EAACI

European

Position Paper on Rhinosinusitis

and Nasal Polyps

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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). 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 (4-6).

Data on (chronic) rhinosinusitis is limited and the disease entity is badly defined. Therefore, the available data is difficult to interpret and extrapolate. Although of considerable assistance, the available consensus documents on chronic rhinosinusitis and nasal polyps do not answer a number of relevant questions that would unify the information and current concepts that exist in epidemiology, diagnosis, treatment and research. To add to this, none of these documents are evidence based.

There is considerable interest in guidelines as tools for implementing health care based on proof of effectiveness. Guidelines should be informative, simple and easy to use and in a form that can be widely disseminated within the medical community in order to improve patient care.

Evidence-based medicine is an important method of preparing guidelines (7, 8). Moreover, the implementation of guidelines is equally important.

The European Academy of Allergology and Clinical Immunology (EAACI) has created a Taskforce to consider what is 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 EP3OS document is also approved by the European Rhinologic Society (ERS).

The present document is intended to be state-of-the art 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 revision of the diagnostic methods;
- to provide an evidence-based revision 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.

Table 1-1. Category of evidence (8).

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

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 one definition aims at all practitioners (4-6, 9).

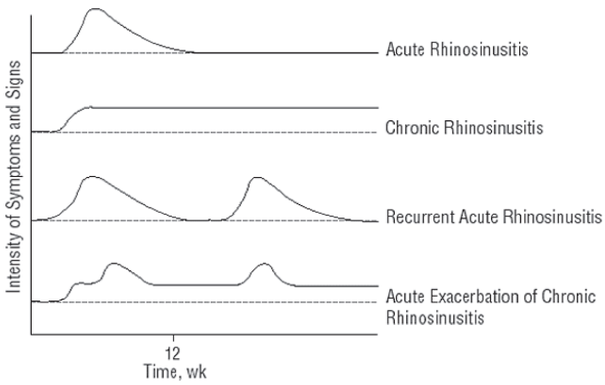
In 2001 the WHO put together a working group on rhinitis and its impact on asthma (ARIA)(10). In this group rhinitis was classified according to duration and severity.

Table 2-1. Classification of allergic rhinitis (10).

1-	"Intermittent" means that the symptoms are present: • Less than 4 days a week, • And for less than 4 weeks.
2-	"Persistent" means that the symptoms are present: • More than 4 days a week, • Or for more than 4 weeks. (should it be "and", not or?)
3-	"Mild" means that there are none of the following items: • No sleep disturbance, • No impairment of daily activities, leisure and/or sport, • No impairment of school or work, • Symptoms are not troublesome.
4-	"Moderate-severe" means that there are one or more of the following items: • Sleep disturbance, • Impairment of daily activities, leisure and/or sport, • Impairment of school or work, • Troublesome are symptoms.

Until recently rhinosinusitis was usually classified based on the duration into acute, subacute, chronic and acute on chronic (see figure 1). Yet this division does not correlate with the classification of rhinitis. Moreover it does not incorporate the severity of the disease. Also due to the long timeline of 12 weeks in chronic rhinosinusitis it can be difficult to discriminate between recurrent acute rhinosinusitis and chronic rhinosinusitis with or without exacerbations.

Figure 2-1. Former classification of Rhinosinusitis (11).



Due to the large differences in technical possibilities to diagnose and treat rhinosinusitis/nasal polyps by various professions, 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 giving definitions that can be applied in appropriate studies. In this way the taskforce hopes to improve the comparability of studies and thus enhance 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

Rhinosinusitis (including nasal polyps) is defined as:

- Inflammation of the nose and the paranasal sinuses characterised by two or more symptoms:
  - blockage/congestion;
  - discharge: anterior/post nasal drip;
  - facial pain/pressure,
  - reduction or loss of smell;

and either

- Endoscopic signs:
  - polyps;
  - mucopurulent discharge from middle meatus;
  - oedema/mucosal obstruction primarily in middle meatus,

and/or

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

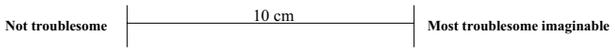
2-2-2 Severity of the disease

The disease can be divided into MILD and MODERATE/SEVERE based on total severity visual analogue scale (VAS) score (010 cm):

MILD = AS 0-4
MODERATE/SEVERE = VAS 5-10

To evaluate the total severity the patient is asked to indicate on a VAS the question:

How troublesome are your symptoms of rhinosinusitis?



2-2-3 Duration of the disease

Acute/Intermittent
< 12 weeks
Complete resolution of symptoms.

Chronic/Persistent
>12 weeks symptoms
No complete resolution of symptoms.

2-3 Definition for epidemiology/General Practice

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

Acute/Intermittent Rhinosinusitis is defined as
sudden onset of two or more of the symptoms:
- blockage/congestion;
- discharge anterior/post nasal drip;
- facial pain/pressure;
- reduction/loss of smell;

for <12 weeks,
with symptom free intervals if the problem is intermittent,
with validation by telephone or interview.
Questions on allergic symptoms i.e. sneezing, watery rhino rhea, nasal itching and itchy watery eyes should be included.

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

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

Persistent/Chronic Rhinosinusitis/nasal polyps is defined as:
nasal congestion/obstruction/blockage with
- facial pain/pressure, or
- discoloured discharge(anterior / posterior nasal drip), or
- reduction/loss of smell

for >12 weeks,
with validation by telephone or interview.
Questions on allergic symptoms i.e. sneezing, watery rhino rhea, nasal itching and itchy watery eyes should be included.
Also include questions on intermittent disease (see definition above).

2-4 Definition for research

For research purposes Chronic Rhinosinusitis (CRS) is the major finding and Nasal Polyposis (NP) is considered a subgroup of this entity. 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 Definitions when no earlier sinus surgery has been performed

Polyposis: bilateral, endoscopically visualised in middle meatus

Chronic rhinosinusitis: bilateral, 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 Definitions when sinus surgery has been performed

Once surgery has altered the anatomy of the lateral wall, the presence of polyps is defined as 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:
- aspirin sensitivity based on positive oral, bronchial or nasal provocation or an obvious history;
- asthma/bronchial hyper-reactivity /COPD based on symptoms, respiratory function tests;
- allergy based on specific serum IgE or SPTs;
- finding of purulent discharge/pus.

2-4-4 Exclusion from general studies

Patients with the following diseases should be excluded from general studies on chronic rhinosinusitis and/or nasal polyposis:
- cystic fibrosis based on positive sweat test or DNA alleles;
- gross immunodeficiency (congenital or acquired);
- congenital mucociliary problems e.g. primary ciliary dyskinesia (PCD);
- non-invasive fungal balls and invasive fungal disease;
- systemic vasculitic and granulomatous diseases.

3. Chronic rhinosinusitis and 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 optimal sinus ventilation and clearance. Specifically, ostial patency significantly affects mucus composition and secretion; moreover, an open ostium allows mucociliary clearance to easily remove particulate matters and bacteria eventually come in contact with the sinusal mucosa.
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 (URI), 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 acute rhinosinusitis.

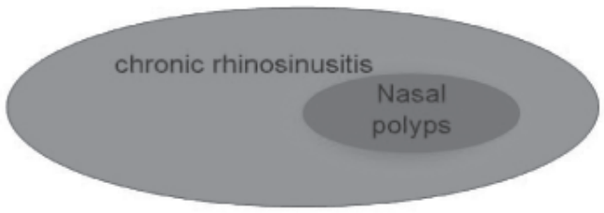
3-2 Rhinosinusitis

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 (12). Factors contributing can be mucociliary impairment (13, 14), (bacterial) infection (15), allergy (16), swelling of the mucosa for another reason, but only rarely physical obstructions caused by morphological/anatomical variations in the nasal cavity or paranasal sinuses (17, 18). A role in the pathogenesis of rhinosinusitis is certainly 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. An in depth discussion on factors contributing to chronic rhinosinusitis and nasal polyps can be found in chapter 4-4 and 4-6.

3-3 Nasal polyps and chronic rhinosinusitis

Nasal polyps and chronic rhinosinusitis are often taken together as one disease entity, because it seems impossible to clearly differentiate between them (19-21). Nasal Polyposis is therefore considered a subgroup of Chronic Rhinosinusitis (fig. 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 (22). 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 (23-27). 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 (28).

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% (29). 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 (30, 31). 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 (31, 32).

4. Epidemiology and predisposing factors

4-1 Introduction

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. More reliable data are available on acute rhinosinusitis. As mentioned earlier acute non-viral rhinosinusitis 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: blockage/congestion, discharge, anterior/post nasal 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 (33). Signs and symptoms of bacterial infection may be mild and often resolve spontaneously (34, 35). In spite of the high prevalence and significant morbidity of chronic rhinosinusitis and 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 EPOS document is to give an overview of the currently available epidemiologic data on rhinosinusitis and nasal polyps, and illustrate the factors which are believed to predispose to the development.

4-2 Acute bacterial rhinosinusitis

When describing the incidence of acute bacterial rhinosinusitis there has been a lot of debate about the definition of acute bacterial rhinosinusitis. For example in the Cochrane Review on antibiotics for acute sinusitis, studies were included if sinusitis was proven by a consistent clinical history, and radiographic or aspiration evidence of acute sinusitis (36). 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 clinical diagnosis of acute rhinosinusitis less than half have significant abnormalities at X-ray examination (37). Based on sinus puncture/aspiration (considered diagnostically the most accurate), 49-83% of symptomatic patients had acute sinusitis (38). 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 (38).

An average of 8.4% of the Dutch population reported at least one episode of acute rhinosinusitis per year in 1999 (39). The incidence of visits to the general practioner for of acute sinusitis in the Netherlands in 2000 was 20.0 per 1,000 men and 33.8 per 1,000 women (40). According to National Ambulatory Medical Care Survey (NAMCS) data in the USA rhinosinusitis is the fifth most common diagnosis for which an antibiotic is prescribed. Rhinosinusitis accounted for 9% and 21% of all paediatric and adult antibiotic prescriptions, respectively, written in 2002 (5).

4-3 Factors associated with acute rhinosinusitis

4-3-1 Pathogens

Superinfection of bacteria on mucosa damaged by viral infection (common cold) is the most important cause of acute rhinosinusitis. The most common bacterial species isolated from the maxillary sinuses of patients with acute rhinosinusitis are Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, the latter being more common in children (41, 42). Other streptococcal species, anaerobic bacteria and Staphylococcus aureus cause a small percentage of cases. Resistance patterns of the predominant pathogens vary considerably (43, 44). 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 (45).

4-3-2 Ciliary impairment

Normal mucociliary flow is a significant defence mechanism in the prevention of acute rhinosinusitis. Viral rhinosinusitis results in the loss of cilia and ciliated cells, with 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 microns in length) were often seen (46). The impaired mucociliary function during viral rhinosinusitis results in an increased sensitivity to bacterial infection.

Also in animal experimental work it was shown that early 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 was found (47).

4-3-3 Allergy

Review articles on sinusitis have suggested that atopy predisposes to rhinosinusitis (48). This theory is attractive given the popularity of the concept that disease in the ostiomeatal area contributes to sinus disease in that the mucosa in an individual with allergic rhinitis might be expected to be swollen and more liable to obstruct sinus ostia, reduce ventilation, lead to mucus retention that might be more prone to become infected. Furthermore there has been an increase in the body of opinion that regard the mucosa of the nasal airway as being in a continuum with the paranasal sinuses and hence the term rhinosinusitis (49). The number of studies determining the occurrence of acute rhinosinusitis in patients with and without allergy is very limited.

Savolainen studied the occurrence of allergy in 224 patients with verified acute rhinosinusitis 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 prior acute sinusitis episodes or of previously performed sinus irrigations. Bacteriological and radiological findings did not differ significantly between the groups (50). Alho showed that subjects with allergic IgE-mediated rhinitis had more severe paranasal sinus changes in CT scans than nonallergic subjects during viral colds. These changes indicate impaired sinus functioning and may increase the risk of bacterial sinusitis (51).

In conclusions: although an attractive hypothesis we can repeat the statement made a decade ago, there remain no published prospective reports on the incidence of infective rhinosinusitis in populations with and without clearly defined allergic rhinosinusitis (52).

4-4 Chronic rhinosinusitis (CRS)

CRS is one of the most common health care problems, with significant direct medical costs and severe impact on lower airway disease and general health outcomes (53, 54). The paucity of accurate epidemiologic data on CRS and 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 (55), ranking this condition second in prevalence among all chronic conditions. Later, the high prevalence of CRS was confirmed by another survey suggesting that 16% of the adult US population has CRS (56). However the prevalence of doctor diagnosed CRS is much lower; a prevalence of 2% was found using ICD-9 codes as an identifier(57).

Of note, the prevalence rate of CRS was substantially higher in females with a female/male ratio of 6/4 (55). In Canada, 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 (58). 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% (58). In a nationwide survey in Korea, the overall prevalence of chronic sinusitis, defined as the presence of at least 3 nasal symptoms lasting more than 3 months along with the endoscopic finding of a nasal polyp and/or mucopurulent discharge within the middle meatus, was 1.01% (59), without differences neither in age groups nor in sexes. By screening a non-ENT population, which may be considered representative of the general population in Belgium, Gordts et al. (60) reported that 6% of subjects suffered from chronic nasal discharge and 40% had signs of mucosal swelling of more than 3 mm on MRI . Notwithstanding 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)

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 (61) It will be clear that in patients with Kartagener's syndrome and primary ciliary dyskinesia, chronic rhinosinusitis is a common problem. 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 chronic rhinosinusitis. Nasal polyps are present in about 40% of patients with CF (62). These polyps are generally more neutrophilic than eosinophilic in nature but may respond to steroids as well, as inhaled steroids in patients with CF reduce neutrophilic inflammation (63-65).

4-5-2 Allergy

Review articles on rhinosinusitis have suggested that atopy predisposes to its development (48, 66). 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 (67, 68) and are frequently associated.

It has been postulated (69) that swelling of the nasal mucosa in allergic rhinitis at the site of the sinus ostia may compromise ventilation and even obstruct sinus ostia, leading to mucus retention and infection. Furthermore, there has been an increase in the body of opinion that regard the mucosa of the nasal airway as being in a continuum with the paranasal sinuses and hence the term 'rhinosinusitis' was introduced (49). 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 (27, 70-74). A number of studies report that markers of atopy are more prevalent in populations with chronic rhinosinusitis. Benninger reported that 54% of outpatients with chronic rhinosinusitis had positive skin prick tests (75). Among CRS patients undergoing sinus surgery, the prevalence of positive skin prick tests ranges from 50 to 84% (50, 76, 77), of which the majority (60%) have multiple sensitivities (77). As far back as 1975, Friedman reported an incidence of atopy in 94% of patients undergoing sphenoethmoidectomies (78).

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 (52). In a small prospective study, no difference in prevalence of purulent rhinosinusitis was found between patients with and without allergic rhinitis (79). 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 acute sinusitis episodes (50). 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 (80). Finally, Emanuel et al. (77)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. (81) reported that the prevalence and extent of sinus mucosa involvement on CT was not determined by the atopic state.

Taken together, epidemiologic data show an increased prevalence of allergic rhinitis in patients with CRS, but the role of allergy in CRS remains unclear.

Radiological studies are unhelpful in unravelling the correlation between allergy and rhinosinusitis. High percentages of sinus mucosa abnormalities are found on radiological images of allergic patients, e.g. 60% incidence of abnormalities on CT scans among subjects with ragweed allergy during the season (82). However, one should interpret this data with caution in view of the fact that high percentages of incidental findings are found on radiological images of the sinus mucosa in individuals without nasal complaints, ranging from 24.7% to 49.2% (83-86), that the normal nasal cycle induces cyclical changes in the nasal mucosa volume (87), and that radiological abnormalities contribute minimally to the patient's symptoms (82).

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 (88). 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 (88).

4-5-3 Lower airway involvement

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 summarized in the ARIA document (10). Rhinosinusitis and lower airway involvement are also frequently associated in the same patients, but their interrelationship 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 7-6). In short, improvements in both asthma symptoms and medication have been obtained after surgery for rhinosinusitis in children with both conditions (89-91).

Studies on radiographic abnormalities of the sinuses in asthmatic patients have shown high prevalences of abnormal sinus mucosa (92, 93). All patients with steroid dependant asthma had abnormal mucosal changes on CT compared to 88% with mild to moderate asthma (94). 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 paediatric 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 (95). 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 respectively 18, 17 and 5% 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 not responding to conservative treatment. In a cross-sectional study to assess the overall prevalence of otolaryngologic diseases in patients with HIV-infection, Porter et al. (96) 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 persons. 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. (97) reported a lower incidences 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 (98).

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 (99). The most common mutation, DF508, is found in 70 to 80% of all CFTR genes in Northern Europe (100, 101). 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 (102-105). Interestingly, Jorissen et al. (106) reported that DF508 homozygosity represents a risk factor for paranasal sinus disease in CF.

4-5-6 Pregnancy and endocrine state

During pregnancy, nasal congestion occurs in approximately one-fifth of women (107). 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. (108) 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% (109).

In addition, thyroid dysfunction has been implicated in CRS, but there is only limited data on the prevalence of CRS in patients with hypothyroidism.

4-5-7 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 (110). However, Bolger et al. (111) found no correlation between CRS and bony anatomic variations in the nose. Also in the survey by Min et al. (112), no correlation was found between septal deviation and the prevalence of CRS. 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 (113) 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 (17, 18, 114, 115). One area where conjecture remains is the effect of a deviated septum. 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 (116, 117)whilst others have not (18, 118). 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 aetiology of CRS. Obtaining accurate epidemiologic data on the incidence of CRS of dental origin is not possible as the literature is limited to anecdotal reports.

4-5-8 Micro-organisms

4-5-8-1 Bacteria

Although it is often hypothesized that CRS evolves from acute rhinosinusitis, 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.

Arouja isolated aerobes from 86% of the middle meatus samples CRS patients, 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. (119).

Some authors suggest that as chronicity develops, the aerobic and facultative species are gradually replaced by anaerobes (120, 121). 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.

4-5-8-2 Fungi

Fungi have been cultured from human sinuses with many different ramifications (122). Their presence may be relatively benign, colonizing normal sinuses or forming saprophytic crusts. They also may cause a range of pathology, ranging from non-invasive fungus balls to invasive, debilitating disease (123).

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 (124). 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. Using this new culture technique, the same percentage of positive fungi cultures was also found in normal controls (125).

A broad array of fungi has been identified in the sinus cavities of patients with sinusitis through varied staining and culture techniques (124, 125).

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.

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. However, the effect during the initial phases of a severe chronic rhinosinusitis 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 chronic rhinosinusitis, it has been suggested that that this irregular bony thickening is sign of inflammation of the bone. This inflamed bone might maintain mucosal inflammation (126).

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 (127, 128). It is certainly possible that these changes, if further confirmed in patients, may at least in part, explain why chronic rhinosinusitis is relatively resistant to therapy.

4-5-10 Environmental factors

Cigarette smoking was associated with a higher prevalence of rhinosinusitis in Canada (58), whereas this observation was not confirmed in a nationwide survey in Korea (59). Other lifestyle-related factors are undoubtedly involved in the chronic inflammatory processes of rhinosinusitis. For instance, low income was associated with higher prevalence of CRS (58). 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 expansion of endoscopic sinus surgery procedures. Among a group of 42 patients with mucocoeles, 11 had prior surgery within 2 years before presentation (129). Another reason for failure after surgery can be the recirculation of nasal mucus out of the natural maxillary ostium and back through a separate surgically created antrostomy resulting in an increased risk of persistent sinus infection (130).

