42.

959. Clayman GL, Adams GL, Paugh DR, Koopmann CF, Jr. Intracranial complications of paranasal sinusitis: a combined institutional review. Laryngoscope. 1991;101(3):234-9.

960. Lerner DN, Choi SS, Zalzal GH, Johnson DL. Intracranial complications of sinusitis in childhood. Ann Otol Rhinol Laryngol. 1995;104(4 Pt 1):288-93.

961. Rumelt S, Rubin PA. Potential sources for orbital cellulitis. Int Ophthalmol Clin. 1996;36(3):207-21.

962. 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;36(6):1165-83, xi.

963. Chandler JR, Langenbrunner DJ, Stevens ER. The pathogenesis of orbital complications in acute sinusitis. Laryngoscope. 1970;80(9):1414-28.

964. Josephson JS, Rosenberg SI. Sinusitis. Clin Symp. 1994;46(2):1-32.

965. Gordts F, Herzeel R. Orbital involvement in sinus pathology: often without ocular pain. Bull Soc Belge Ophtalmol. 2002(285):9-14.

966. Wald ER. Sinusitis in children. N Engl J Med. 1992;326(5):319-23.

967. Dunham ME. New light on sinusitis. Contemp Pediatr. 1994;11(10):102-6, 8, 10 passim.

968. Berenholz L, Kessler A, Shlomkovitz N, Sarfati S, Segal S. Superior ophthalmic vein thrombosis: complication of ethmoidal rhinosinusitis. Arch Otolaryngol Head Neck Surg. 1998;124(1):95-7.

969. Bergin DJ, Wright JE. Orbital cellulitis. Br J Ophthalmol. 1986;70(3):174-8.

970. Mitchell R, Kelly J, Wagner J. Bilateral orbital complications of pediatric rhinosinusitis. Arch Otolaryngol Head Neck Surg. 2002;128(8):971-4.

971. Jones NS, Walker JL, Bassi S, Jones T, Punt J. The intracranial complications of rhinosinusitis: can they be prevented? Laryngoscope. 2002;112(1):59-63.

972. Low DE, Desrosiers M, McSherry J, Garber G, Williams JW, Jr., Remy H, et al. A practical guide for the diagnosis and treatment of acute sinusitis. Cmaj. 1997;156(Suppl 6):S1-14.

973. Giannoni CM, Stewart MG, Alford EL. Intracranial complications of sinusitis. Laryngoscope. 1997;107(7):863-7.

974. Albu S, Tomescu E, Bassam S, Merca Z. Intracranial complications of sinusitis. Acta Otorhinolaryngol Belg. 2001;55(4):265-72.

975. Gungor A, Adusumilli V, Corey JP. Fungal sinusitis: progression of disease in immunosuppression--a case report. Ear Nose Throat J. 1998;77(3):207-10, 15.

976. Skouteris CA, Velegrakis G, Christodoulou P, Helidonis E. Infantile osteomyelitis of the maxilla with concomitant subperiosteal orbital abscess: a case report. J Oral Maxillofac Surg. 1995;53(1):67-70.

977. Bromberg Tea. Devastating complications of acute pediatric bacterial sinusitis. Otolaryngol Head Neck Surg. 1999;120:575-9.

978. 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.

979. Siberry GK, Costarangos C, Cohen BA. Destruction of the nasal

980. Birrel J. Pediatric Otolaryngology. The nose and sinuses. Chapter 9 Embryology and developmental anatomy. . Bristol: ohn Wright and Sons Ltd; 1978.

981. Gordts F, Clement PA, Destryker A, Desprechins B, Kaufman L. Prevalence of sinusitis signs on MRI in a non-ENT paediatric population. Rhinology. 1997 Dec;35(4):154-7.

982. Kristo A, Alho OP, Luotonen J, Koivunen P, Tervonen O, Uhari M. Cross-sectional survey of paranasal sinus magnetic resonance imaging findings in schoolchildren. Acta Paediatr. 2003;92(1):34-6.

