Current conservative treatments in chronic rhinosinusitis with or without nasal polyps: review and analysis of reports on controlled clinical trials

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Abstract

Background: Chronic rhinosinusitis (CRS) implies inflammation of the nose and paranasal sinuses which may or may not have an infectious component and includes nasal polyposis (NP). Chronic rhinosinusitis signs and symptoms persist over 12 weeks and may involve acute exacerbations. It affects around 15% of the population and causes significant reduction in quality of life. The diagnosis is based largely on symptoms with confirmation by nasendoscopy. Computerized tomography scans may confirm mucosal abnormalities in the paranasal sinuses. Various underlying conditions such as infections, anatomical variations, immunodeficiency, aspirin intolerance, mucociliary impairment and allergic fungal rhinosinusitis may present as CRS. Recently found Staphylococcus aureus enterotoxin superantigens, their intracellular long-term persistence, and the production of biofilms may contribute to the pathogenesis of CRS with and without NP. No one single causative factor has been identified that fully accounts for all CRS variations. Various inflammatory processes are involved in the pathogenesis of CRS. Characteristic histomorphological [...]
CURRENT CONSERVATIVE TREATMENTS
IN CHRONIC RHINOSINUSITIS
WITH OR WITHOUT NASAL POLYPS:

review and analysis of reports
on controlled clinical trials

Travail présenté par le
Docteur Roland Giger
pour obtenir le titre de Privat Docent

Genève

2010
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<td>CRS: chronic rhinosinusitis</td>
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<td>NaNIPER: non-allergic, non-infectious perennial rhinitis</td>
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<td>NP: nasal polyps or polyposis</td>
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<td>INS: intranasal steroids</td>
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I would like to thank:

Prof. J.-S. Lacroix. I have to say that working with somebody with all this knowledge and extraordinary experience in the field of rhinology research was a step forward for my academic career. I am so grateful to him for all his enthusiasm during the years of research we did together. I am deeply indebted to him for his immeasurable professional and emotional support, personal guidance, fruitful discussions, continuous encouragement, and friendship.

Prof. J.P. Guyot for his encouragement during my years of apprenticeship in the Department of ENT and Head & Neck Surgery in the University Hospital of Geneva and for his still excellent advices in editoring articles.

Dr. B. N. Landis for his indefatigable working capacity, his huge enthusiasm and encouragement in this field of research, and for being my best friend. His motivation and excellent collaboration helped me many times to finish my research projects mentioned in this work.

Prof. Th. Landis for his critical remarks, advices and personal support on the way on my academic career.

Dr. N. W. Stow, my Australian friend, whose editorial experience and professional expertise clarified several passages and greatly improved the English text.

My girlfriend Christiane Valterio for her comprehension and patience during the endless hours that this work required.
I wish to extend my warmest thanks to all those collaborators who helped me directly and indirectly with my different scientific works cited and discussed in here:

Prof. P. Dulguerov, Prof. D.R. Morel, Prof. E. Grouzmann, Prof. P. Pasche, Prof. P. Montandon, Prof. W. Lehmann, Dr. J.P. Friedrich, Dr. A. Ricchetti, Dr. K. Nicoucar, Dr. A.M. Kurt, Dr. C. Zeng, Dr. D.D. Malis, Dr. D. Leuba, Dr. D. Quinodoz, Dr. A. Hänggeli, M. Hugentobler, G. Rizzo, P. Lorenzo, Y. Bosshard.
ABBREVIATIONS USED

AERD: Aspirin exacerbated respiratory disease
AFRS: Allergic fungal rhinosinusitis
AR: Allergic rhinitis
AS: Aspirin
CGRP: Calcitonin gene-related peptide
CO: Carbon monoxide
COX: Cyclooxygenase
CRS: Chronic rhinosinusitis
CS: Corticosteroids
CT: Computed tomography
CVID: Common variable immunodeficiency
DPPIV: Dipeptidylpeptidase IV
ECP: Eosinophil cationic protein
ESS: Endoscopic sinus surgery
GS: Glucocorticosteroid
GER/GERD: Gastroesophageal reflux/Gastroesophageal reflux disease
GM-CSF: Granulocyte-macrophage colony-stimulating factor
GR: Glucocorticosteroid receptor
HIV: Human immunodeficiency virus
HLA-DR: Human leukocyte antigen-D receptor
IB: Ipratropium bromide
ICAM-1: Intracellular adhesion molecule-1
Ig: Immunoglobulin
IL: Interleukin
INS: Intranasal steroids
LAS: Lysine-acetylsalicylate
LT: Leukotriene
LTRAs: Leukotriene receptor antagonists
LTSIs: Leukotriene synthesis inhibitors
MBP: Major basic protein
MCT: Mucociliary transport
MMP: Matrix metalloproteinase
MRI: Magnetic resonance imaging
NANIPER: Non-allergic, non-infectious perennial rhinitis
NF-κB: Nuclear factor-κB
NKA: Neurokinin A
NKCC: Sodium chloride co-transporter channel
NO: Nitric oxide
NOS: Nitric oxide synthase
NP/NPs: Nasal polyp or polyposis/nasal polyps
NSAIDs: Non-steroidal anti-inflammatory drugs
OMC: Ostiomeatal complex
PG: Prostaglandin
QoL: Quality of life
RANTES: Regulated upon activation normal T-cells expressed and secreted
SAEs: Staphylococcus aureus enterotoxins
SP: Substance P
TNF-α: Tumour necrosis factor-α
VCAM-1: Vascular adhesion molecule-1
SUMMARY

Background: Chronic rhinosinusitis (CRS) implies inflammation of the nose and paranasal sinuses which may or may not have an infectious component and includes nasal polyposis (NP). Chronic rhinosinusitis signs and symptoms persist over 12 weeks and may involve acute exacerbations. It affects around 15% of the population and causes significant reduction in quality of life. The diagnosis is based largely on symptoms with confirmation by nasendoscopy. Computerized tomography scans may confirm mucosal abnormalities in the paranasal sinuses. Various underlying conditions such as infections, anatomical variations, immunodeficiency, aspirin intolerance, mucociliary impairment and allergic fungal rhinosinusitis may present as CRS. Recently found Staphylococcus aureus enterotoxin superantigens, their intracellular long-term persistence, and the production of biofilms may contribute to the pathogenesis of CRS with and without NP. No one single causative factor has been identified that fully accounts for all CRS variations. Various inflammatory processes are involved in the pathogenesis of CRS. Characteristic histomorphological features of CRS without NP are a neutrophilic inflammation and goblet cell hyperplasia, thickening of the basement membrane, limited subepithelial oedema, and prominent fibrosis. Nasal polyps show a predominant eosinophilic inflammation and the destruction of connective tissue. Recent research has focused on cytokines, chemokines, growth factors and metalloproteinases to explain these features, but the aetiology of NP remains largely unclear.

Because of the complex pathogenesis of CRS and the multiplicity of factors playing a role in the aetiology, the current management of CRS remains a challenge. The evidence of a few good quality trials in this area suggests that treatment is primarily medical, involving corticosteroids, antibiotics, saline douching, antileukotrienes, and antihistamines and that surgery should be considered for complications, anatomical variations causing local obstruction, allergic fungal disease or for patients who remain very symptomatic despite maximal medical treatment.

Objectives: To review the literature on conservative, non-surgical treatments for CRS with or without NP, to evaluate their effectiveness and safety, and to analyse their strength of evidence, recommendations and clinical usefulness in the
management of these chronic disease. A succinct update of CRS definition and classification and its pathophysiology is provided.

Search strategy: The search included MEDLINE (1950 – 2009) and THE COCHRANE LIBRARY. The date of the last search was June 2009.

Selection criteria: Randomised controlled and prospective, clinically-relevant trials in which any non-surgical treatment was evaluated in patients with CRS with or without NP, and after surgery to prevent disease recurrence. The diagnosis of seasonal or perennial allergic rhinitis was an exclusion criterion.

Data collection and analysis: Trials were graded for methodological quality and assigned an evidence level based on the modified Sekelle’s evidence scale. Each category of articles was then assigned an overall grade for the strength of evidence [I (strongest) to IV (weakest)], a grade for recommendation [A (strongest: consistent level I studies) to D (weakest: level IV evidence or extrapolated recommendation from any level)], and the clinical relevance.

Results: Two hundred and eight trials were identified that satisfied the inclusion criteria. The retained studies could be grouped as followed: antibiotics (22 trials), antifungal agents (10 trials), antihistamines (11 trials), antileukotrienes (11 trials), aspirin desensitisation and maintenance (16 trials), bacterial lysate preparations (3 trials), capsaicin (12 trials), corticosteroids (36 trials), cromolyn sodium (5 trials), decongestants (4 trials), furosemide (4 trials), gastroesophageal reflux therapy (4 trials), immunotherapy (4 trials), ipratropium bromide (21 trials), nasal irrigation (20 trials), mucoactive agents (7 trials), phytopreparations (7 trials), homeopathies (2 trials), acupuncture (6 trials) and immunomodulatory agents (3 trials).

There is strong evidence [Ib-evidence] that long-term intranasal steroids are beneficial in the treatment of the signs and symptoms of CRS with and without NPs and for the prevention of disease recurrence after surgery. Short-course systemic corticosteroids should only be used as rescue medication in cases of severe NP [Ib-evidence]. Strong evidence also exists in favour of systemic long-term macrolides in CRS without [Ib-evidence] and with NPs [III-evidence], long-term saline irrigation’s in CRS without NPs [Ib-evidence] and less, of topical capsaicin [Ib/III-evidence] in CRS
with and without NPs. Strong evidence has been demonstrated for the long-term systemic antileukotriene [Ib-evidence], and aspirin desensitisation/maintenance [Ib-evidence] treatments in the management of the aspirin exacerbated respiratory disease (asthma, NPs and aspirin or non-steroidal anti-inflammatory drug intolerance); a specific subgroup of CRS with NPs. Antileukotrienes seem evidently prevent NP recurrence after surgery [Ib-evidence]. Short-course systemic treatment of decongestants and mucoactive agents show evidently an improvement of CRS symptoms [Ib-evidence]. Good evidence also exists in favour of long-term courses of topical and systemic antihistamines [Ib-evidence] and intranasal ipratropium bromide [Ib-evidence] in the treatment of rhinorrhea and less, nasal congestion in non-allergic, non-infectious perennial rhinitis (vasomotor rhinitis); a subclass of CRS without NPs. Bacterial lysate preparations show good evidence in the treatment of symptoms and particularly reduce the frequency of acute infectious episodes in CRS without NPs [Ib-evidence]. Studies dealing with olfaction and QoL outcome are rare, demonstrating significant improvement in the treatment groups of AS desensitisation and topical/systemic steroids, and in the treatment groups of long-term macrolides, antileukotrienes, systemic steroids, topical ipratropium bromide and saline irrigations, respectively. An excellent safety profile could be demonstrated for these drug categories.

Intranasal antibiotics [Ib(-)-evidence], topical and systemic antifungal agents [Ib(-)-evidence], intranasal cromolyn sodium [Ib(-)-evidence], topical decongestants [Ib(-)-evidence], topical mucoactive agents [Ib(-)-evidence], homeopathy [Ib(-)-evidence], and acupuncture [Ib(-)-evidence] cannot be recommended due to evidenced negative outcome in randomized trials or bad safety profile. Due to the lack of randomized, placebo controlled studies or unclear outcome, the other treatment categories like topical furosemide, gastroesophageal reflux therapy, immunotherapy, topical and systemic phytopreparations and immunomodulators cannot be retained as first-choice therapy options or are not clinically relevant in the management of CRS with or without NPs.

**Conclusions:** The often imprecise definitions of CRS, complex pathogenesis and uncertainties regarding the precise role played by the involved processes and a lack of well designed trials render an analysis of the retained data difficult. The initial management of CRS is medically with endoscopic sinus surgery reserved for
refractory CRS. First-choice drug treatment in CRS with or without NPs comprises long-term topical steroids and short-term systemic corticosteroids for severe disease. Intranasal steroids also prevent NP recurrences after surgery. Long-term systemic, low-dose macrolides with their anti-inflammatory, immunomodulatory, anti-mucous and less, antimicrobial actions seem to be a good alternative treatment modality in steroid non-responders. Long-term saline irrigation’s may be used singly or as adjunct therapy. Antileukotriene and aspirin desensitisation / maintenance therapy can be considered for aspirin exacerbated respiratory disease. Promising anti-inflammatory agents include topical capsaicin and systemic bacterial lysate preparations. Topical and systemic antihistamines and intranasal ipratropium bromide demonstrated improvement in the treatment of rhinorrhea and less, nasal congestion in vasomotor rhinitis; a specific subclass of non-allergic, non-infectious perennial rhinitis. New approaches are currently evolving, specifically targeting eosinophilic recruitment (chemokine receptor 3, eotaxins) and inflammation (interleukin-4, -5, -13), immunoglobulin E, or tissue remodelling by reducing the activity of metalloproteinases.

Better uniform definitions and classifications of CRS with and without NPs and further well conducted trials in clearly defined patient groups are needed to progress in the management of this chronic and complex inflammatory disease.
1. INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common healthcare complaints in the US and Europe. Because of its prevalence of 14 – 16%, almost 2 per cent of outpatient visits to primary care offices, speciality practices or emergency departments are due to complaints of rhinosinusitis. This disease incurred costs of approximately US$ 7.19 billion in 1996 in the USA.

Rhinitis and sinusitis usually coexist and are concurrent in most individuals; thus the correct terminology is now rhinosinusitis. Chronic rhinosinusitis is defined by mucosal inflammation of the nose and paranasal sinuses of at least 12 weeks’ duration. Various inflammatory processes are involved, and recent innovations in endoscopy, imaging and biology have considerably improved the knowledge of its pathogenesis. Its treatment still remains to be well defined. Medical treatment and surgical treatment aimed at correcting anatomical abnormalities are often inadequate in therapy when used alone.

This work is intended to be a state-of-the-art review to provide an evidence-based report of the available medical and other non-surgical treatment modalities in CRS.

1.1. DEFINITIONS AND CLINICAL PRESENTATION OF CHRONIC RHINOSINUSITIS WITH AND WITHOUT NASAL POLYPS

1.1.1. Background

Chronic rhinosinusitis is defined as an inflammation of the nose and the paranasal sinus mucosa which persists for 12 weeks or longer. Figure 1 shows the clinical definition of CRS. Chronic rhinosinusitis is characterised by at least two of the following symptoms: nasal obstruction, nasal discharge (anterior or posterior nasal drip), facial pain or pressure, and a reduction in or loss of smell; along with endoscopic signs like oedema, polyps, swelling, crusting and erythema of the middle meatus mucosa, mucopurulent discharge, or nasal polyps (NP) and/or the presence of mucosal changes within the ostiomeatal complex (OMC) and the paranasal sinuses documented by computed tomography (CT) techniques. For epidemiology
studies and in general practice, the above mentioned definition is used without endoscopy or CT-scan confirmation of the disease. For research purposes, CRS is defined as above mentioned. The differentiation between CRS with and without NP must be based on endoscopical examination. A CT-scan is advised, but not obligatory. Chronic rhinosinusitis represents a clinically heterogeneous group of diseases which are sometimes divided into three subtypes: CRS without NP (60 – 65%), CRS with NP (20 – 33%), and allergic fungal rhinosinusitis (AFRS) (8 – 12%). Allergic fungal rhinosinusitis may actually belong to the NP subtype.

**Figure 1. Clinical definition of chronic rhinosinusitis / nasal polyposis following the European Position Paper on Rhinosinusitis and Nasal Polyps 2007**

<table>
<thead>
<tr>
<th>Definition</th>
<th>Symptoms</th>
<th>Other</th>
</tr>
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<tbody>
<tr>
<td>Inflammation of the nose and the paranasal sinuses characterised by two or more symptoms,</td>
<td>one of which should be either</td>
<td>Endoscopic signs of:</td>
</tr>
<tr>
<td></td>
<td>- nasal blockage / obstruction / congestion or</td>
<td>- polyps and/or</td>
</tr>
<tr>
<td></td>
<td>- nasal discharge (anterior/posterior nasal drip)</td>
<td>- mucopurulent discharge from middle meatus and/or</td>
</tr>
<tr>
<td></td>
<td>( ± facial pain / pressure</td>
<td>- oedema/mucosal obstruction primarily in middle meatus</td>
</tr>
<tr>
<td></td>
<td>± reduction or loss of smell)</td>
<td></td>
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<td></td>
<td>and either</td>
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<tr>
<td>Severity:</td>
<td></td>
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<tr>
<td>- use of visual analogue scale (VAS) score (0 – 10 cm):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MILD = VAS 0 – 3</td>
<td></td>
<td></td>
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<tr>
<td>MODERATE = VAS &gt;3 – 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEVERE = VAS &gt;7 - 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &gt; 12 weeks symptoms without complete resolution</td>
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</tr>
</tbody>
</table>

**1.1.2. Chronic rhinosinusitis without nasal polyps**

Chronic rhinosinusitis without NP is the most frequent form of CRS. It is a heterogeneous entity that may be due to a number of different contributing factors. Allergic rhinitis (AR), anatomical abnormalities, and chronic bacterial infections may contribute to the aetiology of this CRS entity. Non-allergic, non-infectious perennial rhinitis (NANIPER) of unknown aetiology is an entity of CRS without NP. Several studies of AR have shown CT-changes of the paranasal sinus mucosa in up to 77% of the examined individuals. The NANIPER would probably show similar
mucosal changes, but unfortunately, no trial with a CT-evaluation of the paranasal sinuses of this CRS entity exists strengthening this hypothesis. The terminology rhinitis should be replaced by rhinosinusitis.

1.1.3. Chronic rhinosinusitis with nasal polyps

Chronic rhinosinusitis with NP is characterised by the presence of grape-like structures in the upper nasal cavity or paranasal sinuses (Figure 2). This entity may be associated with aspirin (AS) or non-steroidal anti-inflammatory drug (NSAID) sensitivity and asthma and is called aspirin-exacerbated respiratory disease (AERD) or AS triad disease (Widal syndrome, Samter’s triad), first reported by Widal in 1922. In patients with asthma, a prevalence of 7 – 15% has been noted whereas in NSAID sensitivity, NP were found in 36 – 60% of patients. Immundeficiency, mucociliary dysfunction, and chronic bacterial infections may contribute to the aetiology of this CRS subtype. The pathophysiology of this disease remains elusive, but may be related to a disturbance in the biosynthesis of eicosanoids. Nasal polyps contain high numbers of eosinophils, high levels of interleukin (IL)-5 and -13, and high levels of histamine. Neutrophils are dominant inflammatory cells in Chinese NP and NP caused by a chronic bacterial infection.

Figure 2. Endoscopic view (0° Storz telescope, left nasal cavity), nasal polyp in the middle meatus.
1.1.4. Allergic fungal rhinosinusitis

Allergic fungal rhinosinusitis was mentioned as the third subtype of CRS. It had been characterised by the presence of « allergic mucin », a thick inspissated mucus with eosinophils and fungal hyphae. This entity was first described in 1980s as a distinct pathologic subgroup by Miller et al. (1981) and Katzenstein et al. (1983). The five criteria needed to fulfil the definition of AFRS are: type I hypersensitivity by history, skin tests or serology; NPs; characteristic CT-scan findings; eosinophilic mucus; and positive fungal stain of mucin or on the surface of tissue removed during surgery with no fungal tissue invasion. Attempts have been made to differentiate AFRS from the other subtypes of CRS. Eosinophilic mucus chronic rhinosinusitis (EMCRS) comprises CRS patients with eosinophilic mucin. Eosinophilic mucus chronic rhinosinusitis is further subclassified into non-allergic fungal eosinophilic rhinosinusitis; non-allergic, non-fungal eosinophilic rhinosinusitis; and AFRS. Non-allergic fungal eosinophilic rhinosinusitis is characterized by positive fungal culture and eosinophilic mucin but not noted fungal allergy. Non-allergic, non-fungal eosinophilic rhinosinusitis comprises patients with EMCRS who are negative for fungal allergy and fungal culture. However, current evidence and authors question this classification regarding the fact that positive fungal culture and fungal allergy in these patients are unlikely to be primary pathogenic events, and propose that all these subtypes may represent different phases of the same disease process - the CRS with NP.

Another, and probably less confusing way to classify CRS will be the underlying inflammatory process. There is a clear distinction between eosinophilic and non-eosinophilic inflammation (Figure 3). Eosinophilic CRS includes the following entities: Aspirin exacerbating respiratory disease (AERD), AFRS, and AFRS without fungus, Staphylococcus aureus-induced superantigen sinusitis with NP and eosinophilic CRS with undetermined cause. The non-eosinophilic CRS encompasses inflammatory processes due to mechanical obstruction and chronic bacterial infection without mucin or tissue eosinophilia. The primary distinction between the two categories is that once the mechanical obstruction in non-eosinophilic CRS is relieved and all sequestered bacteria are removed, the patients have a higher rate of symptomatic improvement. As many eosinophilic CRS patients do not develop their
disease until the fourth to sixth decade of their life, an external trigger that activates or upregulates a silent, genetically-coded ability to mount the eosinophilic inflammatory response could be postulated. This may explain the late onset and the difficulty in controlling this subtype of disease\textsuperscript{19}.  

**Figure 3.**  
CRS – Classification overview.  
AERD: Aspirin exacerbated respiratory disease; AFRS: Allergic fungal rhinosinusitis; NARES: Non-allergic rhinitis with eosinophilia syndrome; NANIPER: Non-allergic, non-infectious perennial rhinitis

### 1.2. EPIDEMIOLOGY AND PREDISPOSING FACTORS

Chronic rhinosinusitis is one of the most common health problems, with significant direct medical costs and severe impact on lower airway diseases and general health
outcomes. An accurate estimate of the prevalence of CRS remains speculative, because of the heterogeneity of this disorder. It was estimated that CRS, defined as having "sinus symptoms" for more than 12 weeks, affects 14 – 16% of the population in the USA. A screening of the population in Belgium without sinonasal complaints demonstrated that approximately 6% of the individuals suffered from chronic nasal discharge and 40% had signs of mucosal swelling of more than 3 mm on magnetic resonance imaging (MRI). Epidemiologic data show an increased prevalence of allergy (25 – 30%), asthma (43%), and organ transplantation respectively immunosuppressive treatment (37%) and AIDS (54 – 68%), in patients with CRS, but their etiology role remains unclear.

1.3. HISTOPATHOLOGY

1.3.1. Histopathology of chronic rhinosinusitis without nasal polyps

In CRS without NP, the mucosal lining is characterised by goblet cell hyperplasia, thickening of the basement membrane, limited subepithelial oedema, and prominent fibrosis. The inflammatory cells are predominantly neutrophils. Eosinophils and mast cells can also be found, but their number is much lower than in NPs. A range of inflammatory mediators such as interleukins (ILs) and cytokines have been shown to be increased (IL-1, IL-3, IL-5, IL-6, IL-8, tumour necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), intracellular adhesion molecule-1 (ICAM-1), myeloperoxidase, eosinophil cationic protein (ECP), and major basic protein (MBP)). These cytokines and inflammatory mediator profiles are similar to that one found in acute rhinosinusitis. Dipeptidylpeptidase IV (DPPIV) has been described as playing a role in the in vivo modulation of the inflammatory response of CRS. Dipeptidylpeptidase IV enzymatic activity in nasal tissue biopsies taken from patients suffering from CRS was correlated inversely with the density of inflammatory cells in the nasal mucosa, and the DPPIV activity rose when CRS was treated. A pig animal model showed that intranasal administration of recombinant DPPIV decreased the vasodilatation induced by exogenous substance P (SP), a proinflammatory peptide released by sensory nerves. In contrast, an inhibitor of
DPPIV enhanced the vasodilator effect of low doses of SP. Dipeptidylpeptidase IV is involved to modulate non-adrenergic and non-cholinergic substrates in CRS. These findings suggest that the underlying pathological process might involve yet unknown inflammatory pathways, after both acute and chronic infection, or an immune response to chronic infection.

1.3.2. Histopathology of chronic rhinosinusitis with nasal polyps

In CRS with NP, changes referred to as polypoid degeneration of the nasal and paranasal sinus mucosa develop. Epithelial cells become flattened and colloidal fluid, composed of albumin and other plasma proteins, accumulates in the subepithelial layer. A large accumulation of fluid in the subepithelial layer leads to epithelial damage and development of « empty » pseudocysts which can bulge the epithelium producing polyps. These developed pseudocysts are connected by a network of fibronectin fibres surrounded by fibroblasts and eosinophils. Among the inflammatory cells, activated eosinophils are a prominent and characteristic feature in about 80% of the NP in Caucasian patients. Large accumulations of both mature eosinophils and their progenitor cells and mast cells are found in NPs. At the same time, other structures of the subepithelial layer such as vessels, glands and neural structures tend to be reduced. The NPs show an increased concentration of the following cytokines and chemokines: IL-1β, IL-3, IL-5, IL-8, IL-13, TNF-α, GM-CSF, RANTES (regulated upon activation normal T-cells expressed and secreted), eotaxins as well as increased expression of adhesion molecules ICAM-1, vascular cell adhesion molecule-1 (VCAM-1) and selectins. The cytokine profile in NPs corresponds to that one of a mixed T_helper1 / T_helper2. Nasal polyposis also manifests a high concentration of the following mediators: histamine, tryptase and ECP. Neutrophils are also present and their number is increased compared to controls. Chinese NP and a small percent of NP in Caucasian patients do not demonstrate an eosinophilic inflammation, but a highly increased presence of neutrophils. The histological type of NP is therefore quiet different according to the races. Neutrophilic cellular population in NP develops primarily in the course of CRS accompanying disturbances of the paranasal sinus ventilation as well as congenital and acquired disturbances of the local and systemic immune response. Classic examples of this NP category include...
cystic fibrosis and primary ciliary dyskinesia. In all these disorders, a chronic bacterial infection may play an essential role in the development of NP and may determine the domination of neutrophils in the NPs. The cytokine profile of the neutrophil-dominated NP is similar to the profile encountered in acute rhinosinusitis\textsuperscript{8,34}.

1.4. PATHOGENESIS

1.4.1. Background

The pathogenesis of CRS with and without NP is multifactorial and comprises a vicious circle of pathophysiological, anatomical and constitutive factors. Three factors, however, appear crucial for the normal physiologic working of the paranasal sinuses: patency of the OMC, normal mucociliary transport and normal amount and quality of mucus secretion. Disturbance of one or more of these three factors can predispose to endonasal and paranasal sinus infections followed by a chronic inflammation\textsuperscript{6}. Various causative agents and circumstances may play a role in the pathogenesis of CRS:

a. Environmental factors:
   - Infection (bacteria, fungi and viruses).
   - Medications, irritants, toxic substances, pollutants.

b. Systemic host factors:
   - Specific hyperreactivity (allergic inflammation, asthma, AS and NSAIDs hypersensitivity).
   - Non-specific hyperreactivity.
   - Hormonal rhinitis.
   - Gastroesophageal reflux disease (GERD).
   - Immunodeficiency.
   - Congenital mucociliary dysfunction.
   - Dysfunction of the autonomic nervous system.

c. Local host factors:
   - Anatomical conditions.
- Acquired mucociliary dysfunction.
- Tumours.

d. Injuries:
- Trauma.
- Surgery.

1.4.2. Anatomic obstruction of the ostiomeatal complex

Impairment of sinus drainage caused by obstruction of the OMC results in a pathologic accumulation of mucus in the sinuses that may serve as a medium for bacterial overgrowth. The sinus cavity develops an acidic pH and an anaerobic environment evolves. Inflammation of the sinonasal mucosa provokes a further swelling of nasal and OMC mucosa, damaging of the mucosa layer, impairing of the mucociliary function and poor or absent sinus ventilation with negative intrasinus pressure. Thus, the obstruction triggers the development of a vicious cycle of ciliary dysfunction, retention of secretions with abnormal rheological properties, obstruction of lymph drainage followed by oedema, as well as mucosal hyperplasia, which may lead to chronic inflammation

The most common anatomical variations with partial or complete OMC obstruction include severe nasal septal deviations (Figure 4), hypertrophied and pneumatised middle turbinate (concha bullosa) and atypical migration of ethmoid air cells during sinus development (agger nasi cells, Haller's cells). These anatomical variations do not correlate by themselves with the prevalence of CRS, but they compromise self cleaning mechanisms and OMC and may be the main determinant of resultant sinus disease.
The mucociliary transport (MCT) system represents the self cleaning mechanism and the first barrier of the airway against various biological and physical pathogens. The MCT time is significantly decreased in CRS. This may be caused by an augmentation in the viscoelasticity of the mucus following the acute release of inflammatory mediators, together with a reduction in the periciliary stratum, which slows down the metachronous movement of the MCT. Additionally, the increase in the mucous viscosity may be due to an augmentation of the number of goblet cells and their secretory activity, which correlates well with a decreased ciliary beating frequency. However, there is evidence that in most patients with CRS, ciliary impairment is the consequence rather than the origin. This secondary ciliary dysfunction found in CRS patients is probably reversible after healing.

There exist three hereditary disorders, primary ciliary dyskinesia (immotile cilia syndrome or Kartagener's syndrome), cystic fibrosis and Young syndrome, which have been demonstrated to be always associated with ciliary impairment and MCT dysfunction.
failure, leading to infertility and chronic upper and lower airway inflammations and infections.

### 1.4.4. Bacteria

Although it is often hypothesised that CRS evolves from acute rhinosinusitis, the role of bacteria is unclear. There are 3 categories of bacteria involved in CRS. The first category includes bacteria also cultured in acute rhinosinusitis (Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis) playing a role in the exacerbations of CRS. The second category includes bacteria particular to CRS, including Staphylococcus aureus and Pseudomonas aeruginosa. These microorganisms have frequently been cultured in CRS patients who did not show any improvement after both antibiotic and surgical therapy. The third category includes Staphylococcus epidermidis, other coagulase-negative staphylococci, Corynebacterium species, and anaerobes. Some authors suggested that as chronicity develops, the aerobic and facultative species are replaced by anaerobes. This change may result from the development of anaerobic conditions with decreased oxygen tension and increased acidity within the paranasal sinuses under inflammatory conditions. The contribution of the different microorganisms to the disease remains unclear.

Another intriguing finding is the presence of immunoglobulin (Ig) E antibodies against Staphylococcus aureus enterotoxins (SAEs) in 60 – 80% of patients with NPs and asthma. The SAEs are superantigens that interact with T cells directly, bypassing the antigen-presenting cells, thereby increasing the frequency of immune response. Patients with NPs who have IgE to SAEs in the nasal mucosa also have more severe eosinophilic inflammation and are more likely to have asthma and AS sensitivity.
Figure 5: Pathophysiology of *Staphylococcus aureus* superantigen-driven multiclonal IgE formation in NP. Enterotoxins from *Staphylococcus aureus* act as superantigens on T lymphocytes and induce multiclonal B-cell activation. Release of cytokines (IL-5) from T_{helper} 2 cells will result in an eosinophilic activation with release of eosinophil cationic protein (ECP). ECP causes tissue damage, oedema formation and albumin accumulation. B-cell activation will result in the production of multiclonal IgE by plasma cells (modified from 44).

Several authors have recently demonstrated the role of bacterial biofilms in CRS. Bacteria in natural environment exist in two states, free-floating planktonic bacteria and matrix-enclosed bacteria, which are attached to a surface, the so called biofilm 45. It is defined as organised community of bacteria adherent to a surface and embedded in an extracellular polymeric substance made of exopolysaccharides, nucleic acids and proteins 46,47. The biofilm forming capacity of Staphylococcus aureus and Pseudomonas aeruginosa is associated with their poor medical treatment results and plays an important role in the chronicity of the disease 48.
Another mechanism that may contribute to long-term persistence of Staphylococcus aureus in the nose and paranasal sinuses is its intracellular reservoir, which was demonstrated recently and seemed to be associated with a high rate of recurrences in CRS with persistence of monoclonal Staphylococcus aureus infection and poor antibiotic treatment outcomes.49,50

1.4.5. Fungi

Fungal presence may be relatively benign, colonising normal paranasal sinuses or forming saprophytic crusts. Fungi may also cause potentially life threatening invasive disease. In the past, allergic fungal rhinosinusitis, a subgroup of CRS, typically demonstrated high eosinophilic mucin production containing non invasive fungal hyphae.8 This fungal presence was thought to play an alternate role in the development of CRS, whereby it has been hypothesized that patients became sensitised by colonising fungi through a non-IgE mediated mechanism. This pathway would lead to a local eosinophilic chemotaxis, inflammation, and tissue damage causing NPs.8 The base of this assertion was the finding of positive fungal culture by using a new culture technique in 96% of patients with CRS. However, the same percentage was found in normal controls and there was no increase in type I mediated hypersensitivity in patients as compared with controls. In conclusion, positive fungal cultures do not prove that these pathogens directly create or perpetuate CRS with and without NP. The presence of fungi in the nose should be considered as a “normal” component of the nasal flora and may be a “normal” component of the paranasal sinus flora.

1.4.6. Allergy

The contribution of atopy in CRS has long been controversial. It has been postulated that swelling of the nasal mucosa in AR at the site of OMC and sinus ostia may compromise ventilation, leading to mucus retention and infection.6 Allergic rhinitis is a common condition, affecting 10 – 20% of the population in the USA 51-54. The prevalence of subjects with clinically confirmable AR in Europe ranged from 17% in Italy to 29% in Belgium, with an overall value of 23% 55. Among CRS patients undergoing sinus surgery, the prevalence of positive skin prick tests ranges from 50
– 94%, of which the majority (60%) has multiple sensitivities. However, other epidemiological studies showed no increase in the incidence of infectious rhinosinusitis in the pollen season in allergic individuals. In a small prospective study, no difference in prevalence of purulent rhinosinusitis was found between patient with and without allergic rhinosinusitis.

Although an allergic origin of NPs had been presumed since the early 1930s, this suggestion was challenged in the 1970s, when a retrospective study demonstrated that more NP were found in non-allergic patients than in patients with atopy, and consecutive trials showed that sensitivities were less frequent in patients with NPs compared with controls of the general population. However, increased NP tissue IgE concentrations have been found irrespective of skin test results, suggesting a local IgE production. Specific IgE to SAEs A and B were found in 50% of eosinophilic NPs, suggesting a possible role of superantigens in the development of CRS with NPs.

### 1.4.7. Aspirin sensitivity

The presence of AS-intolerance in CRS is associated with a particularly persistent and treatment-resistant form of NP, coexisting generally with severe asthma and referred to as « AS triad » (Widal syndrome, Samter’s triad). The prevalence of NPs in AS-sensitive asthma may be as high as 60 – 70%, as compared to less than 10% in the population of AS-tolerant asthmatics. In AS-sensitive patients, acute rhinitis symptoms may be induced by a challenge with oral or intranasal AS but also with other cross-reacting NSAIDs. This mechanism has been attributed to inhibition of the enzyme cyclooxygenase (COX)-1 by AS or NSAIDs, with subsequent inflammatory cell activation and release of both lipid and non-lipid mediators. The AS-induced nasal reaction is accompanied by an increase in both glandular (lactoferrin, lysozyme) and plasma (albumin) proteins in nasal secretions indicating a mixed response, involving both glandular and vascular sources. Concomitant release of both mast cell (tryptase, histamine) and eosinophil (ECP) specific mediators into nasal washes clearly indicates activation of both types of cells. Increased concentration of cysteinyl leukotrienes (LT) in nasal secretion was also observed in the acute phase of AS-induced reactions. In parallel with inflammatory mediator release, an influx of leukocytes into nasal mucosa occurred with significant
enrichment in eosinophils. The high-degree of marked tissue eosinophilia is a prominent feature of CRS in AS-hypersensitive patients. The increased number of eosinophils has been linked to a distinctive profile of cytokine expression with up-regulation (e.g. IL-5, GMC-SF, RANTES, eotaxin). Interleukin-5 seems to be a major factor responsible for an increased survival and increased inflammation of eosinophils in NPs of AS-sensitive patients. A relation of SAEs presence and increased expression of IL-5 and ECP in polyp tissue from AS-sensitive patients seems to be particularly evident and the presence of SAEs may have direct effects on eosinophil proliferation and survival or may act as a superantigen to trigger a T-cell mediated inflammatory reaction. Mast cells are also found to be abundant in the NP tissue from AS-sensitive patients. Their density was significantly higher in asthmatic patients with AS-hypersensitivity as compared to AS-tolerant patients.