4-6 Nasal polyps

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 routine examination. On the other hand, polyps that become symptomatic may remain undiagnosed, either because the patient is not investigated properly or because they are missed on anterior rhinoscopy. Endoscopy of the nasal cavity makes it possible to visualize NP and to give a reliable estimate of the prevalence of NP.

In a population-based study in Skövde, Sweden, Johansson et al. (131) 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 (112). Based on a postal questionnaire survey in Finland, Hedman et al. (29) found that 4.3% of the adult population

answered positively to the question as to whether polyps had been found in their nose. However, nasal endoscopy appears to be a prerequisite for an accurate estimate of the prevalence of NP, as 1.4% of the sample population studied by Johansson et al. (131) said to have NP, did not actually have any polyps on nasal endoscopy. From autopsy studies, a prevalence of 2% has been found using anterior rhinoscopy (132). After removing whole naso-ethmoidal blocks, nasal polyps were found in 5 of 19 cadavers (133), and in 42% of 31 autopsy samples combining endoscopy with endoscopic sinus surgery (134). 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 nasal polyps at some stage (135). In a prospective study on the incidence of symptomatic NP, Larsen and Tos (136) 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 5000 patients from hospitals and allergy clinics in the US in 1977, the prevalence of NP was found to be 4.2% (137), with a higher prevalence (6.7%) in the asthmatic patients.

In general, NP occur in all races (138-141) and becomes more common with age. The average age of onset is approximately 42 years, which is 7 years older than the average age of the onset of asthma (142-144). NP are uncommon under the age of 20 (145) and are more frequently found in men than in women (29, 136, 146), except in the population studied by Settipane (137).

4-7 Factors associated with NP

4-7-1 Allergy

0.5-4.5% of subjects with allergic rhinitis have NP (31, 32, 147), which compares with the normal population (135). In children the prevalence of NP has been reported to be 0.1% (31) and Kern found NP in 25.6% of patients with allergy compared to 3.9% in a control population (148). On the other hand, the prevalence of allergy in patients with nasal polyps has been reported as varying from 10% (149), to 54% (150) and 64% (151). Contrary to reports that have implicated atopy as being more prevalent in patients with NP, others have failed to show this (31, 147, 152-154). Recently, Bachert at al. (155) found an association between levels of both total and specific IgE and eosinophilic infiltration in nasal polyps. These findings were unrelated to skin prick test results. Positive intradermal tests to food allergies have been reported in 81% of polyp patients compared to 11% of controls (156). Food and drug sensitivities have been reported in 31% of patients with nasal polyposis and this was more common in men (43% vs. 24%) (140).

4-7-2 Asthma

In patients with asthma 7% have nasal polyps (31) with a prevalence of 13% in non-atopic asthma (skin prick test and total and specific IgE negative) and 5% in atopic asthma (145). Late onset asthma is associated with the development of nasal polyps in 10-15% (31). Asthma develops first in approximately 69% of patients with both asthma and NP and NP take between 9 and 13 years to develop. Ten percent develop both polyps and asthma simultaneously and the remainder develop polyps first and asthma later that (between 2 and 12 years) (138). However, not all patients with nasal polyps have lower respiratory tract symptoms (157).

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 (141).

4-7-3 Aspirin sensitivity

In patients with aspirin sensitivity 36-96% have nasal polyps (32, 145, 158-163) and up to 96% have radiographic changes affecting their paranasal sinuses (164). Patients with aspirin sensitivity, asthma and nasal polyposis are usually non-atopic and the prevalence increases over the age of 40 years.

The children of probands with asthma, nasal polyps and aspirin sensitivity had nasal polyps and rhinosinusitis more often than the children of controls (165). Concerning hereditary factors, HLA A1/B8 has been reported as having a higher incidence in patients with asthma and aspirin sensitivity (166).

4-7-4 Genetics

An interesting observation is that NP are frequently found to run in families, suggestive of an hereditary or shared environmental factor. In the study by Rugina et al. (140), 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 patients had undergone sinus surgery for NP. A lower percentage (14%) of familial occurrence of NP was reported earlier by Greisner et al. in smaller group ($n = 50$) of adult patients with NP (59). Thus, these results strongly suggest the existence of a hereditary factor in the pathogenesis of NP. In this regard, recent genetic studies found a significant correlation between certain HLA alleles and NP. Luxenberger et al. (167) reported an association between HLA-A74 and nasal polyps, whereas Molnar-Gabor et al. (168) report that subjects carrying HLA-DR7-DQA1*0201 and HLA-DR7-DQB1*0202 haplotype had a 2 to 3 times odds ratio of developing NP.

Of note, studies of monozygotic twins have not shown both siblings always develop polyps, indicating that there are likely to be environmental factors influencing their development (169, 170). Nasal polyps 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 (171).

4-7-5 Environmental factors

The role of environmental factors in the development of NP is unclear. No difference in the prevalence of NP has been found in the patient's habitat or pollution at work (140). One study found that a significantly smaller proportion of the population with polyps were smokers compared to an unselected population (15% vs. 35%) (140) whilst another found an association between the use of a woodstove as a primary source of heating and the development of NP (172).

4-8 Epidemiology and predisposing factors for rhinosinusitis in children

4-8-1 Epidemiology

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 in a CT scan study showed that in children with a history of chronic purulent rhino rhea and a nasal obstruction 64% showed involvement of the sinuses (173). In a MRI study of a non-ENT paediatric population (60) 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 (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 (174). 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.

Unfortunately, most studies in the paediatric ENT literature deal with patient populations (children with nasal complaints attending outpatient clinics) and few involve normal populations. Very few prospective studies are available and practically no documentation exists on the natural history of the disease.
The first prospective epidemiologic and long-term longitudinal study was performed by Maresh and Washburn (175) (see Table 4.1). It was started in 1925 and these authors followed on a regular basis 100 healthy children from birth to maturity, looking at the history, and performing a physical examination and routine postero-anterior radiograph of the paranasal sinuses 4 times a year (a total of 3,501 roentgenograms). The oldest children underwent over 50 radiographs. It was noted that there existed a relatively constant percentage (30%) of "pathologic" antra in the films taken between 1 and 6 years of age, the range being 23% to 35%. From 6 to 12 years, this percentage dropped steadily to approximately 15%. Interestingly, the authors noted that variations in size of the sinuses occur frequently, without any demonstrable relation to the amount or frequency of infections as seen on the radiographs and without following any definitive pattern. When there was a recent upper respiratory tract infection ("URI") (in the previous 2 weeks), less than 50% showed clear sinuses. Tonsillectomy had no demonstrable effect on the radiographic appearance of the sinuses.

Although this is one of the only long term follow-up studies one has to realize that a postero-anterior standard X-ray of the sinuses in a child gives only information about the maxillary sinuses and gives little information about the ethmoids so it may well be that the prevalence of sinusitis was under- or over-estimated.

In an MRI study of 60 children (mean age 5.7 years) with symptoms of uncomplicated URI for an average of 6 days, Kristo et al. found in 60% major abnormalities in maxillary and ethmoidal sinuses, 35% in sphenoidal sinuses, and 18% in the frontal sinuses (174). The MRI scores correlated significantly with the symptom scores, especially nasal obstruction, nasal discharge and fever. Of the 26 children with major abnormalities in the first MRI, these findings subsequently (after 2 weeks) improved significantly, showing that these abnormalities after an URI do not need antimicrobial therapy.

Therefore, it seems from all these studies that in younger chil-

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

Author/year	*Included group*	*Examination method*	*Result*	*Conclusion*
Maresh, Washburn 1940 (175)	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 (URI) in the last two weeks	high rate of pathology, can be under or over estimated because of the examination technique
Bagatsch 1980 (176)	24 000 children in the area of Rostock followed up for 1 year		one or more URI in the year: 0-2 years: 84% 4-6 years: 74% > 7years: 80%	

dren with chronic rhinosinusitis, there exists a spontaneous tendency towards recovery after the age of 6 to 8 years. This finding of a decrease in prevalence of rhinosinusitis in older children was also confirmed by other authors in patient populations (177).

4-8-2 Predisposing factors

In an extensive prospective study Bagatsch et al. (see Table 1) saw an influence of day-care (176). If children stay in day care centres, 72% in the group from 0 to 5 year develop one or more episodes of upper airway infection per year compared to 27% of the children staying at home.

Lind (178) and Bjuggren et al. (179) found a much higher prevalence of up to 100% of maxillary sinusitis in children staying in day care centres compared with the same age group staying at home or older children in schools.

The relationship between poor nasal patency and rhinosinusitis was confirmed by Van Cauwenberge (180) , who showed a significant relationship between the results of passive anterior rhinomanometry and pronounced oedema of the nasal mucosa ($p=0.09$ for the rights side, 0.03 for the left side) and the presence of purulent rhinitis ($p=0.006$ for the right side and <0.05 for the left side).

Breast feedings seems to have a beneficial influence on lower respiratory disease, but such an influence on sinusitis in infants and young children has not yet been demonstrated (181-183).

Passive smoking is a putative risk factor, especially in allergic children (183). There is a clearly increased risk for recurrent coryza (odds ratio 3.00) and sinus problems (odds ratio 4.73) in children with smoking mothers compared with children from non-smoking families (184).

4-9 Conclusion

The overview of the currently available literature illustrates the paucity of accurate information on the epidemiology of CRS and NP, especially in European countries, and highlights the need for large-scale epidemiologic research exploring their prevalence and incidence. Only by the use of standardized definitions for CRS 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.

5. Inflammatory mechanisms in acute and chronic rhinosinusitis and 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

Sinus mucosal tissue from subjects with acute bacterial rhinosinusitis (ARS) is difficult to sample, with the exception of acute complications of ARS, resulting in emergency sinus surgery. As a consequence, there is a relative lack of studies on cytokines and mediators in ARS. One of the first studies reported in 10 subjects undergoing surgery for complications, with mucosal tissue sampled from the maxillary sinus, which demonstrated significantly elevated protein concentrations of IL-8 compared to 7 controls (185) . 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. Recently, IL-8 and also TNF-alpha and total protein content were increased in nasal lavage from subjects with ARS compared to controls and allergic rhinitis subjects (186).

Proinflammatory cytokines such as IL-1ß, IL-6 and TNF play a prominent role in ongoing inflammatory reactions by activating endothelial cells, T-lymphocytes and others, inducing the expression of cell adhesion molecules and the release of other cytokines such as IL-8. IL-8 belongs to the CXC-chemokine group and is a potent neutrophil chemotactic protein, which is constantly synthesized in the nasal mucosa (187). The cytokine pattern found in ARS resembles that in naturally acquired viral rhinitis lavage (188).

5-3 Chronic rhinosinusitis

5-3-1 Histopathology

In the sinus fluid of patients with chronic rhinosinusitis undergoing surgery, the inflammatory cells are predominantly neutrophils, as observed in acute rhinosinusitis, but a small number of eosinophils, mast cells and basophils may also be found (189, 190). 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%) (191). 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 both sinus diseases.

5-3-2 Pathomechanism: cytokines, chemokines and adhesion molecules

A highly potent chemoattractant for neutrophils, IL-8 has been demonstrated in chronic rhinosinusitis tissue (192) 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 (193). 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 acute rhinosinusitis, and IL-3 in chronic rhinosinusitis mucosa compared to inferior turbinate samples (194). 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 (195).

A range of mediators and cytokines has been described to be increased in CRS versus control tissue, mostly inferior turbinates, which comprises IL-1, IL-6, IL-8, TNF-a, IL-3, GM-CSF, ICAM-1, MPO and ECP (194, 196-198). Interestingly, VCAM-1, an adhesion molecule involved in selective eosinophil recruitment, and IL-5, a key cytokine for eosinophil survival and activity, have been shown not to be increased (194, 197). This cytokine and mediator profile resembles very much the profile found in viral rhinitis or acute rhinosinusitis, with the exception of a small though significant increase of

ECP. This profile is different from the pattern in nasal polyposis (see below).

The expression of transforming growth factor beta 1 (TGF-b1) at protein and RNA level is significantly higher in CRS versus NP and linked to a fibrotic cross anatomy (199). In CRS, MMP-9 and TIMP-1, a natural antagonist, but not MMP-7 are increased (200), probably resulting in a low MMP-9 activity.

5-4 Nasal polyps

5-4-1 Histopathology

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 (201-203). 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 polyps (204), whereas lymphocytes and neutrophils are the predominant cells in cystic fibrosis and in CRS. Eosinophils are localised around the vessels, glands, and directly beneath the mucosal epithelium (202).

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 (205). 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.

5-4-2 Pathomechanism: cytokines, chemokines and adhesion molecules

5-4-2-1 Eosinophilic inflammation

A large body of studies has focussed on eosinophilic mediators in nasal polyp tissue, and demonstrated that different cell types generate these mediators. Early studies by Denburg et al. (206, 207) 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 (71, 208, 209). According to Hamilos et al. (27), polyp tissue samples from patients with or without allergy contained different cytokine profiles.
They found by in situ hybridization studies that patients with "allergic" polyps had higher tissue densities of GM-CSF, IL-3, IL-4, and IL-5 transcripts than controls, whereas patients with non-allergic polyps had higher tissue densities of GM-CSF, IL-3, and IFN-gamma transcripts. From these results, distinct pathomechanisms for allergic versus non-allergic polyps were suggested. Other studies involving protein measurements in tissue homogenates could not support these findings (28, 194).

In contrast, IL-3 and GM-CSF protein were found in only a small number of polyp and control turbinate samples. However, 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 (155). 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 (210).

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 (211, 212). Furthermore, Wagenmann et al. (213) 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 (214). Whereas the probably antagonistic soluble isoform is upregulated, the signal transducing transmembrane isoform is down-regulated in nasal polyps, especially if associated with asthma.

Recent studies have also shown that nasal polyps also express high levels of RANTES and eotaxin, the predominant recognised eosinophil chemoattractants. Bartels and colleagues (215) 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, Jahnsen and colleagues (216) demonstrated an increased mRNA expression for eotaxin, eotaxin-2, and MCP-4. The expression of eotaxin-2, another CCR3-specific chemokine, was found to be the most prominent of the three chemokines investigated. According to other data (28, 155, 205), 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 (217).

Studies of cell adhesion molecules are relatively few. Early studies by Symon and colleagues (218) 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. (219), 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 (220). 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 (221).

5-4-2-2 Extracellular matrix regulation

The expression of TGF-β_1 and TGF-β_2, 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 again 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-β_1. In contrast, corticosteroid treatment significantly reduced IL-5, ECP and albumin concentrations, whereas TGF-β_1 was increased (205).

These observations suggest IL-5 and TGF-β_1 represent cytokines with counteracting activities, with a low TGF-β protein concentration in IL-5 driven nasal polyps. Furthermore, they supported the deposition of albumin and other plasma proteins as a possible pathogenic principle of polyp formation, regulated by the subepithelial eosinophilic inflammation.

TGF-β_1 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). Staining of nasal polyp tissue shows that TGF-β_1 is mainly bound to the extracellular matrix, where it is found in its latent, inactive form.

Oedema and pseudocyst formation characterize NP, with only a few areas of fibrosis. An imbalance of metallo-proteinases with an upregulation of MMP-7 and MMP-9 in nasal polyps has been recently demonstrated(200). This results in the enhancement of MMP-9 in NP, which may account for oedema formation with albumin retention.

5-4-2-3 Role 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 (226). 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 (155, 205, 227). 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%) (228). If aspirin sensitivity, including asthma, accompanied nasal polyp disease, the Staph. aureus colonization rate was as high as 87.5%, and IgE antibodies to enterotoxins were found in 80% of cases.

Total and specific IgE in polyp homogenates is only partially reflected in the serum of these patients. In contrast, 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(229).

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 (230, 231).

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 (232). 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(229). 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 (233). SAEs furthermore activate antigen presenting cells to increase antigen uptake. 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. 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 nasal polyposis (233). Interestingly, similar findings have recently been reported in asthma, which is known to be associated with NP (234). IgE antibody formation to SAE can be seen in nasal polyp tissue, but rarely in CRS.

5-5 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 remodelling processes. In NP, but not in CRS, staphylococcus-derived superantigens may at least modulate disease severity and expression. For these reasons, CRS and NP should probably be considered as distinct diseases.

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 (21, 235-239).

The symptoms are principally the same in intermittent and persistent rhinosinusitis as well as in nasal polyposis, but the symptom pattern and intensity may vary. Acute forms of infections, both acute intermittent and acute exacerbations in persistent, 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 (22).

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) (240, 241).

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 4 to 0 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.

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 (e.g. 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 (239), 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.

6-1-3 Validation of subjective symptoms assessment

Validation of the rhinosinusitis symptoms to show the relevance in distinguishing disease modalities and repeatability between ratings of the same patient (intrapatient) and between different patients (interpatient) 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 (242, 243) or are disease specific (240, 241).

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.

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 (244-248). However, there are also some studies where this correlation is not seen (249) or the correlation was poor (250, 251).

The interpatient variation in subjective scoring suggests that every nose is "individually calibrated", which makes interpatient comparisons less reliable but still significant (244, 246).

Subjective nasal obstruction correlates better with objective functional measurements of nasal airflow resistance (rhinomanometry, peak flow) than with measurements of nasal cavity width, such as acoustic rhinometry (248, 252).

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 handkerchiefs in plastic bags for weighing have been used in acute infective rhinitis (253) and in "autonomic (previously termed vasomotor) rhinitis" (254).

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) or degenerative alterations in the olfactory mucosa due to the disease or its treatment e.g. 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 (255-257) 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 (235) or paranasal sinus radiographs (258). In CRS 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 (259). However, rhinosinusitis disease specific quality of life studies also include facial pain-related parameters, which have been validated (260).

6-4-3-5 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 (261). QoL methods have produced validated questionnaires which measure the impact of overall rhinosinusitis symptoms on everyday life (240).

Objective experiments to differentiate patient groups according to rhinosinusitis severity or aetiology have been done using nasal provocation with histamine or metacholine (262, 263) 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. Grading of CT findings, both structural and mucosal, do not reflect the rhinosinusitis symptom severity either (264).

Validation of classical overall rating scores for rhinosinusitis against objective criteria is insufficient, but quality of life evaluations of these criteria have been validated.

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 (237) for polyps, oedema, discharge, crusting and scarring (post-operatively) can be obtained (Table 1). A number of staging systems for polyps have been proposed (264-266). 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).

Table 6-1. Endoscopic appearances scores.

Characteristic	Baseline	3 mo	6 mo	1 y	2 y
Polyp left (0,1,2,3)					
Polyp, right (0,1,2,3)					
Oedema, left (0,1,2,)					
Oedema, right (0,1,2,)					
Discharge, 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. (237, 267)

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 (271)	21	chronic	Endoscopic tap (MM) v maxillary aspiration during ESS	85.7%
Klossek et al., 1998 (270)	65	chronic	Endoscopic swab (MM) v maxillary aspiration during ESS	73.8%
Vogan et al., 2000 (272)	16	acute	Endoscopic swab (MM) v maxillary sinus tap	93%
Casiano et al., 2001 (273)	29	acute (intensive care)	Endoscopic tissue culture (MM) v maxillary sinus tap	60%
Talbot et al., 2001 (274)	46	acute	Endoscopic swab (MM) v maxillary sinus tap	90.6%

MM: middle meatus; ESS: endoscopic sinus surgery

6-2-3 Nasal cytology, biopsy and bacteriology

A positive nasal smear may be helpful in indicating the aetiology of disease (268, 269) but a negative smear is not conclusive. The advantage of the technique is its cheapness. However, quantification and changes as a result of therapy in chronic rhinosinusitis/nasal polyposis have not been routinely used

A biopsy may be indicated to exclude more sinister and severe conditions such as neoplasia and the vasculitides.