983. Wald ER, Milmoe GJ, Bowen A, Ledesma-Medina J, Salamon N, Bluestone CD. Acute maxillary sinusitis in children. N Engl J Med. 1981 Mar 26;304(13):749-54.

984. Gwaltney JM, Jr., Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. N Engl J Med. 1994;330(1):25-30.

985. Anon JB. Acute bacterial rhinosinusitis in pediatric medicine: current issues in diagnosis and management. Paediatr Drugs. 2003;5 Suppl 1:25-33.

986. Aitken M, Taylor JA. Prevalence of clinical sinusitis in young children followed up by primary care pediatricians. Arch Pediatr Adolesc Med. 1998 Mar;152(3):244-8.

987. Orobello PW, Jr., Park RI, Belcher LJ, Eggleston P, Lederman HM, Banks JR, et al. Microbiology of chronic sinusitis in children. Arch Otolaryngol Head Neck Surg. 1991;117(9):980-3.

988. Riding KH, Irvine R. Sinusitis in children. J Otolaryngol. 1987 Aug;16(4):239-43.

989. Clement PA, Bijloos J, Kaufman L, Lauwers L, Maes JJ, Van der Veken P, et al. Incidence and etiology of rhinosinusitis in children. Acta Otorhinolaryngol Belg. 1989;43(5):523-43.

990. Wald ER. Beginning antibiotics for acute rhinosinusitis and choosing the right treatment. Clin Rev Allergy Immunol. 2006 Jun;30(3):143-52.

991. Sacco O, Tarantino V, Lantero S, Silvestri M, Spallarossa D, Barretta MA, et al. Nasal brushing: a clinically useful procedure in pediatric patients with rhinosinusitis? Int J Pediatr Otorhinolaryngol. 1999;50(1):23-30.

992. Lusk RP, Lazar RH, Muntz HR. The diagnosis and treatment of recurrent and chronic sinusitis in children. Pediatr Clin North Am. 1989;36(6):1411-21.

993. Manning SC. Pediatric sinusitis. Otolaryngol Clin North Am. 1993;26(4):623-38.

994. Willner A, Lazar RH, Younis RT, Beckford NS. Sinusitis in children: current management. Ear Nose Throat J. 1994;73(7):485-91.

995. 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.

996. 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.

997. Lesserson JA, Kieserman SP, Finn DG. The radiographic incidence of chronic sinus disease in the pediatric population. Laryngoscope. 1994;104(2):159-66.

998. April MM, Zinreich SJ, Baroody FM, Naclerio RMl. Coronal CT scan abnormalities in children with chronic sinusitis. Laryngoscope. 1993;103(9):985-90.

999. Iwens P, Clement PA. [Sinusitis in atopic children]. Acta Otorhinolaryngol Belg. 1994;48(4):383-6.

1000. 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.

1001. Albegger Kl. [ENT aspects of rhino-sinusitis in children (author's transl)]. Hno. 1980;28(10):321-8.

1002. Oxelius VA. IgG subclass levels in infancy and childhood. Acta Paediatr Scand. 1979 Jan;68(1):23-7.

1003. Milczuk HA, Dalley RW, Wessbacher FW, Richardson MA. Nasal and paranasal sinus anomalies in children with chronic sinusitis. Laryngoscope. 1993;103(3):247-52.

1004. Polmar SH. The role of the immunologist in sinus disease. J

Allergy Clin Immunol. 1992;90(3 Pt 2):511-4; discussion 4-5.

1005. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinusitis in the allergic child. Pediatr Clin North Am. 1988;35(5):1091-101.

1006. Mickle JE, Cutting GR. Genotype-phenotype relationships in cystic fibrosis. Med Clin North Am. 2000 May;84(3):597-607.

1007. Neely JG, Harrison GM, Jerger JF, Greenberg SD, Presberg H. The otolaryngologic aspects of cystic fibrosis. Trans Am Acad Ophthalmol Otolaryngol. 1972;76(2):313-24.