Arachidonic acid metabolism abnormalities have been considered a distinctive feature of NPs in the AS-sensitive patients. A significantly lower production of prostaglandin (PG) E2 and a decreased expression of COX-2 in NPs of these patients were reported. Since PGE2 has significant anti-inflammatory activity, including inhibitory effect on eosinophil chemotaxis and activation, it has been speculated that an intrinsic defect in local generation of PGE2 could contribute to development of more severe eosinophilic inflammation in AS-sensitive patients. On the other hand, NPs of AS-sensitive asthmatics demonstrated an increased production of cysteinyl LTs when compared to AS-tolerant patients in vitro, but these observations could not be reproduced in vivo. However, the production of cysteinyl LTs correlated with tissue ECP concentration in both, the AS-sensitive and AS-tolerant NPs, suggesting that these mediators may be linked to tissue eosinophilia rather than to AS-hypersensitivity. An increased level of LT-1 receptors was found in nasal mucosa of AS-sensitive patients suggesting a local hyperresponsiveness to LTs in these individuals. More recently, other arachidonic acid metabolites have been associated with NPs in AS-sensitive patients.

1.4.8. « Osteitis » - the role of underlying bone

Clinical and experimental evidence suggest that the underlying bone of the paranasal sinuses may be involved in the development of CRS. Recent work has demonstrated that patients undergoing surgery for CRS were found to have marked acceleration in
bone physiology with histological changes including new bone formation, fibrosis and presence of inflammatory cells. These findings are consistent with some degree of chronic osteomyelitis. The term « osteitis » was used to describe these findings because of the lack of a marrow space in the thin bone walls of the sinus cavities. These findings may, at least in part, explain why CRS is relatively resistant to therapy. However, to date bacteria have not been found and cultured in the sinus bone in either humans nor animal models of CRS.

1.4.9. Gastroesophageal reflux

Recent attention has been directed toward the role of gastroesophageal or oesophago-nasopharyngeal reflux in the pathogenesis of CRS. Three hypothetical mechanisms have been proposed. The first mechanism proposed direct reflux of gastric secretions into the nasopharynx causing mucosal oedema and inflammation, leading to secondary obstruction of OMC and sinus ostia. The second mechanism suggests a sensory mediated neurogenic inflammation, stating that chronic stimulation of the afferent nerve fibres may result in sinonasal oedema and secondary obstruction of the OMC and sinus ostia. The final theory hypothesises about the role of Helicobacter pylori in CRS. Helicobacter pylori DNA has been detected in 11 – 33% of sinus samples from patients with CRS, but not from controls. However, this does not prove a causal relationship.

1.4.10. Genetic factors

Although chronic sinus disease has been observed in family members, no genetic abnormality has been identified with a link to CRS. However, the role of genetic factors in CRS has been implicated in patients with cystic fibrosis and primary ciliary dyskinesia (Kartagener's syndrome). Genetic aetiology is also suspected in the pathogenesis of NPs, on the basis of familial accumulation. According to several studies, human leukocyte antigen-D receptors (HLA-DR) are expressed on the surfaces of inflammatory cells in the paranasal sinus mucosa and NPs. Nasal polyps represent therefore a multifactorial polygenic disease. In NPs, as compared to normal control tissue, a number of genes with altered expression were
identified. Overexpression of IL-17 may play an important role in the development of NPs.

1.4.11. Immunocompromised state

Among deficiencies in the immune system, both local and systemic immunocompromised states, can contribute to CRS. The similarities of CRS symptoms in patients with and without immunodeficiency make it difficult to distinguish between these two categories. Many immunocompromised patients, particularly those with a humoral defect, have benefited of repeated antibiotic treatments and sinus surgery before their immunodeficiency was recognised. However, a recurrent or persistent CRS despite appropriate treatment may raise suspicion of an immunodeficiency. The often encountered immunodeficiencies associated with increased incidence of sinonasal infections include selective IgA deficiency (SIAD), common variable immunodeficiency (CVID), IgG subclass deficiencies, selective antibody deficiency, X-linked agammaglobulinemia (XLA) and human immunodeficiency virus (HIV) infection. The detection of immune defects is important; prophylactic antibiotic therapy can reduce or resolve symptoms in patients with mild immunodeficiency and intravenous immunoglobulin can be added in more persistent and refractory disease with some beneficial outcome. The testing of the immunologic state of patients with persistent or refractory CRS should be integrated in their evaluation.

1.5. DIAGNOSES

1.5.1. Assessment of chronic rhinosinusitis symptoms

1.5.1.1. Nasal obstruction

Nasal obstruction is a common major symptom associated with CRS. The sense of nasal obstruction is usually caused by mucosal oedema and congestion. The oedema of the nasal mucosa is secondary to acute and chronic inflammation and extravasation of plasma proteins from veins. Nasal congestion is caused by dilation
of nasal blood vessels, mainly erectile venous sinusoids that expand to restrict or sometimes completely obstruct the nasal cavities. Inflammatory causes of nasal obstruction can be distinguished from anatomical origin by applying an intranasal decongestant (sympathicomimetic vasoconstrictor). The remaining restriction after administration of topical decongestant is due to fixed anatomical abnormalities such as deviated nasal septum, tissue adherences, NPs or tumours.

The subjective sensation of nasal congestion, however, is thought to be due to a combination of factors, including nasal resistance to airflow and more subjective changes including psychological factors, Eustachian tube function and cold air thermoreceptors in the nasal mucosa. The objective nasal resistance to airflow, as measured by rhinomanometry, and subjective nasal sensation of airflow are two separate, indirectly related modalities. A study evaluating subjective and objective nasal resistance could demonstrate a statistically significant correlation between the objectively measured nasal resistance by active anterior rhinomanometry and the evaluation of subjective nasal congestion before and 2 years after endoscopic sinus surgery (ESS) (p < 0.001). However, inhalation of aromatics, especially L-menthol, has been shown to improve the subjective nasal airflow without decreasing the objectively measured resistance. This effect is due to the stimulation of the cold air receptors of the trigeminal nerve in the nasal vestibule and nasal cavity mucosa. The same effect could be observed by sucking L-menthol lozenges stimulating the palatal mucosa branches of the trigeminal nerve.

Nasal congestion is caused by swelling of specialised erectile vessels named capacitance veins in the nasal mucosa. These are also called venous sinusoids, venous sinuses, or venous erectile tissue. They are innervated by a dense network of sympathetic nerves, supplied via the cervical sympathetic nerves, which are distributed to the nose via branches of the maxillary and ophthalmic divisions of the trigeminal nerve. The sympathetic nerves release neurotransmitters as noradrenalin and neuropeptide Y that cause an intense vasoconstriction. Stimulation of the nasal parasympathetic nerves induces vasodilatation, glandular secretion and increased blood flow. Nasal congestion by nasal infection and inflammation can be explained by the effects of local vasodilator mediators on nasal blood vessels and nerves. These mediators include histamine, PGs, cytokines and ILs, which are synthesised locally in the nasal mucosa. Histamine and PGE₂ inhibit the release of noradrenalin from the sympathetic nerve endings which may be a further
cause of nasal congestion. On the other hand, most of the inflammatory mediators stimulate the sensory nerve endings, which are very abundant in the nasal mucosa, leading to an additional neurogenic inflammation.

There are several methods of objective assessment of nasal obstruction:

a. Rhinohygrometry
A cold mirror or shiny metal surface is placed beneath the nose and the size of the resultant condensation spot is measured. This was first described by Zwaardemaker in 1894. This test is a qualitative clinical test of the nasal airway. However, in studies of nasal physiology, the semi-quantitative nature of the technique renders it useless for scientific studies.

b. Nasal peak flow
Measurement of either inspiratory or expiratory maximal air flow. These methods have the disadvantages of alar collapse on forced inspiration and expulsion of secretions on expiration. Both methods are effort dependent and assume normal function of the lower airways.

c. Rhinostereometry
A method for measurement of the distance between the medial and lateral wall of the nasal cavity. The distance is determined using an inbuilt scale in a microscope, and the head position has to be fixed to assure measurements at the same position during repeated measurements. This gives only limited information of isolated structures and not of the larger part of the nasal airway. Changes of 0.18 mm can be detected but this technique remains principally an experimental method.

d. Acoustic rhinometry
A method to estimate the nasal anatomy and cavity volume changes associated with congestion. In this method, sound is presented to the nose via a nosepiece and the reflected sound is recorded by means of a microphone. The amplitude and delay of the reflected sound is then calculated by computer analysis. The minimum cross-sectional area of the nose and hence the anatomy can then be estimated. However, this method does not offer any information about the dynamics of nasal airflow.
e. Rhinomanometry
It measures the pressure encountered by air passing through the nasal cavity\textsuperscript{127}. Active anterior rhinomanometry (the patient is actively breathing through one nasal cavity while the narino-choanal pressure difference is assessed in the contralateral nasal cavity) is the most commonly used method of rhinomanometry. However, it cannot be used in case of septal perforation or in subjects with total nasal obstruction. Active posterior rhinomanometry (the choanal pressure is measured via a tube placed in the back of the mouth while the airflow is measured for both nasal cavities simultaneously) is frequently hampered by gag and suction reflexes and is therefore limited to physiological studies or assessment of the nasal patency in the presence of septal perforations or if one nasal cavity is completely obstructed\textsuperscript{128}. Passive anterior rhinomanometry (the pressure is measured for each nasal cavity separately at a given airflow of 250 cm\textsuperscript{3}/sec) is fast but less accurate than both other types of rhinomanometry and is mainly used for nasal provocation tests.

f. Spirometry
This is a portable device which is easy to use and has shown a good correlation with rhinomanometry in investigating airflow. However, nasal spirometry does not give a measurement of nasal airflow resistance but provides a measure of nasal airflow partitioning\textsuperscript{120}.

Generally, the subjective sensation of nasal obstruction (visual analog scale) and rhinomanometric or nasal peak flow evaluations show a good intra-individual correlation in a number of studies considering normal controls, patients after ESS, patients with structural abnormalities, hyperreactivity or infective rhinitis\textsuperscript{107,109,129-132}, and correlate better than with measurements of nasal cavity width, such as acoustic rhinometry\textsuperscript{133,134}.

1.5.1.2. Olfactory dysfunction
Chronic rhinosinusitis is a common cause of olfactory dysfunction, like reduced smell capacity, hyposmia, or total loss of smell. However, the mechanism of olfactory dysfunction in CRS remains controversial. Traditionally, olfactory dysfunction in CRS has been attributed to nasal congestion and mucosal edema explaining a diminished
airflow to the olfactory cleft, making them conductive or transport disorders. More recently, it was speculated that also a direct effect of inflammatory processes on the olfactory epithelium, the surface of the olfactory receptors or the olfactory mucus bathing the receptors may be causative for olfactory troubles. The observation that in anosmic patients with NPs undergoing sinus surgery alone, 50% had a persistent postoperative olfactory deficit, which was successfully treated by oral corticosteroids, underlined the second hypothesis\textsuperscript{135,136}. Biopsy studies of olfactory epithelium obtained from patients undergoing sinus surgery demonstrated the involvement of the olfactory mucosa in CRS with and without NPs resulting in hyposmia and anosmia \textsuperscript{137}. Acute and chronic inflammation within the olfactory neuroepithelium could contribute to olfactory dysfunction by different mechanisms. Apoptotic pathological changes have been found in the olfactory cleft biopsies \textsuperscript{137}. Mediators released by lymphocytes and macrophages trigger hypersecretion in respiratory and Bowman's glands \textsuperscript{138}. Hypersecretion changes and disturbs the ion concentration of olfactory mucus, affecting the microenvironment of olfactory neurons and possibly the transduction processes \textsuperscript{139}. These released mediators may be toxic to neurons and when released by lymphocytes, macrophages and eosinophils, they most likely trigger caspase-3 activation in olfactory sensory neurons, contributing to their damage and destruction \textsuperscript{140}. In summary, it seems that smell disorders secondary to CRS involve direct effects on the olfactory epithelium (sensory disorders) in addition to any blocking changes (transport disorders) of the olfactory cleft in the nose \textsuperscript{141}. Alterations of mucus ion concentration, inflammatory changes as well as direct loss of olfactory neurons may explain partially the sensory component of olfactory impairment. The fact that both steroids and surgery are often required together to improve olfactory impairment supports the theory that smell dysfunction is most often a mixed pathology.

Modern methods evaluating the olfactory function fall into three general categories: psychophysical, electrophysiological and psychophysiological. Psychophysical tests are those in which the stimulus is presented and the individual is asked to report some element of perception (e.g., detection threshold, discrimination, identification). Electrophysiological methods are those in which a stimulus is presented and its influence on the olfaction is measured by electrical changes in the olfactory pathway in the central nervous system. Examples include the odour evoked potential, measured from electrodes placed on the scalp, and the
electro-olfactogram, measured from electrodes placed near or upon the olfactory neuroepithelium. Psychoph ysiological tests rely on stimulus-related changes in measures typically controlled by the autonomic nervous system. Included are tests that measure changes in heart rate, blood pressure, respiration rate and various indices of inhalation after odorant stimulation. Because electrophysiological testing techniques are rarely practised in most centers, psychophysical techniques have remained the most simple and applied olfactory tests for the common use. Several screening tests were developed and standardised. Well-known examples are the University of Pennsylvania smell identification test (UPSIT®) and the sniffing' sticks®, where the odorants are liberated by scratching microencapsulated odour labels mounted on paper or liberated through the tip of a odorant pen, respectively. A cruder screening test, the Zurich Smell Diskette test may also be used and has the advantages of pictorial representation of the items. Because each test has its own merits in terms of facility of application, costs and reproducibility, no globally accepted gold standard smell test exists.

Damm et al. (2004) showed that 72% of all olfactory troubles are due to sinonasal disease, the most common cause of olfactory disorders. Overall, studies suggest that the degree of olfactory loss is usually associated with the severity of sinonasal disease, with the greatest loss occurring in patients who have concurrent CRS and NP. The onset of olfactory loss in sinonasal diseases is often slow, what means that patients are often unaware of, and not disturbed by, the olfactory impairment, explaining the underestimation of smell dysfunction by these patients and it also facilitates the retro-olfactory routes of sensory stimulation because of the impaired orthonasal route. The medical and surgical treatment of inflammatory sinonasal diseases aim to alleviate the smell disorder in parallel with the other nasal functions, primarily nasal congestion, secretions and NP size. Alongside nasal obstruction, discharge and facial pain, smell impairment is a key symptom of CRS definition. Preoperative testing of the olfactory function demonstrated an impaired olfaction in up to 65 – 87% of patients with CRS, whereby up to 34% were anosmic.

Olfactory dysfunction can result in problems concerning safety, hygiene, loss of appetite, interpersonal relations, and disturbances in emotional and sexual behaviour. Despite the significant impact on QoL with deterioration in up to
80% of the patients caused by smell impairment, and the frequent nature of this condition, only few of the studies included in this work (26 of all 208 retained articles) have been conducted dealing with the outcome and improvement of olfactory dysfunction as a primary or secondary outcome in sinonasal disorders. Several studies provided evidence that olfactory function after sinus surgery in patients suffering from CRS with and without NP improved up to 80%. Unfortunately, this effect often seems to be only transient, and the real rate of improvement following surgery was generally lower than assumed. Clinical trials of medical conservative treatments of CRS including smell testing have mostly dealt with the effects of nasal and oral corticosteroids, and lesser studies have been performed on aspirin desensitisation, antileukotrienes, furosemide, and nasal irrigations. About 62% of these studies showed significant improvement of olfactory impairment. Heilmann et al. (2004) conducted a study confirming most current knowledge about the efficacy of corticosteroids for smell loss. The comparison of topical and systemic administered steroids in patients with olfactory loss due to sinonasal disease but also in idiopathic and post-infectious disorders showed a lesser benefit of intranasal steroids than systemic treatment. Table I provides an overview of the studies dealing with conservative medical treatments and the effects on smell dysfunction.

Table I. Summary table of olfactory evaluation and outcome in CRS with and without NP

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total articles number</th>
<th>Articles number showing statistically significant improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antileukotrienes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Aspirin Desensitisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- systemic</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- topical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- topical</td>
<td></td>
<td></td>
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<tr>
<td>11</td>
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</tr>
<tr>
<td>- systemic</td>
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<td></td>
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<tr>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td></td>
<td></td>
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<tr>
<td>- topical</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- topical (short- and long-term)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Irrigations</td>
<td></td>
<td></td>
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<tr>
<td>- saline (short-term)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td></td>
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<tr>
<td>- diverse non–saline</td>
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<td></td>
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<tr>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>26</td>
<td>16</td>
</tr>
</tbody>
</table>

CRS: chronic rhinosinusitis; NP: nasal polyposis

Although improvement in the management of smell disorders is often possible, it is frequently transient or incomplete. In addition to sinus surgery, systemic and topical


corticosteroids are helpful in alleviating olfactory disturbances in CRS. Systemic corticosteroids are usually more effective than intranasal steroids, but long-term courses of systemic steroids are not recommended due to the increased risk of the well-known side effects. Long-term intranasal corticosteroids with short-term courses of systemic steroids may be a helpful regimen. Nevertheless, smell dysfunction is one of the four key symptoms of CRS and its assessment should be incorporated in all future clinical studies.

1.5.1.3. Nasal discharge
Nasal discharge (anterior or posterior rhinorrhea) is often mucopurulent in CRS. Techniques for objective measurement are not as good as for nasal congestion. Counting the nose blowing or using a new handkerchief from a counted reservoir and possibly collecting the used ones in plastic bags for weighing have been used in trials about acute infectious rhinosinusitis and in autonomic, so called vasomotor rhinitis. Validating correlation studies between « objective » discharge measures and subjective scoring of nasal discharge or posterior rhinorrhea have not been done.

1.5.1.4. Facial pain and pressure
Facial or dental pain, especially unilateral, have been found to be predictive of acute maxillary sinusitis with liquid retention in patients with suspected infection, when validated by maxillary antral aspiration or paranasal sinus radiographs. However, facial pain in CRS is more diffuse and fluctuating which renders the clinical correlation with objective assessments unconvincing. There was found a poor correlation between facial pain localisation and CRS signs in CT-scan in patients with acute and chronic symptoms. However, rhinosinusitis disease specific quality of life (QoL) questionnaires include validated, facial pain-related parameters.

1.5.1.5. Overall rating of rhinosinusitis severity, chronic sinusitis survey, chronic rhinosinusitis type specific questionnaire and 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) or more accurately health-related QoL. Although CRS is not a life-threatening disease, it can significantly decrease patients QoL. Comorbidities such as asthma and atopy have an accumulative negative effect. The QoL questionnaires can provide either general or disease specific health
assessment. Quality of life is a very important outcome in the evaluation of CRS severity and its measurements reflect the effect that symptoms and disease have on the patient’s daily life. However, it is of great interest that the severity of nasal and paranasal symptoms or findings do not always correlate with QoL scales. Overall rating of rhinosinusitis severity can be obtained as such or by total symptom’s scores, which are summed scores of the individual symptom scores. Quality of life methods have been produced validated questionnaires which measure the impact of overall rhinosinusitis symptoms on everyday’s life. Quality of life is a general term integrating several aspects of life such as physical, psychological, social, economical, emotional, cognitional, and sexual dimensions. Several of these questionnaires are CRS-specific and include the evaluation of symptoms for CRS such as nasal blockage, loss of smell, rhinorrhea, headache, facial pain, and sneezing, clinical classification of sinus disease, and nasal and paranasal sinus symptoms after sinus surgery. They are usually more sensitive than general health status instruments. However, no validated disease-specific instruments were available to assess patient-oriented QoL in patients with NP. In addition, there were insufficient data to assess the effect of gender, duration of therapy, or comorbidity with asthma or aspirin sensitivity on QoL.

The measures of QoL have evolved as the emphasis on medical care has shifted from symptom scores and objective test results to an assessment of patient-centered effect of disease and response to treatment. The QoL instruments have proved to be very useful providing comparative data with other medical conditions, which could be regarded as more serious. The assessment of patient-reported outcomes is important in clinical trials, and in some cases symptomatic outcome should be the primary treatment outcome. Therefore, a need exists for validated instruments to assess patient-based outcomes.

Several general and specific questionnaires for patients with CRS are available, but most of these questionnaires are not yet validated:

a. **Chronic sinusitis survey (CSS)**
   The CSS is a 6 item duration based monitor of sinusitis specific outcome which has both systemic and medication-based sections, but it is rather better at determining the relative impact of CRS compared to other diseases than as a measure tool of improvement after therapeutic intervention.
b. **Medical Outcomes Study Short Form 36 (SF-36)**
General measurements enable the comparison of patients suffering from CRS with other patient groups including physical functioning, role-functioning physical, body pain, general health, vitality, social functioning, role-functioning emotional and mental health \(^ {210-212}\).

c. **Rhinosinusitis Outcome Measure (RSOM-31)**
A well validated questionnaire allowing measurements of symptom severity and importance to the patient \(^ {213,214}\).

d. **Sinonasal Outcome Test-20 (SNOT-20)**
A validated and easy to use modified RSOM instrument, but it does not contain questions on nasal congestion and loss of smell and taste \(^ {196,211,215}\).

e. **Sinonasal Outcome Test-16 (SNOT-16)**
A rhinosinusitis specific QoL health-related instrument \(^ {216}\).

f. **Rhinosinusitis Disability Index (RSDI)**
A validated questionnaire where the patient is asked to relate nasal and paranasal sinus symptoms to specific limitations on daily functioning \(^ {204,217}\).

g. **Rhinoconjunctivitis QoL questionnaire (RQLQ)**
A well-validated questionnaire with specific focuses on allergy, it is not validated in acute and CRS \(^ {218}\); a newer standardised version RQLQ(S) is available in CRS \(^ {219}\).

h. **RhinoQoL**
A sinusitis specific instrument which measures symptom frequency, bothersomeness and impact (acute and CRS) \(^ {220}\).

i. **Rhinitis Symptom Utility Index (RSUI)**
A questionnaire on the severity and frequency of a stuffy or blocked nose, runny nose, sneezing, itching, watery eyes and itching throat \(^ {221}\).
j. **SN-5**

A validated health-related QoL instrument for children with CRS; the domains are sinus infection, nasal obstruction, allergy symptoms, emotional distress and activity limitations\textsuperscript{222,223}

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 a severity rating of the symptom scale\textsuperscript{224}.

Using a generic SF-36 survey, patients with CRS were compared with a healthy population in Canada and demonstrated to have a statistically significant difference in seven of eight domains\textsuperscript{225}. In a study by Gliklich and Metson (1995), patients with CRS had significantly worse scores for social functioning, body pain, vitality and general health when compared with the general population, with similar results regarding patients with back pain, chronic obstructive pulmonary disease, and angina\textsuperscript{25}. Radenne et al. (1999) looked specifically at NP with the SF-36 and showed a greater impairment in QoL than with perennial rhinitis\textsuperscript{200}. In general, patients with NP, smokers, and asthmatics have worse symptoms and QoL than CRS patients without NP, non-smokers, and non-asthmatics.

Although CRS has a significant impact on general well-being, its very chronicity may mitigate against demonstration of dramatic improvement with therapeutic intervention when compared with seasonal AR\textsuperscript{199}. Nonetheless, several surgical studies have been able to show significant changes and QoL amelioration with return to almost or full normality that was generally maintained up to three years after ESS\textsuperscript{109,209,212,224,226-228}. Significant improvement in symptoms and medications requirements were also demonstrated.

Assessment of QoL changes have also been performed in studies about medical conservative treatments in patients with CRS. **Table II** provides an overview of the studies. In a recent prospective study of patients with CRS with and without NP, patients were randomized to either ESS or three months’ treatment with a macrolide. The patients were followed-up and demonstrated a significant improvement in all subjective and objective parameters 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\textsuperscript{211}. Similar results were
observed in a study of Alobid et al. (2005) with QoL improvement after medical and surgical treatment in patients with NP with one year follow-up. Aside from these studies, there have been several prospective trials included in this work (30 of all 208 retained articles) assessing the QoL outcome after conservative medical treatment in CRS patients (Table II). About 60% of these studies showed significant improvement of QoL, including therapies with long-term macrolides, antileukotrienes, systemic steroids, topical ipratropium bromide, and saline irrigations.

Table II. Summary table of quality of life evaluation and outcome in CRS with and without NP

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total articles number</th>
<th>Articles number showing statistically significant improvement</th>
</tr>
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<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
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<td>- topical</td>
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<td>0</td>
</tr>
<tr>
<td>- systemic long-term macrolides</td>
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<tr>
<td><strong>Antifungals</strong></td>
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<tr>
<td>- topical</td>
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<td>0</td>
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<tr>
<td>- systemic</td>
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<td>1</td>
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<tr>
<td><strong>Antihistamines</strong></td>
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<td><strong>Antileukotrienes</strong></td>
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<td><strong>Corticosteroids</strong></td>
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<td>- topical</td>
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<tr>
<td>- systemic</td>
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<tr>
<td><strong>Gastroeso. Reflux Therapy</strong></td>
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<tr>
<td><strong>Ipratropium bromide</strong></td>
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</tr>
<tr>
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<tr>
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<tr>
<td>- saline (long-term)</td>
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<td>5</td>
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<tr>
<td>- diverse non–saline</td>
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<td>0</td>
</tr>
<tr>
<td><strong>Phytotherapy</strong></td>
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<td></td>
</tr>
<tr>
<td>- systemic</td>
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<td>1</td>
</tr>
<tr>
<td><strong>Homeopathy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- systemic</td>
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<td>1</td>
</tr>
<tr>
<td><strong>Acupuncture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- systemic</td>
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<td>0</td>
</tr>
<tr>
<td><strong>Immunomodulation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- systemic</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>30</td>
<td>17</td>
</tr>
</tbody>
</table>

CRS: chronic rhinosinusitis; NP: nasal polyposis

In conclusion, CRS has a huge impact on patient’s perception of well-being and functional status. Its impact on QoL has been examined in the context of surgical or medical treatment with significant improvement depending the treatment modality. Thus, QoL assessment should be incorporated in all future clinical studies.
1.5.2. Examination

1.5.2.1. Endonasal visualisation

Anterior rhinoscopy with a nasal speculum alone is inadequate, but remains the first and most simple step of clinical examination.

Nasal endoscopy may be performed without and with decongestion and topical anaesthesia for semi-quantitative scoring of NPs, oedema, discharge, crusting and scarring (post-operatively) for the outcome evaluation. A number of staging systems for NPs have been evaluated. A system for classifying and staging NP should be universally adopted to allow for accurate comparison of different therapies and of the same therapies in different series. At an international workshop on NP in Davos, Switzerland, in March 1996, the system described by Lund and Mackay in 1993 and accepted at the International Conference on Sinus Disease: Terminology, Staging and Therapy was updated. This system grades polyps according to their expansion: no visible polyps (Grade 0); polyps confined to middle meatus (Grade 1); polyps beyond middle meatus but not completely obstructing the nasal cavity (Grade 2); and polyps completely obstructing the nasal cavity (Grade 3). Johansson et al. (2000) showed good correlation between a 4 steps staging system ad modum Lildholdt et al. (1997) and their own system in which they estimated the percentage projection of NPs from the lateral wall and the percentage of the nasal cavity volume occupied by the NPs. Unfortunately, no correlation between the size of NPs and subjective symptoms was demonstrated. An endoscopic scoring system for postoperative staging has been evaluated and used in a long-term outcome study after functional ESS in patients with CRS without NP. The results showed a significant correlation between the endoscopic scores and the subjective global amelioration of the nasal symptoms (p < 0.0001).

1.5.2.2. Nasal cytology and biopsy

In general, cytology has not proved as useful tool in diagnosis of CRS although a biopsy may be indicated to exclude more sinister and severe conditions such as vasculitides and neoplasia. However, correlation between the density of inflammatory cells, nasal obstruction (p < 0.001) and quality of life scores (p < 0.001) has been demonstrated.
One of the primary factors dividing CRS into different categories is the patient’s underlying inflammatory process. Recent investigations on the pathogenesis of CRS have emphasised the role of eosinophils. There is a clear distinction between neutrophilic and eosinophilic inflammation. Once this determination is made, the lines of distinction may begin to blur, because various other factors such as anatomic mechanical restriction or SAEs superantigen may cloud the vision. If, however, the above mentioned division of eosinophilic versus non-eosinophilic CRS would be made, a number of seemingly different entities could be grouped in the same category and it would be helpful to diminish the amount of the multiple and often confusing definitions of CRS.

1.5.2.3. Endonasal bacteriology
Several microbiological studies have shown a reasonable correlation between specimen taken from the OMC under endoscopic control and proof maxillary sinus puncture leading to the possibility of microbiological confirmation of both the pathogen and its response to therapy. A meta-analysis showed an accuracy of 87% with a lower end confidence level of 81.3% for the endoscopically directed OMC culture when compared with maxillary sinus taps in acute maxillary sinusitis.

1.5.2.4. Radiographic diagnosis
The role of radiographic modalities is to provide an accurate display of the nasal and paranasal sinus morphology and show the nature and type of OMC obstruction. Since an increasing number of patients undergo ESS as a therapeutic regimen for their pathology, appropriate radiological imaging is critical in providing a « roadmap » for the surgeon. It helps to delimit the surgical procedure as well as ensure its safety and accuracy.

Although standard plain film technology might be less costly than other diagnostic modalities with a lower dose of radiation exposure, it is insensitive and of limited usefulness for the diagnosis of rhinosinusitis. Plain films fail to provide information of patient's anatomical variations, the paranasal sinus perimeter and the extent of inflammatory disease. The plain film is inadequate for guidance of surgery. This technique has only its place nowadays in the detection of acute maxillary sinusitis.
The CT-scan is the imaging modality of choice showing the anatomy and extent of mucosal disease. Given its resolution of the nasal and paranasal sinus bony anatomy and mucosa, it has proven to be the optimal diagnostic imaging technique in providing the anatomic landmarks for the surgeon performing functional ESS. Information afforded by the coronal plane correlates the best with the endoscopic vision and it is the favoured plane to study the nasal and paranasal sinus’ anatomy and plan a surgical procedure (Figure 6). The axial CT sections provide more adequate assessment of the posterior ethmoid and sphenoid sinuses, as well as the exact location of the optic nerve and internal carotid artery. Several authors have attempted to use the CT-scan information, specifically the presence and volume of inflammatory mucosa within the paranasal sinuses to stage the CRS radiologically. The most accepted staging system is the one proposed by Lund-Mackay. One concern regarding the performance of routine CT-scans of the paranasal sinuses is that of radiation exposure, particularly to the lens of the eye. Conventional CT-scan is performed at 225 - 390 milli-Amperes (mAs), corresponding to a level of moderate radiation dose exposition. However, it was possible to reduce the dose during scanning to levels between 80 -160 mAs without compromising the diagnostic value of the scan or precluding its utility in preoperative planning. This low-dose CT scan shows slightly decreased soft tissue contrast. However, this decrease does not affect the sensitivity and specificity of the scan and the use of low-dose CT is highly recommended in patients with CRS.
Although magnetic resonance imaging (MRI) is superior to CT-scan in the delineation of soft tissue pathologies, it is not routinely used in evaluating nasal and paranasal sinuses for ESS. Poor delineation of the bone-air interface results in poor visualisation of the OMC $^{264}$. The MRI may be useful together with the CT-scan in cases of suspected neoplasia, encephalocele, meningocele, intracranial extension of diseases or intracranial complications. However, it is not the imaging modality of primary choice in CRS. Three-dimensional reconstruction software that allows the fusion of CT-scan and MRI helps in preoperative planning of complex cases suffering from tumours or lesions in close proximity to major vascular and neurological structures $^{267}$. 

Figure 6.
CT-scan of the paranasal sinuses showing mucosal swelling and right-side septal deviation.
1.5.2.5. Mucociliary function

The use of saccharine, dye, vegetable charcoal powder or radioactive particles to measure mucociliary transport (MCT) time has been available since about 30 years \cite{268-270}. It allows recognising early alterations and prolongation of MCT in rhinosinusal disturbances. The measurement considers the entire mucociliary system and the MCT time is normal when lesser than 35 minutes. A prolongation of MCT time cannot distinguish between primary or secondary mucociliary impairment. Chronic rhinosinusitis patients show a prolonged MCT time \cite{37}. Specific measurements of ciliary activity using a phase contrast microscope with photometric cells have been used in a number of trials to evaluate therapeutic success \cite{271-273}. Children with suspicion of primary ciliary dyskinesia benefit of this technique. Finally, the gold standard examination of ciliary function involves culture techniques for 6 weeks \cite{274}. Electron microscopy may be used to confirm the presence of specific inherited diseases of the mucosal cilia as in primary ciliary dyskinesia.

1.5.2.6. Nasal nitric oxide

Nitric oxide (NO) is a potent biological mediator that plays an important role in a variety of physiologic and pathophysiologic mechanisms. It has been proposed as a bronchodilator \cite{275}, vasodilator \cite{276} and major neurotransmitter \cite{277}. Antimicrobial \cite{278}, antiviral \cite{279} and antitumour actions \cite{280} are also suggested. In addition, it may act as an airborne messenger \cite{281,282}.

Nitric oxide is synthesised from the semi-essential amino acid L-arginine by the action of nitric oxide synthase (NOS) with the production of L-citrulline. Oxygen and nicotinamide dinucleotide phosphate (NADPH) are important co-factors during the NO synthesis \cite{283}. The NOS exists in at least 2 isotypes: the constitutive NOS (cNOS) (= endothelial NOS) and inducible NOS (iNOS).

It is not known with certainty whether the majority of NO released from the adult nose is derived from the epithelium lining of the nasal cavity or whether it comes also from the paranasal sinuses. Nitric oxide levels in the paranasal sinuses have been demonstrated to be several times higher than those in the nose and it was suggested that the majority of nasal NO originates in the sinuses \cite{284}. Other studies, however, demonstrated that 90% of nasal NO derived from the nasal cavities \cite{285}. Nitric oxide regulates the mucociliary function in the nasal airway. Animal studies have shown a dose-dependent increase in maxillary sinus ciliary beat frequency with
the addition of L-arginine. Very low or almost absent levels of nasal NO were found in children with primary ciliary dyskinesia and cystic fibrosis. The nasal NO was found to be normal or increased in allergic rhinitis and asthma. Decreased NO resulted in acute and CRS. Recent studies have reported that the nasal NO level was inversely correlated with the extent of sinus disease as documented by CT-scan scores, endoscopic score, and NP stage. On the other hand, nasal NO levels increased significantly after a successful medical or surgical therapy of CRS. This would be explained by the normalisation of the ciliated epithelium in the nasal cavities and paranasal sinuses, which regains its normal ability to synthesise NO that passes through open ostia. Ragab et al. (2006) demonstrated a high correlation between changes of the nasal NO and changes of the saccharine clearance test which strongly suggests the potential use of NO measurements in diagnosis and even therapeutically follow-up of diseases affecting sinonasal mucociliary function.

NO can be measured directly or indirectly. Indirect methods have been used to measure NO levels in the fluid phase where it has a very short half life time. These include the measurement of nitrate and nitrite which are the stable end products of NO metabolism or the use of immunohistochemical techniques to localise NOS. Direct measurement of exhaled NO is done by means of chemiluminescence. There is no standardised technique for measuring nasal NO and several methods have been used. The commonest method in use is that of direct nasal aspiration using the NO analyser pump.