Several microbiology studies (270-273) [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).

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 (275-277).

Transillumination was advocated in the 1970 as an inexpensive and efficacious screening modality for sinus pathology (278). The insensitivity and unspecificity makes it unreliable for the diagnosis of rhinosinusitis (279)

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 but rather corroborates history and endoscopic examination after failure of medical therapy.

Table 6-3. CT scoring system (264).

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

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 (80, 264, 280-284).

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 3) (264).

This has been validated in several studies (285) [Evidence Level IIb] and was adopted by the Rhinosinusitis Task Force Committee of the American Academy of Otolaryngology Head and Neck Surgery in 1996 (6). However, the correlation between CT findings and symptom scores has been shown to be consistently poor and is not a good indicator of outcome (286) [Evidence Level IIb]. 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 (287-289). It allows if altered, 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 (< 30 minutes). However, if it is prolonged, it does not distinguish between primary or secondary causes of ciliary dysfunction.

6-2-5-2 Ciliary beat frequency

Specific measurements of ciliary activity using a phase contrast microscope with photometric cell (290, 291) have been used in a number of studies to evaluate therapeutic success (292, 293) [Evidence Level IIb]. The normal range from the inferior turbinate is between 12 and 15 Hz but these techniques are available in only a few centres and therefore largely experimental. The final gold standard of ciliary function are culture techniques (294).

6-2-5-3 Electron microscopy

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

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. It requires little patient co-operation and is quick and easy to perform 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) and therefore may be low even in the presence of normal activity if the sinus ostia are blocked e.g. nasal polyposis (295) [Evidence Level IIb]. It can be used however, as an outcome measure after therapy (296) [Evidence Level IIa]

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 polyposis and compares well with rhinomanometry (297, 298) [Evidence Level IIb]. Expiratory peak flow is less often used as mucus is expelled into the mask and the technique may be associated with eustachian dysfunction.

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 nasal polyposis but can be useful in confirming that improvement in nasal congestion is the result of reduction in inflammation in the middle meatus rather than mechanical obstruction (292) [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 (296, 298-300)[Evidence Levels IIa,IIb,III].

6-2-6-4 Rhinostereometry
This also measures subtle changes in mucosal swelling, largely in the inferior turbinates (301, 302) [Level IIb] and is therefore not directly applicable to assessment of chronic rhinosinusitis and nasal polyposis.

6-2-7 Olfaction
6-2-7-1 Threshold Testing
The estimation of olfactory thresholds by the presentation of serial dilutions of pure odorants such as pm carbinol have been used in a number of studies (293, 299, 303-305) [Evidence Levels IIb, III].

6-2-7-2 Other quantitative olfactory testing
Scratch and sniff test using patches impregnated with micro-encapsulated odorants are available (306) and have been utilised in studies of both chronic rhinosinusitis and nasal polyposis (298). A cruder screening test, the Zurich test may also be used and has the advantage of pictorial representation of the items (307, 308). More complex tests exist (309) e.g. 'Sniff 'n' sticks' which limit their application to the research setting. Recently a combined supra-threshold detection and identification test has been devised as a cross-cultural tool in the European population. The results are presented in the appendix (310) [Evidence Level III].

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

6-2-8 Laboratory assessments – 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 (311). 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) (312).

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 (313).
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 (312).

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) (241). However, it is of interest that the severity of nasal symptoms do not always correlate with QoL scales (314) [Evidence Level IIb]. The QOL questionnaires can provide either general (generic) or disease specific health assessment.

6-3-1 General health status instruments
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) (242) is by far the most widely used and well validated and this has been used both pre- and post-operatively in chronic rhinosinusitis. (296, 315) [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 (243).

6-3-2 Disease specific health status instruments
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.

6-3-2-1 Rhinosinusitis outcome measure (RSOM)
This contains 31 items classified into 7 domains and takes approximately 20 minutes to complete (316). A modified instrument referred to as the Sinonasal Outcome Test 20 (SNOT 20) is validated and easy to use (260). This has been used in a number of studies both medical and surgical (286, 296) [Evidence Levels Ib, IIb].

The Sinonasal Outcome Test 16 (SNOT 16) is also a rhinosinusitis specific quality of life health related instrument (317) as is the 11 point Sinonasal Assessment Questionnaire (SNAQ-11) (318).

6-3-2-2 Chronic Sinusitis Survey (CSS)
This is a 6 item duration based monitor of sinusitis specific outcomes which has both systemic and medication-based sections (319). 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 (241, 320) [Evidence Level IIb].

6-3-2-3 Rhinosinusitis Disability Index (RSDI)
In this 30 item questionnaire the patient is asked to relate nasal and sinus symptoms to specific limitations on daily functioning (240, 321). 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.

6-3-2-4 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 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 (322).

6-3-2-5 Rhinoconjunctivitis quality of life questionnaire (RQLQ)
This is a well-validated questionnaire but specifically focuses on allergy and is of less relevance in chronic rhinosinusitis and nasal polyposis (323).

6-3-2-6 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 two-week reproducibility of the RSUI was weak, probably reflecting the day to day variability of rhinitis (324).

6-3-2-7 General
Most questionnaires concentrate on the duration of the symptoms and not on the severity of the symptoms. A QoL questionnaire developed by Damm et al.includes the severity of the symptom scale (239). The domains in the questionnaire are the overall quality of life, nasal breathing obstruction, post-nasal drip or discharge, dry mucosa, smell, headache and asthmatic complaints.

6-3-3 Results
6-3-3-1 Generic
In a generic SF-36 survey 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 (325). Gliklich and Metson (53) 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, or back pain.

Winstead and Barrett (315) confirmed a similar degree of impact on general quality of life in chronic rhinosinusitis with the SF-36. Following endoscopic sinus surgery they demonstrated a return to normality in all eight domains six months post-operatively which was maintained at twelve months.

6-3-3-2 Disease specific
In a study by Gliklich and Metson the effect of sinus surgery on QoL was studied (320). After the surgery significant improvements were found in reduction of the symptoms and medications needed. Significant improvements in general health status were noted in six of eight categories, and most attained near-normative levels. A disease-specific questionnaire seems to be more sensitive than a general questionnaire in following patients after ethmoid sinus surgery (319). 76% patients reported relief of the symptoms at least in two of the domains studied after FESS surgery (239).

The Chronic Sinusitis Survey has been used in QoL outcomes after osteoplastic frontal sinus obliteration (326). Most patients were satisfied with the results and had significant improvements in their survey scores. The number of clinic visits and antibiotic use also declined.

Mean scores one year after endoscopic frontal sinus surgery showed a significant improvement in symptoms of pain, congestion, and drainage as measured by the Chronic Sinusitis Survey. Medication use was also significantly reduced (327).

Radenne et al.have studied the QoL of nasal polyposis patients using a generic SF-36 questionnaire (314). 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 (328).

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 (296). 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).

Quality of life 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] (260, 329-332) and this has also been shown to improve significantly with treatment [Level IIb] (239, 320, 333, 334).

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 (207, 335-337) or indirectly reducing the secretion of chemotactic cytokines by nasal mucosa and polyp epithelial cells (208, 338-340). 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 (337, 338).

The biological action of glucocorticoids is mediated through activation of intracellular glucocorticoid receptors (GR) (341), expressed in many tissues and cells (342). Two human isoforms of GR have been identified, GR? and GR?, which originate from the same gene by alternative splicing of the GR primary transcript (343). Upon hormone binding, GR? enhances anti-inflammatory or represses pro-inflammatory gene transcription, and exerts most of the anti-inflammatory effects of glucocorticoids through protein-protein interactions between GR and transcription factors, such as AP-1 and NF-?B. The GR? isoform does not bind steroids but may interfere with the GRa function. There may be several mechanisms accounting for the resistance to the anti-inflammatory effects of glucocorticoids, including an overexpression of GR? or a downexpression of GR? . Increased expression of GR? has been reported in patients with nasal polyps (344, 345) while downregulation of GRa levels after treatment with glucocorticoids (346, 347) 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 persistent RS (348).

Potential indications for corticosteroids in rhinosinusitis:

- Acute/Intermittent rhinosinusitis without nasal polyposis (NP);
- Persistent rhinosinusitis without NP;
- Persistent rhinosinusitis with NP;
- Postoperative treatment of persistent rhinosinusitis to prevent recurrences of NP;
- Prophylactic treatment of intermittent rhinosinusitis;
- Oral steroids in persistent rhinosinusitis with NP;
- Oral steroids in acute intermittent rhinosinusitis.

7-1-1 Acute/Intermittent Rhinosinusitis without nasal polyps

Qvarnberg et al. (349) measured the clinical effect of budesonide (BUD)/placebo as a complement to erythromycin and sinus wash out in a randomized, double-blind study on patients referred for sinus surgery due to persistent or intermittent 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 intermittent from persistent rhinosinusitis but all cases were reported to have intermittent “episodes of sinusitis for the last two years”.

Melzer et al. (350) gave mometasone furoate (MF) 400 ?g to 200 patients and placebo to 207 patients with acute intermittent RS as adjunctive therapy to amoxicillin/clavulanate potassium for 21 days. Total symptom score and individual symptom scores as congestion, facial pain, headache and rhino rhea 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 not statistically significant. No side effects of treatment were seen.

Nayak et al. (351) compared MF 200 and 400 ?g to placebo in 325, 318 and 324 patients with intermittent RS (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, rhino rhea 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.

In a study by Dolor et al. (352) 200 µg 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 acute intermittent rhinosinusitis. 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 ($p=0.01$)

Barlan et al. (353) used BUD as adjunctive therapy to amoxillin clavulanate potassium for three weeks in a randomized, placebo controlled study in children with acute intermittent rhinosinusitis. 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.

In a multi centre study Meltzer et al. (354) used flunisolide as adjunctive therapy to amoxicillin clavulanate potassium in patients with intermittent or persistent RS 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.

All these studies were on study groups where intra nasal steroids have been used as an additional treatment to antibiotics and no studies are found where nasal steroids have been compared to antibiotics as a single treatment in intermittent RS. Studies are underway which compare nasal steroids, as a single treatment to antibiotics in patients with acute rhinosinusitis. The first data (only published as abstract) show significant reduction of symptomatology in acute rhinosinusitis over placebo and an antibiotic. The evidence level as adjunctive therapy to systemic antibiotics is I, but as a single therapy no (published) data are available.

7-1-2 Persistent rhinosinusitis without nasal polyps

Parikh et al. (355) performed a randomized, double blind, placebo-controlled trial on patients with persistent 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 symptom 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 persistent RS (without NP) with allergy to house dust mite and who had recently been operated on but still had signs of persistent RS, 256 µg budesonide (BUD) or placebo was instilled into the maxillary sinus once a day through a sinus catheter for three weeks (356). 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. (357) tixocortol pivalate was given as endonasal irrigation in combination with neomycin for 11 days in a double blind placebo controlled in patients with persistent RS. Maxillary ostial patency and nasal obstruction was significantly improved in the tixocortol group compared to placebo. Patients with persistent RS without allergy responded better to local steroids than those with allergy.

Sykes et al. (358) looked on 50 patients with chronic mucopurulent RS 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 place-

Table 7-1. Treatment with nasal corticosteroids in acute/intermittent rhinosinusitis without nasal polyposis.

Study	*Drug*	*Antibiotic*	*Number*	*Effect*	*X-ray*
Qvarnberg, 1992 (349)	budesonide	erythromycin	20	significant effect on nasal symptoms, facial pain and sensitivity; final clinical outcome did not differ	mucosal thickening = no effect
Meltzer, 2000 (350)	mometasone furoate	amox/clav	407	significant effect in congestion, facial pain, headache and rhino rhea. no significant effect in postnasal drip	no statistical difference in CT outcome
Nayak, 2002 (351)	mometasone furoate	amox/clav	967	total symptom score (TSS) was improved (nasal congestion, facial pain, rhino rhea and postnasal drip)	no statistical difference in CT outcome
Dolor, 2001 (352)	fluticasone propionate	cefuroxime axetil	95	significant effect. effect measured as clinical success depending on patients self-judgment of symptomatic improvement	not done
Barlan, 1997 (353)	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
Meltzer, 1993 (354)	flunisolide	amox/clav	180	significant effect: overall score for global assessment of efficacy was greater in the group with flunisolide	no effect on x-ray

bo (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 (excluding 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 (359). Quality of life assessments did not change however.
There is some evidence for an effect of local intranasal steroids in persistent RS, particularly with intramaxillary instillation of steroids. No side effects were seen, including any increased signs of infection with intranasal corticosteroid treatment.

7-1-3 Persistent 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.

Mygind et al. (360) 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 (361) 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. (362) showed in a randomized, double blind, parallel, placebo controlled study with 400 mcg 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. (363) also showed that budesonide in spray (128 mcg) and powder (140 mcg) 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 (364) tested BUD 400µg daily compared to placebo for three months in a multi-centre, 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. (265) compared BUD 400 or 800 µg daily with placebo for four weeks (n=40, 34, 42 resp.). 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. (365) used FP 400µg, BDP 400 µg and placebo for 26 weeks in a double blind, parallel group, single centre study. Patients with bilateral polyps, grade 1-2, n= 19, 18 and18 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. (366) compared fluticasone propionate (FP) nasal drops (FPND) 400 µg daily to placebo in a placebo controlled, parallel-group, multi-centre, 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.

Table 7-2. Treatment with nasal corticosteroids in persistent rhinosinusitis without nasal polyposis.

Study	*Drug*	*Number*	*Time*	*Symptoms*	*Other effects*
Parikh, 2001 (355)	fluticasone propionate	22	16 wks	not significant	acoustic rhinometry not significant.
Lavigne, 2002 (356)	intrasinus budesonide	26	3 wks	total symptom score significant improved	T-cells, eosinophils mRNA for IL-4, and IL-5 significantly improved
Cuenant, 1986 (357)	tixocortol irrigation	60	11 days	nasal obstruction significantly improved	maxillary ostial patency significantly improved
Sykes, 1986(358)	dexametasone + tramazoline	50	4 wks	discharge, obstruction and facial pain significantly improved	plain x-ray and nasal airway resistance and mucociliary clearance significant improved
Lund et al. 2004 (359)	budesonide	134	20 wks	significant symptom improvement	significant improvement in airway using PNIF

Penttila et al. (367) 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. (298) 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. (368) looked on 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.

Local corticosteroids 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 (I) 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.

7-1-4 Postoperative treatment with topical corticoidsteriods 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. (369) used flunisolide 200 mg 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 7-3. Treatment with nasal corticosteroids in persistent rhinosinusitis with nasal polyposis.

Study	*Drug*	*Number*	*Treatment time (weeks)*	*Effect on nasal symptoms (*stat sig)*	*Objective measures (*stat sig)*	*Effect on polyps*
Mygind, 1975 (360)	beclomethasone dipropionate	35	3	total symptom score*		not seen
Deuschl, 1977 (361)	beclomethasone dipropionate	20	2x4weeks	blockage*	rhinomanometry*	not seen
Holopainen, 1982 (362)	budenoside	19	16	total symptom score*	nasal peak flow* eosinophilia*	yes
Tos, 1998 (363)	budenoside	138	6	total symptom score* sense of smell*		yes
Vendelbo Johansen, 1993 (364)	budenoside	91	12	blockage* sneezing* secretion* sense of smell N.S.	nasal peak inspiratory flow *	yes
Lildholt, 1995 (265)	budenoside	116	4	blockage* sneezing* secretion* sense of smell N.S.	nasal peak expiratory flow*	yes
Holmberg, 1997 (365)	fluticasone propionate/ beclomethasone dipropionate	55	26	over all assessment*	nasal peak inspiratory flow*	yes in beclomethasone dipropionate
Keith, 2000 (366)	fluticasone propionate nasal drops	104	12	blockage* rhinitis* sense of smell N.S.	nasal peak inspiratory flow* olfactory test N.S.	not seen
Penttilä, 2000 (367)	fluticasone propionate	142	12	blockage* rhinitis* sense of smell N.S.	nasal peak inspiratory flow* olfactory test*	yes
Lund, 1998 (298)	fluticasone propionate/ beclomethasone dipropionate	29	12	blockage* rhinitis N.S. acoustic rhinometry*	nasal peak inspiratory flow*	yes fluticasone propionate
Hadfield, 2000 (368)	betametasone	46 CF children	6	not seen		yes

Virolainen and Puhakka (370) tested 400 µg 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 (371) 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 mg daily for the first month and then 200 mg 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. (372) used flunisolide 2x25 mcg on both sides twice daily (200 mcg) 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. (373) used budesonide 6 months after polypectomy in a double blind parallel-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. (374) performed a double-blind placebo-controlled randomized study in 162 patients with chronic sinusitis with or without nasal polyps after FESS after failure of nasal steroid treatment. Patients were randomized and given FPANS 400 microg b.i.d., FPANS 800 microg 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 of FPANS compared with placebo in several subgroups such as patients with nasal polyps, high score at FESS or no previous sinus surgery.

Postoperative effect on recurrence rate of NP after polypectomy with intranasal steroids is well documented and the evidence level is Ib. Only one study describes the effect after FESS in a group of patients who underwent FESS after inadequate response to at least three months local corticosteroid treatment It did not show a positive effect of local corticostoroids over placebo.

7-1-5 Prophylactic treatment of intermittent rhinosinusitis

In a study by Puhakka et al. (375) FP (200 mg 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 acute rhinosinusitis. Frequency of sinusitis at day 7 in subjects positive for rhinovirus, based on x-ray, was 18,4% and 34,9% in FP and placebo group respectively (p=0.07) thus indicating a non significant effect of FP.

Cook et al. randomized, as a continuation of an acute episode of rhinosinusitis, patients with at least 2 episodes of rhinosinusitis in the previous 6 months or at least 3 episodes in the

Table 7-4. Nasal corticosteroids in the post operative treatment of persistent rhinosinusitis with nasal polyps to prevent recurrences of nasal polyps.

Study	*Drug*	*Number*	*Treatment time (weeks)*	*Effect on nasal symptoms (*stat sig)*	*Effect on polyp recurrence (method of test)*
Drettner, 1982 (369)	flunisolide	22	12	total nasal score (blockage, secretion sneezing)*	anterior rhinoscopy not seen
Virolainen, 1980 (no statistics) (370)	beclomethasone dipropionate	40	52	blockage	- yes anterior rhinoscopy
Karlsson, 1982 (371)	beclomethasone dipropionate	40	120	not described	- yes anterior rhinoscopy
Dingsor, 1985 (372)	flunisolide	41	52	blockage* sneezing*	- yes anterior rhinoscopy
Hartwig, 1988 (373)	budenoside	73	26	blockage not seen	- yes anterior rhinoscopy
Dijkstra 2004 (374)	fluticasone propionate	162	52	not seen	nasal endoscopy not seen.

Table 7-5. Treatment with nasal corticosteroids in prophylaxis of intermittent rhinosinusitis.

Study	*Drug*	*Number*	*Time (weeks)*	*Effect*	*Comments*
Puhakka, 1998 (375)	fluticasone propionate	199	1	not seen	common cold
Cook, 2002 (376)	fluticasone propionate	227	7	increased time to first recurrence. decreased frequency of intermittent rhinosinusitis	

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) (376).