1008. Yung MW, Gould J, Upton GJ. Nasal polyposis in children with cystic fibrosis: a long-term follow-up study. Ann Otol Rhinol Laryngol. 2002;111(12 Pt 1):1081-6.

1009. Brihaye P, Clement PA, Dab I, Desprechin B. Pathological changes of the lateral nasal wall in patients with cystic fibrosis (mucoviscidosis). Int J Pediatr Otorhinolaryngol. 1994;28(2-3):141-7.

1010. 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.

1011. Sleigh MA. Primary ciliary dyskinesia. Lancet. 1981 Aug 29;2(8244):476.

1012. Narang I, Ersu R, Wilson NM, Bush A. Nitric oxide in chronic airway inflammation in children: diagnostic use and pathophysiological significance. Thorax. 2002 Jul;57(7):586-9.

1013. Jorissen M. Differential diagnosis of local defense mechanism diseases in ENT. Acta Otorhinolaryngol Belg. 2000;54(3):413-5.

1014. Jorissen M, Willems T. Success rates of respiratory epithelial cell culture techniques with ciliogenesis for diagnosing primary ciliary dyskinesia. Acta Otorhinolaryngol Belg. 2000;54(3):357-65.

1015. Barbero GJl. Gastroesophageal reflux and upper airway disease. Otolaryngol Clin North Am. 1996;29(1):27-38.

1016. Morris P, Leach A. Antibiotics for persistent nasal discharge (rhinosinusitis) in children (Cochrane Review). Cochrane Database Syst Rev. 2002(4):CD001094.

1017. Finkelstein JA, Davis RL, Dowell SF, Metlay JP, Soumerai SB, Rifas-Shiman SL, et al. Reducing antibiotic use in children: a randomized trial in 12 practices
A randomized, placebo-controlled trial of antimicrobial treatment for children with clinically diagnosed acute sinusitis
A randomized controlled trial of azithromycin and amoxycillin/clavulanate in the management of subacute childhood rhinosinusitis
Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children
Conservative treatment of chronic maxillary sinusitis in children. Long-term follow-up
Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics
Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children
Is antibiotic treatment of chronic sinusitis effective in children?
Acute rhinosinusitis : a pharmacoeconomic review of antibacterial use
Treatment of pediatric sinusitis
Antibiotics for persistent nasal discharge (rhinosinusitis) in children
Antimicrobial guidelines for the treatment of acute bacterial rhinosinusitis in immunocompetent children
Technical report: evidence for the diagnosis and treatment of acute uncomplicated sinusitis in children: a systematic overview
Disorders of ciliary motility
Diagnosis and treatment of uncomplicated acute sinusitis in children
Medical management of pediatric chronic sinusitis
Judicious use of antibiotics for common pediatric respiratory infections
Short course antibiotic therapy for respiratory infections: a review of the evidence
Antibiotics for persistent nasal discharge (rhinosinusitis) in children
Medical management of acute bacterial sinusitis. Recommendations of a clinical advisory committee on pediatric and adult sinusitis

Acute and chronic sinusitis in children
Current concepts in the management of paediatric rhinosinusitis
Pediatric rhinosinusitis
Infectious intracranial complications of sinusitis, other than meningitis, in children: 12-year review. Pediatrics. 2001;108(1):1-7.

1018. Otten FW, Grote JJ. Treatment of chronic maxillary sinusitis in children. Int J Pediatr Otorhinolaryngol. 1988;15(3):269-78.

1019. 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 Paediatrica. 2005;94(9):1208-13.

1020. Balatsouras DG, Korres S, Rallis E, Eliopoulos P, Ferekidis E. Twice-daily dosing of loracarbef 15 mg/kg versus 30 mg/kg in the treatment of children with acute sinusitis. Drugs Exp Clin Res. 2005;31 Suppl:1-5.

1021. Clement PA, Bluestone CD, Gordts F, Lusk RP, Otten FW, Goossens H, et al. Management of rhinosinusitis in children: consensus meeting, Brussels, Belgium, September 13, 1996. Arch Otolaryngol Head Neck Surg. 1998 Jan;124(1):31-4.