The value of nasal NO as a measure of the outcome on CRS is still uncertain.

1.5.2.7. Nasal carbon monoxide

Carbon monoxide (CO) has recently emerged as an endogenously produced gaseous mediator that, like NO, appears to be involved in both upper and lower airway inflammatory diseases. A role for CO as a peripheral transmitter involved in non-adrenergic, non-cholinergic relaxation of the intestinal smooth muscles has been proposed. Recent in vivo studies showed that exogenous CO administration may induce bronchodilation by an NO independent, cyclic GMP-related mechanism.

There are many ways for CO synthesis, but the degradation of heme to biliverdin and CO by heme oxygenase appears to be the dominating one in most species. The enzyme heme oxygenase (HO) is seen in nerve cell bodies, in
intrinsic parasympathetic ganglia of guinea pig airways and in local parasympathetic ganglia of human trachea and bronchi. These findings suggest that CO may act as a modulator of synaptic neurotransmission in the lower airway \(^{299}\). The HO has also been found in the airway’s smooth muscle and in the respiratory epithelium of guinea pigs, indicating a direct role for CO in airway regulation \(^{297}\). The exhaled level of CO was found to be increased in asthmatic patients during periods of non-steroid treatment, during asthma exacerbation and after allergen challenge \(^{300,301}\).

Yamaya et al. (1998) proposed that CO, in analogy with NO, also can be produced in the upper respiratory airway, thus contributing to the total CO content of exhaled air \(^{302}\). A recent work demonstrated that CO can be reproducibly measured in the nasal cavities and paranasal sinuses and the enzymes responsible for local CO production are present in the nose. The study also showed equal concentration of CO in the nasal cavities and paranasal sinuses, indicating a uniform production in both sites \(^{295}\). The nasal CO levels were found to be higher in patients with AR than in normal controls with no increase of the lower airway CO production. This observation suggests that the nasal airway may be the primary localisation of inflammation as well as CO production during specific hyperreactivity. The nasal CO production was also found to be increased in patients with upper respiratory tract infections. These patients showed also an increase in the lower airway CO production. The role for CO as a marker or mediator of nasal inflammation has been proposed \(^{303}\).

CO can be quantified by several different techniques. Most of the measurements in humans have been made using electrochemical CO sensors. Exhaled CO can also be measured by an adjustable laser spectrophotometer or by a near-infrared CO analyser \(^{304}\).

### 1.5.2.8. Aspirin and other challenges

Objective experiments to differentiate patient groups according to rhinosinusitis severity or aetiology have been done using nasal provocation tests with histamine or metacholine \(^{305}\) to observe mucosal hyperreactivity. These tests resemble to the corresponding bronchial tests i.e. asthma diagnosis, but have not achieved the equivalent value.

Establishing the diagnosis of AS-hypersensitivity may detect a particular subtype of CRS, the so called AERD, and will allow the introduction of a specific
therapy, i.e. AS desensitisation and maintenance. The oral AS challenge test was introduced to clinical practice in the early 1970s 306. An inhalation test with lysine-acetylsalicylate (LAS), the only truly soluble form of AS, was introduced in 1977 which is safer and faster to perform than the oral challenge, although less sensitive 307,308. A negative inhalation challenge should be followed by oral challenge.

1.6. MANAGEMENT OF CHRONIC RHINOSINUSITIS

1.6.1. Medical treatment of chronic rhinosinusitis

No one single treatment regimen exists for the management of CRS because of its heterogeneity. However, the principles involved in the treatment of CRS include identifying and treating the underlying causes. Goals of treatment are reduction of mucosal oedema, restoration of paranasal sinus ventilation and eradication of infectious pathogens. This often requires a combination of topical and oral medication. Nasal polyps are showing a high recurrence rate, clearly indicating the chronicity of this disease and suggest a reserved surgical approach. Medical therapies have a prominent role in the treatment of CRS and can be valuable in reducing the risk of recurrent NPs especially in patients who previously underwent one or more surgical approaches. Thus, a combined treatment strategy involving surgical and medical methods is recommended for long-term control of this disease 309. Different types of medical therapies are available and used in the management of CRS, including topical and systemic corticosteroids, antibiotics, antifungals, hypertonic and isotonic saline irrigations or sprays, antileukotrienes and more.

The primary goal of treatment is the relief of patients’ symptoms: nasal blockage, congestion, hyposmia or anosmia, hypersecretion, post-nasal drip, facial pain, headache, sleep disturbances and diminished QoL. Secondary goals of therapy include a decrease in the frequency of infectious episodes and disease recurrence, an improvement in associated lower airway symptoms and the prevention of complications such as mucoceles or orbital extension.
1.6.2. Surgical treatment of chronic rhinosinusitis

Surgery is reserved for patients who are refractory to medical treatment and for patients with anatomic obstruction causing CRS. Patients with AFRS usually require surgery to remove the inspissated mucus in order to re-establish sinus ventilation and drainage and to diminish the contact of the mucosa with the fungal allergens. Endoscopy was first applied to the nose and paranasal sinuses in the 1970s by Messerklinger. Since its introduction, ESS has become the standard surgical option in the treatment of CRS. Endoscopic sinus surgery involves minimally invasive techniques and is based on two main principles: 1) obstruction of the narrow clefts of the anterior ethmoid (the ethmoid infundibulum and frontal recess) leads to obstruction and possible inflammation of the maxillary, frontal and anterior ethmoid sinuses and 2) relief of obstruction in the anterior ethmoid may allow the other sinuses to drain and return to normal state with a well functioning mucociliary clearance system. However, as surgery strives to restore functional integrity of inflamed mucosal lining, a conservative mucosa-sparing approach is advocated. Although ESS is a well tolerated procedure, the Cochrane meta-analysis by Khalil and Nunez (2006) demonstrated that there is a lack of good evidence in the literature for its superiority over medical treatment in CRS. However, a number of studies have established the effectiveness of surgical therapy in the short-term and long-term outcome, showing subjective improvement of symptoms as well as ostia patency in patients with medically refractory CRS with and without NPs. Major complications occur in less than 1% and revision surgery is performed in approximately 10% within 3 years. In conclusion, in the majority of CRS patients, appropriate medical treatment would be as effective as surgical treatment, thus sinus surgery should be reserved for patients who do not satisfactorily respond to conservative treatments. Randomised, controlled trials comparing the efficacy of medical treatments and surgery in CRS are needed.
2. OBJECTIVES

The purpose of this work is to:

1) review,
2) evaluate the effectiveness and safety,
   and
3) grade the strength of evidence and recommendations

in the clinically relevant conservative treatment of CRS with and without NP.

This review assesses the evidence for the clinical effectiveness of conservative treatments in the management of the symptoms of CRS with and without NPs. The primary focus of the review is symptom relief. It includes assessment of studies where patients have conditions that produce CRS symptoms, not only those that fulfil a set of modern diagnostic criteria for CRS with and without NPs.
3. METHODS

3.1. CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

3.1.1. Types of studies

Randomised, controlled, prospective trials which fulfil the criteria outlined below. Because of the high number of studies involving intranasal corticosteroids, only randomised, double-blind, placebo controlled trials were retained in this category of drugs for this review.

3.1.2. Types of participants

Adults and children with the symptoms of CRS with and without NPs. The review focuses on the symptoms of CRS disease. Seasonal and perennial allergic rhinitis, recurrent acute sinusitis, atrophic rhinitis, cystic fibrosis, gross immunodeficiency, congenital mucociliary diseases, non invasive fungal balls and invasive fungal disorder, systemic vasculitis and granulomatous pathologies, cocaine abuse and neoplasia were excluded from this review.

3.1.3. Types of interventions

Conservative treatments in CRS with and without NP were considered in this review.

3.1.4. Considered types of outcome measures

a. Primary outcomes
   • Symptoms and QoL
   • Radiological assessments
   • Endoscopic scores
   • Objective assessments of nasal resistance, cytology, etc.
   • Recurrence rate of CRS with and without NP after ESS
b. Secondary outcomes

- Adverse events

In studies on the treatment of CRS without NP, the evaluation of the effect of the therapy on sinonasal symptoms and objective nasal airway assessments was recorded. In NP, the effects on polyp size and subjective symptoms were retained. In trials on the treatment after ESS, prevention of NP recurrence is evaluated.

### 3.1.5. Search methods for Identification

MEDLINE (1950 – 2009) and THE COCHRANE LIBRARY were searched. The date of the last search was June 2009. Searching strategies for MEDLINE and THE COCHRANE LIBRARY were:

1) (rhinitis OR sinusitis OR rhinosinusitis OR sinusopathy OR rhinopathy OR nasal polyps OR nasal polyposis OR paranasal sinus disease) NOT (allergic or allergy) NOT acute

and

2) allergic fungal AND (rhinosinusitis OR rhinitis OR sinusitis)

The abstracts of the retrieved articles have been scanned for clinically relevant, randomised controlled and prospective clinical trials. The full-text articles were obtained and scanned from the clinically relevant abstracts and from the abstracts where the method of the study was not clearly stated.

### 3.1.6. Searching other resources

Reference lists from identified publications were scanned to identify further trials. Non-English language publications were assessed if the translated abstract indicated that the study was a randomised controlled or prospective clinical trial.
3.2. DATA COLLECTION AND ANALYSIS

3.2.1. Selection of studies

The initial search results were scanned to identify trials which loosely met the inclusion criteria. The full text articles of all the retrieved trials of possible relevance were reviewed and the inclusion criteria applied. A flow chart of study retrieval and selection is provided in Figure 7.

![Flow chart illustrating the results of the research strategy.](image)

3.2.2. Data extraction and management

Data from the retained studies were extracted: author(s), methods, participants, interventions, duration of treatment and outcomes of the included studies are listed in tables. Adverse events were recorded.

3.2.3. Data synthesis

Each article was assigned an evidence level based on published standards (Table III), and the group of articles was assigned an overall grade for the strength of
evidence for or against each association. Evidence levels range from I (strongest) to IV (weakest). Recommendation grade summaries range from A (strongest: consistent level I studies) to D (weakest: level IV evidence or extrapolated recommendation from any level) (Table IV) 317,318.

Table III. Sekelle’s evidence scale (modified) 318

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence from meta-analysis of randomized controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence from at least one randomized controlled trial</td>
</tr>
<tr>
<td>Ila</td>
<td>Evidence from at least one controlled study without randomization</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence from at least one other type of quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-controlled studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both</td>
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</table>

Table IV. Strength of recommendation

<table>
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<tr>
<th>Grade</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Directly based on category I evidence</td>
</tr>
<tr>
<td>B</td>
<td>Directly based on category II evidence or extrapolated recommendation from category I evidence</td>
</tr>
<tr>
<td>C</td>
<td>Directly based on category III evidence or extrapolated recommendation from category I or II evidence</td>
</tr>
<tr>
<td>D</td>
<td>Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence</td>
</tr>
</tbody>
</table>
4. RESULTS

There are only few well-conducted clinical trials in CRS treatment. Based on the evidence available, initial therapy is medical and should aim to reduce symptoms and signs, improve QoL and prevent disease progression or recurrence. Chronic rhinosinusitis often responds incompletely to the conservative therapy which may need to be continued for a long-term course.

The conservative treatment categories retained from the literature search and discussed in here are summarized in an alphabetical order in Table V.

Table V. Conservative therapy in CRS

<table>
<thead>
<tr>
<th>1. Medical treatments</th>
<th>2. Complementary and alternative medicine</th>
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</thead>
<tbody>
<tr>
<td>Antibiotics (topical/systemic)</td>
<td>Phytopreparations (topical/systemic)</td>
</tr>
<tr>
<td>Antifungal treatment (topical/systemic)</td>
<td>Homeopathy</td>
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<tr>
<td>Antihistamines (topical/systemic)</td>
<td>Acupuncture</td>
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<tr>
<td>Antileukotrienes (systemic)</td>
<td></td>
</tr>
<tr>
<td>Aspirin desensitization and maintenance (topical/systemic)</td>
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</tr>
<tr>
<td>Bacterial lysate preparations and other immunostimulants</td>
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<tr>
<td>Capsaicin (topical)</td>
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</tr>
<tr>
<td>Corticosteroids (topical/systemic)</td>
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</tr>
<tr>
<td>Cromolyn sodium (topical)</td>
<td></td>
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<tr>
<td>Decongestants (topical/systemic)</td>
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<tr>
<td>Furosemide (topical)</td>
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<tr>
<td>Gastroesophageal reflux therapy</td>
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<td>Immunotherapy (systemic)</td>
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<td>Ipratropium bromide (topical)</td>
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<td>Irrigations (topical)</td>
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</tr>
<tr>
<td>Mucoactive agents (topical/systemic)</td>
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</tr>
<tr>
<td></td>
<td>3. Possible future treatments – Immunomodulatory therapies?</td>
</tr>
<tr>
<td></td>
<td>Anti-interleukin-5 monoclonal antibody</td>
</tr>
<tr>
<td></td>
<td>Interleukin-4 and Interleukin-13 antagonists</td>
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<tr>
<td></td>
<td>CC chemokine receptor-3 antagonists</td>
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<td></td>
<td>Immunoglobulin E-Antagonism</td>
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<tr>
<td></td>
<td>Imatinib</td>
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<tr>
<td></td>
<td>Immunosuppression</td>
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<tr>
<td></td>
<td>Interferon-gamma</td>
</tr>
<tr>
<td></td>
<td>Matrix Metalloproteinase Inhibitors</td>
</tr>
<tr>
<td></td>
<td>Recombinant Human Granulocyte Macrophage – Colony Stimulating Factor</td>
</tr>
</tbody>
</table>

This section provides the background, potential therapeutic action, summary of all controlled clinical trials reviewed for this study and the observed side effects of each conservative treatment category. The retained trials are tabulated with information on the author(s), the year of publication, the number of subjects involved, the study design, the type of drug applied, the mode of drug administration, the subjective and objective outcome and the level of evidence.
4.1. MEDICAL TREATMENTS

4.1.1. Antibiotics - topical and systemic

4.1.1.1. Background

While the etiology of CRS with and without NPs remains uncertain, bacteria have traditionally been regarded as major contributors to the pathogenic processes behind this disease. The microbiology of the middle meatus and sinuses in CRS has been studied extensively, but whether cultured bacteria are pathogenic or merely incidental, remains to be established. Bacteria similar to microorganisms found in acute rhinosinusitis (Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis) may play a role in the acute exacerbations of CRS, but not in the etiology of CRS itself, what denies the role of antibiotics against this group of bacteria in the treatment of CRS beside the therapy of the acute episodes. Despite this, most clinicians prescribe antimicrobial therapy as part of their treatment regimen for CRS.

There are significant differences in the bacteria present in CRS, as compared with acute rhinosinusitis. In CRS, polymicrobial infection is common and organisms may exist synergistically. The predominant bacteria are Staphylococcus aureus, Staphylococcus epidermidis, anaerobes and Gram-negative rods (including Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter spp, and Escherichia coli). The pathogenicity of some of the low-virulence organisms, such as Staphylococcus epidermidis, is questionable. In contrast, Gram negative rods are more likely to play a pathogenic role as they are rarely found in cultures of the middle meatus obtained from healthy subjects. Indeed, there is evidence to suggest that they are more common in patients who have had previous surgery or sinus irrigations. Pseudomonas aeruginosa may be more common in patients who have received systemic steroids.

Some authors suggest that as chronicity develops, the aerobic and facultative species are gradually replaced by anaerobes. This change may result from the selective pressure of antimicrobial agents, enabling resistant organisms to survive or from the development of conditions appropriate for anaerobic growth (including a reduction in oxygen tension and an increase in acidity within the sinuses). Certainly, anaerobic bacteria can be isolated in more than half of all patients with CRS and...
these patients have a greater risk of developing local (such as mucocele, osteomyelitis, abscess formation) and intracranial complications \(^{334}\).

In recent years, there have been three significant developments in the study of the role of bacteria in the pathogenesis of CRS: biofilm formation, intracellular residency of bacteria and SAEs.

Bacterial biofilms were first described on inert surfaces such as prosthetic heart valves, but were later implicated as a potential source of chronic infection on mucosal surfaces, such as bladder epithelium in chronic urinary tract infection and respiratory epithelium in cystic fibrosis \(^{335,336}\). A biofilm consists of clusters of bacteria held together by an extracellular glycocalyx, with interspersed water channels. Perloff and Palmer conducted several studies that confirmed the presence of biofilms on the mucosa of patients with CRS \(^{337-339}\); these biofilms could explain why such patients improved after a course of antibiotics and relapsed after medication was ceased \(^{340}\). Relevant organisms in otorhinolaryngological diseases have been shown to form biofilms, such as Pseudomonas aeruginosa, Haemophilus influenzae, Streptococcus pneumoniae and Staphylococcus aureus \(^{341}\). Biofilm formation may be promoted by antibiotic use, particularly in the setting of poor antibiotic tissue penetration or antibiotic resistance which led to persistent, viable microbes. Using the Calgary Biofilm Assay on swab collected samples in patients with CRS, bacterial biofilms have been detected on the mucosa of 28.6% of this population \(^{342}\). In patients who underwent ESS, which means persistent CRS after conservative treatment, perioperative mucosal samples of the ethmoid sinuses scanned under electron microscopy showed bacterial biofilms in 42 – 80%, compared to 0 – 40% in controls without CRS \(^{45,343-349}\). Studies have correlated the presence of biofilms with a worse prognosis after ESS in patients with CRS \(^{48,343,349}\). Surgical failure may be attributed to biofilms when these are not eradicated. Two studies evaluated the presence of biofilms 6 months after ESS and found persistent biofilms in 60 – 66% of the patients, and concluded that surgery resulted in reduction but not total eradication of biofilms, what might cause the unfavorable outcomes of surgery for certain patients with CRS \(^{350,351}\). The re-appearance of biofilms after surgery may be due to its persistence in the folds of edematous and chronically inflamed mucosa in which cilia are damaged or absent, on postoperative mucosal scars, destructed epithelium, or uncovered bone in the sinus cavities which may lead to rapid reinfection \(^{345}\). Once established, biofilms tend to protect the bacteria within them from the action of antibiotics,
rendering them resistant. The presence of biofilms on the mucosa of patients with CRS offers a possible cause of antimicrobial and surgical therapy failure and could change the approach to treatment. However, the presence of biofilms on healthy control samples implies that biofilms may simply be colonizers. Finally, it remains unclear whether biofilms in the CRS with and without NP are the cause or consequence of persistent infection.

Another mechanism which allows bacteria to escape the effects of antibiotics is the ability of some bacteria to reside within epithelial cells. This intracellular bacterial reservoir seems to play a significant role in recurrent episodes of rhinosinusitis due to persistent bacterial clonotypes. There is also concern that antibiotic use might promote the development of this intracellular reservoir, particularly for Staphylococcus aureus.

Staphylococcus aureus can also secrete enterotoxins (SAEs), substances which can act as superantigens, capable of stimulating an immense inflammatory response. In studies on NPs, SAEs promote a severe eosinophilic inflammation and synthesis of a multiclonal IgE response, with high total IgE concentrations in the polyp tissue. This would suggest that SAEs are at least modifiers of disease in CRS with NPs. The genes for enterotoxins P and Q were detected in CRS with and without NP.

Whilst the common bacteria present in CRS have been studied and various pathogenic mechanisms are being investigated, the evidence for prescribing antibiotics remains unclear. There are only a few randomized, placebo-controlled clinical trials examining this issue.

4.1.1.2. Potential Therapeutic Actions
A description of the mechanism of action of all the antibiotics that may be used in the treatment of CRS is beyond the scope of this chapter. Instead, the topical subject of the mechanisms of action of the macrolide antibiotic agents will be discussed, as much research has recently improved our understanding of this interesting class of medications.

Possible mechanisms of action of macrolides in the therapy of CRS and NPs are shown in Figure 8.
Figure 8.
Potential therapeutic action of macrolide antibiotics. Macrolides reduce inflammation of the sinonasal mucosa by inhibiting the production of proinflammatory cytokines, neutrophil elastase and migration of neutrophils. Macrolides also have antibacterial properties, direct inhibitory effect on mucus hypersecretion and increase mucociliary transportability.

Macrolides possess several anti-inflammatory or immunomodulatory actions. The most crucial one is the inhibition of nuclear factor-κB (NF-κB), especially in airway epithelial cells and fibroblasts. This is a nuclear transcription factor that stimulates the expression of several proinflammatory cytokines. Specifically, macrolides reduce the expression of IL-2, IL-6, TNF-α, ICAM-1 and, importantly, IL-8. Interleukin-8 is instrumental in stimulating neutrophil migration and activation, so macrolides reduce neutrophilic inflammation. In vitro studies of cultured nasal epithelial cells show that clarithromycin is as effective as prednisolone in reducing the concentrations of IL-8, IL-5 and GM-CSF. Clinically, in CRS and NP patients, short-term clarithromycin treatment has been associated with a 41% symptomatic improvement and reduced levels of inflammatory markers, such as macrophages (CD68), elastase, IL-6, IL-8, eosinophil activity, TNF-α and oedema of the nasal mucosa. A significant reduction in the concentration of IL-8 and the number of neutrophils was also correlated with improved sinus aeration in patients with CRS treated with macrolides. A recent study confirmed these findings and showed an
anti-inflammatory effect of the long-term therapy with clarithromycin in CRS\textsuperscript{359}. They demonstrated reduced levels of inflammatory products (IL-8, ECP) and \(\alpha_2^*\)-macroglobulin (a marker of plasma exudation) following the treatment.

Macrolides have well-established antimicrobial activity. They bind to the 50S subunit of the 70S ribosome in prokaryotes, thus inhibiting bacterial protein synthesis. They are primarily bacteriostatic against Gram-positive cocci (including anaerobes, but not enterococci) and have limited Gram-negative activity. At higher concentrations, they are bactericidal. However, some organisms are resistant to the direct antibacterial effect of macrolides. In spite of this, these drugs are sometimes able to attenuate the effect of bacterial virulence factors. For example, erythromycin inhibits the release of elastase, protease, haemolysin, lectins, phospholipase C and eotaxin A produced by \textit{Pseudomonas aeruginosa}\textsuperscript{360}. The effect is a reduction of damage to the surrounding tissue\textsuperscript{361}. In a similar fashion, low dose roxithromycin reduced the virulence of pneumococci in a mouse model of pneumonia. Specifically, expression of MMP-7 and activation of keratinocyte-derived chemokine production was inhibited in the lungs, while mononuclear cell responses were increased, resulting in enhanced bacterial clearance\textsuperscript{362}. Importantly, macrolides are effective against some intracellular pathogens, such as \textit{Corynebacterium diphteriae}, \textit{Bordetella pertussis}, \textit{Legionella pneumophila}, \textit{Mycoplasma pneumoniae} and \textit{Chlamydia pneumoniae}\textsuperscript{363}. Another class of antimicrobials, tetracyclines, also have this effect and, interestingly, evidence is emerging of their immunomodulating activity. Macrolides have also been shown to alter the structure and function of biofilms produced by \textit{Pseudomonas aeruginosa}\textsuperscript{364,365}. Azithromycin inhibits interbacterial communication, also referred to as quorum-sensing\textsuperscript{366}. This is an important bacterial virulence factor in the production and maintenance of biofilms.

Laboratory and clinical studies have provided evidence that macrolides have effects on mucus production and mucociliary clearance. Mechanisms for mucus hypersecretion in CRS are multifactorial and include the effects of cytokines, neurotransmitters and oxygen free radicals from neutrophils. Erythromycin has been shown to inhibit the secretion of glucosamine, a component of mucus, in a concentration-dependent manner\textsuperscript{367}. Clarithromycin and erythromycin inhibited mucus secretion from human mucoepidermoid carcinoma cells and human nasal epithelial cells\textsuperscript{368}. In animal studies, clarithromycin and erythromycin block the infiltration of neutrophils into airway goblet cell clusters, reducing goblet cell
hyperplasia and consequently, mucus secretion \(^{369,370}\). Macrolides may also inhibit expression of the mucin gene MUC5AC, which is found primarily in goblet cells \(^{369,370}\). Clinically, clarithromycin 500 mg twice daily for 2 weeks given to patients with purulent rhinitis, restored nasal secretions to normal, decreased secretion volume 10-fold and increased mucociliary transportability by 30%, compared to healthy controls \(^{371}\).

There are efforts underway to develop a new group of macrolides which lack an antibacterial effect, so called “immunolides” or “designer macrolides” \(^{372,373}\). If they were to prove effective, it would reduce the potential problem of bacterial resistance developing upon long-term macrolide treatment.

### 4.1.1.3. Topical Intranasal Antibiotics

The topical application of antibiotics to the sinonasal mucosa offers the potential benefits of a high concentration of drug at the site of the infection, along with low blood levels and hence, low potential for systemic side effects. Despite this, topical antibiotic agents have not been a part of standard treatment. Also, in sinonasal infections generally, antibiotic choice should be based on actual culture results or should empirically target the usual organisms found in CRS. The optimal goal of this type of therapy is to achieve adequate levels of drug without increasing the incidence of local side effects.

**Topical intranasal antibiotic agents in CRS without NPs (Table VI)**

A prospective, case controlled study evaluated 208 patients with CRS using an ultrasound-type inhaler to deliver a topical aminoglycoside (**fosfomycin**) and **cefmenoxine** three times per week during 8 weeks. There was a clinical efficacy rate of 43 - 72% and a radiologic efficacy rate of 32 - 59%, increasing with the dose of the drugs \(^{374}\).

A similar trial evaluated the effects of **fosfomycin** aerosols in 28 patients with CRS \(^{375}\). Two ml of fosfomycin sodium 2% were administered by nebulizer three times per week for 4 weeks. The overall efficacy of this treatment on the basis of both subjective and objective signs and symptoms, was ‘excellent’ for 28.6%, ‘good’ for 10.7%, ‘fair’ for 39.4%, and yield ‘no change’ for 21.4% of the patients. Both IL-1\(\beta\) and IL-6 concentrations in the nasal lavage were significantly decreased after the treatment (p < 0.01).
Recently, a similar study was performed to examine the efficacy and tolerability of topical mupirocin for the management of surgically recalcitrant CRS associated with positive Staphylococcus aureus culture. Sixteen patients were treated with twice daily nasal lavage containing 0.05% mupirocin and lactated ringers salts. The duration of treatment was 3 weeks. Fifteen of 16 patients had improved nasendoscopy findings after treatment (p < 0.001). Twelve of 16 patients noted overall symptom improvement (p = 0.02). Fifteen of 16 patients had negative swab results for Staphylococcus aureus after treatment.

Studies of better design seem to contradict these data. In a randomized, double-blind, placebo-controlled trial of 50 patients with CRS, three treatment groups was examined: dexamethasone, tramazoline and neomycin or dexamethasone and tramazoline with no antibiotic or placebo. Each treatment was delivered as a nasal spray, four times daily to both nostrils for 2 weeks. Both active preparations were more effective than placebo, but there was no significant difference between the active preparations. Thus, the antibiotic neomycin, provided no additional benefit.

Another randomized, double-blind trial compared the use of tobramycin-saline versus saline-only aerosols three times daily for 4 weeks, in 20 patients with CRS refractory to medical or surgical treatment. A large-particle nebulizer was used. There was no difference in clinical outcomes between the groups, although both groups improved from pre-treatment scores.

A recent similar study evaluated the effect of bacitracin/colimycin aerosol in 14 patients with recalcitrant CRS with a positive culture of Staphylococcus aureus. Nasal irrigation with bacitracin/colimycin or placebo using a nebulizer twice daily for 8 weeks and oral levofloxacin during the first 2 weeks in both groups was evaluated. No significant difference in the improvement of rhinosinusitis symptoms, QoL and endoscopically findings was found comparing with the placebo group.

Topical intranasal antibiotic agents in CRS with NPs

No prospective trials are available dealing with topical antibiotics in the treatment of CRS with NP.

On the available evidence, there is currently no place for topical antibiotics in the treatment of CRS with and without NP. One trial dealing with QoL outcome could not demonstrated a statistically significant improvement. The pharmacokinetic and
pharmacodynamic parameters of topically applied antibiotics need further investigation, so dosing and scheduling of regimens can be better defined.

4.1.1.4. Systemic Antibiotics

If antimicrobial agents are prescribed for the treatment of CRS, the optimal empiric agent is a broad-spectrum antibiotic that is beta-lactamase stable and effective against penicillin-resistant *Streptococcus pneumoniae* and anaerobes. The choice of agents includes the combination of a penicillin (e.g., amoxicillin) and a beta-lactamase inhibitor (e.g., clavulanic acid), clindamycin, chloramphenicol or the combination of metronidazole and, either a macrolide or a fluoroquinolone with minimal anti-anaerobic efficacy (e.g., levofloxacin, moxifloxacin, and gatifloxacin). A fluoroquinolone with adequate anti-anaerobic efficacy (e.g., trovafloxacin) can be administered as single agent therapy for serious hospital-based infections. Fluoroquinolones should only be used in adults and are available in oral and parenteral forms.

For severe or resistant cases, parenteral antibiotics may rarely be considered. These include some of the second-generation cephalosporin (e.g., cefotaxin, cefotetan, and cefmetazole), combinations of penicillin (e.g., ticarcillin, piperacillin, and ampicillin) and a beta-lactamase inhibitor (e.g., clavulanic acid, tazobactam, and sulbactam) and the carbapenems (i.e., imipenem, and meropenem). Extra coverage against aerobic gram-negative organisms, such as *Pseudomonas aeruginosa*, can be provided by parenteral therapy with an aminoglycoside, a fourth-generation cephalosporin (ceftazidime of cefepime) or oral or parenteral treatment with a fluoroquinolone. Specific methicillin-resistant *Staphylococcus aureus* (MRSA) coverage can be attained by agents such as vancomycin or linezolid. The superiority of therapy effective against both aerobic and anaerobic bacteria (amoxicillin-clavulanate (AMX/CA), clindamycin or carbapenem) when compared with therapy effective only against aerobic bacteria has been demonstrated in two retrospective studies of CRS.[326,379]

Short-term (< 2 weeks) antibiotic treatment (Table VII)

In a prospective study on 56 patients with acute exacerbations of CRS with and without NPs, patients were given 500 mg ciprofloxacin twice daily for 9 days and 40 mg prednisolone once daily for 6 days.[380] There was no placebo group. Of the
patients with positive pre-treatment bacteriological nasal swabs, the bacteria were eradicated by the treatment in 90% of cases. The clinical success rate (defined as resolution of rhinorrhea) was 74.5%. It is difficult to draw useful conclusions about the role of ciprofloxacin from this study.

In a study of 25 CRS patients with and without NP, clarithromycin 500 mg twice daily was given for 2 weeks. A significant reduction was seen in eosinophilic activity (EG2), macrophages (CD68), IL-6, IL-8, TNF-α, elastase and mucosal oedema scores. Improvement was observed for all clinical parameters, but follow-up was only 2 weeks. The significant reductions in inflammatory markers support the role of clarithromycin in modulating immunologic responses.

In a prospective, double-blind study, 251 adult patients with CRS were treated with ciprofloxacin or AMX/CA for 9 days. There was no placebo group. Overall, there were no significant differences between the two groups in clinical cure and bacteriologic eradication rates (51% vs. 59% and 89% vs. 91%, respectively). However, amongst patients who had a positive initial culture, ciprofloxacin recipients had a significantly higher cure rate than those treated with amoxicillin/clavulanic acid (83.3% vs. 67.6%, p = 0.043) and tolerance was significantly better with ciprofloxacin (p = 0.012), largely due to a high number of gastro-intestinal related side-effects in the AMX/CA (n = 35). Hence, ciprofloxacin is a useful therapeutic alternative for the treatment of CRS, but as there was no placebo group it is difficult to evaluate whether either antibiotic was beneficial.

The effects of AMX/CA (875/125 mg b.i.d. for 14 days) and cefuroxime axetil (500 mg b.i.d. for 14 days) were compared in a multicenter, randomized clinical trial of 206 adults with CRS or acute exacerbation of CRS. Overall cure rate were similar: 95% for AMX/CA and 88% for cefuroxime. Rates for eradication of the pathogen originally identified were also similar: 65% for AMX/CA and 68% for cefuroxime. However, clinical relapse was significantly higher in the cefuroxime group: 8% compared with 0% in the AMX/CA (p = 0.0049) group.

Thus, short-term (< 2 weeks) oral antibiotic therapy is associated with a 51 - 96% improvement in CRS symptoms, although the studies have no placebo-control arms, and the outcome was evaluated only for a short time (9 days to 2 weeks), so it is difficult to interpret this as a definite therapeutic benefit. It seems to be an efficacious treatment in acute exacerbations of CRS. Unfortunately, a clear separation of CRS
without and with NP has not been done. There is no overall difference between the therapeutic effects of ciprofloxacin vs. AMX/CA and cefuroxime axetil vs. AMX/CA.

**Long-term (> 1 month) antibiotic treatment (Table VIII)**

Long-term courses of antibiotics, particularly macrolide antibiotics have been extensively studied in the treatment of CRS.

**Roxithromycin** (150 mg daily) given for 3 months to 30 patients with CRS with and without NPs, significantly improved all symptoms (p < 0.001), except for the sensation of foul odour (prospective, case controlled trial) 383.

**Roxithromycin** 150 mg daily was given to 12 patients with CRS with and without NPs (prospective, case controlled trial) 384. There were significant improvements in the aeration of all sinuses on CT and the levels of recruited neutrophils and IL-8 was reduced in specimens of nasal discharge collected from these patients.

The effect of **clarithromycin** on refractory cases of CRS has also been examined in a prospective, case controlled study of 45 adult patients, treated with 400 mg/day for 8 to 12 weeks 385. There was a clinical improvement in 71% and clinical efficacy depended upon the duration of treatment.

In a prospective, case controlled study of 16 patients with CRS given 200 mg **clarithromycin** or 150 mg **roxithromycin** daily for 2 to 3 months 358, those with normal levels of serum IgE showed a significantly higher clinical improvement rate than those with high levels of serum IgE (42% vs. 5%). Clinical improvement was inversely correlated with the eosinophil counts in the peripheral blood, nasal smear and sinus mucosa. Computed tomography scores, numbers of interferon-γ-positive cells, IL-4-positive cells and neutrophils in the sinus mucosa and neutrophil counts in the nasal smears failed to correlate with the clinical improvement rate.

Longer-term treatment has also been studied (prospective, case controlled). Initially, 17 patients with persistent CRS after sinus surgery, systemic steroids and long-term (non-macrolide) antibiotics were enrolled in a study and treated with **erythromycin** 250 mg twice daily or clarithromycin 250 mg daily 386. After 3 months, 77% had responded to treatment and this group continued treatment for another 9 months. The 12-month follow-up showed significant improvements in visual analogue scale (VAS) scores for nasal congestion, sticky secretion, runny nose and
headaches. Endoscopic nasal examination scoring and saccharine transit time also improved significantly.

Macrolides have been incorporated into regimens of medical management. In a prospective randomized trial, 90 patients with CRS with and without NPs were randomized to a group receiving oral corticosteroid followed by 3 months of topical corticosteroid plus erythromycin, or a group receiving ESS followed by topical corticosteroids for 3 months. Follow-up at 1 year showed significant improvement in both groups in VAS scores of symptoms, SinoNasal Outcome Test (SNOT-22), Short Form 36 Health Survey (SF36), nasal NO concentration, acoustic rhinometry, saccharine clearance time and nasal endoscopy score. There was no significant difference between the two groups or between CRS with and without NP, except for total nasal volume, which was greater after surgery and in NPs. Due to the multiple treatments involved in this study, it is difficult to interpret if there was a specific benefit from macrolides.