There is very low evidence for a prophylactic effect of nasal corticosteroids to prevent intermittent rhinosinusitis.

7-1-6 Systemic steroids in acute/intermittent rhinosinusitis

Gehanno et al. (377) tried 8 mg metylprednisolone three times daily for 5 days as adjunctive therapy to 10 days treatment with amoxicillin clavulanate potassium in patients with acute RS (criteria: symptoms < 10 days, craniofacial pain, purulent nasal discharge with purulent drainage from the middle meatus, opacities of the sinuses in x-ray or CT scan) in a placebo controlled study. No difference was seen in therapeutic outcome at day 14 between the groups (n=417) but at day 4 there was a significant reduction of headache and facial pain in the steroid group. Evidence level: I b. Recently Klossek showed efficacy of a short course of oral prednisone (3 days), versus a placebo, in the treatment of the functional signs of acute maxillary rhinosinusitis with severe pain in adults in addition to an appropriate antibiotic treatment (378).

7-1-7 Systemic steroids in persistent rhinosinusitis with nasal polyps

There are no studies performed on single treatment with systemic steroids in patients with NP without concomitant treatment with topical steroids. Placebo-controlled studies and dose-effect studies are also lacking but there is a clinical acceptance that systemic steroids have a significant effect on NP supported by open studies where a single injection of 14 mg betametasone have been compared with snare polypectomy surgery (267, 379). In these studies effects are seen on nasal polyp size, nasal symptom score and nasal expiratory peak flow but it is difficult to differentiate the effect of systemic steroids from that of local treatment since both treatments were used at the same time. The control groups 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 (380)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. (381) showed a good effect with combined treatment using local 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 chronic RS 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%.

Systemic steroids are less well documented than intranasal steroids but open studies indicate that they are effective in polyp reduction and nasal symptoms associated with NP, even on sense of smell, in contrast to the effect of intranasal corticosteroids. The effect is reversible. Evidence level :III.

There is also 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.

7-2 Treatment of rhinosinusitis with antibiotics

7-2-1 Acute community acquired rhinosinusitis

Although more than 2000 studies on the antibiotic treatment of acute sinusitis have already been published, only 49, involving 13,660 participants, meet the Cochrane Board criteria for placebo control, statistical analysis, sufficient sample sizes, and the description of clinical improvements or success rates (36).
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) (382-384); 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 vari-

ability between studies. Radiographic outcomes were improved by antibiotic treatment. (36).

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 4,818 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 1,067 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 (36).

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 (43, 44). 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 (45). Thus the choice of agent may not be the same in all regions, as selection will depend on local resistance patterns and disease aetiology (45, 385). 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 (386).

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 chronic rhinosinusitis compared to acute sinusitis, because of the conflicts in terms of terminology and definition of the clinical picture of chronic rhinosinusitis in the literature. In most studies, no radiological diagnosis, such as computer tomography, has been performed to 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.

7-2-2-2 Available studies

In a retrospective study, McNally et al. (387) 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. (388) 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

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

Study	*Drug*	*Number*	*Time/Dose*	*Effect symptoms*	*Effect polyps*	*Evidence*
Lildholt, 1997 (267)	betametamethasone/ budesonide	16	14mg/52w	yes	yes	III
Lildholt, 1988 (379)	betametamethasone/ beclomethasone dipropionate	53	?/52w	yes	yes	III
van Camp, 1994 (380)	prednisolone 60 mg	25	2 weeks	72%	yes 10/22	III
Damm, 1999 (381)	budesonide + fluocortolone	20	?	yes	?	III

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. (389), 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 amoxycillin/clavulanic acid group. The clinical cure and bacteriological eradication rates were 59% and 89% for ciprofloxacin versus 51% and 91% for amoxycillin/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 amoxycillin/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 amoxycillin/clavulanic acid group ($n = 35$). Ciprofloxacin proved to be at least as effective as amoxycillin/clavulanic acid.

The efficacy and safety of amoxycillin/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 (390).

Huck et al. (391) 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 acute rhinosinusitis and 56% of patients with recurrent rhinosinusitis. Patients with chronic sinusitis were too few to allow statistical analysis. The susceptibility of organisms isolated to the study drugs was unrelated to outcome.

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. amoxicillin/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 chronic rhinosinusitis and exacerbations of chronic rhinosinusitis.

7-2-3 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 (392, 393). Subsequently a number of clinical reports have stated that long-term, low-dose macrolide antibiotics are effective in treating chronic rhinosinusitis incurable by surgery or glucocorticosteroid treatment, with an improvement in symptoms varying between 60% and 80% in different studies (20, 392, 394, 395). 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 (396-402).

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 (403). In a prospective RCT from the same group (296) 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 surgical 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.

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

Study	*Drug*	*Number*	*Time/Dose*	*Effect on symptoms*	*Evidence*
McNally et al., 1997 (387)	oral antibiotics + topical steroids + adjunctive therapy	200	4 weeks	yes, subjectively after 4 weeks	III
Subramanian et al., 2002 (388)	antibiotics 10 days corticosteroids	40	4 –6 weeks	yes, pre-/posttreatment CT in 24 patients also improvement after 8 weeks	III
Legent et al., 1994 (389)	ciprofloxacin vs. amoxicillin clavulanate	251	9 days	nasal discharge disappeared: ciprofloxacin 60% amoxicillin clavulanate 56% clinical cure: ciproloxacin 59% amoxicillin clavulanate 51% bacterological eradication: ciprofloxacin 91% amoxicillin clavulanate 89%	no
Namyslowski et al., 2002 (390)	amoxicillin clavulanate vs. cefuroxime axetil	206	875/125mg for 14 days 500mg for 14 days	clinical cured: amoxicillin clavulanate 5% cefuroxime axetil 88% bacterial eradication: amoxicillin clavulanate 65% cefuroxime axetil 68% clinical relapse: amoxicillin clavulanate 0/ 98 cefuroxime axetil 7/89	no
Huck et al., 1993 (391).	ceflaclor vs. amoxicillin	56 acute rhinosinusitis 25 recurrent rhinosinusitis 15 chronic maxillary sinusitis	2x 500mg 3x500mg for 10 days	clinical improvement: acute rhinosinusitis 86% recurrent rhinosinusitis 56% chronic maxillary sinusitis no statistics	no

The benefit of long-term, low-dose macrolide treatment seems to be that it is, in selected cases, effective when steroids 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.

7-2-4 Acute exacerbations of chronic rhinosinusitis: oral antibiotic treatment

In open trials, oral antibiotics have an effect on the symptomatology of acute exacerbations of chronic rhinosinusitis (390, 405). In some of these studies patients with acute or chronic rhinosinusitis are combined with patients with acute exacerbations of chronic rhinosinusitis (406, 407). No studies have shown efficacy of antibiotics in acute exacerbations of chronic rhinosinusitis in a double blind placebo controlled manner.

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

7-2-5 Acute exacerbations of chronic rhinosinusitis: local antibiotic treatment

Some studies have compared the effects of local antibiotics in chronic rhinosinusitis and acute exacerbation of chronic rhinosinusitis (357, 408-410).

Desrosiers studied in a randomized, double-blind trial of tobramycin-saline solution versus saline-only solution administered thrice daily to the nasal passages by means of a large-particle nebulizer apparatus for 4 weeks in twenty patients with chronic rhinosinusitis 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 (411).

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 (358).

However, Mosges and Leonard did find differences between local antibiotics and placebo (408, 410). Mosges showed a positive effect for fusafungine nasal spray as early as the first 24 h of treatment which was not seen in the placebo group. The antimicrobiological effect of this preparation is unclear.

Table 7-8. Long-term treatment with antibiotics in chronic rhinosinusitis.

Study	*Drug*	*Number*	*Time/Dose*	*Effect symptoms*	*Evidence*
Hashiba et al., 1996 (392)	clarithromycin	45	400mg /d for 8 to 12 weeks	clinical improvement in 71%	III
Suzuki et al., 1997 (393)	roxithromycin	12	150mg /d	CT scan pre- and post-therapy: improvement in the aeration of nasal sinuses	III
Nishi et al., 1995 (394)	clarithromycin	32	400mg /d	pre- and post-therapy assessment of nasal clearance	III
Gahdhi et al., 1993 (395)	prophylactic 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
Ichimura et al., 1996 (20)	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
Scadding et al., 1995 (403)	oral antibiotic therapy	10	3 month	increased ciliary beating	III
Cervin et al., (404)	erythromicin or clarithromycin	17	1 year	increase mucociliary clearance and endoscopic signs	III
Ragab et al., 2004 (296)	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 months	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.

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 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 chronic rhinosinusitis who have undergone functional endoscopic sinus surgery and who have failed to respond to oral antibiotics or who do not tolerate them (412).

Further studies with better characterized patient populations are needed.

7-3 Other medical management for rhinosinusitis

Standard conservative treatment for intermittent and persistent rhinosinusitis 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 intermittent 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 persistent rhinosinusitis 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/Intermittent Rhinosinusitis

Nasal decongestants are usually applied in the treatment of acute/ intermittent rhinosinusitis, in order to achieve better sinus ventilation and drainage. Experimental trials on the effect of topical decongestants by CT (413) and MRI scans (414) 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 (415) and anti-oxidant action (416). 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 (417). This is in concordance with previous random-

ized 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 (418). 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/intermittent paediatric rhinosinusitis (Ib) (419). Clinical experience, however, supports the use of topical application of decongestants to the middle meatus in acute rhinosinusitis (evidence level IV).

7-3-1-2 Chronic/Persistent Rhinosinusitis

The use of decongestants for adult chronic/persistent rhinosinusitis has not been evaluated in a randomized controlled trial. Decongestants and sinus drainage did not prove to be superior to saline in chronic paediatric maxillary sinusitis in terms of subjective or x-ray scores (420).

7-3-1-3 Nasal polyps

No controlled trials were used to test the effect of decongestant treatment in nasal polyposis. 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 (421).

7-3-2 Mucolytics

7-3-2-1 Acute/intermittent rhinosinusitis

Mucolytics were used as adjuncts to antibiotic treatment and decongestant treatment in acute/intermittent rhinosinusitis 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 chronic/persistent rhinosinusitis (422).A second RCT (Ib) suggested bromhexine was superior to placebo (423).

7-3-2-2 Chronic/persistent rhinosinusitis

A cohort study in a mixed group of 45 acute and chronic rhinosinusitis patients suggested beneficial effect of adding mucolytic to standard rhinosinusitis treatment in terms of reducing treatment duration (424) (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 intermittent rhinosinusitis

The beneficial effect of loratadine in terms of symptom reduction for the treatment of acute/intermittent sinusitis in patients with allergic rhinitis was confirmed in a multicentre randomized double-blind, placebo controlled trial (Ib)(425). 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 intermittent hyperreactive sinusitis measured by subjective scores and ultrasound scans, leading to 50% improvement in both groups (426). A RCT (Ib) for intermittent paediatric rhinosinusitis did not confirm any benefit of oral antihistamine-nasal decongestant drops (419).

7-3-3-2 Chronic/persistent rhinosinusitis

Although generally not recommended as rhinosinusitis treatment, an evaluation study of chronic rhinosinusits treatment in the USA revealed antihistamines as rather often prescribed medication in patients with chronic rhinosinusitis (an average of 2.7 antibiotic courses; nasal steroids and prescription antihistamines 18.3 and 16.3 weeks, respectively, in a 12-month period) (427). However, no evidence of beneficial effects of antihistamine treatment for persistent rhinosinusitis 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) (428).

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 (429). Surgery is considered the first line treatment for allergic fungal (430) and invasive fungal rhinosinusitis (431). Although the use of antimycotics in the treatment of allergic fungal rhinosinusitis has not been tested in controlled trials, high dose of postoperative itraconazole, combined with oral and topical steroids in a cohort of 139 patients with AFS reduced the need for revision surgery rate to 20.5% (432). 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/intermittent sinusitis

No controlled trials for antimycotic treatment for acute rhinosinusitis was found on the Medline search.

7-3-4-2 Chronic/persistent 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 (124), has led to idea of treating any persistent rhinosinusitis/nasal polyposis with a topical antimycotic. Although the presence of fungus in

sinus secretions was detected in a high proportion (< 90%) of patients with persistent rhinosinusitis, as well as in a control disease-free population in a few study centres (124, 125), it cannot be taken as proof of aetiology. Until now a few case studies (level III) are conducted (433, 434). Ponikau, in a group of 51 patient with chronic rhinosinusitis, including polyposis patients, treated 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 (433). As the authors stated, antifungal treatment should be evaluated in a controlled trial to be justified. In a double blind randomized placebo controlled trial in 60 patients with chronic rhinosinusitis, topical treatment with amphotericine B did not show superior to saline in CT scores (p 0.2) and subjective scores, which were (insignificantly) worse in active treatment group (435). In a recent small randomized, placebo-controlled, double-blind, trial using amphotericin B to treat 30 patients with CRS Ponikau was also not able to show significant effect on symptomatology although he 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 (436).

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 (437) and found 48% disappearance of the polyps at endoscopy in previously endoscopically operated patients.

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 (438). 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).

7-3-5 Bacterial lysate preparations

Altered local (and systemic) immune response to bacterial infection (antigens) may be responsible for frequent recurrence of rhinosinusitis. 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 (439), ribosomal fractions of Klebsiella pneumoniae, Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae and the membrane fraction of Kp (440), and mixed bacterial lystate (441) in terms of the reduction of the number of acute relapses in persistent rhinosinusitis, period between the relapses and need for antibiotic treatment, have been tested in multicentre, placebo controlled RCTs (Ib) (439-441).

7-3-5-1 Acute/intermittent 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. Enteroccocus 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) (439). 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 could meet recurrent rhinosinusitis based on symptoms – 4.3 episodes per year) demonstrated 39% reduction of antibiotic courses and 32% of days with antibiotics during the 6 months treatment period (440).

7-3-5-2 Chronic/persistent 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 (441).

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 persistent rhinosinusitis patients refractory to conventional treatment, which did not confirm significantly improved outcomes after such expensive treatment (331). A pilot study (III) with interferon gamma suggested this treatment may be beneficial in treating resistant persistent rhinosinusitis, but the number of patients was not adequate to provide evidence to justify such treatment (442). Certain groups of antibiotics may be regarded as immunomodulators, like quinolones (443) and macrolides (444).

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/intermittent and chronic/persistent 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 chronic persistent rhinosinusitis. Hypertonic saline is preferred to isotonic treatment for rhinosinusitis by some authors in the USA, mostly based on a paper indicating it significantly improves nasal mucociliary clearance measured by saccharine test, in healthy volunteers (445).

7-3-7-1 Acute/intermittent rhinosinusitis

A randomized trial (Ib) by Adam et al. (446). with two controls, compared hypertonic nasal saline to isotonic saline and no treatment in 119 patients with common cold and acute rhinosinusitis (predominantly rhinosinusitis). 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) acute/intermittent rhinosinusitis, demonstrating approximately 5% better cure rate in each group for washouts than for decongestants, which was not significant (447).

7-3-7-2 Chronic/persistent rhinosinusitis

A randomised controlled trial (RCT) by Bachmann (Ib), comparing isotonic saline and EMS solution (balneotherapeutic water) in the treatment of persistent sinusitis in a double-blind fashion revealed improvement in both groups, with no difference between them (448). 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 ($p = .009$), and quality of life scores ($p = .008$) (449). These measures did not change in a control group ($n = 22$) who received standard treatment for chronic rhinosinusitis, 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 chronic rhinosinusitis 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 ($P < .05$), used less antibiotics ($P < .05$), and used less nasal spray ($P = .06$) (450). On the exit questionnaire 93% of study subjects reported overall improvement of sinus-related quality of life, and none reported worsening ($P < .001$); 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 chronic/persistent rhinosinusitis using cough and nasal secretions/postnasal drip as subjective and a radiology score as objective outcome measures (451). 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.

Nebulised hypertonic saline improves mucociliary clearance in short term clinical trials and appears to increase lung function compared to controls in cystic fibrosis patients (Wark, Cochrane Database Syst Rev. 2003;(1):CD001506 – apropos doubt about general harm of hypertonic saline on lung function. However, it does cause bronchocontriction in the asthmatics).

Comparison of treatment with antral washouts in the treatment of persistent adult (452) and paediatric rhinosinusitis (453) 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 (452).

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.

7-3-8 Capsaicin

Capsaicin, the active substance from red hot chilli peppers, 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 desensitizer 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 lead to trials on capsaicin treatment of nasal polyposis.

7-3-8-1 Acute/intermittent, chronic/persistent sinusitis
No trials of treatment of acute or chronic rhinosinusitis with capsaicin could be found.

7-3-8-2 Nasal polyps
A case study (III) by Filiaci et al. has demonstrated significant reduction of the size of nasal polyps after five (weekly) topical applications of capsaicin (30 mmol/L) solution in patients with nasal polyposis (454). 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) (455). 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. (456). The authors used 70% ethanol 3x10-6E 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 NF kappa B antagonist in vitro, some other modes of action may be proposed (457).

7-3-9 Furosemide
The protection of hyperreactive response to different challenges (propranolol (458); metabisulphite (459); exercise (460)) in asthmatics was demonstrated after inhalation of furosemide, suggesting bronchoprotective effects, similar to the effect of cromones. Histamine exocytosis from rat mast cells was protected by furosemide in vitro (461). It exhibited an anti-inflammatory effect through inhibition of production and release of cytokines, interleukin (IL)-6, IL-8, and tumor necrosis factor-alpha from peripheral mononuclear cells in vitro (462).

7-3-9-1 Acute/intermittent, chronic/persistent sinusitis
No trials of treatment of acute or chronic rhinosinusitis with furosemide have been found.

7-3-9-1 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 vs. mometasone furoate in 33 patients, in a prospective non-randomized controlled trial (IIa) by Passali et al. (463), 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 in polyp recurrence protection treatment. Randomized trials however are lacking.

7-3-10 Proton pump inhibitors
7-3-10-1 Acute/intermittent rhinosinusitis
There are no trials with proton pump inhibitors for acute rhinosinusitis

7-3-10-2 Chronic/persistent rhinosinusitis
There is no evidence for benefits in the general population suffering from rhinosinusitis following treatment with proton pump-inhibitors, while 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-morbidity (57 articles screened, 14 articles included) (464, 465). A number of case trials of rhinosinusitis, especially paediatric (464), has tested the efficacy of antireflux treatment with proton pump inhibitors on the clinical course and symptoms of rhinosinusitis. Increased rates of reflux were detected in persistent rhinosinusitis in adults unresponsive to standard treatment (466). A beneficial effect of proton pump inhibitors on sinusitis symptoms in patients with resistant persistent sinusitis was demonstrated in an open label clinical trial (III) (467). Further research is expected in this field, and such treatment should be justified by randomized controlled trials.

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

7-3-11 Antileukotrienes
The role of leukotriens in the pathogenesis of bronchial asthma has been well documented, and increased levels of these mediators have been detected in patients with rhinosinusitis and nasal polyps. Antileukotrienes have been evaluated in the treatment of asthmatics, especially in those with ASA triad. The effect of leukotrienes was evaluated in a randomized con-

trolled trial of patients with seasonal allergic rhinitis and was not found to be superior to placebo in terms of daily nasal symptoms score, and was significantly inferior to nasal steroid (468).
The effect of antileukotriens was not tested in controlled trials for rhinosinusitis and nasal polyposis. However, a few case-controlled trials indicate that antileukotriene treatment may have beneficial effect on nasal symptoms in patients with chronic/persistent rhinosinusitis and nasal polyposis.