1022. Yilmaz G, Varan B, Yilmaz T, Gurakan B. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. Eur Arch Otorhinolaryngol. 2000;257(5):256-9.

1023. Passalacqua G, Albano M, Canonica GW, Bachert C, Van Cauwenberge P, Davies RJ, et al. Inhaled and nasal corticosteroids: safety aspects. Allergy. 2000 Jan;55(1):16-33.

1024. Scadding GK. Corticosteroids in the treatment of pediatric allergic rhinitis. J Allergy Clin Immunol. 2001 Jul;108(1 Suppl):S59-64.

1025. Fokkens WJ, Cserhati E, dos Santos JM, Praca F, van Zanten M, Schade A, et al. Budesonide aqueous nasal spray is an effective treatment in children with perennial allergic rhinitis, with an onset of action within 12 hours. Ann Allergy Asthma Immunol. 2002 Sep;89(3):279-84.

1026. Fokkens WJ, Scadding GK. Perennial rhinitis in the under 4s: a difficult problem to treat safely and effectively? A comparison of intranasal fluticasone propionate and ketotifen in the treatment of 2-4-year-old children with perennial rhinitis. Pediatr Allergy Immunol. 2004 Jun;15(3):261-6.

1027. Baena-Cagnani CE. Safety and tolerability of treatments for allergic rhinitis in children. Drug Saf. 2004;27(12):883-98.

1028. 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.

1029. Poole MD. Pediatric endoscopic sinus surgery: the conservative view. Ear Nose Throat J. 1994 Apr;73(4):221-7.

1030. Bothwell MR, Parsons DS, Talbot A, Barbero GJ, Wilder Bl. Outcome of reflux therapy on pediatric chronic sinusitis. Otolaryngol Head Neck Surg. 1999;121(3):255-62.

1031. 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. Ann Allergy Asthma Immunol. 2003;91(1):71-8.

1032. Tsao CH, Chen LC, Yeh KW, Huang JL. Concomitant chronic sinusitis treatment in children with mild asthma: the effect on bronchial hyperresponsiveness. Chest. 2003;123(3):757-64.

1033. Maes JJ, Clement PA. [The value of maxillary sinus irrigation in children with maxillary sinusitis using the Waters film]. Acta Otorhinolaryngol Belg. 1986;40(4):570-81.

1034. Lund VJ. Inferior meatal antrostomy. Fundamental considerations of design and function. J Laryngol Otol Suppl. 1988;15:1-18.

1035. Hebert RL, 2nd, Bent JP, 3rd. Meta-analysis of outcomes of pediatric functional endoscopic sinus surgery. Laryngoscope. 1998;108(6):796-9.

1036. Jiang RS, Hsu CY. Functional endoscopic sinus surgery in children and adults. Ann Otol Rhinol Laryngol. 2000;109(12 Pt 1):1113-6.

1037. Fakhri S, Manoukian JJ, Souaid JP. Functional endoscopic sinus surgery in the paediatric population: outcome of a conservative approach to postoperative care. J Otolaryngol. 2001;30(1):15-8.

1038. Bothwell MR, Piccirillo JF, Lusk RP, Ridenour BDl. Long-term

outcome of facial growth after functional endoscopic sinus surgery. Otolaryngol Head Neck Surg. 2002;126(6):628-34.

1039. Lieu JE, Piccirillo JF, Lusk RP. Prognostic staging system and therapeutic effectiveness for recurrent or chronic sinusitis in children. Otolaryngol Head Neck Surg. 2003;129(3):222-32.

1040. Chan KH, Winslow CP, Abzug MJ. Persistent rhinosinusitis in children after endoscopic sinus surgery. Otolaryngol Head Neck Surg. 1999;121(5):577-80.

1041. Ramadan HH. Relation of age to outcome after endoscopic sinus surgery in children. Arch Otolaryngol Head Neck Surg. 2003;129(2):175-7.