In the first double-blind, randomized, placebo-controlled clinical trial, 64 patients with CRS without NPs received either 150 mg roxithromycin daily for 3 months or placebo. There were statistically significant improvements regarding SNOT-20 scores, nasal endoscopy scores, saccharine transit time and IL-8 levels in lavage fluid (P < 0.05) in the macrolide group compared to the control group. A correlation was noted between improved outcome measures and low IgE levels. No significant improvements were noted for olfactory function, peak nasal inspiratory flow or α2-macroglobulin levels in nasal lavage fluids. These findings suggest that macrolides have a beneficial role in the treatment of CRS without NP, particularly in patients with low levels of IgE.

Other antibiotic treatments were tried and showed positive effects. Gandhi et al. (1993) followed 26 children with CRS who were treated prophylactically for more than 1 year in a prospective, non placebo-controlled open single centre study. The 12-month period before the use of different prophylactic antibiotics was taken as the control period for each child for comparison. Nineteen of 26 (73%) children had a good outcome (greater than a 50% reduction in the number of exacerbations of sinusitis during a 12-month period compared with the previous year) on prophylactic antibiotics with a reduction in exacerbations of sinusitis from 9.8 episodes per year to 2.7 episodes per year. In contrast, 7/26 (27%) had a poor outcome (p < 0.0001) on prophylactic antibiotics (from 12.6 exacerbations per year to 8.7 exacerbations per
year on prophylactic antibiotics). Treatment outcome correlated inversely with the number of sinus infections before prophylactic antibiotics. They conclude that the use of prophylactic antibiotics is an effective treatment modality in children with CRS, even in patients with selective immune abnormalities.

Scadding et al. (1995)\cite{388}, in a non-placebo controlled single centre study, observed nasal symptoms and measured the ciliary beat frequency in 10 patients with CRS before and after 3 months of treatment with different antibiotics. They showed that patients with CRS have lowered ciliary beat frequencies, with a variation between cilia which probably reflects their proximity to bacterial products and that long-term antibiotic therapy was not only associated with a decrease in symptoms, but also with a significant increase in ciliary beat frequency.

Recently, Dubin et al (2007), in a prospective, case controlled trial, evaluated the Lund-Mackay CT-score before the treatment and after 3 and 6 weeks, respectively, in 35 patients with CRS without NPs treated with a culture-directed antibiotic or clinamycin during 6 weeks\cite{389}. Only 16 patients completed the study and showed a statistically significant CT-score improvement between the pre-treatment and 6-week CT-scan (p = 0.006). Unfortunately, rhinosinusitis symptoms were not assessed in the study.

Systemic antibiotic agents in CRS with NPs (Table VIII)
One study examined the effect of roxithromycin (150 mg a day) for at least 8 weeks on 20 patients with NPs. There was a polyp size decrease in 52% of patients and those with smaller NPs were more likely to improve. Associated allergic conditions and the extent of eosinophilic infiltration had no relation to the treatment result\cite{390}.

Another prospective, case controlled study (n = 20) showed that IL-8 levels in nasal lavage from patients with NPs were reduced during clarithromycin treatment (2 x 200 mg daily during 3 months) and this reduction was significantly correlated with a reduction in the size of the NPs\cite{391}.

Thus, long-term, low-dose macrolide antibiotics (clarithromycin: 200 – 400 mg/day; erythromycin: 500 mg/day; roxithromycin: 150 mg/day) for at least 2 - 3 months seem to be effective in treating CRS without NP and neutrophilic NP. No trial exists comparing the effectiveness of different doses and types of macrolide antibiotics. The available prospective studies show improvement in symptoms varying from 71 - 80%.
Two trials demonstrated a statistically significant improvement of QoL. Recent trials showed also a reduction of eosinophil activity in the sinonasal mucosa after macrolide treatment, and a symptom improvement in patients with CRS and eosinophilic NP. Unfortunately, no study exists documenting a macrolide treatment in eosinophilic NP exclusively, which makes a macrolide cure in this class of CRS less evident. Additional trials, clearly separating CRS and eosinophilic NP, are needed to evaluate whether a treatment with macrolide antibiotics is indicated or not in eosinophilic CRS and NP.

4.1.1.5. Antibiotics after Surgery
One problem with the use of topical antibiotic agents in CRS is the lack of access to the affected sinus mucosa, due to obstructed sinus ostia. After surgery, however, the ostia should be patent to allow drug delivery to the sinuses. However, no prospective trial involving intranasal or systemic antibiotics in the postoperative treatment to prevent recurrences of CRS with and without NPs is available.

4.1.1.6. Side Effects
Common side effects of antibiotics include nausea, diarrhea, and in women, vaginal yeast infections. Severe side effects may involve kidney, liver or bone-marrow function. Blood tests may be used to monitor drug levels and the effects of adverse reactions. Pseudomembranous colitis results from *Clostridium difficile* toxin-related injury. This microbe may grow opportunistically when other bacteria are killed by antibiotics. Antibiotics can also cause allergic reactions. Most are mild and consist of an itchy rash or slight wheezing. Severe reactions, such as anaphylaxis, can be life-threatening. Most adverse events related to antimicrobials are reversible rapidly after cessation of the medication. Irreversible toxicities include aminoglycoside-induced ototoxicity, Stevens-Johnson syndrome and toxicity secondary to nitrofurantoine. Some serious adverse side effects occur more commonly with fluoroquinolones than with other antibiotic drug classes, including central nervous system toxicity, phototoxicity, cardiotoxicity, arthropathy and tendon toxicity. Children and the elderly are at greater risk. Quinolones in comparison to other antibiotic classes rank amongst the highest for risk of causing colonisation with methicillin resistant *Staphylococcus aureus* and *Clostridium difficile*. As a result of this, a general avoidance of fluoroquinolones is recommended.
Topical antibiotic treatment have demonstrated side effects in 10 - 21% of patients, including sore throat, cough, dry skin around the nose and upper lip, tinnitus and joint pain/myalgias. All of these side effects resolved after stopping the drug. No serious side effects were described. Ciliotoxicity occurs with ofloxacin and the effect of long-term and repeated dosing on ciliary beat frequency is unknown. In the randomized placebo controlled, double-blind, single center study by Desrosiers et al. (2001), no difference in adverse effects between tobramycin and saline solution was showed.

Short-term oral antibiotic (AMX/CA, ciprofloxacin, cefuroxime) treatments of CRS have demonstrated side effects in 12 - 25% of patients. Most frequent were gastrointestinal adverse effects (diarrhea, loose stools, abdominal pain, nausea/vomiting). Other adverse events were facial oedema, asthma, vagal discomfort, genital herpes, skin pruritis and medicamentous urticaria. Severe or life-threatening adverse events reported were described in up to 2.5% of patients, with only one considered related to the study drug (urticaria, cefuroxime). All of these adverse events resolved after stopping the administered antibiotic.

Adverse events reported after long-term low-dose oral macrolide antibiotics in CRS treatment were rare (0 - 3%). Two patients suffered from nausea/vomiting and another two patients had epistaxis. All of these adverse events resolved after ceasing the antibiotic. If treating with high doses for several years, there is the potential of ototoxicity. Audiograms at regular intervals are recommended. Possible interactions exist between macrolides and dicumarol, anti-epileptic drugs, terphenadine, methotrexate and anti-depressant drugs.

Another important consequence of the use of antibiotics is the development of bacterial resistance. This is a major public-health problem. Prescription of antibiotics in Europe varies greatly: the highest rate was in France and the lowest was in the Netherlands. A shift from the old narrow-spectrum antibiotics to the new broad-spectrum antibiotics is being seen. Higher rates of antibiotic resistance are found in high consuming countries, probably related to this higher consumption.
Table VI. Topical antibiotic treatment in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Solvent</th>
<th>Dose</th>
<th>Duration</th>
<th>Method</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sykes et al (1986)</td>
<td>CRS</td>
<td>50</td>
<td>Dexamethasone, tramazoline with/without neomycin</td>
<td>Saline water</td>
<td>Dexamethasone 20 µg, tramazoline 120 µg, neomycin 100 µg 4 times daily each nostril</td>
<td>2 weeks</td>
<td>Spray</td>
<td>Randomized, placebo controlled, double-blind single centre study</td>
<td>Improvement: 70% vs. 60% vs. 20% (placebo)</td>
<td>Improvement: 70% vs. 60% vs. 20% (placebo)</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Kobayashi et al (1992)</td>
<td>CRS</td>
<td>208</td>
<td>Aminoglycoside, fosfomycin, cefmenoxine</td>
<td>Saline water</td>
<td>Aminoglycoside 5 mg, 10 mg, 20 mg, fosfomycin 30 mg, 50 mg, cefmenoxine 20 mg, 40 mg, 3 times per week</td>
<td>8 weeks</td>
<td>Aerosol</td>
<td>Prospective, case controlled</td>
<td>Improvement (43% - 72%)</td>
<td>Improvement on x-ray (32% - 59%)</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Kamijyo et al (2001)</td>
<td>CRS</td>
<td>28</td>
<td>Fosfomycin 3%</td>
<td>Saline water</td>
<td>2 ml, 3 times weekly</td>
<td>4 weeks</td>
<td>Aerosol</td>
<td>Prospective, case controlled</td>
<td>Improvement: 60%</td>
<td>Improvement in endoscopy in 60%, decrease in IL-1β * and IL-6 *</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Desrosiers et al (2001)</td>
<td>Refractory CRS after ESS</td>
<td>20</td>
<td>Tobramycin</td>
<td>Saline water</td>
<td>80 mg, 3 times daily</td>
<td>4 weeks</td>
<td>Aerosol</td>
<td>Randomized, placebo controlled, double-blind single centre study</td>
<td>Improvement in both groups without difference</td>
<td>Improvement in both groups without difference</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Uren et al (2008)</td>
<td>Refractory CRS after ESS</td>
<td>16</td>
<td>Mupirocin 0.05%</td>
<td>Lactated ringers salts</td>
<td>400 ml, daily</td>
<td>3 weeks</td>
<td>Lavage</td>
<td>Prospective, case controlled</td>
<td>Improvement *</td>
<td>Improvement in endoscopy *, decrease in bacterial presence</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Videler et al (2008)</td>
<td>Refractory CRS after ESS</td>
<td>14</td>
<td>Bacitracin/colimycin vs. saline solution</td>
<td>Saline water</td>
<td>2 x 8 ml daily (830/640 µg/ml)</td>
<td>8 weeks</td>
<td>Aerosol</td>
<td>Randomized, crossover, placebo controlled, double-blind</td>
<td>No difference of rhinosinusitis symptoms and QoL</td>
<td>No difference in endoscopy</td>
<td>Ib</td>
<td>Negative</td>
</tr>
</tbody>
</table>
### Table VII. Systemic short-term (< 2 weeks) antibiotic treatment in CRS and NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Solvent</th>
<th>Dose</th>
<th>Duration</th>
<th>Method</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legent et al (1994)</td>
<td>CRS</td>
<td>251</td>
<td>Ciprofloxacin vs. amoxicillin/clavulanate</td>
<td>-</td>
<td>Ciprofloxacin 500 mg twice daily, amoxicillin/clavulanic acid 500 mg three times daily</td>
<td>9 days</td>
<td>Oral</td>
<td>Non-placebo controlled, double blind, single centre study</td>
<td>Improvement in both groups (59% vs. 51%)</td>
<td>Improvement in both groups on endoscopy (91% vs. 82%), bacteriological eradication (89% vs. 91%)</td>
<td>Ib</td>
<td>Negative (but improvement in both groups)</td>
</tr>
<tr>
<td>Fombeur et al (1994)</td>
<td>CRS + NP + acute episodes of CRS</td>
<td>56</td>
<td>Ciprofloxacin + prednisolone</td>
<td>-</td>
<td>Ciprofloxacin 500 mg twice daily, prednisolone 40 mg once daily</td>
<td>9 days</td>
<td>Oral</td>
<td>Prospective, case controlled</td>
<td>Improvement (74.5 %)</td>
<td>Bacteriological eradication (90 %)</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>McLeod et al (2001)</td>
<td>CRS + NP</td>
<td>25</td>
<td>Clarithromycin</td>
<td>-</td>
<td>500 mg twice daily</td>
<td>2 weeks</td>
<td>Oral</td>
<td>Non-placebo controlled, single centre study</td>
<td>Improvement</td>
<td>Reduction in CD68, EG2, elastase, IL-6, IL-8, TNF-α, and edema score</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Namyslowski et al (2002)</td>
<td>CRS + acute episodes of CRS</td>
<td>206</td>
<td>Amoxicillin/clavulanate vs. cefuroxime axetil</td>
<td>-</td>
<td>Amoxicillin/clavulanate 875/125 mg twice daily, cefuroxime axetil 500 mg twice daily</td>
<td>2 weeks</td>
<td>Oral</td>
<td>Non-placebo controlled, multi centre study</td>
<td>Clinically cured: 95% vs. 88%</td>
<td>Bacterial eradication: 65% vs. 68%, relapse higher in cefuroxime group</td>
<td>Ib</td>
<td>Negative (but improvement in both groups)</td>
</tr>
</tbody>
</table>

CD68: marker of macrophages, EG2: marker of eosinophilic activity

### Table VIII. Systemic long-term (> 1 month) antibiotic treatment in CRS and NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Solvent</th>
<th>Dose</th>
<th>Duration</th>
<th>Method</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gandhi et al (1993)</td>
<td>CRS in children</td>
<td>26</td>
<td>Amoxicillin, amoxicillin/clavulanate, trimethoprim/ sulfamethoxazole, cefaclor</td>
<td>-</td>
<td>Dose not mentioned, once daily</td>
<td>12 months</td>
<td>Oral</td>
<td>Non placebo controlled, single centre study</td>
<td>Decrease of acute exacerbation by 50% in 73% *</td>
<td>-</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Scadding et al (1995)</td>
<td>CRS</td>
<td>10</td>
<td>Amoxicillin, flucloxacillin, cefadroxil, co-trimoxazole</td>
<td>-</td>
<td>Dose not mentioned</td>
<td>3 months</td>
<td>Oral</td>
<td>Non placebo controlled, single centre study</td>
<td>Improvement (80%)</td>
<td>Increasing in ciliary beating *</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Hashiba et al (1996)</td>
<td>CRS</td>
<td>45</td>
<td>Clarithromycin</td>
<td>-</td>
<td>200 mg twice daily</td>
<td>2 – 3 months</td>
<td>Oral</td>
<td>Non placebo controlled, single centre study</td>
<td>Improvement (71%)</td>
<td>-</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Kimura et al (1997)</td>
<td>CRS + NP</td>
<td>30</td>
<td>Roxithromycin</td>
<td>-</td>
<td>150 mg once daily</td>
<td>3 months</td>
<td>Oral</td>
<td>Non placebo controlled, single centre study</td>
<td>Improvement (80%)</td>
<td>Improvement on x-ray (53%)</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Author et al. (Year)</td>
<td>Indication</td>
<td>N</td>
<td>Drug name</td>
<td>Solvent</td>
<td>Dose</td>
<td>Duration</td>
<td>Method</td>
<td>Study design</td>
<td>Symptoms (stat. signif. *)</td>
<td>Objective (stat. signif. *)</td>
<td>Level of evidence</td>
<td>Outcome</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td>Suzuki et al (1997)</td>
<td>CRS + NP</td>
<td>12</td>
<td>Roxithromycin</td>
<td>-</td>
<td>150 mg once daily</td>
<td>4 – 11 months</td>
<td>Oral controlled, single centre study</td>
<td>Non placebo controlled, single centre study</td>
<td>Decrease in neutrophil score *, reduction of nasal IL-8 * and improvement CT score *</td>
<td>III</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Suzuki et al (2000)</td>
<td>CRS</td>
<td>16</td>
<td>Clarithromycin, roxithromycin</td>
<td>-</td>
<td>Clarithromycin 200 mg once daily, roxithromycin 150 mg once daily</td>
<td>2 – 3 months</td>
<td>Oral controlled single, centre study</td>
<td>Non placebo controlled single, centre study</td>
<td>-</td>
<td>Higher response rate in patients with normal Ig E and lower eosinophil counts in the peripheral blood</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Cervin et al (2002)</td>
<td>Refractory CRS</td>
<td>17</td>
<td>Erythromycin, clarithromycin</td>
<td>-</td>
<td>Erythromycin 250 mg twice daily, clarithromycin 250 mg once daily</td>
<td>12 months</td>
<td>Oral controlled, single centre study</td>
<td>Non placebo controlled, single centre study</td>
<td>Improvement (77%), improvement in VAS * (nasal congestion, sticky secretion, runny nose, headache)</td>
<td>III</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Ragab et al (2004)</td>
<td>CRS + NP</td>
<td>90</td>
<td>Erythromycin vs. ESS</td>
<td>-</td>
<td>500 mg twice daily for 2 weeks, 250 mg twice daily for 10 weeks</td>
<td>3 months</td>
<td>Oral prospective, non placebo controlled, single centre study</td>
<td>Randomized prospective, non placebo controlled, single centre study</td>
<td>Improvement * (VAS) without difference between the 2 groups</td>
<td>Ib</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Wallwork et al (2006)</td>
<td>CRS without NP</td>
<td>64</td>
<td>Roxithromycin vs. placebo</td>
<td>-</td>
<td>150 mg once daily</td>
<td>3 months</td>
<td>Oral randomized placebo controlled, double-blind, single centre study</td>
<td>Randomized placebo controlled, double-blind, single centre study</td>
<td>Improvement * in global patient rating compared to placebo</td>
<td>Ib</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Dubin et al (2007)</td>
<td>CRS without NP</td>
<td>35</td>
<td>Cultured-directed antibiotics or clindamycin</td>
<td>-</td>
<td>?</td>
<td>1.5 months</td>
<td>Oral Prospective case controlled</td>
<td>Prospective case controlled</td>
<td>Improvement of CT score *</td>
<td>III</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Ichimura (1996)</td>
<td>NP</td>
<td>20</td>
<td>Roxithromycin</td>
<td>-</td>
<td>150 mg once daily</td>
<td>2 months</td>
<td>Oral controlled, single centre study</td>
<td>Non placebo controlled, single centre study</td>
<td>Decrease of polyp size (52%)</td>
<td>III</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Yamada et al (2000)</td>
<td>NP</td>
<td>20</td>
<td>Clarithromycin</td>
<td>-</td>
<td>200 mg twice daily</td>
<td>3 months</td>
<td>Oral controlled, single centre study</td>
<td>Non placebo controlled, single centre study</td>
<td>Correlation between reduction of IL-8 and decrease of NP size *</td>
<td>III</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

SF36: Short Form 36 Health Survey, SNOT: SinoNasal Outcome Test, VAS: Visual Analogue Scale
4.1.2. Antifungal treatment - topical and systemic

4.1.2.1. Background
Many causes may be involved in the etiology of CRS: anatomical variants, microbial infection and/or colonization, fungal stimulation, atopic response, AS-intolerance and a combination of all. Most recently, the role of fungal implication has been discussed and investigated. The presence of fungus in sinonasal secretions was detected in a high proportion of patients with CRS (mean: 54.7%, range: 6.2 – 100%), as well as in a control disease-free population (mean: 56.1%, range: 0 – 100%). Thus, it can hardly be taken as proof for a fungal etiology of CRS. However, what has been hypothesized is not a fungal infection, but rather fungal presence in sinonasal secretions, colonization following from an allergic or an altered local (non-allergic) T helper 2-type immunologic reaction in predisposed individuals, resulting in the generation of chronic eosinophilic rhinosinusitis and NPs. If the inflammation observed in CRS with and without NPs is an immune reaction to fungi, reducing the presence of this inflammatory trigger might improve the course of the disease. Ideally, treatment should eliminate the fungus without causing harm to the host. In 1996, Bent and Kuhn studied 22 fungal cultures grown from 15 AFRS patients in vitro, for their susceptibility to five common antifungal drugs, (ketoconazole, amphotericin B, itraconazole, nystatin and fluconazole). Ketoconazole and amphotericin B were shown to be most effective, independent of the fungal organism tested. Amphotericin B is active against most fungi frequently identified within the nose and paranasal sinuses. Despite its clinical effectiveness, the use of systemic amphotericin B is limited by adverse systemic reactions, including fevers, chills, nausea, diarrhea and neutropenia, as well as damage to kidneys and liver. To bypass this systemic toxicity, the use of irrigation and sprays of amphotericin B has been proposed. An added advantage is the local application, in relatively high concentrated amounts, directly to the sinonasal mucosa. Although the injectable formulation of amphotericin B carries US Food and Drug Administration-approved labeling solely for intravenous administration, several alternative routes of application that use the injectable formulation have been reported including the administration of amphotericin B into the pleural cavity, bladder, synovial joints and peritoneal space.
Various studies investigating the effectiveness of topical and systemic antifungals in CRS with and without NPs have been published within the last decade.

### 4.1.2.2. Potential Therapeutic Actions

Topical amphotericin B treatment has been suggested to reduce fungal load, thereby reducing the inflammatory response in the nasal cavities and paranasal sinuses and, ideally, resulting in the improvement of CRS and NPs. In middle to the controversy in the literature regarding the use of amphotericin irrigation in CRS and NP patients, Shirazi et al. (2007) published an *in vitro* study on the use of amphotericin B against 10 fungal species commonly found in nasal cavities. Each fungus was exposed to 20 ml of amphotericin B at concentrations of 100, 200 or 300 µg/ml or sterile water for 6 weeks. They reported that the currently recommended and commercially available 100 µg/ml solution was ineffective in killing fungi *in vitro* during the 6-week period. The 200 and 300 µg/ml solutions, however, had a fungicidal effect after 5 and 6 weeks, respectively. Consequently, they recommended that higher concentrations of topical amphotericin B would be needed to be tested *in vivo* for a shorter time interval than 6 weeks. The shortened time could decrease treatment costs for the patient and increase compliance. The authors did recognize, however, the difficulty in administering amphotericin *in vivo*. Obstructive disease such as NPs, in particular, poses huge difficulty in drug delivery. Since most authors believe that CRS with NPs has a greater association with fungus than CRS without NPs, Shirazi et al. (2007) recommended primary ESS in patients with obstructive disease, followed by nasal irrigation therapy. Additionally, it was suggested that nasal saline rinse before topical antifungal therapy could improve results by removing gross mucopurulence and fungal debris. Unfortunately, the so different study designs and used solvents, in the *in vivo* trials make a comparison on the therapeutic effect of the different concentrations of the antifungal solutions almost impossible.

Recent data suggest that amphotericin B, besides having an antifungal effect, may have some other properties. In common with other polyene antibiotics and antimycotics, amphotericin B acts on cellular membrane permeability. Amphotericin B is a sterol-binding agent with high affinity for ergosterol (the dominant fungal sterol) and low affinity for cholesterol (the mammalian sterol) and is known to modify cell membrane structure by forming aqueous pores in lipid membranes, resulting in an increase in membrane permeability to small ions (inward leak of Na+,...
outward leak of K+) and, consequently, activation of the Na+ K+ - ATPase pump and modifications in transepithelial resistance. By treating human NPs epithelial cells with amphotericin B (50 M, 4 hours daily for 5 days), Jornot et al. (2003) observed an increase in cell permeability and, as consequence, a disruption of the integrity of epithelial monolayer derived from NPs (as demonstrated by 60% drop in transepithelial resistance). In addition, a significant loss in cell number and expression of the tight junction protein occludin was demonstrated using immunofluorescence microscopy. The integrity of turbinate epithelial cells, however, was conserved (i.e. no change in transepithelial resistance), suggesting a different effect on both cell types. For turbinate epithelial cells, Jornot et al. (2005) observed that amphotericin B treatment results in a decrease in transepithelial potentials, short-circuit currents and Na+ absorption. This inhibition of Na+ transport was associated at first with decreased apical sodium channel (EnaC) activity and followed by a decrease in basolateral Na+K+-ATPase pump activity and K+ conductance, possibly reflecting a feedback mechanism that aims to limit cellular Na+ overload and K+ depletion subsequently to formation of amphotericin B pores in the cell membrane. Whether an aberrant feedback mechanism results in the disruption of cell monolayer integrity and cell death in NPs epithelium remains unclear.

In addition to a possible cytotoxic effect on epithelial cells of CRS and NPs, it has been suggested that amphotericin B may have anti-inflammatory properties. However, a 4-week treatment regimen with topical amphotericin B (50 or 100 mg/l, 10 ml twice daily), did not show to result in a significant reduction in IL-5, IL-8, IFN-γ and RANTES (regulated upon activation of normal T-cell expressed and secreted) levels. In addition, an 8-week treatment regimen with a topical amphotericin B spray (3 mg/ml, 200 μl per nostril, 4 times daily) did also not show to result in a significant reduction in ECP and tryptase levels in nasal lavage fluid from patients with NPs. Neither topical amphotericin B therapy nor fungal state before and after treatment had any significant influence on ECP and tryptase levels, although a slight improvement in ECP level was observed in those patients with successful elimination of fungus when compared to those patients with persistent fungus. A randomised, placebo-controlled, double-blind trial has studied the anti-inflammatory hypothesis by testing the effect of nasal antifungal treatment on the inflammatory cytokine levels in NPs. Nasal polyps were collected before and 4 weeks after irrigation treatment.
with topical amphotericin B or placebo. The cytokine - IL-5, IL-8, INF-γ, RANTES content of polyp homogenates was determined by means of ELISA (enzyme-linked immunosorbent assay). They found that NPs contain large amounts of cytokines (IL-5, IL-8 and RANTES) compared with normal inferior turbinate mucosa and that after 4 weeks of treatment with topical agents, IL-5 levels tended to decrease in comparison with those of the other cytokines, but there was no statistically significant reduction in IL-5 concentration with either amphotericin B or with normal saline. They concluded that intranasal antifungal irrigation similar to 0.9% sodium chloride irrigation tends to reduce cytokine expression (IL-5) in NP and that long-term treatment and evaluations is needed to establish the efficacy and anti-inflammatory effects of antifungal treatments in CRS/NP patients. However, a most recent randomized, double-blind, placebo controlled study examining the effect of nasal antifungal treatment on secreted anti-inflammatory mediators in the nasal lavage of patients with CRS with and without NP did not show any significant effect on these markers after a treatment of topical amphotericin B for the duration of 3 months. The anti-inflammatory effect may not be relevant in the antifungal therapy of CRS. These are possible mechanisms for the clinical effect of amphotericin B that are independent of its antifungal role, reducing the size of NPs by decreasing edema and leading to subjective improvement.

4.1.2.3. Topical Intranasal Antifungal Agents

Topical intranasal antifungal agents in CRS and NPs (Table IX)

In 2002, Ponikau et al. published a prospective open-label trial using amphotericin B in 51 randomly selected patients with CRS with NPs. The authors reasoned that since antibiotics and antihistamines did not help these patients it was worthwhile to study the effects of an antifungal drug. Furthermore, although systemic corticosteroids provide some benefit, their utility is somewhat limited in their long-term and repeated use by their side effects. The patients were treated with topical amphotericin B as sinonasal washing, without placebo or other control treatment. The antifungal agent was applied intranasally as 20 ml of a 100 μg/ml solution twice daily for at least 3 months. This study found symptomatic improvement in 75% and endoscopic improvement in 74%, mainly after long lasting treatment (3 – 17 months). Substantial improvement in maxillary sinus CT-scan findings was shown in 12 of 13 patients (92%). Since this pioneer work by Ponikau et al., the debate about
amphotericin B treatment in NP remains an ongoing debate. Critical authors put forward the bias this study had: only 13 of the 51 patients were selected for a post-treatment sinus CT-scan and the lack of a placebo controlled comparison, while the authors themselves concluded that sinonasal administration of amphotericin B was both safe and effective.

Similar to the upper mentioned study, an unblinded, uncontrolled study with 115 patients having medically resistant NPs was published in the same year. They combined topical steroid treatment with amphotericin B and they found a 40% cure rate after a 4-week period of amphotericin nasal irrigation. An average of 48% of patients with stages I and II of NPs were cured, but the treatment was not effective in patients with stage III of NPs; suggesting that polyp stage is a relevant factor for treatment success. Patients who had previously undergone functional ESS showed better response rates (54% cured) than patients without surgery (22% cured). The higher efficacy of the treatment after surgery could be due to a better penetration and deeper accessibility of the drug to the surgically opened sinus cavities.

Another, prospective, case controlled study tested fluconazole nasal spray in addition to systemic steroids and itraconazole unblinded on 16 patients having CRS with and without NPs. They found stabilisation or improvement endoscopically and for the subjective patients’ perception (75%). They interpreted these results as a success of the antifungal spray, although no comparison with a placebo treatment was performed.

In contrast to these studies, randomised, double-blind, placebo controlled trials have been conducted. In a study, 200 µl per nostril of amphotericin B (3 mg/ml) saline spray four times daily was applied over an 8-week period in patients with NPs. The spray was used to avoid artifacts possibly caused by the irrigation itself. They found that the described dosing and time schedule was ineffective and actually worsened symptom scores in the active treatment group when compared to the placebo group. All other investigated parameters, including CT-scan scores for maxillary sinus opacity, QoL scores, endoscopy scores and presence of fungal elements in nasal lavages, did not differ between the two treatment groups. Most importantly, none of the investigated outcome measures improved in the subgroup of patients in whom fungal elements had been detected before but not after treatment with amphotericin B. This raises the question of the causality between CRS/NP and fungi presence. At least the hypothesis that elimination of the supposed causative
agent improves the course of the disease is challenged by this finding. Similar to the above mentioned study, the same authors published data on the effect of nasal antifungal treatment on the levels of ECP and tryptase in the patients with NPs already enrolled in the above mentioned trial. The purpose was to take another objective look at whether or not amphotericin B could reduce the inflammation in the nasal mucosa of patients with NPs. They did not reveal differences between amphotericin B and placebo treatments in the reduction of ECP (p = 0.17) and tryptase (p = 0.09) and no difference was found between cellular activation markers whether fungal elimination was achieved or not (for fungal positive patients). Their conclusion was that neither amphotericin B nor fungal state before and after treatment had any influence on activation markers of inflammatory cells in NPs. Consequently, they found no benefit for the use of amphotericin B intranasal therapy and they hypothesized that fungi are innocent bystanders and not the trigger for inflammatory cell activation (eosinophils).

In response to all these findings consecutive to his pioneer study, Ponikau et al. conducted a randomised, placebo-controlled, double-blind trial in 2005 in order to test intranasal amphotericin B for a longer period of time. Amphotericin B solution was applied twice daily for 6 months at 20 ml (250 μg/ml). Only 24 of the 30 enrolled patients completed the trial and were monitored objectively with CT-scan and endoscopy. This time, no significant effect could be shown on symptoms, although a significant reduction of inflammatory mucosal thickening on both CT-scan and endoscopy as well as decreased levels of intranasal markers of eosinophilic inflammation (eosinophil derived neurotoxin) could be found. However, blood tests did not reveal any decrease of IL-5 and eosinophil levels.

With regard to these confounding data on the suitability of topical amphotericin, a large, multicentre trial was done in 2006. One hundred and sixteen patients were randomly selected to use 25 ml amphotericin B (100 μg/ml) or placebo in each nostril twice daily for 13 weeks, in a large, double-blind, placebo-controlled, multicentre study. Subjective symptom scores were assessed with the visual analogue scale, the amount of nasal obstruction by peak nasal inspiratory flow, nasal endoscopy scores, polyp scores and QoL scores [Rhinosinusitis Outcome Measure-31 (RSOM-31), Short Form-36 (SF-36)] were done before and after 3 months of treatment. The study failed to show any significant improvement or differences between the groups after 3 months using both objective and subjective
measures. The authors concluded that amphotericin B, in the above regimen, showed no additional benefit to intranasal steroids and irrigations and that extramucosal fungi are innocent bystanders in the upper respiratory tract and play no crucial role in the pathophysiology of CRS and NPs in patients with a normal immune status.

These results were repeated in a prospective, non-placebo controlled single centre 3-month trial looking at the effect of amphotericin B on NPs. They also did not find significant improvement in symptoms or decreased NP stages at the nasal endoscopy.

The most recent study evaluated the efficacy of intranasal amphotericin B in patients who have CRS without NP. Sixty-four patients diagnosed with CRS were enrolled in this study. They were assigned randomly to receive irrigation with amphotericin B solution (20 mg of amphotericin B in 500 mL of normal saline) or placebo (yellowish dye in 500 mL of normal saline) for 4 weeks. There was significant improvement in the amphotericin B group (n = 32) both in endoscopic (p = 0.013) and in the Chinese version of the Rhinosinusitis Outcome Measure 31 (CRSOM-31) scores (p < 0.0001). The placebo group (n = 32) showed also significant improvement in CRSOM-31 scores (p < 0.0001). CRSOM-31 scores were lower in the amphotericin B group than in the placebo group after 2-week treatment and remained lower after 4-week treatment, although the difference was not significant (p = 0.091). There were no significant differences in endoscopic scores and bacterial or fungal culture rates between the two groups after treatment.

Taken together, topical amphothericin B treatment has so far not been shown to be more suitable than saline lavage in CRS and NPs, although preliminary work was promising. One study dealing with QoL outcome could not prove statistically significant improvement.

4.1.2.4. Systemic Antifungal Agents
Systemic antifungal agents in CRS and NPs (Table X)
Only one prospective trial was available. This randomised, double-blind, placebo-controlled, multicentre trial studied the use of high-dose oral terbinafine on CRS and NPs. Fifty-three adults with CRS and NPs received either 625 mg/day (n = 25) terbinafine or placebo (n = 28) once daily for 6 weeks. Computed tomography scan
was graded for opacity at baseline and at 6 weeks. They did not find any subjective nor objective benefits after terbinafine treatment and concluded that treatment failed to improve the radiographic appearance, the symptoms, and QoL even when nasal irrigation samples were positive for fungus on culture at the beginning of the trial. This trial seemed to confirm the results of trials with topical antifungal treatments in that the presence of fungi in nasal mucus does not make any difference regarding the treatment outcomes. Terbinafine levels were measured in post-treatment sinus biopsies of selected patients. Although tissue terbinafine levels were well within minimum inhibitory concentration ranges for fungal isolates in CRS, questions arise as to whether tissue bioavailability of oral terbinafine is similar to mucus bioavailability. As has been suggested by Ponikau et al. (1999) 407, fungi reside extramucosally outside the range of the drug circulation. In order to produce an effect, a systemic antifungal should then be secreted into the sinonasal mucus, a phenomenon that has not been documented and may not occur. Their cited reasons for failure were that fungus might not be an exacerbating factor in CRS and NPs, that terbinafine is inadequately secreted into the sinonasal mucus or less, that the duration of therapy was inadequate.

4.1.2.5. Antifungal agents after Surgery (Table XI)
A recent open randomized trial comparing protective effects of lysine AS (LAS) and LAS combined with amphotericin B on NP recurrences in 89 patients who underwent medical polypectomy applied as intramuscular steroids or ESS, suggested that adding amphotericin B to LAS in a long-term topical treatment may add benefit in terms of recurrence protection 424. Recurrence after 20 months was found in 52% treated with LAS after surgery, in 60% after medical treatment and LAS, while 31% after surgical polypectomy and 30% after medical treatment protected with LAS and amphotericin B, respectively. The recurrence of NPs in the groups treated with amphotericin B plus LAS was significantly lower (p = 0.018) than in the two groups treated only with LAS post-“polypectomy”. They concluded that the presence of fungi could be a secondary co-factor in NPs, acting by the way of enhancing the inflammatory response of the NPs and that long-term topical treatment with LAS and amphotericin B may be clinically effective in the treatment of this disease.
A prospective study evaluating any systemic antifungal treatments in CRS with and without NP after ESS to prevent recurrences was not available.