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

7-3-11-2 Chronic/persistent rhinosinusitis and nasal polyps
The antileukotriene treatment in 36 patients with chronic rhinosinusitis and nasal polyposis, 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 (469). 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 (470). 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 (471).

Results of these three studies indicate that there is a need for controlled trials of antileukotriene treatment in chronic persistent rhinosinusitis and nasal polyposis.

7-3-12 Aspirin desensitisation
7-3-12-1 Acute/intermittent and chronic/persistent rhinosinusitis
No controlled trials of systemic aspirin desensitisation or topical aspirin lysine treatment for acute and chronic rhinosinusitis were found.

7-3-12-2 Nasal polyps
Systemic aspirin desensitisation or topical lysine-aspirin treatment may be implicated in protection against chronic rhinosinusitis with nasal polyposis recurrence. However, no randomized controlled trials have been done, and only one non-randomized controlled trial showed doubtful control.

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 (472-474).

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 (475).

A case controlled trial of treatment 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 (476).

These data indicate that systemic aspirin desensitisation and topical aspirin lysine treatment in nasal polyposis needs to be tested in randomized controlled trials to obtain proper evidence of recurrence protection.

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 chronic rhinosinusitis and asthma revealed that 24% were taking herbal preparation (477). 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/intermittent rhinosinusitis
A standardized myrtol oil preparation was proven superior to other essential oils, and both were superior to placebo in the randomized placebo controlled trial for uncomplicated acute

rhinosinusitis. A need for antibiotic treatment after myrtol was 23%, compared to 40% for placebo (478).

With andrographis paniculata in a fixed combination Kan Jang showed significantly improved nasal symptoms and headache in acute rhinosinusitis compared to placebo (479).

7-3-13-2 Chronic/persistent rhinosinusitis

Guaifenesin, a phytopreparation known for its mucolytic properties, was tested in a RCT on a selected population of HIV patients with chronic/persistent rhinosinusitis, demonstrating 20% higher improvement in subjective scores compared to placebo in this population (480).

7-3-13-3 Nasal polyps

No controlled trials on nasal polyp treatment with phytopreparations were found.

7-3-14 Conclusion

The results are summarized in table 7-9.

There is research-based evidence (level B) for adjunctive use of hypertonic/normotonic saline in the treatment of persistent rhinosinusitis (<4 controlled trials [CT]), but not intermittent rhinosinusitis.

There is no evidence for the use of decongestants and antral lavage in the treatment of intermittent rhinosinusitis (481). There is research-based evidence (level B) in children for selective use of bacterial lysates in the treatment of recurrent intermittent rhinosinusitis (3 multicentre RCTs). There is level C (limited) evidence for the use of mucolytics in the treatment of intermittent rhinosinusitis (controlled clinical trial, 1 RCT for and 1 RCT against in paediatric rhinosinusitis). There is level B evidence for the use of antihistamines in intermittent rhinosinusitis in patients with allergic rhinitis (1 multicentre placebo controlled RCT).

There is level C (limited) evidence for the use of antimycotics in eosinophilic mucin rhinosinusitis (2 case trials).

There is level B evidence for the use of capsaicin and furosemide in protection against recurrence of nasal polyposis (1 RCT for capsaicin, 2 CT for furosemide). There is also level C evidence for aspirin lysine as a protection against polyp recurrence. There is level C evidence for use of antileukotrienes in patients with nasal polyposis for the alleviation of nasal symptoms.

There is level C evidence for the use of proton pump inhibitors in patients with persistent rhinosinusitis and gastroesophageal reflux.

7-4 Evidence based surgery for rhinosinusitis

7-4-1 Introduction

Nowadays surgery, although minimally invasive, is generally reserved for acute/intermittent rhinosinusitis and chronic/persistent rhinosinusitis un-responsive to conservative medical treatment or where there are complications associated with these conditions. The concept of functional endoscopic sinus surgery (FESS), the Messerklinger technique, spread worldwide by the efforts of Stammberger and Kennedy, was broadly accepted in the 80's and evaluated in numerous prospective and retrospective case controlled studies or non randomized clinical trials. The functional approach to rhinosinusitis hypothesized recovery of the diseased sinus mucosa by enabling ventilation through the natural ostia and restoring mucociliary clearance achieved by minimally invasive endoscopic technique (482, 483).

7-4-2 Surgery in acute /intermittent rhinosinusitis.

To date there are no data available to judge the role of surgery in acute/intermittent rhinosinusitis.

Table 7-9. Other medical management for rhinosinusitis. Results from the treatment studies summarised.

Treatment	*Acute*	*Evidence*	*Relevance*	*Chronic*	*Evidence*	*Relevance*	*Nasal polyp*	*Evidence*	*Relevance*
decongestant	1 RCT, 1 CT	B	no.	no trial			no		
trial									
mucolytic	1 RCT	B	no	1 case	no	no	no trial		
phytomedicine	1 RCT (myrtol)	B	no	1 CT	C	no	no trial		
bacterial lysate	2 RCT recurrent	A	yes	1 RCT	B	no	no trial		
immunomodulation	no trial			1 RCT	B	no	no trial		
antihistamine	1 RCT allergic	B	no	no trial			1 RCT allergic	B	no
antimycotic	no trials			1 case trial	C	no	1 case trial	C	no
antral lavage	1 RCT	B	no	1 RCT	B	no	no trial		
isotonic douche	no trial			3 RCT	A	yes	no trial		
hypertonic douche	1 RCT	B	yes	2 RCT	A	no	no trial		
antileukotriene	no trial			1 case	C	no	3 case	C	no
proton pump inhibitor	no trial			3 case	C	no	no trial		
aspirin lysate	no trial			no trial			1 CT 1 case	B	no
furosemide	no trial			no trial			1 CT 1 case	B	no
capsaicin	no trial			no trial			1 RCT 1 case	B	no

7-4-3 Surgery in chronic /persistent rhinosinusitis and nasal polyposis unresponsive to medical treatment

7-4-3-1 Introduction

Table 7-10 summarizes some of the larger studies with follow up ranging from six months to ten years. Virtually all of these offer only Level III evidence.

Treatment outcomes for ESS were reviewed by Terris and Davidson in 1994 (499), analysing 10 large series (II and III level) with a total of 1,713 patients, which showed a mean 91% (73-97.5%) improvement rate. 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 major complications occurred in 1.6% of patients.

7-4-3-2 Comparing ESS and Caldwell/Luc in the short and long term

Some evidence has been provided by studies either comparing different surgical techniques (radical vs. endoscopic sinus surgery (ESS)), or considering the use of new technology- e.g. powered instrumentation applied to the Messerklinger technique. Penttila and co-workers randomized patients to either endoscopic sinus surgery or a Caldwell Luc approach (C-L) and considered outcomes one year following surgery (500); and in the longer term (501) (Level Ib)

Interestingly, the first study revealed significant improvement for obstruction, rhino rhea and improved smell in the ESS group compared to C-L group (global evaluation showed marked improvement in 50.7% of the C-L group and in 76.7% of the ESS group), (500) but the outcomes in the second trial demonstrated a different improvement rate 5-9 years postoperatively, with 82% of the C-L and 76% of the ESS patients respectively deriving benefit. Long term revision surgery was done in 20% of ESS group and 18% of C-L group (501). However, postoperative cheek pain and altered sensation to changes in temperature were noted in 23% of C-L group. The histopathology of similar groups was studied by Forsgren et al. (IIb level), indicating a greater reduction in inflammatory parameters in the mucosa of the maxillary sinus after C-L than ESS one year after the surgery (502). Another randomized controlled (485) clinical study (503) (level Ib), has revealed superiority of ESS (40 patients) to C-L (37 patients) when both CT scans and endoscopy were used as outcome measures (Level III).

7-4-3-3 Comparing inferior antrostomy with middle meatal antrostomy

A cohort controlled trial (38 patients, bilateral disease, sides randomized) comparing outcomes of chronic maxillary sinusitis following middle (MMA) and inferior meatal antrostomy (IMA) did not reveal significant differences, (504) in contrast to the results of Lund, (505) (Level III) who analysed long-term nasal symptoms scores for two types of antrostomies, proving superiority of MMA.

Table 7-10. Subjective results following endoscopic sinus surgery.

First author	*Year reported*	*Number of Patients*	*Improvement*	*Follow-up*
Kennedy et al. (483)	1987	75	92%	0.3-2.75 years
Hosemann et al. (484)	1988	220	81.8%	4.3 years
Hoffman and May (485)	1989	100	98% (10 revised)	0.75 years
Rice (486)	1989	100	83% (7% revised)	2 years
Schaefer et al. (487)	1989	100	83%	0.4 years
Levine (488)	1990	221	80% (CRS) 88% (NP)	1.4 years
Mathews et al. (488 a)	1991	155	91%	1 year
Stammberger and Posawetz (489)	1990	500	95%	0.75-10 years
Wigand and Hosemann (490)	1991	84	83%	1 year
Kennedy (281)	1992	120	85%	1:5 years (mean)
Vleming (491)	1993	92	85%	3.6 years
Schaitkin et al. (492)	1993	100	98%	0.75 years
Lund and Mackay (493)	1994	650	87%	0.5 years
Danielson and Olofsson (494)	1996	226	49% asymptomatic 25% improved 15% slightly improved 0% worse	1-5 yrs mean 3y 5 mo
Weber et al. (495)	1997	170	89%	1.6 - 10 years
Senior et al. (496)	1998	72 (from original cohort of 120 Kennedy)	98% (18% revised)	Mean 7.8 years
Sobol et al. (497)	1998	393	81% 70% (4% revised)	6 months 12 months
Jakobsen and Svendstrup (498)	2000	237	45% totally satisfied 44% improved	1 year

7-4-3-3 Comparing endoscopic sinus surgery with conventional surgery

In a randomized study of 50 patients comparing endoscopic sinus surgery with conventional surgery (506), follow up ranged from 15-33 months with a mean of 19 months, at the end of which 76% of the endoscopic group had complete relief of symptoms, 16% partial relief and 8% no relief as compared to 60%, 16% , 24% in the conventionally treated group. Outcomes for purulent discharge and loss of smell showed significant improvement following ESS when preceded by maxillary sinus irrigation as compared with those obtained by sinus irrigation alone after one year's observation for chronic maxillary sinusitis in a trial (Level III) conducted by Hartog et al. (507). Scores for other sinusitis symptoms did not differ significantly and as sinus irrigation avoided surgery in 58% of the patients at one year follow up, it was suggested that this method, combined with broad spectrum antibiotics should precede ESS.

There are no direct comparisons between endoscopic sinus surgery and conventional intranasal ethmoidectomy and only an historical comparison is possible. In these earlier studies improvement was judged in a fairly crude subjective manner and would appear to be somewhat worse than that reported with endoscopic sinus surgery though that might reflect the predominance of nasal polyposis in these patient groups.

More recently a systematic review of the clinical effectiveness of endoscopic polypectomy was conducted by the University of Exeter in 2002. This considered 33 published studies which had enrolled more than 50 patients, comprising three RCTs, three non-randomised control trials and twenty seven case series including many of the references already discussed. The RCTs and controlled trials reported an overall symptomatic improvement that ranged from 78% to 98% for FESS compared to 43 to 84% for comparative techniques (including polypectomy, Caldwell-Luc and intranasal ethmoidectomy). Disease recurrence was 8% for FESS compared to 14% for Caldwell-Luc and polyp recurrence was 28% for endoscopic ethmoidectomy compared to 35% for polypectomy. The percentage of overall complications was 1.4% for FESS compared to 0.8% for conventional procedures. The case series studies reported overall symptomatic improvement for patients with nasal polyps that ranged from 37% to 99% (median 89%). For the mixed patient groups with and without polypoid disease, overall symptomatic improvement ranged from 40% to 98% (median 88%). The authors concluded that FESS may offer some advantages in effectiveness over comparative techniques but there is enormous variation in the range of results reported and severe methodological limitations (514).

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 538 ENT surgeons (both consultants and trainees) working in 87 hospitals in England and Wales. Patients undergoing surgery were prospectively enrolled and followed up at 3 and 12 month intervals post-operatively using the SNOT-22 as the main outcome measure. Three thousand one hundred and twenty eight patients participated in the audit of whom two-thirds had nasal polyps. This included all forms of surgery though the majority were performed endoscopically. Overall there was a high level of satisfaction with the surgery irrespective of whether it was performed endoscopically or not and clinically significant improvement in the SNOT-22 scores were demonstrated at 3 and 12 months although there was some deterioration during this interval. All polyp patients benefited more from surgery than the chronic rhinosinusitis with benefit increasing as polyp extent increased. 8.7% of patients had or were waiting for revision surgery at 12 months. Overall the surgery was safe with a CSF leak of 0.064% and peri-orbital haematoma rate of 0.2% with no long term visual problems. Patients with aspirin sensitivity and patients with a history of previous surgery tended to derive less benefit from sinonasal surgery in terms of symptom improvement (515) (Level II).

Modifications to standard FESS technique have been studied in several randomized controlled clinical trials. A multicentre study (Ib) compared extended versus limited ESS approach in 65 patients with a long-term follow up evaluating subjective symptom scores, nasomucociliary transit time and endoscopic findings which showed no significant difference between the two groups although the number of patients was small for statistical analysis (516). Nayak et al. have tested so-called functional nasosinusal surgery (FENS – limited ethmoid approach combined with endoscopic septal surgery) for what they described as allergy-associated chronic rhinosinusitis in a randomized controlled trial (Ib) by means of visual analogue symptom scores and endoscopy. The results indicated FENS to be superior to FESS for this selected population with CRS (517). More conservative procedures e.g. minimal invasive sinus surgery (MIST) had similar subjective outcomes as con-

Table 7-11. Subjective results following conventional intranasal ethmoidectomy.

First author	*Year reported*	*Number of Patients*	*Improvement*	*Follow-up*
Eichel (508)	1982	46	83%	3-8 years
Taylor et al. (509)	1982	80	70%	1-10 years
Stevens and Blair (510)	1988	87	75%	0.5-11 ears
Friedman and Katsantonis, 1990 (511)	1990	1037	85%	8 years
Sogg, 1989 (512)	1989	146	69%	6-13 years
Lawson, 1991 (513)	1991	90	73%	3.5 years

ventional ESS, in a prospective non-randomized study in 85 patients with persistent rhinosinusitis (level III) but the results should be validated by a RCT (518).

A randomized controlled trial (Ib) tested the outcomes for holmium-YAG laser in 32 patients with CRS undergoing ESS (randomization - one side conventional, contralateral laser) (519). 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 difference between the methods. Similarly in a prospective randomized study Selivanova et al.were unable to demonstrate an advantage of mechanical debriders over conventional instrumentation (520).

7-4-3-5 Endoscopic surgery in special situations

From a cohort of 650 patients undergoing ESS for CRS, 28 patients suffered for cystic fibrosis and14 from immune deficiency (493) (Level III). Whilst overall subjective improvement was less than in the cohort as a whole (91% improved), 54% of the cystics and 79% of those with immune deficiency derived significant benefit at six month follow-up. No studies specifically focusing on primary ciliary dyskinesia or congenital immune deficiency were found in the literature. However, a number of authors have considered acquired immune deficiency, mainly related to HIV. These have been by definition a relatively small series (98) , (Level III). The bacterial profile may mirror that seen in conventional rhinosinusitis but can also includes pseudomonas aeruginosa and toxoplasma. A range of surgical approaches have been used in this group with high relapse rates reported of 76-81%.

The small number of papers concentrating on cystic fibrosis have mainly concerned the paediatric population. Halvorsen et al. (521) reported 16 adults with cystic fibrosis and chronic rhinosinusitis/nasal polyposis combined with pulmonary complications. The study considered pulmonary function following endoscopic sinus surgery and preliminary findings suggested an improvement in both the symptoms of rhinosinusitis and exercise tolerance (Level III). However, again there was a high chance of relapse, 50% in the study by Rowe-Jones and Mackay (522) (Level III) within two years of the procedure.

The relationship of asthma/aspirin-sensitivity on surgical results and the effects of surgery on the lower respiratory tract are debated. A prospective study of 120 patients maintained that when extent of disease was taken into account, asthma per se did not adversely affect outcome (281) (Level II). However, as a corollary of this, recurrence particularly in the aspirin-sensitive group is likely to be higher (492) (523) (Level III). This may be off-set to some extent in the short term by the extent of surgery (523, 524) The effect of sinonasal surgery on respiratory function has generally been positive.

7-4-4 Conclusion

In conclusion, trials providing high level statements of evidence for efficacy of surgery for rhinosinusitis are lacking, as already concluded by Lund in 2001 (539). Few sinonasal surgical studies are designed as RCTs, and those that are should be of higher quality. Lack of consistency between the studies (inclusion-exclusion criteria, staging, scores, questionnaires etc.) and inadequate numbers for robust statistics are the main drawbacks of these trials. In addition the experience of an endoscopic rhinosurgeon should be established before one can compare results from different studies (540) though there have been some attempts to look at the 'learning curve' through complication rates (Stankiewicz). We have a large amount of low level evidence that ESS is a safe procedure that improves rhinosinusitis symptom scores, HRQL and some objective criteria (see Chapter 7-5-3) in low-risk adult patients. However, at least two studies have shown that aggressive medical therapy offers similar results over a one year period (296, 541) (Level IIb) underlining the need to reserve surgery for those who have failed medical therapy. 'High-risk' patients should be treated with aggressive long-term medication pre- and postoperatively and represent a different group when evaluating studies.

7-5 Surgical treatment vs. medical treatment in CRS /NP

7-5-1 Surgical treatment vs. steroids in NP

In the two open studies by Lildholt et al. (267, 379) single injections of 14 mg betametasone have been compared to intranasal polypectomy without any difference in outcome 12 months after treatment with subsequent local steroids in both groups, as measured by mean nasal score or mean score of sense of smell. In a study by Blomqvist et al. (542) 32 patients were pre treated with systemic steroids (prednisolone for fourteen days) and budesonide for 4 weeks after which unilateral FESS was performed and intranasal steroids given for an additional 12 months to both sides. The sense of smell improved after treatment with systemic and local steroids. Surgery had an additional beneficial effect on nasal obstruction and secretion that persisted over the study period but no additional effect was observed on sense of smell. The authors conclude that surgical treatment is indicated after steroid treatment, if nasal obstruction persists but not if hyposmia is the primary symptom (Level III).

To date there is too little data available to determine if there is any difference between surgery and steroid therapy in the long-term outcome of patients with nasal polyposis.

7-5-2 Surgical vs. steroids in CRS

To our knowledge no studies have been published to date comparing surgery and topical corticosteroids in the treatment of CRS.

Table 7-12. Chronic rhinosinusitis and bronchial asthma: Effects of various paranasal sinus procedures on lung function (Level II/III).