1042. Ramadan HH, Hinerman RA. Smoke exposure and outcome of endoscopic sinus surgery in children. Otolaryngol Head Neck Surg. 2002;127(6):546-8.

1043. Ramadan HH. Timing of endoscopic sinus surgery in children: is there an impact on outcome? Laryngoscope. 2001;111(10):1709-11.

1044. Ramadan HH. Corticosteroid therapy during endoscopic sinus surgery in children: is there a need for a second look? Arch Otolaryngol Head Neck Surg. 2001;127(2):188-92.

1045. Duplechain JK, White JA, Miller RH. Pediatric sinusitis. The role of endoscopic sinus surgery in cystic fibrosis and other forms of sinonasal disease. Arch Otolaryngol Head Neck Surg. 1991;117(4):422-6.

1046. 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;28(1):25-32.

1047. Rosbe KW, Jones DT, Rahbar R, Lahiri T, Auerbach AD. Endoscopic sinus surgery in cystic fibrosis: do patients benefit from surgery? Int J Pediatr Otorhinolaryngol. 2001 Nov 1;61(2):113-9.

1048. Hibbert J. The occurrence of adenoidal signs and symptoms in normal children. Clin Otolaryngol. 1981 Apr;6(2):97-100.

1049. McClay JE. Resistant bacteria in the adenoids: a preliminary report. Arch Otolaryngol Head Neck Surg. 2000;126(5):625-9.

1050. Wang D, Clement P, Kaufman L, Derde MP. Fiberoptic evaluation of the nasal and nasopharyngeal anatomy in children with snoring. J Otolaryngol. 1994 Feb;23(1):57-60.

1051. 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. Arch Otolaryngol Head Neck Surg. 2001;127(9):1093-8.

1052. Ungkanont K, Damrongsak S. Effect of adenoidectomy in children with complex problems of rhinosinusitis and associated diseases. Int J Pediatr Otorhinolaryngol. 2004 Apr;68(4):447-51.

1053. Ramadan HH. Adenoidectomy vs endoscopic sinus surgery for the treatment of pediatric sinusitis. Arch Otolaryngol Head Neck Surg. 1999;125(11):1208-11.

1054. Hens G, Hellings PW. The nose: gatekeeper and trigger of bronchial disease. Rhinology. 2006 Sep;44(3):179-87.

1055. Carayol N, Crampette L, Mainprice B, Ben-Soussen P, Verrecchia M, Bousquet J, et al. Inhibition of mediator and cytokine release from dispersed nasal polyp cells by mizolastine. Allergy. 2002;57(11):1067-70.

1056. Johansson A, Bende M, Millqvist E, Bake B. Nasobronchial relationship after cold air provocation. Respir Med. 2000 Nov;94(11):1119-22.

1057. Denburg JA, Keith PK. Systemic aspects of chronic rhinosinusitis. Immunol Allergy Clin North Am. 2004 Feb;24(1):87-102.

1058. Barnes KC. Genetic epidemiology of health disparities in allergy and clinical immunology. J Allergy Clin Immunol. 2006 Feb;117(2):243-54; quiz 55-6.

1059. Braunstahl GJ, Hellings PW. Nasobronchial interaction mechanisms in allergic airways disease. Curr Opin Otolaryngol Head Neck Surg. 2006 Jun;14(3):176-82.

1060. Senior BA, Kennedy DW, Tanabodee J, Kroger H, Hassab M, Lanza DC. Long-term impact of functional endoscopic sinus surgery on asthma. Otolaryngol Head Neck Surg. 1999;121(1):66-8.

1061. 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? Journal of Allergy & Clinical Immunology. 2003;112(5):877-82.

1062. 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. J Allergy Clin Immunol. 2002;109(4):621-6.

1063. 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;17(4):215-9.

1064. Nishioka GJ, Cook PR, Davis WE, McKinsey JP. Functional endoscopic sinus surgery in patients with chronic sinusitis and asthma. Otolaryngol Head Neck Surg. 1994;110(6):494-500.