4.1.2.6. Side effects
Although the advantages are clear, topically applied drugs may have cytotoxic effects. To rule out this possibility, Hofer et al. (2004) studied the effect of topical amphotericin B on ciliary beat frequency \(^ {425}\). When diluted in saline, no effect of amphotericin B (0.1 mg/ml) on ciliary beat frequency was observed. When diluted in distilled water, ciliary beat frequency was irreversibly lowered to about 50%, suggesting that physiologic solvents should be used. Confirming these findings, Gosepath et al. (2002) observed minimal ciliotoxicity upon treatment with low concentration of amphotericin B (2.5%, 5%) \(^ {396}\). After increasing the concentration to a 10% solution, ciliary beat frequency dropped. The effect of long-term and repeated dosing on ciliary beat frequency is unknown. Amphotericin B is a cytotoxic drug and long-term topical application may have systemic effects. Frequency of minor adverse events during 3 months of topical amphotericin B treatment in a randomised, placebo controlled trial was similar in the active and placebo group \(^ {231}\). However, major adverse events were more common in the active treatment group (9% in active vs. 0% in placebo group, respectively), although only one event was judged to be drug-related (asthma attack). In a similar trial, Ponikau et al. (2005) could not show any difference in the frequency of minor adverse events between the active and placebo group during 6 months of topical amphotericin B therapy \(^ {421}\). However, similar to Ebbens et al. (2006) \(^ {231}\), there were more major adverse events noticed in the active treatment group (13% vs. 0%), both of them were judged to be drug related (asthma attack). In the other, non placebo controlled trials of topical antifungal agents, adverse events were showed between 0% and 20%, mostly describing a burning sensation and nasal blockage during drug application \(^ {417}\).

Another concern regarding the use of amphotericin B as topical treatment for CRS and NPs is the possibility that widespread use may lead to resistances. Amphotericin B remains a valuable antifungal systemic treatment for potentially life-threatening invasive mycoses and increased selective pressure with topical treatment may give rise to increase drug resistance in common fungal pathogens which still demonstrate low resistance, like Candida and Mucor \(^ {426-428}\). This is a real possibility due to different drug distribution pattern in the sinus cavities (some spaces have sub-
therapeutic drug concentrations) and, in time we may lose a valuable antifungal systemic drug, which still demonstrates low resistance.

The most frequent adverse events reported after long-term oral antifungal treatments are nausea, headache, skin rash, vomiting, abdominal pain and diarrhea. Major adverse events, like serious liver dysfunction are rare and mostly seen in patients at risk and due to drug interactions. Congestive heart failure has resulted in death with itraconazole (Sporanox®). Transient visual changes are common with voriconazole (Vfend®) and it may carry a risk of permanent visual acuity. In the randomised, placebo controlled trial from Kennedy et al. (2005), oral treatment with terbenafine for 6 weeks did not induce more adverse events than placebo, none were drug-related and no difference in liver function was observed between the active and placebo group after 6 weeks 232. In case that systemic antifungal treatment reveals to be appropriate, pretreatment blood analyses and possibly vision checks will be required for good safety and monitoring reasons. Follow-up blood test every 1 - 2 months is indicated, along with patients understanding of the risks, benefits and alternatives.
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Solvent</th>
<th>Dose</th>
<th>Duration</th>
<th>Method</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ponikau et al (2002)</td>
<td>NP</td>
<td>51</td>
<td>Amphotericin B</td>
<td>Sterile water</td>
<td>100μg/ml, 20 ml twice daily each nostril</td>
<td>3 – 17 months</td>
<td>Nasal lavage</td>
<td>Non-placebo controlled, single centre study</td>
<td>Improvement *(75%)</td>
<td>Improvement *(74%) and CT *(92%)</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Ricchetti et al (2002)</td>
<td>NP</td>
<td>115</td>
<td>Amphotomoronal (Bristol-Myers Squibb) + topical corticosteroids</td>
<td>Sterile water</td>
<td>100μg/ml, 20 ml twice daily each nostril vs. 200 μl twice daily each nostril</td>
<td>4 weeks</td>
<td>Nasal lavage vs. nasal spray</td>
<td>Non-placebo controlled, single centre study</td>
<td>-</td>
<td>Improvement on endoscopy *(40%), improvement * on endoscopy in Stage I and II *(48%)</td>
<td>III</td>
<td>Negative</td>
</tr>
<tr>
<td>Jen et al (2004)</td>
<td>CRS + NP</td>
<td>16</td>
<td>Fluconazole (SinuCare, Inc.)</td>
<td>Saline water</td>
<td>200 μg/ml, 2500 μl twice daily each nostril</td>
<td>3 months</td>
<td>Nasal spray</td>
<td>Non-placebo controlled, single centre study</td>
<td>Stabilisation or improvement *(75%)</td>
<td>Stabilisation or improvement on endoscopy *(75%)</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Weschta et al (2004 and 2006)</td>
<td>NP</td>
<td>60</td>
<td>Amphotericin B (Bristol-Myers Squibb)</td>
<td>5% glucose solution (sodium phosphate buffered)</td>
<td>3 mg/ml, 200 μl four times daily each nostril</td>
<td>8 weeks</td>
<td>Nasal spray</td>
<td>Randomised, placebo controlled, double-blind, single-blind study</td>
<td>Worsening *</td>
<td>No difference on CT, ECP or tryptase levels</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Ponikau et al (2005)</td>
<td>CRS + NP</td>
<td>24</td>
<td>Amphotericin B</td>
<td>Sterile water</td>
<td>250 μg/ml, 20 ml twice daily each nostril</td>
<td>6 months</td>
<td>Nasal lavage</td>
<td>Randomised, placebo controlled, double-blind, single centre study</td>
<td>No difference</td>
<td>Less mucosal thickening on CT, less EDN, but not IL-5, Alternaria protein, and eosinophils in lavage</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Helbling et al (2006)</td>
<td>NP</td>
<td>21</td>
<td>Amphotericin B</td>
<td>Sterile water</td>
<td>10mg/ml, 100 μl three times daily each nostril, total daily dose: 3 mg</td>
<td>3 months</td>
<td>Nasal spray</td>
<td>Non-placebo controlled, single centre study</td>
<td>Improvement *(33%)</td>
<td>Improvement on endoscopy *(14%)</td>
<td>III</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Table IX. Continued.

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Solvent</th>
<th>Dose</th>
<th>Duration</th>
<th>Method</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebbens et al (2006) 231</td>
<td>CRS + NP</td>
<td>116</td>
<td>Amphotericin B</td>
<td>2.5% glucose</td>
<td>100 µg/ml, 25 ml twice daily each nostril</td>
<td>13 weeks</td>
<td>Nasal lavage</td>
<td>Randomised, placebo controlled, double-blind, multicentre study</td>
<td>No difference</td>
<td>No difference on polyp scores, PNIF, RSOM-31 and SF-36</td>
<td>lb</td>
<td>Negative</td>
</tr>
<tr>
<td>Liang et al (2008) 423</td>
<td>CRS without NP</td>
<td>64</td>
<td>Amphotericin B</td>
<td>Sterile water</td>
<td>0.04 mg/ml, 500 ml</td>
<td>4 weeks</td>
<td>Nasal lavage</td>
<td>Randomised, placebo controlled, double-blind study</td>
<td>No difference</td>
<td>No difference</td>
<td>lb</td>
<td>Negative</td>
</tr>
</tbody>
</table>


Table X. Systemic antifungal treatment in CRS and NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Solvent</th>
<th>Dose</th>
<th>Duration</th>
<th>Method</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy et al (2005) 232</td>
<td>CRS + NP</td>
<td>53</td>
<td>Terbinafine</td>
<td>Not applicable</td>
<td>625 mg/day</td>
<td>6 weeks (+ 9 weeks follow-up)</td>
<td>Oral</td>
<td>Randomised, placebo controlled, double-blind, single centre study</td>
<td>No difference</td>
<td>No difference on CT, MRI, endoscopy and RSDI patient and physician</td>
<td>lb</td>
<td>Negative</td>
</tr>
</tbody>
</table>

RSDI: Rhinosinusitis Disability Index

Table XI. Antifungal treatment after ESS in CRS with NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Solvent</th>
<th>Dose</th>
<th>Duration</th>
<th>Method</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corradini et al (2006) 424</td>
<td>NP</td>
<td>89</td>
<td>After ESS or medical polypectomy (triamcinolone i.m., total dose: 120 mg); topical lysine acetylsalicylate + amphotericin B</td>
<td>5% glucose solution</td>
<td>3.3mg/ml, 0.5 mg/day</td>
<td>20 months</td>
<td>Nasal lavage</td>
<td>Non-placebo controlled, single centre study</td>
<td>-</td>
<td>Lower recurrence rate * on endoscopy</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

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4.1.3. Antihistamines – topical and systemic

4.1.3.1. Background

Rhinosinusitis is classified as allergic if symptoms correlate with a specific IgE-mediated response, as non-allergic if symptoms are induced by irritant triggers in the absence of specific IgE-mediated responses, and as mixed if specific IgE-mediated responses are present in conjunction with symptoms induced by both, allergens and non-allergenic irritant triggers \(^{429}\).

Although many chemical mediators can induce one or more symptoms of allergic rhinitis (AR), histamine remains its quintessential mediator, especially during the early-phase response. Acting at the H\(_1\)-receptors, histamine can induce most of the allergic symptoms (eg, sneezing; itching of the nose, throat, and palate; and rhinorrhea) through stimulation of the sensory nerves, increase in vascular permeability and mucus production (Figure 9).

**Figure 9.**
The effects of histamine on the nasal mucosa.
Non-allergic, non-infectious perennial rhinitis (NANIPER), a subgroup of CRS without NP, is characterized by sporadic or persistent perennial nasal symptoms that may be triggered by environmental conditions, such as strong smells; changes in temperature, humidity, and barometric pressure; strong emotions; ingesting alcoholic beverages and changes in hormone levels. These triggers do not involve an IgE-mediated immunopathologic pathway and do not require histamine or other allergic mediator release. The symptoms may resemble AR, but usually with less prominent nasal or palatal itching, less sneezing and less conjunctival irritation. Most patients with NANIPER experience nasal congestion, rhinorrhea and postnasal drip as their primary symptoms. Non-allergic, non-infectious perennial rhinitis can be classified into 6 subtypes: drug-induced rhinitis, gustatory rhinitis, hormonal rhinitis, non-AR with eosinophilia syndrome, occupational rhinitis and vasomotor rhinitis. The prevalence of NANIPER ranges from 17 - 52% of all patients with rhinitis. Vasomotor rhinitis is the most common subtype of NANIPER. It is believed to result from disturbed regulation of the parasympathetic and sympathetic systems in which the parasympathetic system dominates, resulting in vasodilation, increased secretion and oedema in the nasal mucosa. Some investigators believe that the sensory nervous system is also involved, with triggering of the release of nasal neuropeptides secondary to environmental irritations as the underlying pathophysiologic events. These patients may also have concomitant AR, and in fact, as many as 60% of patients with AR have a non-allergic component, now known as mixed rhinitis. In the past, vasomotor rhinitis was incorrectly diagnosed by exclusion; nasal symptoms plus negative skin test results led to the diagnosis. We now recognize that vasomotor rhinitis is defined by elicitation of nasal symptoms on exposure to environmental irritants, with or without skin test positivity.

In classifying the available antihistamines, the « first-generation » antihistamines were those that historically were the first on the market (e.g. chlorpheniramine, diphenhydramine, hydroxyzine). Many of these are still available as over-the-counter medications.

There are four major types of histamine receptors: H1, H2, H3 and H4. All are hepta-helical structures that transduce extracellular signals via G-proteins and all have constitutive activity, which is defined as the ability to trigger downstream events, even in the absence of ligand binding. The H1 receptors are the most important in
allergic rhinitis. They have about 45% homology with muscarinic receptors, and this explains why some antihistamines induce anticholinergic side effects. Second-generation antihistamines are less lipophilic than some of the older, first-generation antihistamines, and do not cross the blood brain barrier.

Some of the «second-generation» antihistamines, like fexofenadine, are actively transported into the lumen of the gut, kidney and brain by p-glycoproteins, which restrict their ability to accumulate and cause unwanted side effects. However, agents such as rifampicin, which induce p-glycoprotein, may increase the clearance of fexofenadine and reduce its efficacy. The second-generation antihistamines were therefore developed as H1 blockers, which have fewer unwanted side effects than first-generation antihistamines, particularly sedation. However, two of these, astemizole and terfenadine, have serious cardiac side effects, resulting in prolonged Q-T intervals and arrhythmias and were withdrawn from the market. Effective and safe second-generation antihistamines developed include cetirizine and loratadine. Neither of these have significant cardiac side effects.

Recently, new formulations that are related to previous second-generation antihistamines have become available. These include desloratadine, fexofenadine (= the active metabolite of terfenadine), levocetirizine, and rupatadine, and are currently referred to as “new-generation” antihistamines. The mechanism of histamine receptor antagonism has recently been carefully explored in vitro and in vivo, and it is now understood that the new generation antihistamines, such as levocetirizine, are actually “inverse agonists” rather than receptor antagonists, i.e. they do have intrinsic activity at the histamine receptor site, other than competing for histamine 1 binding. The important new issues pertaining to antihistamines were identified as follows: 1. anti-inflammatory properties, 2. potency, efficacy and effectiveness, 3. lack of cardiotoxicity, 4. lack of drug interactions, and 5. lack of CNS interactions.

New classes of antihistamines are theoretically possible and would act by binding to histamine and competing with histamine for the H1 receptors. Other possible mechanisms would be by influencing the synthesis or metabolism of histamine or possibly by down regulating the expression of histamine receptors. Such new compounds are being explored in drug development programmes, but are not yet available commercially. This type of antihistamine would have the potential to
represent a “third-generation” antihistamine in the future. It is hoped that the development of these new antihistamines, which act differently to current receptor antagonists and are devoid of all side effects, will soon be completed.

Oral antihistamines are efficacious and safe in the management of AR. Some oral antihistamines have certain anti-inflammatory actions. This effect could be helpful by treating patients suffering from NANIPER with this drug, rather than its antihistamine potency. Although generally not recommended as first choice treatment in CRS, an evaluation study of therapy of this chronic disease in the USA revealed antihistamines as rather often prescribed medication (during a 12-month period: an average of 2.7 antibiotic courses; 18.3 weeks of nasal corticosteroids and 16.3 weeks of antihistamines).

Recently, a great deal of important evidence has been generated that suggests that intranasal antihistamines might have certain advantages over oral ones by treating both AR and NANIPER. The intranasal administration delivers drug directly to the target organ, thereby minimizing the potential for the systemic adverse effects. Furthermore, the topical route of delivery enables the use of lower doses of medication. This topical antihistamine is called azelastine, a second-generation nasal antihistamine approved in the treatment of AR. Azelastine hydrochloride has a broad spectrum of anti-allergic and anti-inflammatory activities. Thus, the additional anti-inflammatory action may, at least theoretically, be a pathophysiological basis for the use of intranasal azelastine in the treatment of NANIPER.

4.1.3.2. Potential Therapeutic Actions

Oral antihistamines

Antihistamines are chemically different groups of compounds with similar pharmacologic property of competitively antagonizing histamine at its H₁-receptor site due to the core ethylamine moiety. The radicals or side chains adjoining the core determine their absorption and how they are distributed and eliminated. H₁-antihistamines antagonize the H₁-receptors on smooth muscle cells, sensory nerve endings and glandular cells, leading to a reduction in sneezing, itching of nose, palate and throat, and rhinorrhea. However, they only have mild effect on nasal congestion. Certain antihistamines may also inhibit mediator release such as histamine and PGs from basophils and mast cells, and reduce the production of
mediators such as LTs and chemokines (including interference with the vasoactive neuropeptide substance P; inhibition of production of LTB₄, C₄, and D₄, PGD₂, TNF-α, GM-CSF; and possibly decrease of NF-κB, a transcription factor for multiple pro-inflammatory substances), explaining the anti-inflammatory properties in addition to their H₁-receptor effect. Furthermore, some antihistamines decrease the release of the chemokines IL-8 (fexofenadine) and RANTES (desloratadine) by inhibition of TNF-α. Histamine, which may be released from mast cells in NP tissue, significantly increases the number of epithelial cells expressing ICAM-1 and HLA-DR. This mechanism is blocked by certain antihistamines (cetirizine, loratadine, rupatadine). Antihistamines have also been shown to reduce significantly the inflammatory cell influx of eosinophils and neutrophils after allergen challenge. Desloratadine inhibits in vitro the activation of both eosinophils and mast cells derived from NP. Loratadine, cetirizine, and rupatadine, another second-generation oral antihistamine, have additional anti-platelet-activating factor (PAF) activities inhibiting PAF-induced eosinophil chemotaxis which could be favorable in the treatment of eosinophilic CRS. Rupatadine endowed with anti-histamine, anti-PAF, and anti-mast cell cytokine secretion activity has actually not yet been studied in the treatment of CRS and NP, but could be a promising and safe candidate for further development.

Many of the first-generation antihistamines (available in the USA before 1985) also possess anticholinergic effects that can be of further benefit in the reduction of rhinorrhea. However, H₂-antihistamines which block some vascular dilation, have not been shown to potentiate the action of H₁-antihistamines in the management of rhinitis.

Intranasal antihistamines
In contrast to oral antihistamines, intranasal azelastine has a rapid onset of action (within minutes) and also effectively reduces nasal congestion. Azelastine hydrochloride is a pharmacologically distinct, second-generation H₁-receptor antagonist, with some affinity for H₂-receptors. Azelastine blocks histamine release from rat mast cells and from rabbit and human basophils, and inhibits the response to histamine via antagonism of airway H₁-receptors. Azelastine inhibits generation and release of LTs, which are primary biochemical mediators of the late-phase allergic response, in the nose and from human eosinophils.
(LTB₄/C₄) by blocking phospholipase A₂ and LTC₄ synthase. Oral azelastine also reduces significantly the substance P and bradykinin in nasal secretion, which may play a role in the nasal itching and sneezing associated with AR and NANIPER. In cultured mast cells, azelastine inhibits the release of TNF-α and, in human blood cells, it reduces the generation of GM-CSF, TNF-α, as well as both IL-1β and IL-6. Patients treated with azelastine showed significant decrease in blood cytokine levels and exhaled NO levels. A single dose of intranasal azelastine reduces neutrophil and eosinophil counts and decreases expression of ICAM-1 on nasal epithelial cell surfaces in the early- and late-phase of the allergic, inflammatory response. In vitro, azelastine demonstrated an inhibition of free-radicals produced by human eosinophils and neutrophils, and a reduction of calcium influx induced by platelet-activating factor.

In NPs, azelastine showed an in vitro anti-inflammatory action in therapeutically relevant concentrations as assessed by its ability to reduce TNF-α release as well as to inhibit LTC₄ production in allergenic stimulated human NP cells. In vivo, intranasal azelastine showed nasal symptom reduction and decreased concentrations of myeloperoxidase, ECP and tryptase in nasal secretions, confirming an inhibitory effect on eosinophil and neutrophil activation in NPs.

4.1.3.3. Topical Intranasal Antihistamines (Table XII)

Chronic rhinosinusitis without NPs

One multicentre, randomised, double-blind, placebo controlled study has evaluated the efficacy of intranasal azelastine (1.1 mg/day) in 426 patients with CRS / NANIPER during 3 weeks. Azelastine spray significantly reduced the total nasal symptom score (p = 0.005) from baseline when compared with placebo.

In a similar trial, 89 patients with CRS / NANIPER were treated with azelastine spray (0.84 mg/day) for 2 weeks. A significant decrease was found in nasal obstruction (p = 0.017) and rhinorrhea (p = 0.023) after 2 weeks and also 2 weeks after the end of the treatment. In the azelastine group, rhinoscopy showed a significantly higher reduction of the inflammation and oedema of the nasal mucosa (p = 0.03 and 0.02, respectively). General efficacy assessment by the physician and the patient was in favour of azelastine (p < 0.01).
Chronic rhinosinusitis with NPs

One prospective, case controlled study showed amelioration in nasal symptoms after the intranasal application of azelastine (3 weeks) in 10 patients with NPs. Reduction of rhinorrhea, sneezing and itching was seen in 90%, 100%, and 90%, respectively. Endoscopic findings could not show polyp size reduction.

In another, similar trial, 16 patients with recurrent NPs were treated with azelastine spray for 25 weeks. An important reduction of nasal secretion and itching was showed. Mean concentrations of myeloperoxidase (p = 0.0015), ECP (p = 0.0342) and tryptase (p = 0.0574) in nasal secretions decreased, showing an inhibitory effect on eosinophil and neutrophil activation.

Intranasal azelastine for 2 – 3 weeks improves evidentially nasal symptoms like congestion, rhinorrhea and sneezing, and nasal mucosa inflammation in CRS / NANIPER. Long-term application seems also to decrease nasal symptoms in patients with NPs, but no effect on the polyp size could be demonstrated. Unfortunately, no statistics were shown of the symptoms’ outcome in the two trials about NPs.

4.1.3.4. Systemic Antihistamines (Table XIII)

Chronic rhinosinusitis without NPs

A randomised, cross over, double-blind, placebo controlled trial tested the efficacy of 2 different oral antihistamines (dexbrompheniramine maleate and brompheniramine) in combination with a systemic decongestant on 35 patients with chronic vasomotor rhinitis during 2 weeks. Significant better relieve (p < 0.05) of nasal obstruction and rhinorrhea was showed in both antihistamine groups when compared to the placebo group.

A randomised, double-blind, placebo controlled study evaluated the effect of astemizole compared to placebo in the treatment of CRS / NANIPER. From the 55 included patients, only 10 had proven relevant allergy. Twenty-eighth patients received astemizole (10 mg/day) for 4 weeks and the other 27 a placebo tablet. The antihistamine treated group showed significantly improvement in sneezing and rhinorrhea (p < 0.05) when compared with the placebo group. Nasal decongestion effect was limited.

In a randomised, cross-over study, oral astemizole therapy was compared with intranasal beclomethasone dipropionate spray for the treatment of CRS /
The decrease in the visual analogue scale of the symptoms demonstrated significantly more efficacy in the treatment with beclomethasone spray than with astemizole ($p < 0.05$). Sneezing and rhinorrhea were similar. Nasal congestion tended to be less severe after beclomethasone dipropionate treatment.

A similar, randomised, double-blind trial was performed comparing oral terfenadine with intranasal budesonide in 142 patients with CRS. Budesonide, but not terfenadine, significantly reduced all nasal symptoms from baseline ($p < 0.05$). Terfenadine could significantly relieve the nasal obstruction ($p < 0.05$), more than other nasal symptoms. Budesonide provided a better control of nasal symptoms than terfenadine ($p < 0.05$).

A randomized, double-blind, placebo controlled trial has studied the adjunct effect of loratadine in the standard treatment of CRS with intranasal corticosteroids. Thirty patients with CRS were divided in two groups, half receiving flunisolide two 25 µg puffs per nostril morning and night plus loratadine 10 mg/day and half the same doses of flunisolide plus an orally placebo for 3 weeks. The loratadine treated group had significantly better results in nasal symptoms, with a decrease in sneezing ($p < 0.000001$) and rhinorrhea ($p < 0.006$), respectively. No difference was detected regarding nasal obstruction. The eosinophil counts in the nasal secretion decreased significantly in both groups ($p < 0.05$).

A further, prospective, case controlled study evaluated the outcome and the change in QoL of 61 patients with CRS after a 12-week course of desloratadine (5 mg/day). There were significant reductions in median rhinitis symptom score ($p < 0.001$) and in median endoscopic score ($p < 0.001$). Patients’ general health perception was also improved after treatment ($p = 0.022$).

### Chronic rhinosinusitis with NPs

One randomised, double-blind, placebo controlled study has compared the efficacy of orally cetirizine in a dose of 20 mg/day with placebo in 45 patients with residual or recurrent NP after ESS during a 3-month period. There was a statistically significant reduction of nasal obstruction ($p = 0.016$), rhinorrhea ($p = 0.017$) and sneezing ($p = 0.004$) compared to placebo. No effect on polyp size could be shown.

In conclusion, systemic antihistamines improve significantly rhinorrhea and sneezing, and less, nasal obstruction in patients suffering from CRS. One trial even
observed a statistically significant improvement in QoL. A comparison of oral antihistamines with intranasal corticosteroids showed more efficacy in favour of the corticosteroid treatment. Systemic cetirizine improved evidentially nasal symptoms, but could not show any changes in polyp size in patients suffering from NPs treated for 3 months.

4.1.3.5. Antihistamines after Surgery
There were no data available dealing with intranasal or oral antihistamine treatments after ESS to prevent recurrence of CRS with and without NPs.

4.1.3.6. Side Effects
Unlike first generation oral antihistamines (lipophilic), where central nervous system and peripheric muscarinic side effects were significant due to the crossing of the blood-brain barrier and the poor selectivity for H₁-receptors (sedation, mucous membrane drying, vision blurring, constipation, urinary retention, and tachycardia), frequency of adverse events in newer second generation antihistamines (lipophobic) is low. Second-generation H₁-antihistamines have better H₁-receptor selectivity, and thus, less anticholinergic and antiserotoninergic side effects. However, all these agents, with the exception of fexofenadine, have the potential to cross the blood-brain barrier and inhibit N-methyltransferase or block central H₁-receptors. They also can activate central cholinergic serotoninergic or adrenergic receptors. Their actions can produce four types of adverse central nervous system effects: stimulation, neuropsychiatric, peripheral and suppressive reactions (sedation). The most commonly reported events during treatment with second generation oral H₁-antihistamines were upper respiratory tract infections, wheezing, vulvitis, cough, headache, migraine, drowsiness, sedation and injuries, most of them reported in 1 – 14% of the treated population, however, not necessarily related to the drug. The most frequent adverse effect is sedation. In various studies the experience of sedation occurs in 10 – 25% of users of first-generation H₁-receptor antagonists. Cetirizine, a second-generation oral agent causes also an increased incidence of sedation at its recommended dose (11 - 14% vs. 6% receiving placebo). However, sedation was not noted to be more frequent in a large cohort taking desloratadine or rupatadine compared with placebo. A statistically significant increase in appetite was reported in patients treated with astemizole (20% vs. 5%, p < 0.01)
leading to a significant weight gain. Although caution with cardiotoxicity and cardiovascular arrhythmias, applied to older non-sedating antihistamines (eg., terfenadine, astemizole), actually withdrawn from the market; this risk seems to be absent in newer compounds (desloratadine, levocetrizine, fexofenadine, and rupatadine), at least in recommended doses and regimens. Certain antihistamines can either interact with specific drugs (macrolide antibiotics, oral antifungals) or foodstuff, probably due to interaction of their metabolisation by the hepatic cytochrome P450 system. Co-administration of the antifungal ketoconazole with either fexofenadine or desloratadine can increase the plasma concentrations of these antihistamines by 135% and 40%, respectively. Grapefruit juice, in large amounts, has the potential to decrease plasma levels of fexofenadine, putatively through saturation of organic anion-transporting peptide carriers. Tolerance to the beneficial effects of H₁-antihistamines has not been shown to occur.

The incidence of reported side-effects associated with the use of topical azelastine is low. There were no serious or unexpected adverse effects or significant clinical laboratory findings in CRS / NAPAN patients treated with azelastine nasal spray in the above mentioned studies and the number of patients who discontinued treatment because of an adverse experience was similar in the active treatment and placebo groups, respectively. Bitter taste, headache, somnolence, throat irritation, nasal burning and epistaxis were the most frequently reported dose-dependent side effects (0 - 20%), but the majority of these cases were mild or moderate. The incidence of somnolence was shown to be significantly greater with azelastine nasal spray compared with placebo (11.5% vs. 5.4%; p < 0.05) in patients suffering from AR. On the other hand, the incidence of sedation in CRS / NAPAN studies was 3.2% for azelastine nasal spray compared with 1% with placebo and this difference was not statistically significant. Several studies confirmed these results and showed sedation incidence of about 2% of patients treated with azelastine and placebo, respectively. The most common side effect of azelastine nasal spray is a bitter taste (19.4% vs. 2.4%; p < 0.05); however, this problem can be reduced by using the dosing technique recommended in the product labeling from manufacturer (tilting the head slightly forward and not inhaling the drug to avoid deposition in the nasopharynx).
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Banov et al (2001)</td>
<td>CRS / NANIPER</td>
<td>426</td>
<td>Azelastine vs. placebo</td>
<td>Spray, 1.1 mg</td>
<td>3 weeks</td>
<td>Multicentre, randomised, double-blind, placebo controlled</td>
<td>Total nasal symptoms *, rhinorrhea *, sneezing *, obstruction *</td>
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<td>Ib</td>
<td>Positive</td>
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<tr>
<td>Gehanno et al (2001)</td>
<td>CRS / NANIPER</td>
<td>89</td>
<td>Azelastine vs. placebo</td>
<td>Spray, 0.84 mg</td>
<td>2 weeks</td>
<td>Multicentre, randomised, double-blind, placebo controlled</td>
<td>Nasal obstruction *, rhinorrhea *</td>
<td>Endoscopy; inflammation * and edema *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Bussi et al (1995)</td>
<td>NP</td>
<td>10</td>
<td>Azelastine</td>
<td>Spray, daily dose unknown</td>
<td>3 weeks</td>
<td>Prospective, case controlled</td>
<td>Reduction in rhinorrhea (90%), sneezing (100%), itching (100%)</td>
<td>No changes in polyp size</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Mösges et al (1998)</td>
<td>NP</td>
<td>16</td>
<td>Azelastine</td>
<td>Spray, 0.56 mg</td>
<td>25 weeks</td>
<td>Prospective, case controlled</td>
<td>Reduction in rhinorrhea and itching</td>
<td>Decrease of ECP *, myeloperoxidase * and tryptase in nasal secretions</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Author</td>
<td>Indication</td>
<td>N</td>
<td>Drug name</td>
<td>Daily dose</td>
<td>Duration</td>
<td>Study design</td>
<td>Symptoms (stat. signif. *)</td>
<td>Objective (stat. signif. *)</td>
<td>Level of evidence</td>
<td>Outcome</td>
</tr>
<tr>
<td>--------------------------</td>
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<tr>
<td>Löffkvist and Svensson (1978)</td>
<td>CRS / NARIPE</td>
<td>35</td>
<td>Dextromethorphanine maleate + d-isopropylcine sulphate vs. brompheniramine + 2-amino-1-phenyl-propanol- (1)-hydrochloride vs. placebo</td>
<td>12 mg + 240 mg vs. 24 mg + 100 mg</td>
<td>2 weeks</td>
<td>Randomised, double-blind, cross over, placebo controlled</td>
<td>Improvement of nasal symptoms * in both groups</td>
<td>No improvement in nasal endoscopy</td>
<td>Ib</td>
<td>Positive</td>
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<tr>
<td>Wihl et al (1985)</td>
<td>CRS / NARIPE</td>
<td>45</td>
<td>Astemizole vs. placebo</td>
<td>Orally, 10 mg</td>
<td>4 weeks</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Rhinorrhea *, sneezing *, obstruction</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
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<tr>
<td>Sibbald et al (1986)</td>
<td>CRS / NARIPE</td>
<td>21</td>
<td>Astemizole vs. BDP</td>
<td>Orally, 10 – 30 mg, Spray, 8 – 16 puffs (dose ?)</td>
<td>12 weeks</td>
<td>Randomised, prospective, cross-over</td>
<td>BDP: better improvement in symptom VAS * and obstruction, improvement of rhinorrhea and sneezing in both groups</td>
<td>-</td>
<td>Ib</td>
<td>Negative (BDP &gt; astemizole)</td>
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<tr>
<td>Lau et al (1990)</td>
<td>CRS / NARIPE</td>
<td>142</td>
<td>Terfenadine vs. budesonide vs. budesonide + oxymetazoline nasal drops</td>
<td>Orally, 120 mg terfenadine, budesonide 400 µg</td>
<td>3 weeks</td>
<td>Randomised, double-blind, double dummy</td>
<td>Better improvement in nasal symptom score in budesonide group *, nasal obstruction relieve * in terfenadine group</td>
<td>-</td>
<td>Ib</td>
<td>Negative (budesonide &gt; terfenadine)</td>
</tr>
<tr>
<td>Purello-D’Ambrosio et al (1999)</td>
<td>CRS / NARIPE</td>
<td>30</td>
<td>Loratadine and flunisolide vs. placebo and flunisolide spray: 200 µg</td>
<td>Orally, 10 mg, flunisolide spray: 200 µg</td>
<td>3 weeks</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Rhinorrhea *, sneezing *, obstruction</td>
<td>Eosinophils in nasal secretion decreased in both groups</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Lam et al (2007)</td>
<td>CRS / NARIPE</td>
<td>61</td>
<td>Desloratadine</td>
<td>Orally, 5 mg</td>
<td>3 months</td>
<td>Prospective case controlled</td>
<td>Improvement in nasal symptom score * and general health perception *</td>
<td>Improvement * in endoscopic appearance score</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Haye et al (1998)</td>
<td>Recurrent NP</td>
<td>45</td>
<td>Cetirizine vs. placebo</td>
<td>Orally, 20 mg</td>
<td>3 months</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Obstruction *, rhinorrhea *, sneezing *</td>
<td>No changes in polyp size</td>
<td>Ib</td>
<td>Positive</td>
</tr>
</tbody>
</table>

AAR: active anterior rhinomanometry, BDP: beclomethasone dipropionate, VAS: visual analogue scale
4.1.4. Antileukotrienes - systemic

4.1.4.1. Background

Preformed and newly generated mediators cause early-phase allergic rhinitis symptoms when stimulated by an allergen. Parallel to this response, chemotactic factors induce mediator release from eosinophils, basophils, mast cells, macrophages and lymphocytes, probably causing late-phase (AR) symptoms. Histamine, proteases, cysteinyl-LTs, PGs, platelet-activating factor, kinins, ILs, TNF-α and GM-CSF are early-phase mediators. Late-phase inflammatory mediators include cysteinyl-LTs and other cytokines, which are also partially responsible for early-phase responses in allergic sinonasal inflammation.

Cysteinyl-LTs are formed from arachidonic acid by the action of the enzyme 5-lipoxygenase. Their inflammatory action includes mucus secretion by goblet cells, smooth muscle contraction, inflammatory cell recruitment and activation (mainly eosinophils), decrease of mucociliary clearance, vasodilation causing nasal obstruction due to mucosal oedema, and fibrosis and airway remodeling acting by means of smooth muscle cell and epithelial cell proliferation in the distal airways. Leukotrienes do not appear to stimulate the sensory nerves present in the nasal mucosa and thus probably do not contribute significantly to nasal itching and sneezing. Eosinophils, one of the major sources of LTs, are increased locally and peripherally in patients with NPs. Particularly in patients with AS-intolerance and NPs, LTs may play a central role. Several trials, where asthmatic and AR patients were treated with antileukotrienes, showed significant decrease in peripheral blood and sputum eosinophil cell counts, and clinical improvement in mild-to-moderate chronic stable asthma. These results confirm the role of LTs in stimulating eosinophilic inflammation. Patients with NPs also had an elevation in transcription of LT metabolic precursor proteins. Furthermore, the LTC₄ and LTB₄ synthase was found to be upregulated in NPs, as well as the number of leukocytes expressing the cysteinyl-LT-1 receptors. It has been hypothesised that a high level of LTC₄ in NPs may have a negative prognostic value.

Antileukotrienes were first used in the treatment of asthmatic patients without improvement after conventional therapies. Further trials showed good results in the treatment of AR. Leukotriene receptor antagonists (LTRAs) or leukotriene synthesis inhibitors (=5-lipoxygenase inhibitor) (LTSIs) may reduce tissue eosinophilia in inflammatory airway diseases. CysteinyI-LT-1 receptor antagonist montelukast
and the LTSI zileuton have been suggested to have efficacy on signs and symptoms in CRS with NPs, especially in AS-sensitive patients. Several descriptive case series have reported symptom control and improvement in nasal endoscopic findings after treatment with oral antileukotrienes in CRS with NP \(^{505-508}\). But it is known clinically and empirically that there are responders and non-responders, with a better effect in the treatment of the lower airways diseases rather than sinonasal pathologies.