Author	*Patients (age)*	*Procedure*	*Post-operative interval*	*Results*	*Comments*
Brown et al., 1979 (525)	101 patients with ASA triada (10-74y)	polypectomyb	12 mo	clinically[c] 32% better, 53% unchanged, 15% worse.	60% nasal passages free post-operative
Jäntti-Alanko et al., 1989 (526)	34 patients	polypectomy	48 mo	clinically: 59% better, 29% unchanged, 12% worse	
English, 1986 (527)	205 patients with ASA triad[a] (91% adults)	Caldwell-Luc[b]	6-156 mo	lung function: 98% better, 2% unchanged, 0% worse	steroids reduced in 84%
Nishioka et al., 1994 (91)	20 patients (16-72 y)	partial endonasal ethmoidectomy	12 mo	clinically: 95% better	90% nasal obstruction preoperative.
Friedman et al., 1982 (528)	50 patients	endonasal ethmoidectomy	6-36 mo	clinically: 93% cortisone reduced	100% nasal obstruction preoperative
Hosemann et al., 1990 (529)	13 patients (27-75 y)	endoscopic ethmoidectomy	12 mo	lung function/medication: 77% better, 15% unchanged, 8% worse	
Ilberg, 1994 (530)	32 patients	endoscopic ethmoidectomy	36 mo	clinically: 50% better	
Jankowski et al., 1992 (531)	50 patients	endoscopic ethmoidectomy	18 mo	lung function/ clinically: 91% better, 9% unchanged	
Korchia et al., 1992 (532)	25 patients	endoscopic ethmoidectomy	1 y	clinically: 66% unchanged, 29% better, 5% worse	lung function 100% unchanged
Dunlop et al., 1999 (533)	50 patients (17-74 y)	endoscopic ethmoidectomy	1 y	clinically: 40% better 20% less steroid inhaler 28% less bronchodilator sig less oral steroids with hospital admissions	
Goldstein et al., 1999 (534)	13	endoscopic ethmoidectomy	mean 33 months	1/13 showed obj or subj improvement	
Ikeda et al., 1999 (535)	21-15 6	endoscopic sinus surgery controls	6 months	ESS: ?peakflow ? steroids controls: no change	
Palmer et al., 2001 (536)	15	endoscopic sinus surgery	1 y	? steroids ? antibiotics	
Wreesman et al., 2001 (537)	82	Denker's procedure	?	clinical improvement	refractory CRS/polypoids
Batra et al., 2003 (538)	17 9 ASA triad	endoscopic ethmoidectomy	1 y	clinically 76% better FEV_1[d] better 71% less steroid	ASA triad did worse

a ASA triad: asthma + chronic rhinosinusitis + aspirin intolerance; b Additional endonasal procedures to the ethmoidal; c Clinically: clinical investigation (assessment based on questioning of patient, consumption of medication, admissions to hospital etc); d FEV1: forced expiratory volume (1/s);e Variable: various procedures, operating technique unclear, mo: months; y: years

7-5-3 Surgical vs. antibiotics in CRS

Only one recent study in the literature compares surgery versus long term antibiotic treatment in patients with CRS with and without NP (296). Ninety patients with CRS were equally randomized either to medical or surgical therapy. Each patient had three assessments: before starting the treatment, after 6 months, and at 1 year. Both the medical and surgical treatment of CRS significantly improved almost all the subjective and objective parameters of CRS ($P<.01$), with no significant difference being found between the medical and surgical groups ($P>.05$), except for the total nasal volume in CRS with ($P<.01$) and without polyposis ($P<.01$) groups, in which the surgical treatment demonstrated greater changes.

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 (543). 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% (544).

Complications of rhinosinusitis are classically defined as **orbital**, **osseous** and **endocranial** (544) though rarely some unusual complications can develop (table 2) (545-549).

An extremely useful test, although not specific, is the white cell count which, if elevated in acute rhinosinusitis 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 (551) 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 give in his work (555).

8-3 Orbital complications

8-3-1 Systemic

If there is a complication in rhinosinusitis, the eye is often involved (552) especially in ethmoiditis, whereas this is rare in sphenoidal infection (557). The spread of infection directly via the thin and often dehiscent lamina papyracea (557); or by veins (558) occurs with relative ease.

According to Chandler's classification orbital complications may progress in the following steps (559):
periorbital cellulitis (preseptal edema),
orbital cellulitis,
subperiosteal abscess,
orbital abscess or phlegmon and
cavernous sinus thrombosis (543, 560).

Moreover orbital complications especially in children, often occur without pain (561). Orbital involvement is manifested by swelling, exophthalmos, and impaired extra-ocular eye move-

Table 8-1. Epidemiological data of complications in rhinosinusitis.

Author	*Country*	*Age*	*Pathology*	*Pts*	*Total % of complications*	*Orbital*	*Intracranial*	*Osseous*	*Soft tissue*
Mortimore, 1999 (550)	South Africa	adults	acute pansinusitis	87	72.4% (63/87)				
Ogunleye, 2001 (551)	Nigeria	adults	acute/chronic pansinusitis	90	37% (33/90)	41%	5%	32%	18%
Eufinger, 2001 (552)	Germany	adults/ children	acute pansinusitis	36	75% (27/36)	58% (20+1/36)	11% (3+1/36)		8.4% (3/36)
Kuranov, 2001 (553)	Russia	adults	rhinosinusitis			0.8%	0.01%		
Gallagher, 1998 (554)	USA	adults	rhinosinusitis	176			8.5% (15/176)		
Clayman, 1991 (555)	USA	adults	acute/chronic rhinosinusitis	649			3.7% (24/649)		
Lerner, 1995 (556)	USA	children	rhinosinusitis	443			3% (14/443)		

ments (562). 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 (560).

8-3-2 Periorbital cellulitis

Periorbital cellulitis (inflammation of the eyelid and conjunctiva) (549) 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 (563) and it manifests itself as orbital pain, blepharal edema and high fever (564). Periorbital cellulitis usually responds to an oral antibiotic appropriate to common sinus organisms but if not aggressively treated, may spread beyond the orbital septum (563).

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 extra ocular muscles (549, 565).

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 abscess 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 (563).

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 abscess** generally results from diagnostic delay or to immunosuppression of the patient (564) with a frequency of 9% and 8.3% (566, 567) 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 (563).

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 (568).

8-4 Endocranial complications

These include epidural or subdural abscesses, brain abscess, meningitis (most commonly), cerebritis, and cavernous sinus thrombosis (563, 569, 570).

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 (554) while intracranial abscesses are often heralded by signs of increased intracranial pressure, meningeal irritation, and focal neurological deficits (562). Although an intracranial abscess is relatively asymptomatic, subtle affective and behavioural changes often occur showing altered neurological function, altered consciousness, gait instability, and severe, progressive headache.
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 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 (554).

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 essential when there are some degrees of soft tissues involvement such as in cavernous sinus thrombosis (554). Moreover, if meningitis is suspected, a lumbar puncture could be useful (554) once an abscess has been excluded.

Table 8-2. Endocranial complications in rhinosinusitis.

Author	*Number of patients with endocranial complications*	*Complications*	*Mortality/Further Defects*
Gallagher 1998 (554)	176 patients	meningitis represented 18% cerebral abscess 14% epidural abscess 23%	Mortality 7% Morbidity 13%
Albu 2001 (571)	16 patients	6 had meningitis 6 frontal lobe abscess 5 epidural abscess 4 subdural abscess 2 cavernous sinus thromb-ophlebitis	
Dunham 1994 (563)		subdural empyema in 18%	Mortality 40% Surviving patients often have neurological disability
Eufinger 2001 (552)		together meningitis, empyema and brain abscess constitute 12% of all the intracranial complications	

High dose long term i.v. antibiotic therapy followed by craniotomy and surgical drainage are usually required for successful treatment (566). Pathogens most commonly involved in the pathogenesis of endocranial complications are Streptococcus and Staphylococcus species and anaerobes (570).

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 (563). Such a complication has been estimated at 9% of intracranial complications (554, 571) and is a fortunately rare and dramatic complication of ethmoidal or sphenoidal sinusitis. 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 (560).
The cornerstone of diagnosis is high-resolution CT scan with orbit sequences (572) which show low enhancement compared to normal (573). 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% (574). The use of anticoagulants in these patients is still controversial (560) but is probably indicated if imaging shows no evidence of any intracerebral haemorrhagic changes (575).

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 (560). The most common osseous complications are osteomyelitis of the maxillary (typically in infancy) or frontal bones (573).

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 (560).

In this context, Gallagher (554) 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 (551). 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 (544).

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 contralaterally. 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 (560).

8-7 Unusual complications of rhinosinusitis

Table 8-3. Unusual complications of rhinosinusitis.

Complication	*Author, year*
Lacrimal gland abscess	Mirza 2001 (545)Patel 2003 (546)
Nasal septal perforation	Sibbery 1997 (576)
Visual field loss	Gouws 2003 (548)
Mucocoele or mucopyocoele	Low 1997 (569)
Displacement of the globe	Low 1997 (569)

8-8 Complications of surgical treatment

8-8-1 Introduction

After the introduction of endoscopic paranasal 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 (577).

8-8-2 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 8-4.

8-8-3 Epidemiology of complications of sinus surgery using non-endoscopic techniques

Table 8-5. presents the number of complications in several studies using non-endoscopic sinus surgery.

8-8-4 Epidemiology of complications of sinus surgery using endoscopic techniques

The Table (8-6) 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 1% and minor complications in about 5-6% of cases. Further analysis with the available data is not possible because of different classification and data presented in these studies.

8-8-5 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, 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. (594), 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

Table 8-4. Complications following paranasal sinus surgery.

Location	*Minor complications*	*Major complications*
Orbital	Orbital emphysema Ecchymosis of the eyelid	Orbital haematoma Loss of visual acuity/blindness Diplopia Nasolacrimal duct damage
Intracranial	CSF leak - uncomplicated	CSF leak Pneumcephalus (Tension) Encephalocoele Brain abscess Meningitis Intracranial (subarachnoid) bleeding Direct brain trauma
Bleeding	Small amount of bleeding Stopped with packing No need for blood transfusion	Lesion of anterior ethmoidal artery Lesion of sphenopalatine artery Lesion of internal carotid artery Bleeding which requires transfusion
Other	Synechiae Slight exacerbation of pre-existent asthma Hyposmia Local infection (osteiitis) 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-existent asthma or broncospasm Death

Table 8-5. Epidemiology of complications following paranasal surgery, using non-endoscopic techniques.

Author/Year	*N*	*Orbita*	*Intracranial*	*Bleeding*	*Others*	*Minor*
Freedman and Kern, 1979 (578)	565	4	2	2	1	16
Taylor et al, 1982 (509)	284	1	3	-	-	8
Stevens and Blair, 1988 (510)	87	3	-	3	-	8
Eichel, 1982 (508)	123	1	2	1	-	no numbers
Sogg, 1989(512)	146	-	-	-	-	4
Friedman and Katsantonis, 1990 (511)	1163	-	4	3	-	25
Lawson, 1991 (513)	600	2	3	-	2	5
Sogg and Eichel, 1991 (579)	3000	-	5	2	-	288

Table 8-6. Epidemiology of complications following paranasal surgery, using endoscopic techniques.

Author/Year	*N*	*Orbita*	*Intracranial*	*Bleeding*	*Others*	*Minor*
Schaefer et al., 1989 (487)	100	-	-	-	-	14
Toffel et al., 1989 (580)	170	-	-	1	-	6
Rice, 1989 (486)	100	-	-	-	-	10
Stammberger & Posawetz, 1990 (489)	500	-	-	1	-	22
Salman, 1991 (581)	118	-	-	-	-	28
Wigand and Hoseman, 1991 (490)	500	-	10	-	-	no numbers
Lazar et al., 1992 (582)	210	-	-	-	3	16
Vleming et al., 1992 (583)	593	2	2	2	1	38
Weber and Draf, 1992 (584)	589	20	15	1	-	no numbers
Kennedy, 1992 (281)	120	-	-	-	-	1
May et al., 1993	1165	-	4	3	-	94
Smith and Brindley, 1993 (585)	200	1	-	-	-	16
Dessi et al., 1994 (586)	386	3	2	-	-	no numbers
Cumberworth et al., 994 (587)	551	1	2	-	-	no numbers
Lund and Mackay, 1994 (493)	650	1	1	-	-	no numbers
Ramadan and Allen, 1995 (588)	337	1	3	-	-	34
Danielson and Olafson, 1996 (494)	230	-	-	-	10	6
Castillo et al., 1996 (589)	553	2	2	8	-	36
Weber et al., 1997 (495)	325	4	3	30		no numbers
Rudert et al., 1997 (590)	1172	3	10	10	-	no numbers
Dursum et al., 1998 (591)	415	12	1	12	-	56
Keerl et al., 1999 (592)	1500	2	5	9	-	no numbers
Marks, 1999 (593)	393	1	3	5	-	22
Total amount	10877	53 (0.5%)	63 (0.6%)	82 (0.8%)	14 (0.1%)	399 (3.6%)

42% 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 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: table 8-7.

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

In Australia Kane (595) did an similar review, presenting an overall major complication rate of 0.03% (12 major orbital complications and 22 intracranial complications in 10,000 FESS operations).

Table 8-7. Complications comparison of non-endoscopic and endoscopic techniques.

Technique	*Major complications*	*Patients died*
Endoscopic ethmoidectomy	0.4097%	3
Endonasal ethmoidectomy with headlamp	0.3569%	23
External ethmoidectomy	0.5204%	9
Transantral ethmoidecthomy	0.1765%	3

8-8-6 Risk factors for complications in sinus surgery

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

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

8-8-7 Conclusion

Sinus surgery is well established. 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.

9. Special considerations: Rhinosinusitis in children

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 change with age. The management of rhinosinusitis in children is a controversial and a rapidly evolving issue.

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 (596). 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. In the newborn, two to three ethmoid cells are found bilaterally, and by the age of four the ethmoid labyrinth has been 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 air cell (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.

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 (173) in a CT scan study showed that in children with a history of chronic purulent rhino rhea and nasal obstruction 64% showed involvement of the sinuses. In a MRI study of a non-ENT paediatric population (597) 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 (URI), and to 100% in the presence of purulent secretions. Also Kristo et al. (598) 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.
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 (176, 177)
In temperate climates there is a definite increase in the occurrence of chronic rhinosinusitis in children during the fall and in the wintertime, so that the season seems to be another important factor (176).
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.

Although viruses are uncommonly recovered from sinus aspirates (562, 599), most authors agree (600, 601) that viral infections are the trigger to rhinosinusitis. Although CT scan abnormality can be seen up to several weeks after the onset of a URI, one can assume that only 5 to 10% of the URI in early childhood are complicated by acute rhinosinusitis (602). 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 acute rhinosinusitis are Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, the latter being more common in children (41, 42).

Since antral punctures are not frequently performed in children anymore, it is interesting to know from the studies that in children 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%) (603).

9-4 Symptoms and signs

Several authors studied the presenting symptoms of rhinosinusitis in children (177, 604, 605). Children with acute rhinosinusitis frequently have less specific complaints than adults. Rhino rhea is the most frequent presenting symptom in all forms of rhinosinusitis (71% to 80%). Cough seems to be a frequent symptom (50% to 83%). In acute rhinosinusitis, however, nasal obstruction does not appear to be the most prominent symptom, probably because it is masked by more severe symptoms such as fever (50 to 63%) and pain (29% to 33%). On the other hand, in chronic sinusitis, nasal obstruction and mouth breathing are very frequent (70% to 100%) and is often accompanied by ear complaints (recurrent, purulent otitis media or chronic otitis media with effusion: 40% to 68%). This relationship between rhinosinusitis and otitis is not unexpected, as the middle ear can be considered a kind of specialized paranasal space.

9-5 Examination

Physical examination of a child's nose is often difficult, and only limited anterior rhinoscopy is tolerated by these young patients (606). This examination may be accomplished in a simple way by tilting the tip of the nose upward (young children have wide noses with round nostrils and no vibrissae, allowing easy examination of the condition of the head of the inferior turbinate). Another convenient method is the use of an otoscope (607, 608). Because of the difficulties of performing anterior rhinoscopy in a young child, most studies provide limited information about the condition of the nasal cavity in rhinosinusitis in children. Mostly the nasal (boggy turbinate) and pharyngeal mucosa appears erythematous. Yellow to greenish purulent rhino rhea of varying viscosity can be seen. Lymphoid hyperplasia may be seen in the oropharynx. There may be adenoid and/or tonsillar hypertrophy, cervical lymph nodes may be moderately enlarged and slightly tender (606, 607). The only quantitative data on rhinoscopy in young children is given by Clement et al. (605) showing a postnasal drip in 60% and presence of pus in the middle meatus in 50% and by Riding et al. showing turbinate mucosal swelling in 29% (604).

The value of transillumination and ultrasonography is certainly limited, and these procedures are not recommended for diagnoses of adult rhinosinusitis. The increased thickness of both the soft tissue and bony vault of the palate in children under 10 years of age limits the clinical usefulness of transillumination in the younger age group even more (279).

The value of plain sinus films in assessing the extent of the disease, especially in young children, is questionable. Lusk et al. (607) studied 70 children who had symptoms compatible with chronic rhinosinusitis, and compared plain films with coronal CT scans within a few hours of one another. When all sinuses were evaluated or considered, they found a lack of correlation between both methods in 74% of the patients. Forty five percent of the normal plain radiographs showed abnormalities on CT, and 34% of the abnormal plain radiographs were actually normal on CT. These authors found that plain films both over- and underestimated the amount of sinus disease. Thus, for evaluation of paediatric rhinosinusitis, CT remains the imaging modality of choice, because of its ability to resolve both bone and soft tissue (608). Before defining which CT scan findings are considered abnormal in children, it is interesting to discuss the incidental paranasal sinus abnormalities on CT scans of children and their clinical correlation. A number of authors have shown that radiographic opacification on the CT scan are found in considerable number of asymptomatic children (609).

Looking at the percentage of CT signs of sinus disease in a symptomatic paediatric population, the prevalence of CT abnormalities increases from 64% to 81% (173, 610). Thus most authors are in agreement that an asymptomatic child with an incidental paranasal sinus finding on CT needs no further work-up unless clinical symptoms and signs are elicited (611).
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 (612).

9-6 Systemic disease and chronic rhinosinusitis

The role of atopy in chronic rhinosinusitis is unclear. Many authors attribute a great deal of importance to allergy (73, 604, 608) although others (81, 173, 613) did not find an increased prevalence of rhinosinusitis in allergic children.

All young children have a physiologic primary immune deficiency (608, 614). Defence against polysaccharides encapsulated bacteria via immunoglobulin G subclasses 2 and 4 may not reach adult levels until the age of 10 years (95). IgG subclass deficiency can lead to protracted or chronic rhinosinusitis (74,79,85,94,96). According to Polmar (615) 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 and replacement therapy cannot be provided (616). Patients with primary or acquired immune deficiencies (e.g. treatment for malignancies, organ transplants, maternally transmitted AIDS or blood-transmitted AIDS in hemophilics, 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 rhino rhea, mild congestion, and chronic cough (608).

Cystic fibrosis is caused by a mutation of the gene FES1 encoding the cystic fibrosis transmembrane conductance regulator (CFTR). This gene contains 27 exans encompassing approximately 252 kb of DNA on chromosone 7q 31.2. The most common mutation, deletion of phenylalanine at position 508 (D F508) accounts for nearly 70% of mutuations in European-derived Caucasian population (617).

In children with cystic fibrosis, sinusitis seems to be a common problem. Although the prevalence of nasal polyposis in children with cystic fibrosis was previously estimated to be between 6 and 20% (618), Yung et al. (619) found it to be over 50% and Brihaye et al. (620) 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% (620) 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 polypoidal 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 the study by Brihaye et al. (620) massive polyposis was never found before the age of 5 years. Mucopyosinusitis of 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. The youngest child reported with the disease was a 3 months old infant presenting symptoms similar to those of children with bilateral choanal atresia (nasal blockade, stridor, and feeding problems), except that the symptoms occurred only gradually following a symptom-free period after birth.