1065. Dinis PB, Gomes A. Sinusitis and asthma: how do they interrelate in sinus surgery? Am J Rhinol. 1997;11(6):421-8.

1066. Manning SC, Wasserman RL, Silver R, Phillips DL. Results of endoscopic sinus surgery in pediatric patients with chronic sinusitis and asthma. Arch Otolaryngol Head Neck Surg. 1994;120(10):1142-5.

1067. Schaitkin B, May M, Shapiro A, Fucci M, Mester SJ. Endoscopic sinus surgery: 4-year follow-up on the first 100 patients. Laryngoscope. 1993 Oct;103(10):1117-20.

1068. 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. Laryngoscope. 2003;113(10):1703-6.

1069. Mehanna H, Mills J, Kelly B, McGarry GW. Benefit from endoscopic sinus surgery. Clin Otolaryngol. 2002;27(6):464-71.

1070. Ponikau JU, Sherris DA, Kephart GM, Adolphson C, Kita H. The role of ubiquitous airborne fungi in chronic rhinosinusitis. Current Allergy & Asthma Reports. 2005;5(6):472-6.

1071. 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.

1072. Hurst JR, Wilkinson TM, Donaldson GC, Wedzicha JA. Upper airway symptoms and quality of life in chronic obstructive pulmonary disease (COPD). Respir Med. 2004 Aug;98(8):767-70.

1073. Stankiewicz JA, Chow JM. Cost analysis in the diagnosis of chronic rhinosinusitis. Am J Rhinol. 2003;17(3):139-42.

1074. Franzese CB, Stringer SP. Economic analysis of the use of limited coronal computed tomography scans in the management of sinusitis. American Journal of Rhinology. 2004;18(5):329-34.

1075. 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.

1076. Gliklich RE, Metson R. Economic implications of chronic sinusitis. Otolaryngol Head Neck Surg. 1998;118(3 Pt 1):344-9.

1077. Wasserfallen JB, Livio F, Zanetti G. Acute rhinosinusitis : a pharmacoeconomic review of antibacterial use. Pharmacoeconomics. 2004;22(13):829-37.

1078. van Agthoven M, Uyl-de Groot CA, Fokkens WJ, van de Merwe JP, Busschbach JJ. Cost analysis of regular and filgrastim treatment in patients with refractory chronic rhinosinusitis. Rhinology. 2002;40(2):69-74.

1079. Katz R. FDA: evidentiary standards for drug development and approval. NeuroRx. 2004 Jul;1(3):307-16.

1080. Pfaller MA, Ehrhardt AF, Jones RN. Frequency of pathogen occurrence and antimicrobial susceptibility among community-acquired respiratory tract infections in the respiratory surveillance program study: microbiology from the medical office practice environment. Am J Med. 2001;111(Suppl 9A):4S-12S; discussion 36S-8S.

1081. Cain WS. Testing olfaction in a clinical setting. Ear Nose Throat J. 1989;68(4):316, 22-8.

1082. Cain WS, Gent J, Catalanotto FA, Goodspeed RB. Clinical evaluation of olfaction. Am J Otolaryngol. 1983 Jul-Aug;4(4):252-6.

1083. Cain WS, Gent JF, Goodspeed RB, Leonard G. Evaluation of

olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. Laryngoscope. 1988 Jan;98(1):83-8.

1084. 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;32(3):489-502.

1085. Wright HN. Characterization of olfactory dysfunction. Arch Otolaryngol Head Neck Surg. 1987;113(2):163-8.

1086. Kurtz DB, White TL, Sheehe PR, Hornung DE, Kent PF. Odorant confusion matrix: the influence of patient history on patterns of odorant identification and misidentification in hyposmia. Physiol Behav. 2001 Mar;72(4):595-602.

1087. Hendriks AP. Olfactory dysfunction. Rhinology. 1988 Dec;26(4):229-51.

1088. Corwin J. Olfactory identification in hemodialysis: acute and chronic effects on discrimination and response bias. Neuropsychologia. 1989;27(4):513-22.