### 4.1.4.2. Potential Therapeutic Actions

A number of drugs that selectively modify the LT pathway (or antileukotrienes) have been developped. The effect of LTs can be counteracted in two ways:

1) by blockage of the cysteinyl-LT-1 receptor (montelukast, zafirlukast, panlukast)
2) by inhibition of the LT synthesis by 5-lipoxygenase (zileuton)

The generation of LTs and action of the antileukotrienes are demonstrated in Figure 10. In principle, LTSIs have the same clinical effect as LTRAs, but they have additional effect on the synthesis of LTB\(_4\), which functions primarily as a chemoattractant for T cells and neutrophils (infectious inflammation) \(^{509}\). They act on the above mentioned cysteinyl-LT pathway and decrease their inflammatory actions in the nasal and paranasal sinus mucosa. Antileukotriene agents reduce tissue eosinophils in asthmatic patients \(^{497}\), and inhibit eosinophil recruitment, decrease sinusnasal eosinophil activation and block systemic humoral pathway in NPs.
Figure 10.
The action of antileukotriene agents. Leukotrienes (LT) are generated by the action of cytosolic phospholipase A2 (cPLA2) on plasma membranes to release arachidonic acid (AA), which can then be converted into either prostaglandin (PG), lipoxin (LX), or leukotriene A4 (LTA4). Leukotriene A4 can be released from the cell or converted into either LTB4 or LTC4. Outside the cell LTC4 is rapidly hydrolized to LTD4 and then LTE4; these three leukotrienes are collectively referred to as the cysteinyl leukotrienes (CysLTs). Two receptors exist that can bind LTB4: leukotriene B4 receptor 1 (BLT-1) on T cells and neutrophils, and leukotriene B4 receptor 2 (BLT-2) mainly on neutrophils. Similarly, CysLT-1 receptors (on smooth muscle cells and eosinophils) and CysLT-2 receptors (on mucous glands) can bind the CysLTs (with LTE4 capable of binding only CysLT-1 receptors). Enzymes are shown in boxes and currently available strategies to inhibit the leukotriene pathway are indicated in green circles with large red arrows. The corresponding drugs were mentioned in red quadrangles near the inhibiting strategy. 5-LO: 5-lipoxygenase; 15-LO: 15-lipoxygenase; COX: cyclooxygenase; FLAP: 5-LO activating protein (modified from 510).

Nuclear/plasma membrane

Extracellular

Intracellular

MK 886
AM 103
BAY X1005
(experimental)
4.1.4.3. Antileukotriene Treatments (Table XIV)

Chronic rhinosinusitis without NPs

There are no adequate studies or data available to determine the potential usefulness of antileukotriene agents in the treatment of CRS without NPs.

Chronic rhinosinusitis with NPs

In a prospective, case controlled trial, 44 adult patients with NPs associated with asthma refractory to long-term, conventional medical therapy were treated with montelukast (10 mg once a day) as an add-on therapy to intranasal and inhaled corticosteroids for 3 months. Clinical subjective improvement in NP occurred in 64% (p < 0.01) AS-tolerant and 50% (p > 0.05) of AS-sensitive patients, and asthma improvement in 87% (p < 0.01) and 61% (p < 0.01), respectively. Asthma improved significantly in both types of patients (p < 0.05). However, acoustic rhinometry, peak nasal inspiratory flow and NO levels did not change significantly in any group, and improvement on montelukast therapy was not associated with aspirin sensitivity.

In a similar study (prospective, case controlled), 26 patients with NPs treated with intranasal corticosteroids for at least 6 months, were included. Montelukast (10 mg /day) was given to them for 3 months while INS was continued. The nasal symptoms improved significantly (p < 0.001) in 71% of the patients. In addition, the eosinophilia score in the nasal biopsies decreased significantly (p < 0.01).

One prospective, single-blind, randomised controlled study has evaluated the outcome of montelukast treatment compared with intranasal fluticasone propionate in the treatment of asthma associated with NPs. Of the 12 patients included in the study, 7 were randomised to the montelukast group (10 mg once daily) and 5 to the fluticasone group (600 µg daily). They were treated for one month. Subjects in both treatment groups showed improvement in respiration, nasal symptoms and NP size. Pulmonary function tests did not show any significant improvement in both groups. No significant differences were observed between the 2 groups.

Another prospective, randomised controlled study showed better outcome after antileukotriene treatment than after conventional therapy in patients with NPs associated with asthma. Ten patients were treated with montelukast (10 mg daily) and intranasal beclomethasone (600µg daily) (group 1), 10 patients were treated with a conventional rhinosinusitis regimen (loratadine (5 mg/day) with pseudoephedrine (120 mg/day) (group 2), and another 10 patients first underwent
polypectomy followed by the identical treatment of group 1. Nasal symptoms, eosinophils in nasal mucus, and peak flow improved significantly ($p < 0.05$) in group 1 and 3 at the third, sixth and twelfth month. There was no significant difference within the improvement ($p > 0.05$) obtained in the patients of group 3. Group 2 did not show significant changes regarding the baseline in the studied variables ($p > 0.05$).

A similar prospective, randomised controlled study has also examined the potential of **montelukast** as an adjunct to corticosteroids in patients with NPs. Thirty-eight adult patients were randomised into two groups: 18 patients were treated with oral prednisone for 2 weeks (35 mg per day mane reducing by 5 mg every second day) and budesonide nasal spray twice a day for 8 weeks; 20 patients received similar treatment with additional oral montelukast (10 mg once a day) for 8 weeks. Subjects in both treatment groups showed improvement in all of their nasal symptoms and in QoL. Subjects treated with montelukast reported significantly less headache ($p = 0.013$), facial pain ($p = 0.048$) and sneezing ($p = 0.03$) than controls. No significant differences were recorded between the groups when evaluating nasal obstruction, alteration in sense of smell, nasal secretion, overall symptom score and QoL. The effects were not maintained at the 12-week time-point that is four weeks after stopping the treatment.

A double-blind, placebo-controlled trial with a randomised, crossover design has examined the efficacy of **zileuton** on NPs in patients with additional asthma and NSAID-intolerance. Forty patients were included in this study and underwent treatment for 6 weeks. There was a clinically significant effect on asthma scores and on lung-function parameters ($p < 0.01$). Zileuton caused a small but significant reduction of bronchial hyperresponsiveness to histamine ($p < 0.05$) and inhibited AS-induced bronchoconstriction ($p < 0.05$). In addition, nasal symptom scores showed clear effect of zileuton on the sense of smell ($p < 0.01$), a statistically significant effect on rhinorrhea ($p < 0.05$) and a trend toward an effect on nasal obstruction ($p = 0.63$). Daily measurements of peak nasal inspiratory flow showed changes which did not attain statistical significance.

A trial with the same study design demonstrated similar results after a 6-week period of treatment with **montelukast** (10 mg/day). There was a significant improvement of the nasal symptom score, nasal resistance and decrease of eosinophils (smear) and neuropeptides during the montelukast phase compared to placebo.
Another randomized, double-blind, placebo controlled study has evaluated the
treatment of montelukast (10 mg once a day) on NPs. Thirty patients were
included in this study and underwent treatment for 4 weeks. Patients treated with
montelukast improved significantly their nasal symptoms ($p < 0.01$) and health-
related QoL ($p < 0.05$). Intranasal ECP and polyp size tended to improve as well, but
did not reach statistically significance. Placebo-treated patients revealed no
significant changes.

Evidenced studies on systemic antileukotriene agents in NPs have been published,
giving support to the clinical impression that they are effective after a treatment
course of at least 4 weeks. As well as nasal symptom relief and improvement of QoL
(2 studies), an effect on objective nasal resistance and eosinophil count have been
demonstrated. This effect could be maintained by a long-term treatment with
antileukotrienes. Only two studies have done nasal endoscopy and could
demonstrate a decrease of the size of NPs during the treatment period. Two trials
evaluated the olfactory outcome, but only one showed statistically significant
improvement.

4.1.4.4. Antileukotrienes after Surgery (Table XV)
One prospective, case controlled study has compared the outcome of an additional
6-months’ treatment with montelukast (10 mg/day) with a treatment of intranasal
momethasone furoate (200 μg/day) and loratadine (10 mg/day) after ESS in patients
with NPs associated with asthma and AS-intolerance. Both groups showed
improvement in nasal symptoms and nasal resistance. The CT-scans after 7 months
did not show any NP recurrences in the two groups. There was no significant
difference of the evaluated parameters. Patients taking the montelukast reported a
significant reduction in the use of rescue medications for their associated asthma ($p <
0.05$).

A similar prospective, case controlled trial has evaluated the efficacy of
montelukast for 12 months on NPs after ESS. Eighteen patients were treated
with an intranasal corticosteroid for 3 months and montelukast (10 mg daily) for 12
months. Six patients were treated only with the intranasal corticosteroid for 3 months.
The montelukast-group showed significant improvement in nasal, pulmonary and
QoL-related symptoms after 12 months compared to the group without any
treatment. Reduction in NP size was found in all treated patients and this was significantly different in comparison to the non-treated group which shows NP recurrences of 50% as soon as 6 months after the begin of the study. Serologic ECP- and mucosal IL-5-levels did not show a difference between both groups.

Another prospective, randomized controlled study has compared the efficacy of montelukast with intranasal beclomethasone dipropionate (BDP) after ESS in patients with NPs. This study tested 10 mg of montelukast once a day compared to 400 μg intranasal BDP treatments in 40 patients. After one year of medication, significant reduction in nasal symptom score was recorded in both groups. In the montelukast-treated group improvement was more marked in itching, post-nasal drip and headache. The control of sneezing was comparable in both groups with a marginal advantage of montelukast. Intranasal steroids had a more marked effect on smell disturbances and nasal congestion. There was no difference in the recurrence rate or in the need of rescue medications between both groups.

There are only 3 trials evaluating the outcome of antileukotriene treatments after ESS in patients with NPs. During the treatment period (upon 12 months), these drugs seem to prolong the time to recurrence significantly. Two studies showed decrease in NP relapse similar to the intranasal corticosteroid control group, which is well-known for preventing early NP recurrences. One of these trials demonstrated a statistically significant improvement of QoL.

4.1.4.5. Side Effects
The systemic administration of antileukotriene agents in the treatment of NPs has demonstrated minor drug-related side effects in 0 - 14% of patients, including dryness, headache, myalgias, gastrointestinal symptoms, rashes, dizziness, nausea, lymphocytosis, but also increased salivation, cough, fatigue, palpitations, and elevation of liver enzyme levels. However, no severe adverse side effect was seen in the mentioned studies, nevertheless the prolonged treatment periode up to 12 months.
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Reduction of NP size</th>
<th>Level of evidence</th>
<th>Outcome</th>
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<tr>
<td>Dahlén et al (1998)</td>
<td>NP (+ asthma + NSAID intolerance)</td>
<td>40</td>
<td>Zileuton vs. placebo</td>
<td>4 x 600 mg</td>
<td>6 weeks</td>
<td>Randomised, double-blind, placebo controlled, cross-over</td>
<td>Smell *, rhinorrhea *, obstruction</td>
<td>Pulmonary function (FEV1) *, Histamine and LAS bronchoprovocation *, PNIF</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
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<tr>
<td>Wobst et al (2000)</td>
<td>NP (+ asthma + NSAID intolerance)</td>
<td>24</td>
<td>Montelukast vs. placebo</td>
<td>1 x 10 mg</td>
<td>6 weeks</td>
<td>Randomised, double-blind, placebo controlled, cross-over</td>
<td>Nasal symptom score *</td>
<td>Anterior rhinomanometry *, decrease of eosinophils * and neuropeptides *</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
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<td>Ragab et al (2001)</td>
<td>NP (+ asthma + NSAID intolerance)</td>
<td>44</td>
<td>Montelukast</td>
<td>1 x 10 mg</td>
<td>3 months</td>
<td>Prospective, case controlled</td>
<td>Asthma clinical score *</td>
<td>Polyp clinical score *, pulmonary function, PNIF, acoustic rhinometry, NO</td>
<td>-</td>
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<tr>
<td>Malerba et al (2002)</td>
<td>NP (+ asthma)</td>
<td>12</td>
<td>Montelukast vs. intranasal fluticasone propionate</td>
<td>1 x 10 mg</td>
<td>1 month</td>
<td>Prospective, single-blind, randomised controlled</td>
<td>Nasal symptoms improved in both groups, difference not statistically significant.</td>
<td>FEV1, PEF, metacholine bronchoprovocation</td>
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</tr>
<tr>
<td>Kieff and Busaba (2005)</td>
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<td>26</td>
<td>Montelukast (added to intranasal corticosteroids)</td>
<td>1 x 10 mg</td>
<td>3 months</td>
<td>Prospective, case controlled</td>
<td>Nasal symptom score *</td>
<td>Decrease of eosinophilis in biopsy *</td>
<td>-</td>
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<td>Positive</td>
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<tr>
<td>Almeida et al (2005)</td>
<td>NP (+ asthma)</td>
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<td>Montelukast + nasal beclomethasone vs. loratadine + pseudoephedrine vs. polypectomy + montelukast + nasal beclomethasone</td>
<td>1 x 10 mg</td>
<td>12 months</td>
<td>Prospective, randomised controlled</td>
<td>Nasal symptoms *, difference between (1) and (3)</td>
<td>Eosinophils *, Peak flow *</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Pauli et al (2007)</td>
<td>NP</td>
<td>30</td>
<td>Montelukast vs. placebo</td>
<td>1 x 10 mg</td>
<td>1 month</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Nasal symptoms *, QoL *</td>
<td>ECP</td>
<td>Yes, difference not significant</td>
<td>Ib</td>
<td>Positive</td>
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Table XIV. Continued.

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<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Reduction of NP size</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stewart et al (2008) 108</td>
<td>NP</td>
<td>38</td>
<td>Montelukast + oral steroid → intranasal budesonide vs. oral steroid → intranasal budesonide</td>
<td>1 x 10 mg</td>
<td>8 weeks</td>
<td>Prospective, randomised controlled</td>
<td>Headache *, facial pain *, sneezing *, obstruction, sense of smell, secretion, overall nasal symptoms, QoL.</td>
<td>-</td>
<td>-</td>
<td>Ib</td>
<td>Positive (short-term)</td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in 1 second, PNIF: peak nasal inspiratory flow.

Table XV. Antileukotrienes after surgery to prevent NP recurrences

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Effect on NP relapse</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Rienzo et al (2000) 516</td>
<td>NP (+ asthma + NSAID intolerance)</td>
<td>40</td>
<td>Montelukast, control group with nasal momethasone furoate + loratadine</td>
<td>1 x 10 mg</td>
<td>6 months</td>
<td>Prospective, case controlled</td>
<td>Improvement in nasal symptoms in both groups, no significant difference</td>
<td>Improvement in CT-scan and anterior rhinomanometry (no significant difference), asthma rescue medication *</td>
<td>Yes, difference not significant</td>
<td>III</td>
<td>Positive (Montelukast = control group)</td>
</tr>
<tr>
<td>Grundman and Topfner (2001) 528</td>
<td>NP (+ asthma + NSAID intolerance)</td>
<td>24</td>
<td>Montelukast vs. no treatment</td>
<td>1 x 10 mg</td>
<td>12 months</td>
<td>Prospective, case controlled</td>
<td>Nasal, pulmonary and QoL symptoms *</td>
<td>Reduction of ECP and IL-5</td>
<td>Yes *</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Mostafa et al (2005) 517</td>
<td>NP</td>
<td>40</td>
<td>Montelukast vs. intranasal BDP</td>
<td>1 x 10 mg</td>
<td>12 months</td>
<td>Prospective, randomised controlled</td>
<td>Nasal symptoms * in both groups, no significant difference</td>
<td>-</td>
<td>-</td>
<td>Ib</td>
<td>Positive (Montelukast = BDP)</td>
</tr>
</tbody>
</table>

BDP: beclomethasone dipropionate
4.1.5. Aspirin Desensitisation and Maintenance – topical and systemic

4.1.5.1. Background
Aspirin-exacerbated respiratory disease (AERD) is an acquired pathology characterised by chronic hyperplastic eosinophilic sinusitis with NPs, asthma and airway reactivity following the ingestion of medications that inhibit the COX-1 enzyme, namely AS and other NSAIDs. The acute reaction that results from COX-1 inhibition varies in severity and typically consists of the sudden onset of rhinitis (rhinorrhea, nasal obstruction, sneezing, itching of the nose), bronchospasm (coughing, wheezing, dyspnea, chest tightness) and/or laryngospasm (stridor, dysphonia). These respiratory symptoms may be accompanied by extrarrespiratory manifestations including conjunctivitis, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain and hypotension. Whereas the sensitivity to COX-1 inhibition can develop at any time in the progression of AERD, the chronic upper and lower respiratory manifestations generally become clinically apparent between the 2nd and 4th decades of life. Chronic rhinosinusitis with progression to severe NP formation develops first. Asthma may preexist from childhood or may develop later. In adults, the asthma becomes apparent 2 to 5 years after the beginning of the CRS symptoms \(^519\). In the general population, AS-hypersensitivity ranges from 0.6 – 2.5\%, and in adults with asthma from 4.3 – 11\% \(^520,521\). Up to 78\% of patients with asthma and NPs have AS-intolerance mirrored by exacerbation of their respiratory disease after AS ingestion \(^522\). A systematic review of studies designed to measure the prevalence of AERD in adults with asthma found that the prevalence was higher when determined by oral provocation testing (21\%) than by patient reports (3\%) \(^523\).

The event or series of events leading to the transformation from tolerance to intolerance of medications that inhibit COX-1 is unknown. Analysis of the genetic background of this heterogenous disease are ongoing and may open new diagnostic and therapeutic options \(^524\). However, it is clear that in patients with AERD, both the acute reaction and the chronic inflammatory respiratory disease result from abnormal metabolism of arachidonic acid. Recent studies have shown that AERD is associated with an overproduction of pro-inflammatory cysteinyl-LTs and PGD\(_2\), and a relative deficiency of anti-inflammatory lipoxins and PGE\(_2\) \(^525-527\). An increased recruitment of effector cells such as mast cells and eosinophils results, those are capable of releasing cytotoxic molecules leading to respiratory mucosal inflammation and
An IgE-mediated AS-intolerance, that means a real allergic reaction, is also possible to explain the symptoms of AERD. Figure 11 shows a summary of the pathogenetic mechanisms of the arachidonic acid metabolism.

Cysteinyl-LTs have been well established as important molecules in both the acute respiratory reaction that results from ingestion of medications that inhibit the COX-1

\[\text{AA} \rightarrow \text{COX pathway} \rightarrow \text{PGE2} \rightarrow \text{Reduced inhibition} \]

\[\text{COX-2} \rightarrow \text{Change of COX-2 structure} \]

\[\text{Generation of LO-pathway products} \]

\[\text{CysLT: LTA4, LTC4, LTD4, LTE4} \]

\[\text{LTB4} \]

\[\text{LTA4 hydrolase} \]

\[\text{LTC4 synthase} \]

\[\text{5-LO} \rightarrow \text{LTA4} \rightarrow \text{LTA4 hydrolase} \rightarrow \text{LTB4} \]

\[\text{Shunt from COX-towards LO-pathway} \]

\[\text{COX pathway} \rightarrow \text{COX-1} \rightarrow \text{PGE2} \]

\[\text{Nuclear/plasma membrane} \]

\[\text{cPLA2} \]

\[\text{AA} \]

\[\text{5-LO} \rightarrow \text{LTA4} \]

\[\text{LTA4 hydrolase} \rightarrow \text{LTB4} \]

\[\text{LTC4 synthase} \rightarrow \text{LTC4} \]

\[\text{CysLT: LTC4, LTD4, LTE4} \]

\[\text{LTB4} \]

\[\text{Shunt from COX-towards LO-pathway} \]

\[\text{COX pathway} \rightarrow \text{COX-1} \rightarrow \text{PGE2} \]

\[\text{Nuclear/plasma membrane} \]

\[\text{cPLA2} \]

\[\text{AA} \]

\[\text{5-LO} \rightarrow \text{LTA4} \]

\[\text{LTA4 hydrolase} \rightarrow \text{LTB4} \]

\[\text{LTC4 synthase} \rightarrow \text{LTC4} \]

\[\text{CysLT: LTC4, LTD4, LTE4} \]

\[\text{LTB4} \]
enzyme, and the chronic inflammatory process that leads to the clinical manifestations of AERD. Thus, it is not surprising that LT-modifying drugs, such as the 5-lipoxygenase inhibitor zileuton and the cysteinyl LT receptor type-1 antagonists montelukast and zafirlukast, are particularly helpful in the management of the airway disease processes in AERD.

In AS-sensitive patients with NPs, conservative treatment possibilities consist of: 1) avoidance of AS and other NSAIDs, which prevents exacerbations but not progression of the disease, 2) oral / topical corticosteroids, 3) eventually LT receptor antagonists or synthesis inhibitors, and 4) AS desensitisation and maintenance in selected patients. If the symptoms of AERD persist despite the above mentioned measures, or in the event of one of the following indications for treatment with AS or NSAIDs, AS desensitisation followed by daily AS maintenance should be considered:

- Moderate or severe asthma and/or intractable nasal symptoms that are uncontrolled with topical corticosteroids and leukotriene-modifying drugs
- Severe, nasal blocking NP formations
- Daily or frequent courses of systemic corticosteroids to control nasal symptoms and/or asthma
- Additional medical indication for AS (e.g., atherosclerotic cardiovascular disease)
- Medical indication for other COX-1 enzyme-inhibiting medication (e.g., arthritis refractory to acetaminophen)

It is possible to desensitise AERD patients by means of repeated application of AS. Once they have been desensitised, patients can ingest AS on a continuous basis and no further respiratory reactions to AS will occur. In fact, ingesting daily AS can maintain the AS-desensitised state indefinitely. In this condition, patients can ingest any of the crossreacting NSAIDs without adverse effects. In most cases, oral administration is used for desensitisation, but soluble AS, the lysine-acetylsalicylate (LAS) for the intranasal application exists and data are available.

For almost 60 years after the first report by Widal et al. (1922) of the successful desensitisation to AS in a patient with what is now known AERD, the therapeutic benefit of AS in these patients was not recognized. In 1980, Stevenson et al. 

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published a case report of two patients with AERD who experienced improvement in rhinosinusitis symptoms following AS desensitisation and daily AS treatment for several months. In recent decades, several studies have been published demonstrating the clinical effectiveness of AS desensitisation and maintenance in patients with AERD.

4.1.5.2. Potential Therapeutic Actions
The pathophysiologic mechanisms of desensitisation remain obscure. Different studies observed a change in the balance of inflammatory mediators after desensitisation. Most likely, desensitisation in patients with non–IgE-mediated AS-intolerance reactions (that means reactions related to COX-1 inhibition) and IgE-mediated AS-intolerance reactions differs. In patients with IgE-mediated AS-intolerance, mechanisms similar to desensitisation with penicillin are assumed, in which repeated exposure to AS or NSAIDs leads to saturation of anti-NSAID IgE antibody binding sites on mast cells and basophils. In patients with reactions related to COX-1 inhibition, AS desensitisation leads to decreased LT production, down-regulation of cysteinyll-LT receptor-1, and decreased histamine release due to a mast cell inhibition and a reduction of acute tryptase release within 3 hours of exposition \(^{535}\). The relevance of diagnostic tools to monitor and verify the effect of desensitisation have been evaluated, and a balance between PGE\(_2\) and cysteinyll-LTs and the correlation of these variables with clinical symptoms or changes in thromboxane levels have been observed \(^{536,537}\). A reduction in urinary LTE\(_4\) excretion after 2 weeks and in LTB\(_4\) synthesis in peripheral monocytes after desensitisation have been shown \(^{538}\). Another possible mechanism of AS desensitisation could be a direct modulation of the intracellular biochemical pathway of inflammatory cells, such as activation / inactivation of particular transcription factors \(^{539}\).

4.1.5.3. Oral Aspirin Desensitisation and Maintenance (Table XVI)
The first prospective trial dealing with AS desensitisation and AS maintenance included 19 patients with AERD and NPs \(^{540}\). After desensitisation, the patients were treated daily for 2 weeks or longer with \(> 325\) mg of AS. Seventeen patients were elected to continue AS for an average period of 12.5 months after desensitisation, and 76% experienced improvement in their nasal symptoms.
A randomised, double-blind, placebo-controlled, crossover study of the effectiveness of **AS desensitisation followed by daily maintenance of AS** in 25 subjects with AERD was conducted. They found that treatment with AS (325 - 650 mg/day) for 3 months, resulted in significant improvement in nasal symptoms (p < 0.05) and reduction in INS use (p < 0.03) compared with placebo, with 75% of patients experiencing improvement. There was no significant improvement in asthma symptoms or reduction in systemic corticosteroid medication.

To further investigate the beneficial effect of **AS desensitisation and maintenance** in AERD, the same group examined in a prospective manner the effects of this approach in 65 patients with AERD by comparing pre-treatment and post-treatment clinical status in a number of parameters. After AS desensitisation, patients were asked to maintain AS, 325 mg daily to 650 mg three times daily (mean dose, 1214 mg/d) and they were followed for a mean of 3.1 years. The results demonstrated high statistically significant improvement in the number of sinus infections per year (p < 0.0001), hospitalisations for asthma per year (p < 0.0001), olfaction symptom scores (p < 0.0001) and decrease of systemic (p < 0.0001) and INS (p < 0.004). An association of AS desensitisation and a significant reduction in need for sinus surgery, including nasal polypectomy (p < 0.004), from an average of one operation every 3 years before AS treatment to one operation every 10 years after AS therapy was found.

One prospective, case controlled short-term treatment study (1 month) evaluated how rapidly changes occur in clinical parameters after **AS desensitisation and maintenance**. They studied 16 patients with AERD. These patients were evaluated for 4 weeks before AS desensitisation and 4 weeks after starting treatment with AS 600 mg/day. Histamine inhalation challenges were performed for 13 patients before beginning and at the end of the study. The results were as follows: mean daily nasal symptom scores decreased significantly (p < 0.001), daily asthma scores declined (p < 0.001) and daily use of beta-agonists declined from 370 µg to 249 µg (p = 0.01). Of the 13 patients undergoing histamine challenges, 10 showed a decrease in bronchial responsiveness after AS treatment for 1 month. The use of systemic corticosteroids was reduced.

An other prospective, case controlled study monitored the modulations of the eicosanoid pathway with the help of a practicable *in vitro* assay on mixed leukocyte cultures and compared the results with the clinical outcome. Thirty patients with
AERD and polyps were treated with 100 mg AS for 1 year after AS desensitisation and reassessed every 3 months clinically and in vitro. Twenty-five patients (83%) showed a normalisation of in vitro eicosanoid levels (p < 0.01) during this period, 4 showed some improvement, and 1 showed no therapeutic effect on eicosanoid release. Clinical follow-up revealed a low recurrence rate of NPs, with recurrent disease only in 4 individuals (13%) who also showed no normalisation of eicosanoid release levels. Furthermore, a reduction of the average incidence of purulent episodes of sinusitis was seen after 1 year. Of 12 patients with asthma, 9 experienced marked improvement in pulmonary functions. Of 16 individuals with a marked impairment of nasal breathing, 14 felt an increase of nasal patency and 7 of 11 patients with pre-treatment hyposmia had an improved sense of smell after 1 year.

A prospective, case controlled study demonstrated that the therapeutic benefit of AS desensitisation and maintenance in 38 patients with 1300 mg/day on nasal symptom scores (p < 0.0001), asthma symptom scores (p < 0.0001) and systemic corticosteroid dosages (p < 0.0001) was highly significant as soon as 1 month after AS desensitisation and initiation of daily AS maintenance.

High statistically significant improvement in rhinosinusitis and asthma was observed in an observational cohort study by the same investigators involving 172 patients with AERD referred for AS desensitisation. Forty-six patients (27%) discontinued AS treatment within 1 year for a variety of reasons, including 24 (14%) who did so for known side effects of AS (gastritis, gastritis with bleeding, urticaria and epistaxis). Of the 126 patients who continued AS therapy (mean daily dose, 1138 mg/day) for at least a year, 87% experienced improvement in their clinical courses. Analysis of changes in clinical disease markers after 6 months and 1 year of treatment revealed significant reductions in frequency of sinus infections (p < 0.0001) and sinus operations (p < 0.0001), and improved nasal (p < 0.0001), asthma (p < 0.0001) and smell (p < 0.0001) scores. In addition, significant reductions in the dosages of nasal, inhaled and systemic corticosteroids (p < 0.0001) were observed.

A prospective, case controlled study compared the clinical effectiveness and risk of adverse effects of two commonly used AS doses in 137 patients with AERD. Upon completion of AS desensitisation, patients were randomised into two groups: 325 mg, twice daily or 650 mg, twice daily. After 1 month, patients taking 325 mg, twice daily were asked to increase the dose if symptoms were inadequately
controlled, whereas those initially assigned to 650 mg, twice daily were asked to reduce the dose if symptoms were adequately controlled. Patients in either group could also decrease AS doses if side effects occurred. Patients taking 325 mg, twice daily and those taking 650 mg, twice daily at the end of 1 year had significant improvement in nasal symptom scores (p < 0.03), asthma symptom scores (p < 0.03), and yearly numbers of sinus infections (p < 0.0001), sinus operations (p < 0.0001), and hospitalisations for asthma (p < 0.0001) as compared with baseline. In addition, systemic corticosteroid doses were decreased threefold (p < 0.0001) and a significant reduction in INS applications was observed (p < 0.0005). There was no significant difference between dosage groups.

The most recently, prospective, case controlled trial compared two doses of AS (300 mg/day vs 100 mg/day) during the first year of desensitisation and evaluated long-term effects on nasal/pulmonary symptoms in 14 patients with AERD. In all patients taking 100 mg AS (n = 7) recurrent NPs were observed. No patient experienced reduction of asthma medication or improvement of pulmonary function. In the 300 mg group no recurrent NPs were seen. Asthma medication could be reduced in three patients; pulmonary function was improved in five patients. The 300 mg AS-group showed significantly better follow-up parameters when compared with the 100 mg AS-group: rhinomanometry, smell score, pulmonary function test, reduced asthma medication and need of revision sinus surgery (p < 0.05). In the second part of this study, 39 consecutively desensitised patients, taking 300 mg AS, showed significant improvement of olfaction (p < 0.05) and polyp-free nasal passages (p < 0.05) during the first year of therapy. After a median follow-up of 27 months no sinus revision surgery was necessary. Sinusitis and asthma score improved significantly (p < 0.01).

These trials including more than 500 patients with AERD provide good evidence for a beneficial effect of oral AS desensitisation followed by daily AS maintenance of at least 300 mg on the symptoms, medication burden and need for surgical interventions. However, only one randomised, double-blind, placebo controlled study exists which found significant improvement in nasal symptoms and reduction of INS use, but no decrease in asthma score and systemic corticosteroid need, respectively. Three of the five trials dealing with olfactory outcome showed statistically significant improvement.
4.1.5.4. Intranasal Lysine-Aspirin (Table XVII)

In an early, prospective, case controlled study, 2000 µg of intranasal LAS was applied to one nostril and saline to the other once a week for periods of up to 15 months. This treatment was given to 20 patients with recurrent NPs but without any history of AS-sensitivity. Symptomatic polyp recurrence was delayed compared with a control-group of another study while on INS, with eight patients remaining symptom free at 15 months compared with an expected number of three (p < 0.05). Polyp recurrence was bilateral but there was a tendency for the LAS treated side to have less polyp formation as assessed by nasendoscopy and by acoustic rhinometry.

Another prospective, case controlled trial studied the efficacy of inhaled LAS (4 mg/day) for 1 – 3 years in 49 patients with AERD after medical polypectomy with triamcinolone. There was no significant difference of decrease in nasal symptoms when compared with a surgical polypectomy control-group.

A small, double-blind, placebo controlled, crossover trial failed to demonstrate significant improvement in clinical outcomes (subjective nasal and asthma symptoms, objective airway measurements) in 22 LAS-treated (16 mg / 2 days) AERD patients for 6 months as compared with placebo. However, they showed a significant reduction in nasal mucosa cells with cysteiny-LT-1 receptors in the patients treated with LAS.

A recent prospective, case controlled study in 13 patients with AERD treated with increasing LAS doses (→ 108 mg/day) for 3 months found a significant reduction in polyp size on nasoendoscopic examination (p = 0.031), an improvement in the peak nasal inspiratory flow (p = 0.014) and an increase in nasal NO (p = 0.028), but no improvement in nasal symptoms.

In conclusion, some evidence exists that intranasal LAS is effective to treat NPs in AERD. However, the effectiveness of LAS seems limited to a beneficial effect on NP formation. Whether this treatment modality is effective for reduction in nasal symptoms associated with AERD requires further randomized, double-blind, placebo controlled studies.

4.1.5.5. Intranasal Lysine-Aspirin after Surgery (Table XVIII)

An early prospective, case controlled study evaluating the effectiveness of long-term, intranasal LAS (max. 2000 µg/week) after surgical polypectomy in 43 patients with
and without AERD demonstrated a significantly reduced NP relapse at 24 months compared with untreated controls (21% vs. 76%, p < 0.0001) \textsuperscript{549}.

A similar follow-up study of 1 – 6 years observed a significant decrease in NP recurrences (p < 0.001) after surgical polypectomy in 76 patients treated with long-term, intranasal LAS compared with a similar patient group but without LAS treatment \textsuperscript{546}.

In conclusion, some evidence exists that intranasal LAS is effective to prolong the time until NP relapses in patients with AERD. Unfortunately, randomized, double-blind, placebo controlled studies are lacking.

\textbf{4.1.5.6. Side Effects}

There are six potential shock-organ responses with their clinical presentations of reactions, which can occur during AS challenges: 1) bronchospasm, 2) laryngospasm, 3) rhinitis/conjunctivitis, 4) generalized urticaria, pruritis or flushing, 5) gastric pain, and 6) hypotension. During oral challenges with AS, the most important complication is a severe asthma attack. Bronchospasms were objectively demonstrated in 49 - 89\% of the patients after oral AS challenges \textsuperscript{168,541}. An intensive care unit with all modalities for intubation and mechanical ventilation must be readily available for transfer of patients, if required. The potential danger of AS-induced asthma attacks can be significantly reduced by a pretreatment with corticosteroids, theophyllines and antileukotrienes, all of which ensure optimal baseline bronchial patency and stability. In addition, challenges should begin with small doses of AS (30 mg), and then incrementally increased at minimum intervals of 3 hours \textsuperscript{532}. The most frequent complications of AS maintenance are gastrointestinal troubles. Although any patient can experience gastrointestinal side effects, patients with a prior history of gastritis, ulcers, GERD, particularly those with a remote history of AS / NSAID-induced gastritis, may be more prone to these complications. In the above mentioned studies, gastrointestinal side effects occurred in 61 of 482 patients (13\%) with AS maintenance \textsuperscript{167-170,541,542,544}. An accompanying proton pump inhibitor treatment may decrease the rate of these side effects. Other side effects as urticaria (3\%) and nose bleeding (1\%) were mentioned in a follow-up study for a period of 1 – 6 years including 172 patients treated with oral AS \textsuperscript{169}. 