By definition, patients with Kartagener's syndrome [a hereditary disease involving the classic triad of rhinosinusitis, bronchiectesis, and situs inversus] have chronic rhinosinusitis, but which develops later in life. The neonatal group with Kartagener's syndrome do not have rhinosinusitis and bronchiectesis, and therefore the term "immotile cilia syndrome" was introduced in the seventies. As ultrastructural changes of cilia were also found after chronic infections or polyposis, and situs inversus did not seem to be essential, the name of this autosomal recessive disease was changed to primary ciliary dyskinesia (PCD) (621). One should always consider the diagnosis 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 goes for an infant or older child with atypical asthma, unresponsive to treatment, chronic wet cough, and sputum production in the older child who is able to expectorate, very severe gastro-oesophagal 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.
There are a number of ways to diagnose PCD. Clinically the most useful is the saccharine test, which is a cheap and easy procedure to screen older children and adults. If the child is too young for the test or the results are positive (transport time longer than 60 minutes) or there exists a strong clinical suspicion, the ciliary beat frequency can be tested from a nasal epithelial biopsy.

If the direct inspection of the ciliary beat frequency is abnormal (less than 11-16 Hz) an ultrastructional 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 (622). Many of these abnormalities on TEM (transmission electron microscopy), however, can be transient or occur secondarily after infection. In cilia with patients with PCD specific ultrastructural abnormalities are present, such as dynein and/or spoke deficiency, and absence of the central pair of microtubules. 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 both (294). Therefore the study of cilia after sequential monolayer-suspension culture technique avoids the acquired form (623).

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 (624). 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 potential relationship between GER and otolaryngologic abnormalities. The author found in 17 patients: 1 or more of these endoscopic signs: cobblestoning of the mucosa of the laryngopharynx, inflammation of the upper airway, sinus involvement, rhino rhea, subglottic stenosis, velopharyngeal insufficiency, pharyngeal tracheitis and tracheomalacia. In most of the patients the oesophagus on examination was erythematous. The diagnosis needs to be confirmed by oesophageal 24 hours pH monitoring. In 30 children with chronic sinus disease found after 24 hour pH monitoring in 63% oesophageal reflux and 32% had nasopharyngeal reflux (466).

9-7 Management

9-7-1 Introduction
In 1994 Poole stated that chronic rhinosinusitis in the young child does not necessary have to be treated, as spontaneous resolution is the norm (625). With regard to the natural history of the disease and the growing resistance and b-lactamase production of many microorganisms, one should refrain from overtreating a runny nose in a young child. One should not treat every common cold with antibiotics or smash any minor

self-limiting infection of a common cold with the sledge hammer of broad spectrum antibiotics. Some physicians prescribe antibiotics for minor respiratory infections in the hope of preventing serious complications and/or avoid medical/legal litigations. 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, which proved that complications of rhinosinusitis in a child are uncommon (177).

9-7-2 Treatment of rhinosinusitis

9-7-2-1 Medical treatment of rhinosinusitis

The data on specific treatment of children are very limited.

In a short-term follow-up study Furukawa (626) showed a superior result from erythromycin-sulfisoxazole plus topical decongestants compared with placebo + topical decongestants, and Rachelefsky et al. (85) studying 84 children, demonstrated on the basis of radiographs and clinical response a better result in the group treated with amoxicillin, although trimethoprim-sulfamethoxazole was an adequate alternative, while erythromycin was not any better than an antihistamine-decongestant combination. The only long-term follow-up in the treatment of children with chronic maxillary sinusitis (n=141) comparing oral amoxicillin combined with decongestant nose drops, drainage of the maxillary sinus (antral lavage), a combination of the two previous regimen, and placebo was performed by Otten et al. (627) showing that the therapeutic effects of these four forms of treatment did not differ significantly or have a significant curative effect The usual duration of antimicrobial therapy is 10 to 14 days. This recommendation is based on experience in adults.

One study suggest that 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 acute sinusitis (353). There are a large number of studies showing that local corticosteroids are effective and safe in children with rhinitis (628-632).

Additional therapy consists of topical or oral decongestants. Most authors prefer topical a2 agonists (xylo- and oxymetazoline) in appropriate concentrations. Careful dosage is important when treating infants and young children, to prevent toxic manifestations.

Saline nose drops or nasal douches are popular with paediatricians (606, 608, 616). As long as the saline is isotonic and at body temperature, it can help in eliminating nasal secretions and it can decrease nasal oedema.

In children with chronic rhinosinusitis and proven gastro-oesophageal reflux (GER) after 24 hours of pH monitoring Phipps et al. (466) showed that most children showed improvement of sinus disease after GER treatment and Bothwell et al. (633) suggests that in 89% of the children (25 out of 28) surgery could be avoided. These studies indicate that GER could be evaluated and treated in children with chronic sinus disease before sinus surgical intervention.

9-7-2-2 Surgical treatment of rhinosinusitis

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 (634) showed that nasal obstruction, snoring and speech defects occur more frequently in children with adenoid hypertrophy while symptoms of rhino rhea, 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.

Wang et al. e.g. didn't find any significant correlation between the size of the adenoid and the presence of purulent secretions in the middle meatus on fiberoptic 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 ($p<0.001$) (635). 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. (636). 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 (637).

Antral lavage: with the introduction of antroscopy at the end of the 1970s antral lavage in children became popular. As a trocar of the endoscope has a 4 mm diameter, it was easy to leave a ventilation tube in position, making frequent irrigations of the maxillary sinus possible in children, without any need for repetitive anaesthesia. It was shown, however, that in children with chronic rhinosinusitis, irrigation of the maxillary sinus does not lead to a better cure after 3 weeks, compared with a control group (638) or is not statistically significantly more successful (607).

Inferior antrostomy: as it had been demonstrated that the results of antral lavage in children were not long lasting; the logical consequence in children who required continuous antral lavage was to resort to a permanent antrostomy or nasal antral window in the inferior meatus. Lund (639), however, demonstrated that -especially in children under the age of 16 years there is a higher rate of closure of these antral windows. She concluded that the inferior meatus in children is smaller than in adults, making it impossible to create an adequately sized antrostomy. As a consequence Lusk (607) was able to

show that in a six-month follow-up the success rate of the nasal antral window procedure dropped to 27%. All patients remained symptomatic, and 28% needed further functional endoscopic sinus surgery. So the only current indication for a naso-antral window in the inferior meatus is therefore mainly limited to PCD where one hopes to achieve a kind of gravitational drainage.

Sinus surgery: the Caldwell-Luc operation is contra-indicated in children as it can cause damage to the unerrupted teeth (608, 616). 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 (11):

a. absolute indications:
   1. complete nasal obstruction in cystic fibrosis due to massive polyposis or by 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 exacerbations that persist despite optimal medical management 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 sphenoidectomy may be necessary.

Most results are judged on symptomatic relief and not include endoscopic examination or CT scan. Lusk et al. (640) found a success rate of 88% in 24 children who had only one procedure. They saw a 24% improvement of the purulent rhino rhea (from 100% tot 64%), 33% improvement of fever, usually low grade (from 55% to 22%), and a 13% improvement of cough (from 48% to 35%).

A meta-analysis performed by Hebert et al. (641) focusing on the number of patients per study, length of follow-up, prospective versus retrospective, a separation or exclusion of patients with significant underlying systemic disease, showed in 8 published articles (832 patients) positive outcome rates going from 88 to 92%. The average combined follow-up was 3.7 years. Thus they concluded that FESS is a safe and effective treatment for chronic rhinosinusitis that is refractory to medical treatment.

Similar results were published in a more recent study by Jiang et al. (642) and Fakhri et al. (643) showing a postoperative improvement in 84% of the FESS (n=121). For this indication Bothwell et al. (644) found no statistical 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 didn't, using qualitative antropomorphic analysis of 12 standard facial measurements after a 13.2 years follow-up.

As already mentioned before in a cystic fibrosis population of 48 children, 12% showed on endosocpy a medialisation of the lateral nasal wall and 45% nasal polyps coming out of the middle meatus (620). Initially polyps were removed as they appeared. When nasal obstruction occurred polypectomy was the rule. Regrowth, however, was sometimes observed within 3 weeks and many patients had multiple polypectomies ranging from 1 to 12 procedures per child. Crockett et al. (645) was the first to stress the importance of a long-term follow-up (average 5 years) and showed that when intranasal ethmoidectomy and Caldwell-Luc procedures were combined with polypectomy, fewer recurrences and longer symptom-free intervals resulted. Unfortunately Caldwell-Luc procedures can only be performed in older children and adults. With the introduction of FESS, however, a new approach was possible to achieve radical surgery. Duplechain (646) reported for the first time the results of this kind of surgery in cystic fibrosis children which was soon followed by many more (522, 619, 647, 648).

10. Socio-economic cost of chronic rhinosinusitis and nasal polyps

10-1 Direct Costs

Chronic rhinosinusitis, which 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 acute rhinosinusitis from the chronic form of this disease.

In 2002, Murphy et al. (649) examined a single health maintenance organization to evaluate the cost of chronic rhinosinusitis. 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 filled 43% more prescriptions, yet had fewer hospital stays than the general HMO adult population. In total, the cost of treating patients with CRS was $2,609 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. Chronic rhinosinusitis 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 (56) the overall cost would increase to $6.39 billion annually.

Addressing the cost of pharmacologic management of chronic rhinosinusitis, Gliklich and Metson's (650)1998 study reported an annual expenditure of $1220. This figure is the sum of OTC medications ($198), nasal sprays ($250), and antibiotics ($772).

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 (651). The direct cost of the CRS of these severe patients was €1,861,- per 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 €2,000,- depending on the severity of the disease.

10-2 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(56).

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 (375,000), 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 (427) used patient-completed surveys to determine the direct and indirect costs of chronic rhinosinusitis. 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 totaled $1,539 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 $1,500 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 (53). 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.

11. Outcomes measurements in research

For transparent and equal outcome results, the collection of some specific details is recommended by the Task Force on "Rhinosinusitis".

For acute rhinosinusitis recommended information collection includes:

a. symptoms;
b. endoscopic signs;
c. fluid level or total opacification on a plain x-ray;
d. medication used;
e. dropouts.

For CRS and NP, the following minimum data set describing outcome measures of research should include:

a. Symptoms as above (VAS) for Chronic Rhinosinusitis (CRS); and for Nasal polyps (NP);
b. QOL – general health (SF36) for CRS and NP;
c. Endoscopy – polyps 0-4 (pictures & description) based on the worst detected side for CRS and NP
   0 = no polyps
   1 = cobblestoned mucosa
   2 = pendunculated polyps only visible endoscopically
   3 = pendunculated polyps not protruding under the middle turbinate (equivalent to the back of the inferior turbinate when the middle turbinate is (partially) resected or absent
   4 = pendunculated polyps below the middle turbinate (see 3);
d. CT scan description – following the system of Lund/Mackay for CRS and NP;
e. Smell (validated) for NP;
f. medication used for CRS and NP;
g dropouts for CRS and NP;
h. information about asthma and other lower airway disease for CRS and NP.

Additional information for all types of rhinusinusitis is required on:

a. medication pre/post therapeutic intervention;
b. smoking history;
c. allergy (history and test);
d. history of aspirin intolerance.

Additional tests may be done eg. cells, mediators, mucociliary clearance, microbiology, haematology.

12. Evidence based schemes for diagnostic and treatment

12-1 Introduction

The following schemes for diagnosis and treatment are the result of a critical evaluation of the available evidence.
The tables give the level of evidence and grade of recommendation for the available therapy. Under relevance it is indicated whether the group of authors think this treatment to be of relevance in the indicated disease.

12-2 Level of evidence and grade of recommendation

Table 12-1. Therapy in acute/intermittent rhinosinusitis.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
antibiotic (36).	Ia (49 studies)	A	yes: after 5 days, or in severe cases
topical steroid	1b (1 study not yet published)	B	yes
addition of topical steroid to antibiotic (350-353)	Ib	A	yes
oral steroid (377, 378)	no evidence (1 study +, one -)	D	no
addition of oral antihistamine in allergic patients (425)	2b	B	no
nasal saline douche (446, 447)	no evidence	D	no
decongestion (417-419)	no evidence	D	yes as symtomatic relief
mucolytics (422, 423)	no evidence	D	no
bacterial lysates (439, 440)	2b	B	no
phytotherapy (478, 479)	2b	B	no

Table 12-2. Therapy in chronic rhinosinusitis *.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
oral antibiotic therapy short term < 2 weeks (387-391)	III	C	no
oral antibiotic therapy long term ~ 12 weeks (20, 296, 392, 394, 395, 403)	III	C	yes
antibiotics – topical (412, 358, 408, 410, 411)	III	D	no
steroid – topical (355-359)	Ib	A	yes
steroid – oral	IV	D	no
nasal saline douche (448-451)	III no data on single use	C	yes, for symptomatic relief
decongestant oral / topical	no data on single use	D	no
mucolytics (424)	III	C	no
antimycotics - systemic	no data	D	no
antimycotics – topical (433, 435, 436)	Ib (-)	D	no
oral antihistamine added in allergic patients	no data	D	no
allergen avoidance in allergic patients	IV	D	yes
proton pump inhibitors (464, 466, 467)	III	C	no
bacterial Lysates (441)	2b	C	no
immunotherapy	no data	D	no
phytotherapy	no data	D	no

* Some of these studies also included patients with nasal polyposis in addition to CRS.
* Acute exacerbations of CRS should be treated like acute rhinosinusitis

Table 12-3. Postoperative treatment in chronic rhinosinusitis *.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
oral antibiotics short term <2 weeks (390, 405-407)	IV	D	immediately post-operative, if pus was seen during operation
oral antibiotics			
long term ~ 12 weeks (20, 392, 394, 395)	III	C	yes
topical steroids (374)	1b (negative)	D	yes: immediately post-operative no: long term therapy
oral steroids	no data available	D	yes: immediately post-operative no: long term therapy
nasal douche	no data available	D	yes: immediately post-operative no: long term therapy

* Some of these studies also included patients with nasal polyposis in addition to CRS.

Table 12-4. Therapy in nasal polyposis.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
oral antibiotics short term <2 weeks	no data available	D	no
oral antibiotic long term ~12 weeks (296, 403)	III	C	yes
topical antibiotics	no data available		no
topical steroids (360, 367, 368)	I b (>10)	A	yes
oral steroids (267, 379-381)	III	C	yes
nasal douche	III no data in single use	D	yes for symptomatic relief
decongestant topical / oral	no data in single use	D	no
mucolytics	No data	D	no
antimycotics – systemic	No data	D	no
antimycotics – topical (437, 438)	III (2)	D	no
oral antihistamine in allergic patients (428)	Ib (1)	B	no
capsaicin (454-456)	II	B	
proton pump inhibitors (463)	II	C	no
immunotherapy	no data	D	no
phytotherapy	no data	D	no

Table 12-5. Postoperative care in nasal polyposis *.

Therapy	*Level*	*Grade of recommendation*	*Relevance*
oral antibiotic short term <2 weeks	no data available	D	immediately postoperative, if pus was seen during operation
oral antibiotic long term ~ 12 weeks (296)	III	C	yes
topical antibiotics	no data available	D	no
topical steroid after polypectomy (369-373)	Ib	A	yes
topical steroid after FESS (374)	Ib (negative)	D	yes
oral steroid (652)	III	C	short time in high dose long time low dose
nasal douche	no data available	D	yes, for immediante use no for long time use
decongestant - topical /oral	no data available	D	no

12-3 Evidence based diagnosis and management scheme for GP's

12-3-1 Scheme for GP for adults with acute/intermittent rhinosinusitis

Diagnosis

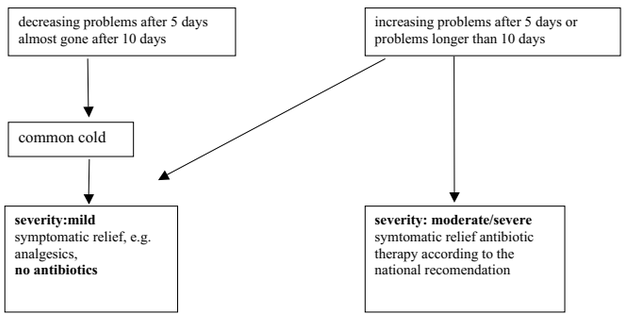
Symptoms

- facial pain or headache (for adults) especially unilaterally,
- plus one or more of the following:
- nasal obstruction;
- smell disturbance.

Treatment

- mild: start with symptomatic relief, analgesics;
- moderate / severe: additional topical steroids.

Treatment scheme for GP for adults with acute/intermittent rhinosinusitis



Failure of treatment for moderate/severe disease:

- persistence of symptoms after 5 days of therapy;
- or increasing symptoms for 2 days during therapy.

Signs of potential complications requiring immediate referral:

- eye swollen/red eyelids;
- displaced globe;
- double vision;
- ophthalmoplegia
- unable to test vision
- reduced vision acuity;
- severe unilateral or bilateral frontal headache;
- frontal swelling;
- signs of meningitis or focal neurologic signs.

12-3-2 Scheme for GP for CRS /NP in adults

Diagnosis

Symptoms present longer than 12 weeks

- nasal obstruction;
- plus one or more of following symptoms:
- discoloured discharge
- frontal pain;
- smell disturbance.

Additional diagnostic information

- questionnaire for allergy should be added and, if positive, allergy testing should be performed.

Not recommended: plain x-ray.

CT-Scan is also **not** recommended **unless** additional problems such as:

- very severe disease;
- immuncompromised patient;
- signs of complications;
- operation recommended.

Severity of symptoms

- (following the VAS score for the total severity) mild/moderate/severe.

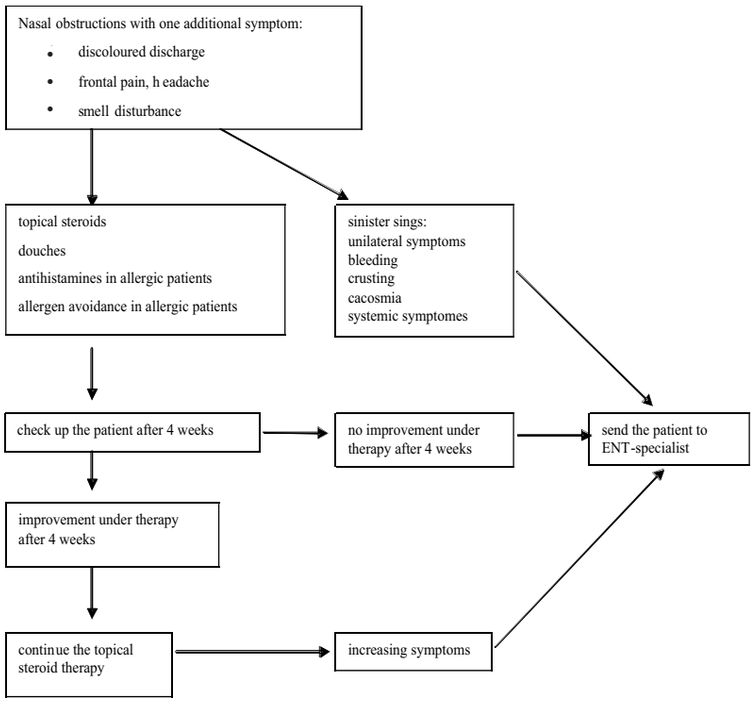
Signs of potential complications requiring immediate referral:

- swelling of eye or lids/eye redness;
- displaced globe;
- double vision;
- reduced vision;
- severe unilateral frontal headache;
- frontal swelling;
- signs of meningitis or focal neurologic signs.