1089. Takagi SF. A standardized olfactometer in Japan. A review over ten years. Ann N Y Acad Sci. 1987;510:113-8.

1090. Eloit C, Trotier D. A new clinical olfactory test to quantify olfactory deficiencies. Rhinology. 1994 Jun;32(2):57-61.

1091. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). Laryngoscope. 1996 Mar;106(3 Pt 1):353-6.

1092. Doty RL, McKeown DA, Lee WW, Shaman P. A study of the test-retest reliability of ten olfactory tests. Chem Senses. 1995 Dec;20(6):645-56.

1093. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S. "Sniffin' sticks": screening of olfactory performance. Rhinology. 1996;34(4):222-6.

1094. Robson AK, Woollons AC, Ryan J, Horrocks C, Williams S, Dawes PJ. Validation of the combined olfactory test. Clin Otolaryngol. 1996 Dec;21(6):512-8.

1095. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses. 1997 Feb;22(1):39-52.

1096. Kobal G, Klimek L, Wolfensberger M, Gudziol H, Temmel A, Owen CM, et al. Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. Eur Arch Otorhinolaryngol. 2000;257(4):205-11.

1097. Davidson TM, Murphy C. Rapid clinical evaluation of anosmia. The alcohol sniff test. Arch Otolaryngol Head Neck Surg. 1997 Jun;123(6):591-4.

1098. Ahlskog JE, Waring SC, Petersen RC, Esteban-Santillan C, Craig UK, O'Brien PC, et al. Olfactory dysfunction in Guamanian ALS, parkinsonism, and dementia. Neurology. 1998 Dec;51(6):1672-7.

1099. Nordin S, Bramerson A, Liden E, Bende M. The Scandinavian Odor-Identification Test: development, reliability, validity and normative data. Acta Otolaryngol. 1998 Mar;118(2):226-34.

1100. Kremer B, Klimek L, Mosges R. Clinical validation of a new olfactory test. Eur Arch Otorhinolaryngol. 1998;255(7):355-8.

1101. McCaffrey RJ, Duff K, Solomon GS. Olfactory dysfunction discriminates probable Alzheimer's dementia from major depression: a cross-validation and extension. J Neuropsychiatry Clin Neurosci. 2000 Winter;12(1):29-33.

1102. Kobal G, Palisch K, Wolf SR, Meyer ED, Huttenbrink KB, Roscher S, et al. A threshold-like measure for the assessment of olfactory sensitivity: the "random" procedure. Eur Arch Otorhinolaryngol. 2001 May;258(4):168-72.

1103. Hummel T, Konnerth CG, Rosenheim K, Kobal G. Screening of olfactory function with a four-minute odor identification test: reliability, normative data, and investigations in patients with olfactory loss. Ann Otol Rhinol Laryngol. 2001 Oct;110(10):976-81.

1104. 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.

1105. May M LH, Schaitkin B, et al. Results of surgery. In: Levine H MM, editor. Rhinology and sinusology. New York: Thieme Medical Publishers, Inc.; 1993.

1106. Oxford LE, McClay J. Complications of acute sinusitis in children. Otolaryngology - Head & Neck Surgery. 2005;133(1):32-7.

1107. Germiller JA, Monin DL, Sparano AM, Tom LW. Intracranial complications of sinusitis in children and adolescents and their outcomes. Arch Otolaryngol Head Neck Surg. 2006 Sep;132(9):969-76.

1108. Quraishi H, Zevallos JP. Subdural empyema as a complication of sinusitis in the pediatric population. Int J Pediatr Otorhinolaryngol. 2006 Sep;70(9):1581-6.

1109. 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.

1110. 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.

1111. Hytonen M, Atula T, Pitkaranta A. Complications of acute sinusitis in children. Acta Otolaryngol Suppl. 2000;543:154-7.

1112. Lim M, Lew-Gor S, Darby Y, Brookes N, Scadding G, Lund V. The relationship between subjective assessment instruments in chronic rhinosinusitis. . Rhinology. 2007;45(2):144-7.