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There were only two studies about intranasal LAS which reported side effects. In 1 of 20 patients gastric pain and in 1 of 13 patients nasal irritation occurred, respectively.\textsuperscript{545,548}
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumry et al (1983)</td>
<td>AERD</td>
<td>19</td>
<td>AS</td>
<td>1056 - 1300 mg</td>
<td>2.1 - 12.5 months</td>
<td>Prospective case controlled</td>
<td>Improvements in nasal symptoms in 76%</td>
<td>-</td>
<td>III (no statistics) Positive</td>
</tr>
<tr>
<td>Stevenson et al (1984)</td>
<td>AERD</td>
<td>25</td>
<td>AS vs. placebo</td>
<td>325 mg – 650 mg</td>
<td>3 months</td>
<td>Randomised, double-blind, placebo controlled, crossover</td>
<td>Improvement in nasal symptoms *, no improvement in asthma</td>
<td>Reduction of nasal CS *, no reduction in systemic CS, no changes in FEV1</td>
<td>Ib Positive</td>
</tr>
<tr>
<td>Kowalski et al (1986)</td>
<td>AERD</td>
<td>16</td>
<td>AS</td>
<td>600 mg</td>
<td>1 month</td>
<td>Prospective, case controlled</td>
<td>Improvement * in nasal and bronchial scores</td>
<td>Decrease of bronchodilatators *, decrease of bronchial responsiveness, reduction of systemic CS</td>
<td>III Positive</td>
</tr>
<tr>
<td>Stevenson et al (1996)</td>
<td>AERD</td>
<td>65</td>
<td>AS</td>
<td>325 – 3 x 650 mg (mean dose: 1214 mg)</td>
<td>3.13 yrs (1 – 6 yrs)</td>
<td>Prospective case controlled</td>
<td>tt. &gt; 1 yr.: improvement in acute sinusitis episodes *, improvements in smell, nasal, sinus and asthma symptoms, hospitalisation for asthma *</td>
<td>Reduction of systemic CS * and nasal CS *, no changes in inhaled CS, reduction of NP size and recurrence rate, reduction in need for operation *</td>
<td>III Positive</td>
</tr>
<tr>
<td>Gosepath et al (2001)</td>
<td>AERD</td>
<td>30</td>
<td>AS</td>
<td>500 – 100 mg</td>
<td>1 year</td>
<td>Prospective, case controlled</td>
<td>Improvement in acute sinusitis episodes, low recurrence rate of NP</td>
<td>Increase in serum PGE2 * and decrease in peptidoleukotrienes *, improvement in pulmonary function</td>
<td>III Positive</td>
</tr>
<tr>
<td>Berges-Gimeno et al (2000)</td>
<td>AERD</td>
<td>38</td>
<td>AS</td>
<td>1300 mg</td>
<td>4 weeks</td>
<td>Prospective case controlled</td>
<td>Improvement * of nasal symptoms, asthma and olfaction</td>
<td>Reduction of systemic CS *</td>
<td>III Positive</td>
</tr>
<tr>
<td>Berges-Gimeno et al (2003)</td>
<td>AERD</td>
<td>172</td>
<td>AS</td>
<td>Mean 1138 mg</td>
<td>1 yr., Follow-up: 1 – 6 yrs.</td>
<td>Prospective, case controlled</td>
<td>Reduction of acute sinusitis episodes *, improvement * in nasal and asthma symptom scores and olfaction</td>
<td>Reduction of systemic, inhaled and nasal CS*, acute sinusitis episodes *, hospitalisations for astma *</td>
<td>III Positive</td>
</tr>
</tbody>
</table>
### Table XVI. Continued.

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al (2007)</td>
<td>AERD</td>
<td>137</td>
<td>AS</td>
<td>650 mg or 1300 mg</td>
<td>1 year</td>
<td>Prospective case controlled</td>
<td>Improvement in nasal symptom score *, asthma symptom score *, episodes of acute sinusitis episodes *, sinus operations *, hospitalisations for asthma</td>
<td>Reduction of systemic *and nasal CS *</td>
<td>III</td>
<td>Positive (650 mg = 1300 mg)</td>
</tr>
<tr>
<td>Rozsasi et al (2008) a</td>
<td>AERD</td>
<td>14</td>
<td>AS 100 vs. AS 300</td>
<td>100 mg vs. 300 mg</td>
<td>&gt; 1 year</td>
<td>Prospective case controlled</td>
<td>300: smell *, nasal score 100: no improvement, no asthma improvements in both arms</td>
<td>Reduction of NP *: 300 &gt; 100, improvement of nasal resistance in AAR * in 300</td>
<td>III</td>
<td>Positive (300 mg &gt; 100 mg)</td>
</tr>
<tr>
<td>Rozsasi et al (2008) b</td>
<td>AERD</td>
<td>39</td>
<td>AS</td>
<td>300 mg</td>
<td>&gt; 1 year</td>
<td>Prospective case controlled</td>
<td>Improvement * of smell, sinusitis and asthma score</td>
<td>Reduction in NP size *, no revision surgery necessary</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

AAR: active anterior rhinomanometry
### Table XVII. Intranasal Lysine-Acetylsalicylate in AERD with NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Scadding et al (1995)</td>
<td>NP (not AERD recurrence s)</td>
<td>20</td>
<td>LAS vs. saline (each nostril)</td>
<td>2000 µg weekly</td>
<td>15 months</td>
<td>Prospective case controlled</td>
<td>Nasal symptoms *</td>
<td>No significant decrease in polyp size by endoscopy and AR</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Nucera et al (2000)</td>
<td>AERD</td>
<td>49</td>
<td>LAS after medical polypectomy with triamcinolone i.m.</td>
<td>Inhalation, 4 mg</td>
<td>1 – 3 years</td>
<td>Prospective case controlled</td>
<td>No significant improvement in nasal symptoms when compared with polypectomy control group</td>
<td>Decrease in NP recurrences</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Parikh and Scadding (2005)</td>
<td>AERD</td>
<td>22</td>
<td>LAS vs. placebo</td>
<td>16 mg/2 days</td>
<td>6 months</td>
<td>Randomised, double-blind, crossover, placebo controlled</td>
<td>No significant improvement in nasal and asthma symptoms</td>
<td>No significant improvement in AR, PNIF and PEFR, reduction * in cell CystLT1 receptors</td>
<td>Ib</td>
<td>Negative (clinical)</td>
</tr>
<tr>
<td>Ogata et al (2007)</td>
<td>AERD</td>
<td>13</td>
<td>Drops → 108 mg</td>
<td>3 months</td>
<td>Prospective, case controlled</td>
<td>No significant decrease of nasal obstruction, other nasal symptoms unchanged</td>
<td>Improvement * in PNIF, nasal NO, NP size</td>
<td>III</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

AR: acoustic rhinometry, PEFR: peak expiratory flow rate, PNIF: peak nasal inspiratory flow

### Table XVIII. Intranasal Lysine-Acetylsalicylate after surgery in AERD with NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patriarca et al (1991)</td>
<td>28 AERD, 15 non-AERD NP</td>
<td>43</td>
<td>LAS</td>
<td>20, 200, and 2000 µg (max. 2000 µg weekly)</td>
<td>2 years</td>
<td>Prospective case controlled</td>
<td>-</td>
<td>Decrease in NP recurrences *</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Nucera et al (2000)</td>
<td>AERD</td>
<td>76</td>
<td>LAS</td>
<td>Inhalation, 4 mg</td>
<td>1 – 6 years</td>
<td>Prospective case controlled</td>
<td>-</td>
<td>Decrease in NP recurrences *</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

AAR: active anterior rhinomanometry, FEV1: forced expiratory volume in 1 second
4.1.6. Bacterial lysate preparations and other immunostimulants - systemic

4.1.6.1. Background
Many predisposing factors are responsible for CRS and recurrent CRS. Chronic inflammation, altered local and systemic immune response to bacterial presence (antigens) may be responsible for frequent recurrences or persistence of CRS with and without NPs. Bacterial superinfections are most frequently the origin of acute exacerbations in patients with CRS, following by aggravation of the preexisting disease. Acute episodes of CRS are often treated by antibiotics, which is discussed controversially. Recurrent acute episodes in CRS are caused by bacteria, including Acinetobacter spp., Enterobacteriaceae, Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella ozenae, Moraxella catarrhalis, Nocardia asteroides, Pasteurella multocida, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pneumoniae and Streptococcus pyogenes (group A). Different immunomodulators or immunostimulants to improve the altered immune system have been tested. A common type of this medication is a bacterial lysate preparation (Broncho-Vaxom®, Luivac®) which is constituted by a mixture of bacterial antigens derived from different species, according to the considered extract. The more often included species are: Staphylococcus aureus, Streptococcus viridans, Streptococcus pneumoniae (6 strains), Streptococcus pyogenes, Klebsiella pneumoniae, Klebsiella ozenae, Moraxella catarrhalis, and Haemophylus influenzae. Antigens are obtained following a mass culture of reference bacterial strains, using a chemical or mechanical lysis of cells and followed by lyophilisation. Another type of immunostimulant medication is RU 41740 (Biostim®), a glycoprotein extracted from Klebsiella pneumonia. A ribosomal extract of immunogenic cellular components, i.e. ribosomes of bacteria, is another form of immunostimulants (Ribomunyl®). Different antigens are mixed and excipients are added in order to prepare the agents. These immuno-stimulant medications are both, a specific and non-specific immunostimulating agent activating different systems in the chain of immunologic defense reaction. They are indicated for the prevention and treatment of recurrent respiratory infections, including sequelae to common cold and influenza. Different studies evaluated the effects of this class of drugs in maintaining the immune system stimulated and in a state of alert, and in raising a defence against microbial
infections, hopefully leading to a reduction in their frequency. Efficacy of immunostimulant medications in terms of reduction of acute episodes of chronic airway diseases and need for antibiotics, have been evaluated in several randomised, double-blind, placebo controlled studies\textsuperscript{555-568}. Those studies are very different and heterogeneous, including patients of all ages suffering from various diseases: recurrent respiratory infections of the upper and lower airway; chronic bronchitis; rhinosinusitis and other ear, nose and throat infections; and chronic obstructive pulmonary diseases. The immunostimulants may also be used for infections resistant to common antibiotics.

4.1.6.2. Potential Therapeutic Actions

The capacity of a virtually intact microbe to activate resting monocytic-macrophage cells is strictly linked to the presence of structures belonging to the bacterial cell wall (for example, protido-glycanes or lipopolysaccharides) against which some receptor structures (such as the so called toll like receptors -TLR) are specific directed. Toll like receptors are expressed on the surface of monocytes membrane. The interaction between bacterial structures and TLR results in the activation of these cells, their differentiation to immature dendritic cells and the following maturation to mature dendritic cells, able to be considered a suitable antigen presenting cell. The use of bacterial antigens obtained by mechanical or chemical lysis is thus able to activate monocytic-macrophagic cells of the intestinal submucosa, inducing the above mentioned differentiation. The activation of such a mechanism results in an immunostimulation. The presentation of bacterial antigens on mature dendritic cells results in the stimulation of the T-cell (with a consequent induction of a powerful T\textsubscript{helper} function) and of the B-cell compartment, followed by the maturation to plasma cells and secretion of specific antibodies. The administration of immunostimulants is thus able to induce the production of serum IgA antibodies in saliva and airway secretions and IgG in serum directed to the administered mixture of antigens\textsuperscript{554,569-571}. These results suggest a stimulation of the mucosa associated immune response which has an essential role in the local combat against bacteria. The secretion of antibodies directed to bacterial antigens has a positive function only in the case where the antibodies will have the capacity to opsonize living bacterial cells, thus favouring the phagocytosis and the annihilation mediated by professional phagocytes, such as granulocytes. These findings represent the actual mechanism of
bacterial lysates, potentiating non-specific (dendritic cells and phagocytes) and specific (T- and B-cells) immune reactions, resulting in a prophylactic effect on recurrent airway infections. The mechanism of action of oral bacterial lysates and other immunostimulants is summarized in Figure 12.

Figure 12.
Mechanism of action of oral immunostimulators (modified from ⁵⁷²). M: M cells; Ag: antigen; APC: antigen presenting cell; Th: T helper cell; Ig: immunoglobulin
4.1.6.3. Bacterial lysate Treatments and other immunostimulants (Table XIX)

Only 3 studies dealing with immunostimulant treatment in CRS were found fulfilling the inclusion criteria.

Chronic rhinosinusitis without NPs

The first randomised, double-blind, placebo controlled trial dealing with Broncho-Vaxom\textsuperscript{®} (= bacterial lysates) included 55 children with CRS suffering from repetitive acute exacerbations\textsuperscript{561}. After a 1-month curative treatment phase (1 capsule/day) a 3-month prophylactic treatment phase followed (1 capsule/day for the first 10 days of each month). The children treated with Broncho-Vaxom experienced a significant decrease in cough (p < 0.05), nasal discharge (p < 0.02), nasal obstruction (p < 0.05) and acute exacerbations of CRS (p < 0.05) when compared with the placebo. An increase of serum IgA was shown at the end of the study period in the Broncho-Vaxom group. The IgA levels showed statistically significant difference between the active and placebo treated children (p < 0.05).

One multicentre, randomised, double-blind, placebo controlled study has evaluated the efficacy of Broncho-Vaxom\textsuperscript{®} (= bacterial lysates) vs. placebo in 284 patients suffering from chronic purulent sinusitis during a 3-month treatment\textsuperscript{558}. They were monitored for 6 months. Reduction in symptom scores and overall-severity score, including cough and expectoration were significant during the treatment period (p < 0.01). The average number of reinfections was significantly lower (p < 0.01) in the Broncho-Vaxom group than in the placebo group at the end of the study. Purulent nasal discharge subsided in the first month of treatment with Broncho-Vaxom and continued to decrease significantly (p < 0.001) until the end of the study. Abnormal radiological examinations decreased by 83% in the Broncho-Vaxom group against 45% in the placebo group.

A similar trial has compared the efficacy of a treatment with a bacterial immunostimulant (3 x 30 drops/day), comprised of cells and autolysates of human Enterococcus faecalis bacteria (Symbioflor 1), to placebo in 157 patients with chronic recurrent sinusitis by investigating the occurrence of acute relapses during the treatment (6 months) and follow-up period (8 months)\textsuperscript{573}. The occurrence of relapses (50 incidents) under bacterial lysate treatment was about half (56%) the number observed under placebo (90 incidents) (p < 0.045). This superiority of the bacterial lysate was found during the treatment period with 17 vs. 33 relapses (p =
0.019) as well as during the follow-up observation with 33 vs. 57 relapses (p = 0.013). The mean time interval to the first relapse was clearly longer under Symbioflor 1 (513 days) than under placebo (311 days). The relative risk for a relapse under the test preparation compared to placebo was 0.49 during the treatment and 0.56 during the follow-up period. Severity of the acute relapses was comparable in both groups.

In conclusion, bacterial lysate therapy decreases evidentially nasal symptoms and the frequency of acute relapses in adults and children suffering from CRS.

Chronic rhinosinusitis with NPs
No data were available treating patients who suffered from NP with bacterial lysate or other immunostimulant preparations.

4.1.6.4. Bacterial lysate Treatments or other immunostimulants after Surgery
No trial was available evaluating bacterial lysate or other immunostimulant treatments after ESS to prevent NP recurrence.

4.1.6.5. Side Effects
In the systematic review of Sprenkle et al. (2005) about clinical efficacy in chronic bronchitis and chronic obstructive pulmonary disease, similar numbers of patients withdrew from the Broncho-Vaxom group (9.2 - 14.5%) and the placebo group (14 - 15.4%) 574. In larger cohort studies, mild adverse events are described in 3 – 15% in the active treatment group and 1 – 16% in the placebo group, respectively 555,558,573,575. The most common reported and mild adverse events were headache, gastrointestinal symptoms (nausea, stomachache, and diarrhea) and exanthema. Major severe adverse events were not observed.
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zagar and Löfler (1988)</td>
<td>Recurrent relapses of CRS (children)</td>
<td>55</td>
<td>Broncho-Vaxom (bacterial lysate) vs. placebo</td>
<td>Orally, 1 cpsl. for 30 days 1 cpsl., 10 days/mth. for 3 mths.</td>
<td>6 months?</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Reduction * of cough, nasal discharge, obstruction and acute sinusitis episodes</td>
<td>Increase of Ig A levels *, reduction of erythrocyte sedimentation rate *, improvement on sinus x-rays *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Heintz et al (1989)</td>
<td>CRS</td>
<td>284</td>
<td>Broncho-Vaxom (bacterial lysate) vs. placebo</td>
<td>Orally, 1 cpsl., 10 days/mth.</td>
<td>3 months</td>
<td>Multicentre, randomized, double-blind, placebo controlled</td>
<td>Reduction * of nasal symptoms, cough, expectorations, acute episodes and purulent nasal discharge</td>
<td>Reduction of radiologic signs: Broncho-Vaxom &gt; placebo</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Habermann et al (2002)</td>
<td>Recurrent relapses of CRS</td>
<td>157</td>
<td>Symbioflor 1 (cells and autolysates of human Enterococcus faecalis) vs. placebo</td>
<td>Orally, 90 drops</td>
<td>6 months</td>
<td>Multicentre, randomized, double-blind, placebo controlled</td>
<td>Less acute episodes *</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
</tbody>
</table>
4.1.7. Capsaicin - topical

4.1.7.1. Background

In the pathophysiology of CRS, an imbalance in the non-adrenergic, non-cholinergic, peptidergic neural system of the human nasal mucosa has been proposed as one underlying mechanism. The distribution of these nerves along mucosal glands and blood vessels strongly suggests their regulatory role of these structures. An activation of sensory nerve receptors in the nasal mucosa leads to a release of neuropeptides from the peptidergic sensory neurons and provokes effects similar to CRS symptoms. These sensory neuropeptides are potential contributors to CRS. Locally released from the peptidergic nerves (antidromic release), mainly unmyelinated sensory C-fibres in the nasal mucosa, after activation by unspecific stimuli like inflammatory mediators (histamine, bradykinin, PGs, LTs) or inhaled irritants (nicotine, cigarette smoke, formaldehyde, capsaicin), neuropeptides may activate several processes leading to CRS signs and symptoms (Figure 13). Activation of nasal sensory nerves can lead to vascular congestion by 3 routes: 1) initiation of axon responses, 2) direct effects on the vasculature, or 3) induction of central nervous reflexes involving the sympathetic and parasympathetic nervous system. These reflexes also provoke sneezing and a sense of nasal irritation, and together with the vascular congestion, they cause nasal obstruction. Sensory nerves respond to the above mentioned « noxious » chemical and mechanico-thermal stimuli by conveying messages of injury (pain) to the central nervous system and by initiating local vascular inflammatory reactions. The peripheral axon responses lead to a release of the neuropeptides CGRP, SP and neurokinin A (NKA). These neuropeptides are the product of a peripheral sensory nerve subpopulation that has been termed capsaicin-sensitive primary afferents, consisting mostly of unmyelinated C-fibres and some myelinated A-fibres. Substance P and NKA receptors are present on human nasal glands, epithelium, and on arterial, venous and sinusoidal vessels. Substance P and NKA stimulate mucous glycoprotein secretion from human nasal mucosa, and SP elicits proliferation of both, human fibroblasts and endothelial cells in culture. Calcitonin gene-related protein receptors are present on arterial vessels and CGRP acts as a potent and long-acting arterial vasodilator. Calcitonin gene-related protein also induces proliferation of human upper airway epithelial cells in cultures, suggesting a role in regulating airway epithelial cell growth, and in stimulating the repair of damaged nasal epithelium and hyperproliferation of the
epithelium in NPs. These neuropeptides are also known to cause plasma extravasation, mucus hypersecretion and activation of mast cells in human respiratory mucosa.

The hypothesis that neurogenic inflammation may play a role in the pathogenesis of CRS with and without NPs has led to trials on capsaicin treatment in these sinonasal diseases. Capsaicin (8-methyl-N-vanillyl-6-nonenamide), the active substance from red hot chilli peppers, is a specific sensory nerve stimulant, activating certain fibres but not others. The unmyelinated sensory C-fibres or « pain receptors » are especially sensitive to capsaicin. Intranasal capsaicin provocation results in rhinorrhea, nasal blockage and sneezing. These effects may be produced either through an *orthodromic, central neural reflex*, associated with efferent, predominantly parasympathetic neurotransmission or via an *antidromic, afferent local release of neuropeptides from sensory neurons* (Figure 13). Repeated applications of capsaicin, however, lead to desensitisation and even degeneration of peptidergic unmyelinated sensory C-fibres. Thus, capsaicin is a « neurotoxin » which depletes SP with some other neurokinins and neuropeptides, leading to long-lasting damages of unmyelinated and thinly myelinated axons when repeatedly applied to the nasal mucosa, and so reducing its hyperreactivity and belonging nasal symptoms.

Intranasal capsaicin administration has been suggested as an alternative to expensive corticosteroids in the treatment of CRS in developing countries. However, intranasal capsaicin causes a great deal of pain and treatment with capsaicin in CRS with and without NPs is still an area of ongoing research.
Figure 13.
Scheme of autonomic and peptidergic innervations of the nasal mucosa. Irritation initiates an afferent sensory signal. After central processing, this leads to an efferent, predominantly parasympathetic signal, giving rise to increased secretion and vasodilatation – the so called orthodromic reflex. The initial irritation also induces the local release of neuropeptides (e.g. substance P, calcitonin gene-related peptide) from sensory nerves in the nasal mucosa, also resulting in increased vasodilatation, vascular permeability and secretion – the so called antidromic reflex (modified from 581).

4.1.7.2. Potential Therapeutic Actions
Capsaicin is the active substance of hot red peppers. Its mode of action is well demonstrated in rodents, where it affects mainly the thin, unmyelinated sensory nerve fibers 591. It acts on nonspecific cation channels and allows the influx of calcium into the cell, leading to depolarization of the neuron, and to pain, neuropeptide release and the axon response. Capsaicin causes initial stimulation evidenced symptomatically by the immediate burning sensation, rhinorrhea, and lacrimation with release of endogenous neuropeptides SP and CGRP, followed by depletion of these fibers and desensitization to capsaicin and other sensory stimuli after repeated applications 592-596. This «pharmacologic» desensitization is
characterized by a progressive decline in response to capsaicin. With higher doses, long-term functional decrease or even morphological destruction of the thin sensory neurons may occur, which may explain the desensitization (reduction or loss of response to capsaicin and other stimuli) lasting for several weeks. In humans, the effect of capsaicin has not been fully documented. Different studies were unable to show a reduction of non-adrenergic, non-cholinergic C-fibres in the nasal mucosa in CRS patients after successful capsaicin treatment. Downregulation of vanilloid receptor subtype 1 (=capsaicin receptor) expression, accompanied by a loss of SP and CGRP showed in treatment of the rat bladder with capsaicin may be an explanation for the effects of capsaicin on upper airway diseases. A marked reduction of sensory neuropeptides content was measured in the nasal mucosa after capsaicin treatment. However, it is difficult to understand how capsaicin receptor downregulation alone can result in the long-lasting therapeutic effect observed in CRS patients. Capsaicin also seems to modulate inflammation of the nasal mucosa. A recent study showed that capsaicin targets specific pathways involved in inflammation (NF-κB inhibition), proving its anti-inflammatory activity. However, the mechanism explaining the therapeutic effect of repeated capsaicin applications remains unclear.

4.1.7.3. Topical Intranasal Capsaicin
Chronic rhinosinusitis without NPs (Table XX)
A prospective, case controlled study has demonstrated significant reduction of nasal symptoms after 3 consecutive days of treatment with daily doses of 0.009 mg of topical capsaicin in 20 patients with CRS / NANIPER (vasomotor rhinitis). The mean nasal symptom score involving nasal obstruction and nasal secretion was significantly reduced (p < 0.01) by capsaicin treatment until at least 30 days after topical application.

A prospective, case controlled study investigated the efficacy of intranasal capsaicin (0.03 mmol/l, once-daily, 3 days) in 10 patients with CRS / NANIPER. Significant improvements were shown for nasal blockage and discharge 1 and 3 months after treatment (p < 0.01). Sneezing did not show statistically significant improvement. After 6 months, patients were observed to revert to the initial symptom score.
Another prospective, case controlled study has evaluated capsaicin spray applications in 16 patients with CRS / NANIPER. They underwent a capsaicin application (0.009 mmol/l) once a week for consecutive 5 weeks. Nasal symptoms like obstruction, rhinorrhea and sneezing improved statistically significant (p<0.05) at 6 months after the end of capsaicin treatment. Both nasal vascular responses (laser Doppler flowmetry) and objectively measured nasal resistance (anterior rhinomanometry) have been markedly reduced after the 5th application (p<0.01). Nasal biopsies showed a 50%-reduction of the CGRP-like immunoreactivity content (p<0.01).

A similar study has evaluated capsaicin applications in increasing concentrations in 27 patients with CRS / NANIPER during 7 weeks (0.01, 0.03, and 0.1 mmol/l; 7 applications). Nasal symptoms did not improve significantly 6 months after the treatment. Patients with nasal hypersecretion and sneezing showed greater improvement than patients with nasal obstruction.

In a prospective, case controlled trial, 84 patients with CRS / NANIPER were treated with capsaicin spray for 4 weeks (1.5 mg/day). Improvement was demonstrated in nasal symptoms, endoscopic mucosal findings and nasal resistance. Unfortunately, no statistical comparisons were done.

Capsaicin applications of increasing concentrations were evaluated in a prospective, case controlled trial in 123 patients with CRS / NANIPER for the duration of 3 weeks (0.01, 0.03, and 0.1 mmol/l; 5 - 7 applications). An improvement of the predominant symptoms was shown in 62 - 72% of the patients. Unfortunately, no statistical comparisons were done. A reduction of unpleasant side effects following application (epiphora, itching, sneezing, mucosal oedema) indicating a desensitising effect could be documented. Immunohistochemical investigations of nasal mucosa biopsies did not demonstrate a reduction of peptidergic neurons within the nasal mucosa.

Another study (prospective, case controlled) compared the long-term effect of two different application regimens with capsaicin spray (0.1 mmol/l). Thirty patients with CRS were included. Patients in group A were first treated with capsaicin 5 times on a single day at intervals of 1 hour. After 2 weeks, they received a total of 5 treatments with placebo once every 2nd or 3rd day. Patients of group B first received placebo 5 times on a single day at intervals of 1 hour followed 2 weeks later by a total of 5 treatments with capsaicin once every 2nd or 3rd day. Both active treatment
regimens showed significant improvement in nasal symptoms, nasal patency (acoustic rhinometry) and cold dry air hyperreactivity (p < 0.05) up to 9 months after treatment (p < 0.05). No significant changes was found in smell and peak nasal inspiratory flow.

One randomised, double-blind, placebo controlled study has evaluated the efficacy of endonasal irrigations of capsaicin (0.1 mmol/l) in 25 patients with CRS / NANIPER during 2 weeks (7 irrigations) 610. Nasal symptoms improved significantly more in patients treated with capsaicin compared with patients treated with placebo (p = 0.0007). The therapeutically effect lasted for more than 9 months. No significant difference was found in the mean concentrations of LTC₄, -D₄, -E₄, PGD₂ and tryptase, which are mediators of various inflammatory cells. This may be explained, as their concentration was low at baseline and comparable with levels observed in nasal lavage obtained from normal controls.

The second randomised, placebo controlled study compared the effect of various capsaicin dosages 611. A total of 208 patients affected by CRS without NPs were enrolled and randomised into 3 groups (groups A, B, and C) receiving increasing doses of capsaicin (1, 2 and 4 μg/puff, respectively) and 1 group (group D) receiving a placebo. One puff per nostril was instilled 3 times a day at 30 minutes intervals for 3 consecutive days. A significant reduction of nasal symptoms was only seen in the 4 μg/puff–group when compared with the placebo treatment (p = 0.006).

In conclusion, intranasal capsaicin improves evidentially sinonasal signs and symptoms associated with CRS / NANIPER, such as nasal obstruction, rhinorrhea and sneezing. Objective nasal airway assessments confirmed these results by showing a decrease of mucosal edema by endoscopy and improvements of nasal patency by rhinomanometric measurements.

**Chronic rhinosinusitis with NPs (Table XXI)**

A randomised, placebo controlled study evaluated the efficacy of intranasal capsaicin (0.1 ml in each nostril, 0.03 mmol/l) once a week for 5 consecutive weeks in 30 patients with NPs 612. They showed significant improvement in nasal symptoms (p<0.01) and objectively measured nasal resistance (p < 0.01) at 1 - 3 months after the treatment compared to placebo. A reduction in the size of NPs was found at the
1- and 3-month controls (p < 0.05). An increased nasal eosinophilia was noted after the treatment period without correlation to the polyp size.

A prospective, case controlled study has demonstrated significant reduction of NP size after 5 consecutive days of treatment with increasing doses (0.03 – 0.1 mmol/l) of topical capsaicin. Nasal symptoms and endoscopy showed significantly improvement (49% and 71%, respectively) (p < 0.05) compared with the pre-trial findings. Computed tomography measures showed statistically significant reduction of inflammatory signs (p < 0.05). The ECP level was not influenced by the treatment.

In conclusion, intranasal capsaicin decreases NP size and reduces nasal symptoms. Objective nasal airway assessments confirmed the subjective findings by showing nasal patency improvements (objectively measured nasal resistance, endoscopical findings, CT-scan measurements). No reduction of tissue eosinophils was found after the treatment, explaining another mechanism than the inhibition or reduction of inflammatory cells. One study dealing with olfactory outcome showed a statistically not significant improvement after the medical treatment. Unfortunately, there is no randomised, double-blind, placebo controlled study confirming these results.

4.1.7.4. Capsaicin after Surgery (Table XXII)

Only one study was found fulfilling the criteria of inclusion. This randomized, double-blind, placebo controlled study has examined the efficacy of intranasal capsaicin (3 μmol/l) after ESS in 51 patients with NPs. Once a week intranasal application of capsaicin for 5 weeks showed significant less NP recurrences and significant better subjective nasal patency (p < 0.001) when compared with placebo treatment at the 9-month follow-up. Nasal polyps were statistically significant smaller in the treated group (p < 0.01): 40% polyp stage 0 (Malm) and 45% stage 1 in the active treatment group; 45% polyp stage 2 and 40% stage 3 in the placebo treated patients, respectively.

4.1.7.5. Side Effects

The published controlled trials indicate that capsaicin can be safely administered with almost no severe adverse effects. The most common side effects following intranasal application are burning sensation in the nose and on the
upper lips, lacrimation, rhinorrhea, and coughing, itching or sneezing and nasal congestion. Topical nasal anesthesia with 10% xylocain spray will reduce these unpleasant sensations. Other, less frequent, but more severe side effects are reported: dyspnea, headache, epistaxis, nasal dryness and skin exanthema (0% - 7.5%). The frequency of these adverse events was increased in patients with higher doses of capsaicin.

However, one has to bear in mind that capsaicin may induce a severe and potentially fatal asthma attack in asthmatic subjects. Therefore, this treatment modality is contraindicated in patients suffering from CRS associated with asthma.
Table XX. Topical capsaicin in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marabini et al (1991)</td>
<td>CRS (NANIPER)</td>
<td>20</td>
<td>Capsaicin (15 µg/100 µl)</td>
<td>0.09 mg/day, 3 days</td>
<td>30 days</td>
<td>Prospective, case controlled</td>
<td>Nasal symptom score *</td>
<td>-</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Stjärne et al (1991)</td>
<td>CRS (NANIPER)</td>
<td>10</td>
<td>Capsaicin (0.03 mmol/l)</td>
<td>Cotton strips, 1x/day</td>
<td>3 days</td>
<td>Prospective, case controlled</td>
<td>Obstruction *, rhinorrhea *, sneezing</td>
<td>-</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Lacroix et al (1991)</td>
<td>CRS (NANIPER)</td>
<td>16</td>
<td>Capsaicin (0.009 mmol/l)</td>
<td>1x/week</td>
<td>5 weeks</td>
<td>Prospective, case controlled</td>
<td>Obstruction *, rhinorrhea *, sneezing</td>
<td>Reduction of nasal resistance response *, reduction of CGRP-LI *</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Riechelmann et al (1993)</td>
<td>CRS (NANIPER)</td>
<td>27</td>
<td>Capsaicin (0.01, 0.03, and 0.1 mmol/l)</td>
<td>0.5 ml/provocation, 7 times</td>
<td>approx. 7 weeks</td>
<td>Prospective, case controlled</td>
<td>No significant improvement in nasal symptom scores</td>
<td>-</td>
<td>III</td>
<td>Negative</td>
</tr>
<tr>
<td>Eberle and Glück (1994)</td>
<td>CRS (NANIPER)</td>
<td>84</td>
<td>Capsaicin</td>
<td>3 x 2 puffs/day, 1.5 mg/day</td>
<td>4 weeks</td>
<td>Prospective, case controlled</td>
<td>Improvement in obstruction, rhinorrhea, sneezing</td>
<td>Improvement in endoscopy and rhinomanometry</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Wolf et al (1995)</td>
<td>CRS (NANIPER)</td>
<td>123</td>
<td>Capsaicin (0.01, 0.03, and 0.1 mmol/l)</td>
<td>0.5ml/provocation 5-7 times</td>
<td>approx. 3 weeks</td>
<td>Prospective, case controlled</td>
<td>Improvement of nasal symptom score (no statistics)</td>
<td>Reduction of nasal resistance response *, no reduction of peptidergic neurons</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Blom et al (1997)</td>
<td>CRS (NANIPER)</td>
<td>25</td>
<td>Capsaicin (0.1mmol/l) vs. isotonic saline (0.9%)</td>
<td>0.3 mg/day, 7 times during 2 weeks</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Overall nasal symptoms *</td>
<td>Tryptase, LTC4/D4/E4, PGD2</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Van Rijswijk et al (2003)</td>
<td>CRS</td>
<td>30</td>
<td>Capsaicin (0.1 mmol/l)</td>
<td>0.27 ml/provocation, 5 times</td>
<td>1 day vs. 2 weeks</td>
<td>Prospective, case controlled</td>
<td>Overall nasal symptoms *, rhinorrhea *, obstruction *</td>
<td>CDAP *, acoustic rhinometry *, smell and PNIF</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Ciabatti et al (2009)</td>
<td>CRS</td>
<td>208</td>
<td>Capsaicin (1, 2 or 4 µg/puff) vs. placebo (?)</td>
<td>3, 6 and 12 µg/provocation, 3x/day</td>
<td>3 days</td>
<td>Randomized, placebo controlled</td>
<td>Symptoms’ resolution * in capsaicin 4 µg/puff</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
</tbody>
</table>

CDAP: cold dry air provocation, HDM: house dust mites, LDF: laser Doppler flowmetry, PNIF: peak nasal inspiratory flow
### Table XXI. Topical capsaicin in CRS with NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filiaci et al</td>
<td>NP</td>
<td>30</td>
<td>Capsaicin (30μmol/l) vs. isotonic saline (0.9%)</td>
<td>0.2ml/day, 1x/week</td>
<td>5 weeks</td>
<td>Randomized, placebo controlled</td>
<td>Symptom scores *</td>
<td>Polyp size *, nasal resistance *, increase of eosinophils *</td>
<td>Iб</td>
<td>Positive</td>
</tr>
<tr>
<td>Baudoin et al</td>
<td>NP</td>
<td>9</td>
<td>Capsaicin (30μmol/l – 100μmol/l)</td>
<td>1 ml/day</td>
<td>5 days</td>
<td>Prospective, case controlled</td>
<td>Symptom score *</td>
<td>NSAV *, polyp size *, ECP: no difference</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

NSAV: nose/sinuses air volume (cm³)

### Table XXII. Topical capsaicin in CRS after surgery to prevent NP recurrences

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al</td>
<td>NP</td>
<td>51</td>
<td>Capsaicin (3μmol/l) vs. placebo (capsaicin vehicle)</td>
<td>Cotton strips, 1x/week</td>
<td>5 weeks → 9 months follow-up</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Obstruction *, rhinorrhea: no difference</td>
<td>Polyp size *</td>
<td>Iб</td>
<td>Positive</td>
</tr>
</tbody>
</table>
4.1.8. Corticosteroids – topical and systemic

4.1.8.1. Background
Chronic rhinosinusitis with and without NPs are the result of complex chronic inflammatory processes of the upper respiratory tract. Nasal polyposis represents an entity of CRS in which severely oedematous mucosa forms pedicled protrusions, usually from the middle meatus. Though the aetiologies of CRS with and without NPs are not well understood, medical and surgical therapy are well-established. However, therapeutic options are not always curative and symptoms frequently recur, especially in NP.