Therapy

- topical steroids;
- nasal douches;
- antihistamines in allergic patients;
- allergen avoidance in allergic patients.

Scheme for GP: therapy for CRS/NP in adults



12-4 Evidence based diagnosis and management scheme for Non-ENT specialist for adults with CRS/NP

Diagnosis

Symptoms present longer than 12 weeks

- nasal obstruction;
- plus one or more additional symptom:
- discoloured discharge;
- frontal pain, headache;
- smell disturbance.

Additional diagnostic information

- anterior rhinoscopy, inspection with otoscope or ideally nasal endoscopy (if available);
- review primary care physician's diagnosis and treatment;
- questionnaire for allergy should be added and, if positive, allergy testing should be performed, if it is not done yet.

Not recommended: plain x-ray.

CT-Scan is also **not** recommended **unless** additional problems such as:

- very severe disease;
- immuncompromised patients;
- signs for complications.

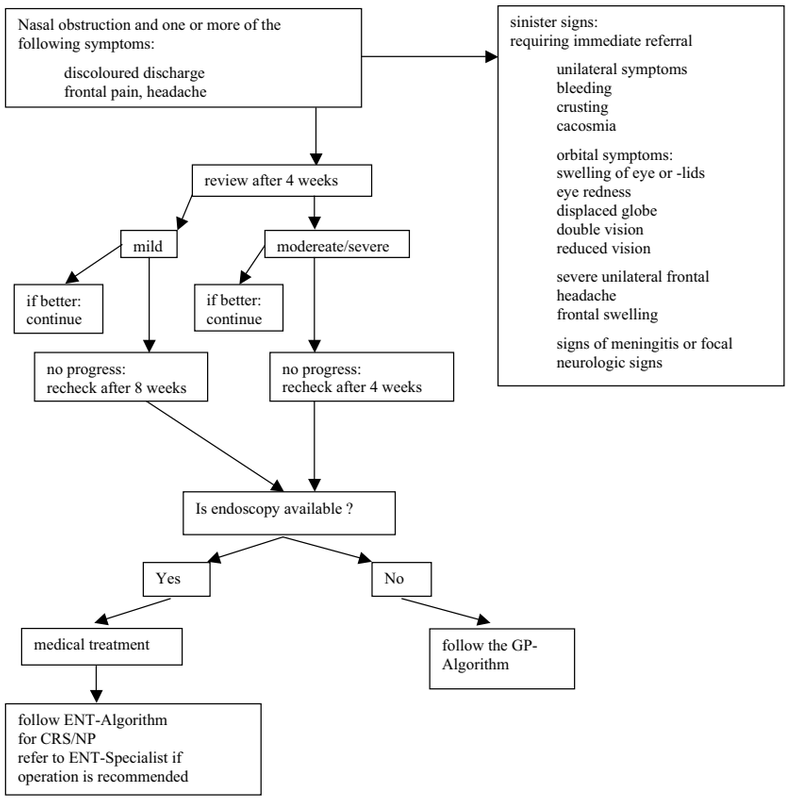
Severity of symptoms

- (following the VAS score for the total severity) mild /moderate /severe.

Treatment

- topical steroids;
- nasal douches;
- antihistamines and allergen avoidance in allergic patients.

Treatment scheme for Non-ENT specialists: therapy for CRS/NP in adults



12-5 Evidence based diagnosis and management scheme for ENT specialists

12-5-1 Scheme for ENT-Specialist for adults with acute rhinosinusitis

Diagnosis

Symptoms

- facial pain (for adults) especially unilaterally; plus one or more of the following symptoms:
- nasal obstruction;
- smell disturbance;
- nasal discharge.

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,
- immuncompromised patients;
- signs for complications.

Severity of symptoms

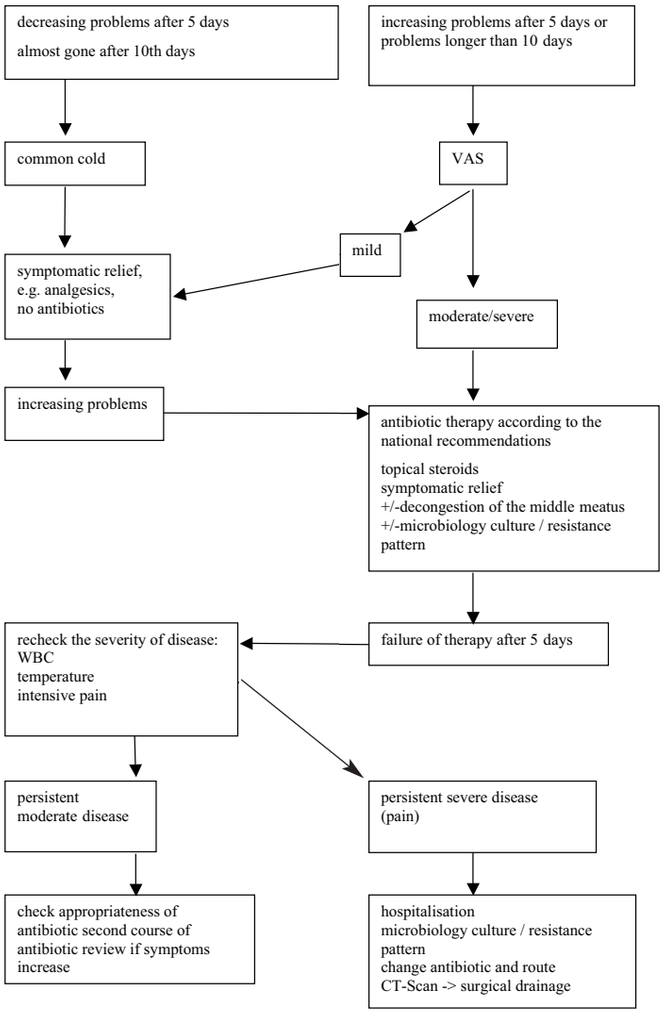
- mild /moderate /severe.

Treatment

Initial treatment depending on the severity of the disease:

VAS: mild -> follow initial treatment for common cold;
moderate -> follow initial treatment for common cold with short follow up;
severe -> follow initial treatment as listed below.

Treatment scheme for ENT specialists: therapy for acute rhinosinusitis in adults



Signs of potential complications requiring immediate intervention:

- eye swollen / red eye or lids;
- displaced globe;
- double vision;
- ophthalmoplegia
- unable to test vision
- reduced vision;
- severe unilateral frontal headache;
- frontal swelling;
- signs of meningitis or focal neurologic signs.

12-5-2 Scheme for ENT-Specialists for adults with CRS

Diagnosis

Symptoms present longer than 12 weeks

- nasal obstruction;
- plus one or more of the following symptoms:
- discoloured discharge;
- frontal pain, headache;
- smell disturbance.

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.

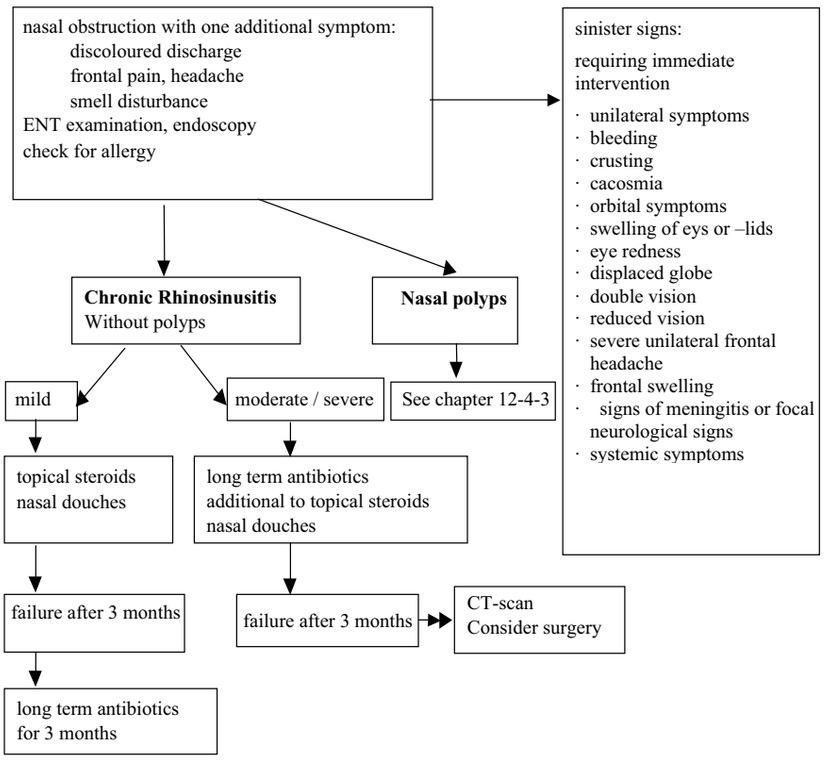
Severity

- (following the VAS score for the total severity) mild / moderate / severe.

Treatment

- topical steroids;
- douches;
- antihistamines in allergic patients;
- allergen avoidance in allergic patients.

Treatment scheme for ENT-Specialists: therapy for CRS in adults



12-5-3 Scheme for ENT-Specialists for adults with NP

Diagnosis

Symptoms for longer than 12 weeks

- nasal obstruction;
  plus one or more of the following symptoms:
- discolourered discharge;
- frontal pain;
- smell disturbance.

Signs

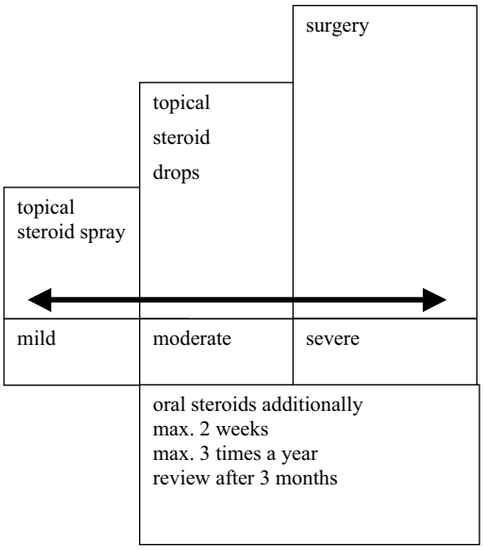
- ENT examination, endoscopy;
- review primary care physician's diagnosis and treatment;
- questionnaire for allergy and if positive, allergy testing if not already done.

Severity of the symptoms

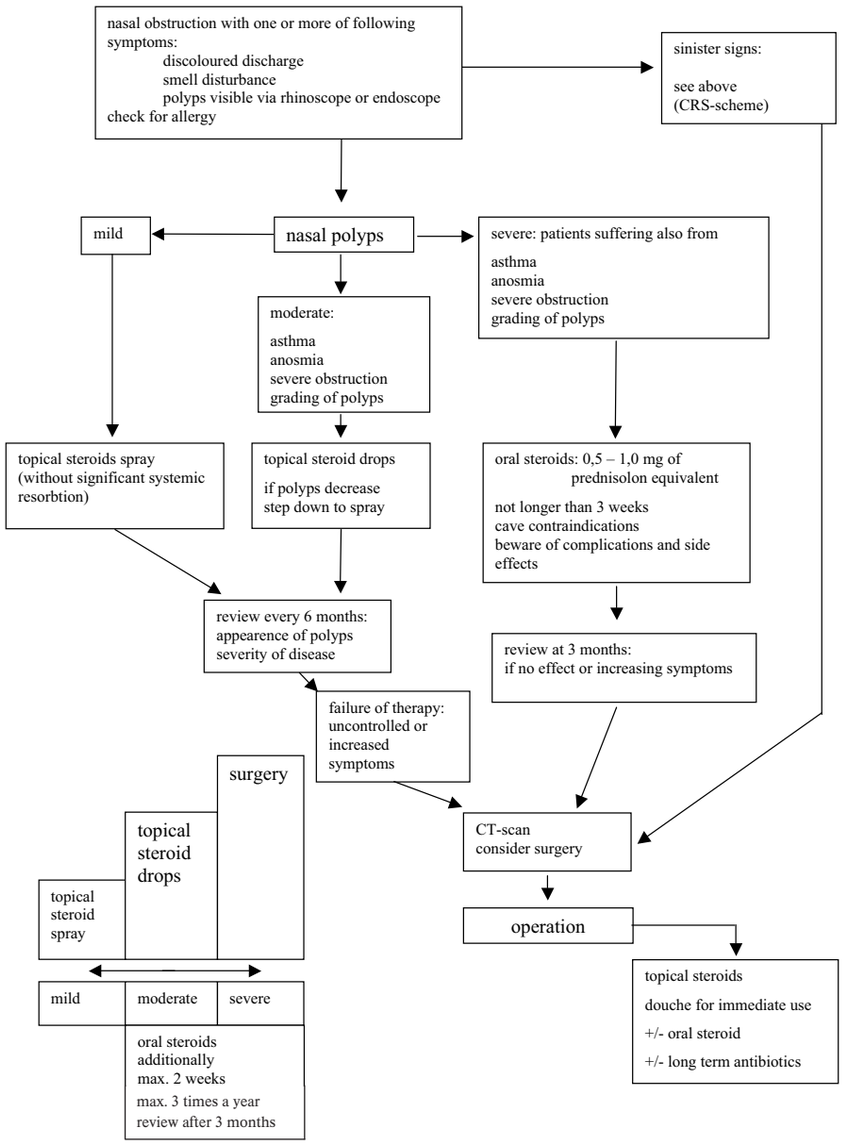
- (following the VAS score for the total severity) mild/moderate/severe.

Treatment

- topical steroids (drops preferred);
- nasal douches;
- antihistamines in allergic patients;
- allergen avoidance in allergic patients.



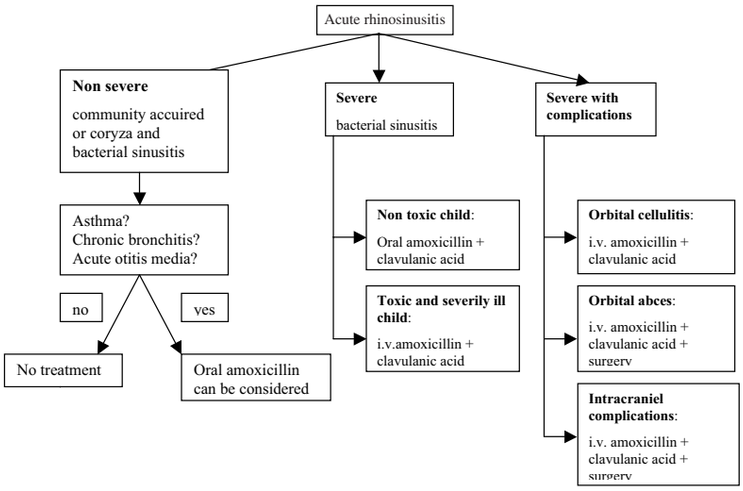
Treatment scheme for ENT-Specialists therapy for nasal polyps in adults



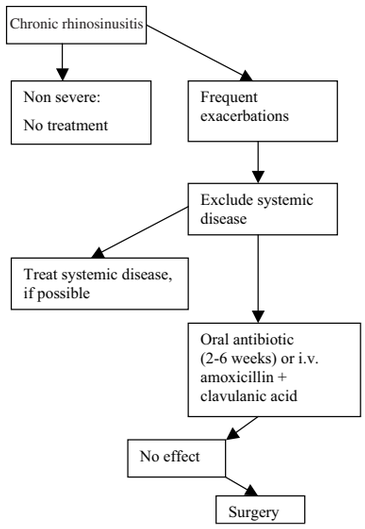
12-6 Evidence based schemes for therapy in children

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.

Treatment scheme for Non-ENT Specialists: therapy for acute rhinosinusitis in children



Treatment scheme for Non-ENT Specialists: therapy for chronic rhinosinusitis in children



13. Research needs and priorities

Although much work has been done on chronic rhinosinusitis and nasal polyps there are many questions still unanswered.

The following suggestions should highlight some areas of interest for further research.

A prospective population study of a group of age- and sex-matched controlled atopic and non-atopic individuals to consider the incidence of all upper respiratory tract symptoms including acute and chronic rhinosinusitis over a 5 year period.

A long-term follow-up of a cohort of patients with nasal polyposis to study the natural history of the condition (a randomised medical and surgical arm could be done at the same time).

A study of the benefit of long term macrolide therapy in nasal polyposis and chronic rhinosinusitis (this needs repeating to verify the work already published on this).

Studies should be performed to compare nasal steroids as a single modality of treatment with antibiotics in patients with intermittent or persistent rhinosinusitis.

There is an urgent need for randomized placebo controlled trials to study the effect of antibiotics in chronic rhinosinusitis and exacerbations of chronic rhinosinusitis.

To provide good evidence for the use of local antibiotic treatment in acute exacerbations of chronic rhinosinusitis, further studies with better characterized patients are needed.

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15. Appendix

15-1 Survey of published olfactory tests

Author(s)	Year	Test name	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Cain	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.	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 Kurtz et al.	1987 2001	Odourant Confusion Matrix (OCM)	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.
Hendriks	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	1989 1992	YN-OIT		USA			Age, disease	Based on 20 UPSIT odours. Yes or no matching of a descriptor to a proposed odour.

Author(s)	Year	Test name	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Takagi	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	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.	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.
Kobal et al.	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.	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. Kobal et al.	1997 2000	Sniffin'Sticks		Germany, Switzer-land, Austria, Australia, Italy, USA	>1000	r=0.72	Age, olfactory disorder. 1/Threshold for n-butanol.	Odours in pens. 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

Author(s)	Year	Test name	Test-Time	Country	Sample size	Test retest	Subject differences	Method
Davidson and Murphy	1997	AST	5 min	USA	100		Olfactory disorder.	Detection of isopropanol. Measure as distance from nose.
Ahlskog et al.	1998	CA-UPSIT		Gua-manian Cha-morro	57		Neuro-degnerative disease. Educational level.	Identification of 20 encapsulated odours. 4AFC. Scratch-and-sniff technique.
Nordin	1998 2001	SOIT	15 min	Sweden Finland	>600	r=0.79	Age, gender, olfactory disorder.	Identification of 16 odours in bottles. 4AFC
Kremer et al.	1998		4 min	Germany Netherlands	>200		Hyposmia.	6 aromas sprayed into open mouth. Odours in nasal sprays.
McCaffrey et al.	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.	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.	2001	"Four-minute 4 min odour identification test"	4 min	Germany	1,012	r=0.78	Age, olfactory disorder.	Identification of 12 odours. 4AFC. Odours in pens.

15-2 Source of some olfactory tests

University of Pennsylvania Smell Identification Test (UPSIT)
Sensonics Inc
125 White Horse Pike
Haddon Heights
New Jersey 08035
USA

Tel: (International +1 609 547 7702
Fax No: (Intrnational +1 609 547 5665
www.smelltest.com.usa

Sniffin' Sticks
Burghart medizintechnik
Tinsdaler weg 175
Tel: +49 (0) 103 800 76-0
Fax: +49 (0) 4 103 800 76-29
Email: sniffin@burghart.net
www.burghart.net

Zurich Test
UniversitätsSpital Zürich
Klinik für Ohren-, Nasen-, Hals- und Gesichtschirugie
Frauenklinikstr 24
CH-8091 Zürich
Tel: +44 1 255 5860
Fax: +41 1 255 4556
Email: simmen@jorl.usz.ch