The potent anti-inflammatory effects of steroids are well known, but so are their potential side effects, especially when administered systemically. In 1972, the introduction of a topical nasal glucocorticosteroi (GCS) formulation was a major therapeutic advance. The avoidance of systemic side effects was a powerful advantage. Topical corticosteroids have made a significant contribution to the treatment of AR and CRS with and without NPs. They have been shown to reduce sinonasal symptoms, improve nasal airflow patency, reduce the size of polyps and decrease polyp recurrence rates. They can be used alone in mild disease, or combined with systemic steroids or surgery in severe cases. Several studies support the efficacy of intranasal steroids (INS) in CRS with and without NPs. Currently, eight INS compounds are approved for the management of inflammatory nasal and paranasal diseases: triamcinolone acetonide, flunisolide, budesonide, beclomethasone dipropionate, ciclesonide, fluticasone propionate, mometasone furoate and fluticasone furoate.

Systemic steroids are only used for short-term therapy, due to their high risks of adverse effects. These effects include glucose intolerance, hypertension, and adrenal suppression, gastro-intestinal bleeding and altered mental states. There is little published data on the frequency of these effects. Adverse effects associated with long-term use of oral steroids include gastrointestinal complications, growth suppression, diabetes mellitus, hypertension, psychotropic effects (e.g. mood changes), glaucoma, osteoporosis and avascular osteonecrosis.

Corticosteroid treatment is a medical therapy with proven effects on the symptoms and signs of CRS with and without NPs and can be used topically or systemically.
4.1.8.2. Potential Therapeutic Actions

The efficacy of corticosteroids may depend partly on their abilities to reduce the recruitment and influx of inflammatory cells into the upper respiratory airway tract. During the late phase of the inflammatory response, they may reduce the secretion of pro-inflammatory mediators and chemotactic cytokines by nasal mucosal cells and epithelial cells in polyps\(^{618-622}\) (Figure 14). Evidence for this includes reduced levels of histamine, LTs, and mast cells in the nasal fluid and mucosa of patients with AR treated with INSs\(^{622-625}\). The anti-inflammatory effects of GCSs could theoretically be expected in non-allergic rhinitis as well. The effects appear to be less in NPs, which may partly explain an induced inflammatory resistance to steroids in CRS with NPs\(^{618,626}\).

Figure 14.
Pathophysiology of the early and late phases of the allergic inflammatory reaction and therapeutic action of corticosteroids. Corticosteroids act primarily during the late phase by inhibiting the inflammatory cell recruitment and secretion of mediators (modified from\(^{622,627}\)). Ig: immunoglobulin; IL: interleukin; TNFα: tumor necrosis factorα, IFNγ: interferon γ.
**The glucocorticoid receptor**

Corticosteroid molecules are derived from the parent molecule, cortisol [456]. The biological actions of GCSs are mediated through activation of intracellular glucocorticoid receptors (GRs), expressed in many tissues and cells [628,629]. Two human isoforms of GRs have been identified, GRα and GRβ, which originate from the same gene by alternative splicing of the GR primary transcript [630]. Upon binding with the hormone, GRα enhances anti-inflammatory or represses pro-inflammatory gene transcription. Most of the anti-inflammatory effects of GCSs occur through protein-protein interactions between GRs and transcription factors, such as activating protein and NF-κB. The inhibition of these two factors leads to downregulation of the production of cytokines and other inflammatory molecules: this is thought to be among the primary mechanisms for the anti-inflammatory effects of GCSs [631,632]. The GRβ isoform does not bind steroids but may interfere with the GRα function. There may be several mechanisms accounting for the resistance to the anti-inflammatory effects of GCSs, including an overexpression of GRβ or a downregulation of GRα. Increased expression of GRβ has been reported in patients with NPs [628,633]. Downregulation of GRα levels after treatment with GCSs [634,635] has been postulated to be one of the possible explanations for the secondary GCSs resistance phenomenon.

The carbon framework of each corticosteroid is made up of three 6-carbon rings (rings A, B and C) and one 5-carbon ring (ring D) ([Figure 15]) [627]. All anti-inflammatory corticosteroids have features in common with cortisol and with each other. The variation in ring D is the greatest differentiating factor between the individual molecules. Structure - activity relationship studies of this region led to the identification of chemical groups that enhanced topical activity and reduced adverse systemic effects (improved anti-inflammatory activity, resistance to degradation by esterases, increased potency) [627,636].
Pharmacodynamic properties of INS
Glucocorticoid potency is thought to be closely related to GR binding affinity. Figure 16 illustrates the relative GR binding affinities for most intranasal compounds. The highest relative receptor affinities were associated with some of the newest compounds (e.g. fluticasone furoate, momethasone furoate, fluticasone propionate), reflecting the improved understanding of the GR complex that has enabled the design of more potent corticosteroid molecules recently.
Nevertheless, there is no evidence of a linear association between glucocorticoid potency and clinical response, nor is there a known plateau beyond which greater potency does not add additional benefit. Likewise, it is not evident that the compound with the highest receptor affinity will have superior clinical efficacy. Although increased potency at intranasal sites would seem desirable, the possibility of greater potency at other sites could theoretically increase the risk of systemic adverse effects, as GRs are similar throughout the body.\textsuperscript{627}

**Pharmacokinetic properties of INS**

The pharmacokinetic properties of an INS determine the concentration and disposition of the drug at the receptor site and the potential for the drug to reach the systemic circulation. The goals of INS therapy are to: deposit the drug at the site of action, keep it there for as long as possible and limit the amount that enters the systemic circulation. Hence, the pharmacokinetic features of particular interest are lipophilicity and systemic availability.\textsuperscript{627}

More highly-lipophilic compounds are absorbed more quickly by the nasal mucosa and remain for longer in nasal tissue, thereby increasing their exposure to the GR.\textsuperscript{638} The addition of lipophilic side chain groups to a corticosteroid molecule facilitates its uptake across the phospholipid cell membranes of the nasal mucosal
cells to their cytoplasm, where the GRs are situated. Lipophilicity also contributes to increase plasma protein binding. Only free drug is pharmacologically active, therefore a high degree of serum protein binding for INSs (range: 71% of triamcinolone acetonide to 99% of ciclesonide / des-ciclesonide) is desirable to limit potential systemic adverse events. On the other side, lipophilicity may contribute to the accumulation of drug in other tissues, possibly contributing to unwanted side effects. The order of lipid solubility for corticosteroids has been reported as: momethasone furoate > fluticasone propionate > beclomethasone dipropionate > budesonide > triamcinolone acetonide > flunisolide. Ciclesonide and des-ciclesonide have greater lipophilicity than fluticasone propionate.

Systemic availability of an INS is dependent on its degree of lipophilicity, oral and local bioavailability and hepatic first-pass effect. Following intranasal administration, a drug can enter the systemic circulation through direct local absorption in the nasal mucosa or oral absorption of swallowed drug. Figure 17 shows the systemic bioavailability of a 200 µg dose of three different INSs. The large proportion cleared from the nose and swallowed becomes available for systemic absorption from the gastrointestinal tract. A high rate of first-pass metabolism will inactivate the absorbed drug, but direct systemic absorption through nasal tissues bypasses this protective hepatic first-pass mechanism. Therefore, careful attention needs to be paid to this direct absorption of potent corticosteroid agents.
Systemic absorption rates are highest among the relatively older compounds (flunisolide, beclomethasone, triamcinolone, budesonide) (Figure 18)\textsuperscript{627,644}. The newer compounds - fluticasone propionate and momethasone furoate - are more lipophilic and undergo rapid and extensive first-pass metabolism following oral administration, contributing to their negligible systemic absorption \textsuperscript{645}. An in vitro study on fluticasone furoate reported very high tissue binding affinity to human lung tissue and, hence, low systemic absorption \textsuperscript{637}.  

Figure 17.
Systemic bioavailability of a theoretical 200 µg nominal dose of three different intranasal steroids. TAA: triamcinolone acetonide, MF: momethasone furoate, FP: fluticasone propionate (modified from 627,642,643).
Lipid conjugation, or fatty acid esterification, is a process through which a corticosteroid molecule forms a reversible chemical bond with fatty acids in the nasal tissues, thus serving as a slow-release drug reservoir within the target area. It is probably partly responsible for the once-daily efficacy of many INSs (budesonide, des-ciclesonide).

One of the most sensitive measures of systemic corticosteroid bioactivity is suppression of endogenous cortisol secretion from the adrenal cortex. These determinations measure basal adrenocorticoid secretion (morning plasma cortisol, 24-h urinary-free cortisol or overnight urinary cortisol) or dynamic function of the hypothalamic-pituitary-adrenal (HPA) axis to determine adrenal reserve (ACTH cosyntropin stimulation or corticotropin releasing factor test). Urinary cortisol measurements are often corrected for creatinine excretion and expressed in terms of urinary : creatinine ratio. One report showed that mean urine cortisol : creatinine ratio was significant lower during treatment with fluticasone propionate 200 µg/day than with triamcinolone acetonide 110 or 200 µg/day or placebo. Apart from this, the use of INSs at recommended doses does not appear to have significant effects on the HPA axis.

In conclusion, it could be argued that the newer INS agents (fluticasone propionate, mometasone furoate, ciclesonide and fluticasone furoate) possess the most...
desirable pharmacokinetic and pharmacodynamic features: 1) high GR affinity, potency and specificity; 2) low systemic availability; 3) high hepatic first-pass clearance and rapid systemic elimination; and 4) once-daily dosing modality.

4.1.8.3. Topical Intranasal Corticosteroids
The therapeutic modality of corticosteroid agents that has been best studied in controlled trials is that of topically applied steroids. The design of topically active INS formulations has provided a much better therapeutic ratio than oral corticosteroids. The pharmacodynamic and pharmacokinetic properties of these agents play an important role in facilitating local anti-inflammatory activity with a low rate of side effects. Based on currently available data, there is no clear evidence that any INS is superior to any other for rhinosinusitis symptom’s relief, despite the pharmacologic differences between many of them. The newer-generation INS fluticasone furoate seems to have characteristics to control more than the other topical corticosteroids the eye symptoms in AR. Fluticasone furoate has not yet been evaluated in the treatment of CRS with and without NP.

Chronic rhinosinusitis without NPs (Table XXIII)
One randomised, double-blind, parallel-group study has evaluated the efficacy of endonasal irrigations of tixocortol pivalate-neomycin and neomycin alone in 60 patients with CRS (including 7 patients with NP) for the duration of 11 days. Nasal obstruction and sinus patency, measured by a ventilometric system, improved significantly more in the patients treated with tixocortol pivalate-neomycin compared with neomycin alone (p < 0.05). Patients with chronic bacterial rhinosinusitis showed better results than patients with allergic CRS (94% vs. 69% of patients showing improvement in nasal obstruction).

Another randomised, double-blind, placebo controlled study compared the effect of various drug combinations with topical dexamethasone (DM) (DM-tramazoline-neomycin, DM-tramazoline, placebo). Fifty patients with mucopurulent CRS were included and applied INS 4 times daily over 4 weeks. Both active treatments showed significant improvement in nasal discharge, obstruction, facial pain and objectively measured assessments (plain x-ray, nasal airway resistance, mucociliary clearance) (p < 0.05). The total response rates were 62% for DM-
tramazoline-neomycin, 60% for DM-tramazoline and 12% for placebo. The addition of neomycin to DM has not shown a difference in the outcome.

One randomised, double-blind, placebo controlled study has evaluated the treatment of fluticasone propionate (FP) on patients with CRS without NPs. There were 22 subjects included in the study (4 patients had CRS with NPs). Fluticasone propionate 160 μg daily was used for 16 weeks. No significant improvement was seen, as measured by nasal symptom scores, diary card, acoustic rhinometry or endoscopy.

Another randomised, double-blind, parallel group study investigated the efficacy and safety of intranasal beclomethasone dipropionate (BDP), 400 μg /day in a once-daily or twice-daily regimen in 112 patients with allergic or non-allergic CRS without NPs for a 12-week treatment period. Significant improvements were measured in the nasal symptom scores (p < 0.05) over the treatment period, but there was no difference between the two groups. The improvements were similar in the two groups, with a mean final decrease over baseline of 59.7% in the twice-daily group and 53.7% in the once-daily group. Similar improvements were also reported for nasal airway patency (p < 0.05), measured by anterior rhinomanometry and acoustic rhinometry. No signs of adrenal suppression were observed and the serum morning cortisol values did not significantly change over the 12-week period.

One randomised, double-blind, placebo controlled, multicentre study has evaluated the efficacy of intranasal Budesonide on CRS without NPs. In this study, Bud 256 μg and placebo were used in 134 patients for 20 weeks. There was a significant improvement in overall nasal symptom scores when compared with placebo (p = 0.005). Budesonide produced significant reductions in nasal obstruction and discharge scores and improved the sense of smell when compared with placebo treatment. At the end of the study, 43.1% of patients treated with Bud reported substantial or total control of their symptoms, compared with 25.9% of placebo treated patients (p = 0.015). The peak nasal inspiratory flow increased significantly in the Bud group (p = 0.003). The study, however, did not show changes in QoL assessments.

In summary, INSs improve evidently nasal symptoms associated with CRS without NPs, such as nasal obstruction, rhinorrhea, discharge and sense of smell. Objective nasal airway assessments have shown improvements in radiological and nasal
patency measures. The only one study dealing with olfactory outcome demonstrated statistically significant amelioration. One study using fluticasone propionate nasal spray \(^{658}\) showed a negative outcome. This is probably explained by the low patient number, an insufficient dosage of INSs when compared with similar studies on CRS with NPs (160 vs. 400 µg daily), and the fact that fluticasone propionate nasal drops are more effective than nasal spray \(^{177-179,660}\).

**Chronic rhinosinusitis with NPs (Table XXIV)**

Two randomised, placebo controlled studies have examined the efficacy of intranasal **beclomethasone dipropionate (BDP)** on CRS with NPs. One study described 3 weeks of topical treatment given to 19 patients compared to a control group of 16 patients treated with placebo aerosol: nasal symptoms, including sneezing, nasal secretion and blockage, were reduced to 52% of the pre-trial level for the whole group \(^{661}\). A similar study reviewed results after a treatment of 4 weeks and found a significant improvement in nasal obstruction (p < 0.05) and nasal patency as measured with posterior rhinomanometry (p < 0.05) \(^{662}\). However, in both studies, a significant difference in size of NPs was not shown.

Seven randomised, double-blind, placebo controlled studies have evaluated the efficacy of intranasal **budesonide (Bud)** on CRS with NPs \(^{173-176,663-665}\). All of them showed significant improvement in nasal symptoms compared to placebo. In two studies, an improvement of the sense of smell was shown \(^{175,176}\). Statistically significant improvements in nasal patency were shown by objective measures (peak nasal inspiratory flow and peak nasal expiratory flow) in five studies \(^{173,174,663,665}\). The polyp size decreased statistically significant in all of the seven studies. Overall, 49 - 77% of patients treated with Bud reported substantial or total control of their symptoms, compared with 26 – 45% of placebo treated patients. Three studies showed no dose-response correlation in symptom relief or reduction in NP size \(^{174-176,664}\). In contrast, one study showed reduction in NP size at a dosage of 280 µg Bud \(^{664}\), but not at 140 µg.

Five randomised, double-blind, placebo controlled studies have evaluated the efficacy of intranasal **fluticasone propionate (FP)** on CRS with NPs \(^{177-179,660,666}\). All of them showed significant improvement in nasal symptoms and objectively-measured peak nasal inspiratory flow compared to placebo. Overall, 29 - 55% of patients treated with FP reported substantial or total control of their symptoms,
compared with 22 – 39% of placebo treated patients. Fluticasone propionate nasal drops, rather than spray, has been compared to placebo: 800 µg, but not 400 µg FP nasal drops daily reduced NP size significantly (p < 0.01)\(^\text{177,178}\). In 54 patients with severe NPs who were on a waiting list for surgery, ESS was no longer required in 48% of those treated with FP nasal drops compared to 22% in the placebo group (p < 0.05). Nasal symptoms were significantly reduced in the FP nasal drops group (p < 0.05). There was a significant increase of peak nasal inspiratory flow (p < 0.01) and a reduction of the size of NP\(^\text{179}\).

Three randomised, double-blind, placebo controlled studies of intranasal momethasone furoate (MF)\(^\text{180-182}\) have shown significant improvements in nasal symptoms and peak nasal inspiratory flow compared to placebo. Overall, 34 - 75% of patients treated with MF reported substantial or total control of their symptoms, compared with 25 - 46% of placebo treated patients. In one study\(^\text{180}\), significant reduction in NP size and improvements in nasal symptoms were observed at dosages of MF 200 µg and 400 µg daily, but the 400 µg-group showed better improvements in subjective nasal blockage. Another study\(^\text{182}\) found that 200 µg MF twice daily had a significant effect in reducing polyp size, but the effect of 200 µg MF once daily was not statistically different to that of placebo group.

Intranasal steroids decrease NP size and improve the nasal symptoms associated with NPs such as nasal obstruction, rhinorrhea, sneezing and the sense of smell. The only one study dealing with QoL outcome could not prove statistically significant improvement. Nasal obstruction seems to exhibit the best response to topical corticosteroids.

How do different corticosteroids compare? (Table XXIV)
Two studies have compared the effect of different INSs (fluticasone propionate (FP) and beclomethasone dipropionate (BDP)). One study compared FP 400 µg, BDP 400 µg and placebo, each given for 26 weeks\(^\text{666}\). There was a significant improvement in nasal symptoms and peak nasal inspiratory flow for both steroid groups compared to placebo but only the BDP-group showed a reduction of the size of NPs. A similar study showed significant improvement in nasal symptoms and nasal patency for both active groups, but only the FP group had a significantly improved polyp score\(^\text{660}\).
4.1.8.4. Systemic Corticosteroids (Table XXV)

Short-course of systemic corticosteroids is widely used in clinical practice to provide rapid relief of symptoms, followed by the use of long-term INSs. Several prospective, case controlled studies have demonstrated efficacy of combined systemic and topical corticosteroids. The efficacy of systemic corticosteroids is supported by two prospective studies where a single, intramuscular injection of 14 mg betamethasone was compared to surgical polypectomy \(^{253,667}\). In these studies, improvements were seen in NP size, nasal symptoms and peak nasal expiratory flow, but it is difficult to differentiate the effect of systemic steroids from that of intranasal treatment since both treatments were used at the same time.

There have been only six prospective trials of short-course systemic corticosteroids to confirm their efficacy on the symptoms of CRS and on the size of NPs \(^{183,184,668-670}\), and only one of them is double-blind and placebo controlled \(^{214}\). Systemic steroids are most often used in high dose for short duration in exacerbations of CRS and severe NP. There is however a lack of evidence regarding the optimal treatment regimen of oral steroids with respect to indication, dose and duration. The optimal usage of steroids is clinically important as it may reduce the need for surgery by providing good symptomatic control.

Chronic rhinosinusitis without NPs

There is only one prospective, non-randomized study dealing with this subject. In this study, 18 patients with CRS without and with NPs underwent a CT-scan before and after receiving 1 mg/kg \textit{prednisone} for 10 days \(^{669}\). The Lund-Mackay CT-score dropped significantly in all patients \((p = 0.016 \text{ for without NPs and } p = 0.03 \text{ for with NPs})\), but the improvement was significantly greater in those without NPs \((p = 0.006)\).

Chronic rhinosinusitis with NPs

In a prospective study \(^{670}\), an \textit{intramuscular suspension of betamethasone dipropionate and betamethasone disodium phosphate} was given as a single dose to 8 patients with NPs. This led to an improvement in the nasal symptom index score and an increase of nasal volume and expiratory peak flow (measured by acoustic rhinometry and peak nasal expiratory flow, respectively). Unfortunately, no statistics were given, and there was a strong tendency to recurrence after 15 weeks.

Oral steroids have also been studied. In one study of 25 patients with severe
NPs, **prednisolone** (at a starting dose of 60 mg/day for 4 days, then decreased by 5 mg per day over 12 days) improved nasal symptoms in 72% and reduced polyp size in 81% \(^{668}\). There was a strong tendency to recur within 5 months of treatment.

Recently, however, two prospective, randomized controlled studies \(^{183,184}\) have shown effects of systemic steroids in NP treatment (78 and 84 patients, respectively). Oral **prednisone** was given for two weeks (30 mg daily for 4 days followed by a progressive reduction until 2 weeks). After the 2-week period, treated patients demonstrated a significant improvement in nasal symptoms, in all impaired QoL domains and a reduction of the NP size compared to both, control group and baseline (p < 0.05). In the study of Benitez et al. (2006), objectively measured nasal patency showed a significant improvement \(^{184}\).

In the only double-blind, randomised, placebo controlled study, 50 mg **prednisolone** daily for 2 weeks was compared with placebo \(^{214}\). Only the prednisolone-treated group showed significant improvement in nasal symptoms (95% vs. 37%) (p < 0.001). The Rhinosinusitis Outcome Measure (RSOM-31) score improved in both groups, but the prednisolone-treated group had significantly greater improvement than the placebo group (p < 0.001). Objectively, there was significant reduction in polyp size, as assessed at nasendoscopy (p < 0.001) and MRI (p < 0.001), only in the prednisolone-treated group. The outcome measures correlated with each other; the highest level of correlation was between the objective measures of nasendoscopy and MRI \((R^2 = 0.76, \ p < 0.001)\). There were no significant adverse events.

Thus, recent studies on systemic steroids in NP have provided evidence that they are effective after a short course of two weeks at doses acceptable for the majority of patients. Relief of nasal symptoms and smell dysfunction, improvement of QoL, and reduction of polyp size in nasendoscopy and on imaging have been reported.

### 4.1.8.5. Intranasal Local Corticosteroid Injection

Anecdotally, steroid injections seem to have an effect on NPs which is more substantial than that of topical INSs, likely due to the higher concentration of the drug at the polyp site. Moreover, the effect seems to last for 6 – 8 weeks, largely because of the depot nature of the steroid suspension \(^{671}\). There is no prospective randomized study available on steroid injection in the management of CRS with and without NPs.
and comparison of its efficacy with topical INSs or oral steroids has never been done. A study of intraturbinate steroid injection showed a transient and mild amount of systemic absorption without lasting adrenal suppression. There is also a risk of fat necrosis at the site of the injection, temporary visual loss and permanent blindness due to embolisation and retinal vessel spasm. Hence, steroid injections have no role in the current medical management of CRS.

4.1.8.6. Corticosteroids after Surgery (Table XXVI)

Patients with NPs frequently need additional surgical procedures because of recurrent NPs. Several studies have found that INSs are effective in reducing and extending time of relapse of NPs after simple polypectomy or ESS.

One study has examined the efficacy of intranasal beclomethasone dipropionate (BDP) after nasal polyp surgery. This study tested 400 μg intranasal BDP in 22 patients compared to a placebo treatment in 18 patients. After one year of therapy, 86% of the patients in the BDP group were asymptomatic compared to 60% in the placebo group. There was normal rhinometry nasal patency in 68% in the BDP group and in 33% in the placebo group. Unfortunately, no statistical comparisons were performed.

In another study of 73 patients, 24 weeks of intranasal budesonide (Bud) was given after polypectomy. In the Bud group, NP scores were significantly lower than in the placebo group after 3 and 6 months of treatment, but only patients with recurrent NPs benefited from the Bud treatment – there was no evidential effect in patients with first time surgery for NPs. There was no significant difference in relief of nasal obstruction between both groups.

Two studies have evaluated the efficacy of intranasal flunisolide for 3 months on NPs after polypectomy. Both of them showed significant improvement in nasal symptoms compared to placebo. In one study, patients treated with flunisolide had fewer recurrences and smaller polyps at 6- and 12-month follow-up. However, the second study was not able to show any significant effect on measured nasal patency or on NP score compared with the placebo group.

Two randomised, double-blind, placebo controlled studies have evaluated the efficacy of intranasal fluticasone propionate (FP) in patients with CRS after ESS. In one study, 162 patients were randomised to daily FP 800 μg, FP 1600 μg or placebo for 1 year after ESS. After 1 year, relapse rates were 1.22-fold higher...
in the 800 μg group and 1.48-fold higher in the 1600 μg group compared to the placebo group. In another study, FP 400 μg or placebo was used for 5 years in 109 patients with CRS after ESS. At 5 years, changes in a visual analogue scale measuring overall symptoms were significantly better in the FP group than in the placebo. Changes in endoscopic oedema, polyp scores and total nasal volumes measured by acoustic rhinometry were also significantly better in the FP group than in the placebo group at 4 years, but not 5 years. The cohort of patients receiving FP contained significantly fewer recurrent polyp cases. Prednisolone was used significantly more frequently as a rescue medication in the patients treated with placebo.

A recently published randomised, double-blind, placebo controlled study evaluated the effect of 200 μg daily intranasal momethasone furoate (MF) for 6 months on NP relapse after ESS in 162 patients. There was significantly longer relapse-free period among the subjects who received MF when compared with the patients who received placebo (median time of relapse: 173 days and 61 days, respectively; p < 0.007). Regarding nasal symptoms, with the exception of rhinorrhea, there were no significant differences between the 2 groups.

A similar study has evaluated topical momethasone furoate (MF) spray (200 μg twice a day) for the duration of 6 months postoperatively in 99 patients with CRS with and without NP. MF led to greater, although not significant, reductions in total endoscopic scores in all subjects, compared with placebo. The endoscopic combination scores (for inflammation, edema, NP), however, indicated significantly improved healing with MF than with placebo for all subjects (median scores: 0.0 vs 2.0, p = 0.02), and particularly for subjects with NP (median scores: 2.0 vs 4.0, p = 0.03). The total symptom scores and percent of subjects requiring rescue medication were similar in the two groups.

Thus, INSs after ESS in CRS patients with and without NPs significantly improve woundhealing and prolong the time to NP recurrence. The inconsistent results of the two studies describing the effect of intranasal fluticasone propionate after ESS may be explained by the fact that not only patients with NPs but also patients with CRS without NPs were included, and so, data analysis was done on patients with varied conditions.
4.1.8.7. Side Effects

Suppression of the HPA axis, osteonecrosis, osteoporosis or changes in bone mineral density, growth retardation in children, cataracts and glaucoma have been reported to be the main adverse effects of corticosteroid treatment \(^{682}\). In relation to adverse effects of corticosteroids, it is obvious that a clear distinction needs to be made between intranasal and oral corticosteroids.

Topical corticosteroids

Nasal corticosteroid treatment represents one of the long-term treatment options in patients with CRS. Several factors influence the systemic absorption of INSs: the molecular characteristics of the corticosteroid, the prescribed dose, the mode of delivery and the severity of the underlying disease \(^{682}\). There is insufficient evidence to relate the use of INSs at recommended doses to changes in bone mineral density, cataracts and glaucoma. Adrenal suppression may occur with some INSs at recommended doses, but the clinical relevance remains uncertain.

Intranasal administration of corticosteroids has demonstrated side effects in 0 - 89% of patients, with drug-related side effects in about 0 – 49%, including epistaxis, dryness, nasal burning, itching, crust formation, stinging, throat irritation, headache, eczema, small ulcers in the nostrils, nausea, abdominal pain, change of taste and hyperglycemia \(^{172,175,177,178,180-182,657,659,660,662,665,666,674-677,680,683,684}\). The frequencies of the side effects are similar in the various compounds. The most common drug-related side effect is minor epistaxis, attributed to the vasoconstrictor activity of the corticosteroid molecules. However, it should be remembered that minor nose bleeds are common in the population, occurring in 16.5% of 2197 women aged 50 – 64 years over a one year study \(^{685}\). Nasal mucosal atrophy is a concern with chronic topical steroid use. A study with topical budesonide treatment during 4 months for NPs did not find significant epithelial changes such as metaplasia or atrophy \(^{683}\). A long-term study with momethasone furoate found no evidence of atrophy or metaplasia following 12 months of intranasal use \(^{174}\). Similar studies with fluticasone propionate also did not identify indications of atrophy and noted only an insignificant increase in metaplasia in one patient \(^{686}\). Moreover, there is no evidence that INS treatment increases the frequency or the severity of viral or bacterial infections in the nose or paranasal sinuses. Nasal septal perforation induced by INSs is rarely described in the literature \(^{687}\). It is unclear if this is caused by repeated traumas to the
nasal mucosa by the nasal device, the vasoconstrictor activity of the corticosteroids or other effects.

The systemic bioavailability of INSs varies from <1% to up to 40 – 50% and influences the risk of systemic adverse effects. Potential adverse events related to the administration of INSs are effects on growth, eyes, bone, and the HPA axis. Because the dose delivered topically is small, this is not a major consideration, and of several studies, only one reported an effect in the HPA axis with continued and prolonged treatment. Studies in adults on long-term intranasal treatment with 200 - 400 µg/day of various INSs have shown that there is no or only a very small risk of systemic corticosteroid adverse effects. One case of candidiasis of the oesophagus was described as serious systemic side effect after topical intranasal corticosteroid administration. There are two cases of cataract after INS use described in the literature, but it may be coincidental. Raised intraocular pressure has been described with INS and patients with a history of glaucoma should be monitored more closely. In theory, even small doses of corticosteroids over a prolonged period may contribute to osteoporosis, especially in postmenopausal women. However, a very large case-controlled study of elderly individuals has failed to show any effect of INS treatment on the number of hip fractures. A short-term study of children receiving an adult dose of budesonide (200 µg twice daily) showed growth inhibition, while this was not the case when 200 µg was given once daily in the morning. Long-term treatment for 1 - 2 years with budesonide 256 - 400 µg in 5 - 15-year-old children showed no negative effect on growth. Also, a double-blind, placebo controlled study of 150 children, aged 3.5 - 9 years, showed no effect on growth rate from treatment with fluticasone 200 µg for 1 year. Another study with momethasone furoate did not demonstrate significant changes in lower leg growth velocity. Among studies of momethasone furoate, fluticasone propionate, budesonide, ciclesonide and beclomethasone given over one year, only the study with beclomethasone reported a smaller mean growth among the treated children. Thus, the risk of growth inhibition in children seems to be very small in the treatment with INSs. However, it seems important to be aware that several patients use inhaled steroids for both, the upper and lower airways. Considering the total systemic steroid exposure for these patients, from a clinical safety point it is important to use the lowest possible steroid dose at which these patients can keep their symptoms under control, and the INS with the lowest
systemic bioavailability. It should also be noted that inhaled steroids for the lower airways can have additional benefits on the upper airways. Hence, the steroid doses can probably sometimes be reduced when concomitant glucocorticosteroids are prescribed for both upper and lower airways\textsuperscript{703}.

In summary, INSs are highly effective. Local side effects have been described (nasal bleeding most frequently). Older-generation INSs could have been associated with some systemic adverse effects, and particularly have had some impact on the growth of children. This is no more the case with the (even prolonged) use of newer-generation INSs, like fluticasone propionate and momethasone furoate, at least at the dosage recommended by the manufacturers.

**Systemic corticosteroids**

Short-course treatments with oral corticosteroids are effective in CRS with NPs. The anti-inflammatory effects of corticosteroids cannot be separated from their metabolic effects as all cells use the same glucocorticoid receptor. Therefore, when systemic corticosteroids are prescribed, measures should be taken to minimize their side effects. The incidence of significant side effects increases with the dose and duration of treatment, so that the minimal dose and period necessary to control the disease should be given. Short-course oral corticosteroids have demonstrated drug-related side effects in 0 - 40\% of patients. Major side effects include insomnia, personality changes, stomach ulcers and diabetes\textsuperscript{214,668-670}. The high incidence of side effects in 40\% of the patients in the study of Hissaria et al. (2006)\textsuperscript{214} may be explained by the slightly higher dose of corticosteroid than that was seen in most previously published studies, and tapering was not used. No clinically significant symptoms or signs of adrenal suppression were found in the mentioned studies.

In summary, short-course oral corticosteroids are effective in patients with CRS with NPs. Nevertheless, major systemic side effects have been described, so this treatment modality should only be used as a rescue medication for very severe NPs or if there has been no improvement after INS treatment.
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<th>Symptoms (stat. signif. *)</th>
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<td>Cuenant et al</td>
<td>CRS</td>
<td>60</td>
<td>Tixocortol pivalate-neomycin vs. Neomycin</td>
<td>50 mg tixocortol pivalate</td>
<td>11 days</td>
<td>Randomized, double-blind, parallel group</td>
<td>Obstruction *</td>
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<td>Sykes et al</td>
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<td>50</td>
<td>Dexamethasone-tramazoline-neomycin vs. Dexamethasone-tramazoline vs. Placebo</td>
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<td>Giger et al</td>
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<td>Parikh et al</td>
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<td>Randomized, double-blind, placebo controlled</td>
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<td>PNIF *</td>
<td>Ib</td>
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<td>Posterior rhinomanometry *</td>
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<td>Nasal peak flow * eosinophilia *</td>
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<td>NP</td>
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<td>Bud</td>
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<td>1 month</td>
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<td>PNIF *</td>
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<td>Bud</td>
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<td>3 months</td>
<td>Randomized, double-blind, placebo controlled, multicenter</td>
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<td>Liidholdt et al (1995) 174</td>
<td>NP</td>
<td>116</td>
<td>Bud</td>
<td>400 μg 800 μg</td>
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<td>PNEF *</td>
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<td>Tos et al (1998) 175</td>
<td>NP</td>
<td>138</td>
<td>Bud</td>
<td>256 μg (aqueous) 400 μg (powder)</td>
<td>1.5 month</td>
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<td>Filiaci et al (2000) 664</td>
<td>NP</td>
<td>157</td>
<td>Bud</td>
<td>140 μg 280 μg</td>
<td>2 month</td>
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<td>-</td>
<td>No: 140 μg daily Yes *. 280 μg daily Yes *</td>
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<td>Jankowski et al (2001) 176</td>
<td>NP</td>
<td>183</td>
<td>Bud</td>
<td>128 μg 256 μg</td>
<td>2 months</td>
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<td>NP</td>
<td>55</td>
<td>FP/BDP</td>
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<td>6.5 months</td>
<td>Randomized, double-blind, placebo controlled</td>
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<td>PNIF *</td>
<td>Yes * in BDP</td>
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<td>Objective (stat. signif. *)</td>
<td>Reduction of NP size</td>
<td>Level of evidence</td>
<td>Outcome</td>
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<td>PNIF * Olfactory test</td>
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<td>FPND</td>
<td>400 μg</td>
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<td>Small et al (2005)</td>
<td>NP</td>
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<td>MF</td>
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<td>Stjarne et al (2006)</td>
<td>NP</td>
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<td>CRS / NP</td>
<td>18</td>
<td>Prednisone</td>
<td>50 – 80 mg</td>
<td>10 days</td>
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<td>CT-scan *</td>
<td>Yes *</td>
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<td>Elbrand et al (1991) 670</td>
<td>NP</td>
<td>8</td>
<td>Betamethasone disodium phosphate</td>
<td>Intramuscular single dose (7 mg)</td>
<td>1 x</td>
<td>Prospective case controlled</td>
<td>Obstruction</td>
<td>PNEF, acoustic rhinometry</td>
<td>-</td>
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<td>Van Camp and Clement (1994) 668</td>
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<td>Prednisolone</td>
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<td>2 weeks</td>
<td>Prospective case controlled</td>
<td>Nasal symptoms improvement (in 72%)</td>
<td>CT-scan improvement (in 52%)</td>
<td>Yes (in 81%)</td>
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<td>Prednisone</td>
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<td>2 weeks</td>
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<td>Anterior rhinomanometry *</td>
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<td>Nasal symptoms *, RSOM-31 *</td>
<td>MRI *</td>
<td>Yes *</td>
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PNEF: peak nasal expiratory flow, RSOM-31: Rhinosinusitis Measure Outcome – 31 questionnaire
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<td>200</td>
<td>6</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Rhinorrhea *, obstruction</td>
<td>PNIF, CT-scan</td>
<td>Yes *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Jorissen and Bachert</td>
<td>CRS / NP</td>
<td>99</td>
<td>MF</td>
<td>400</td>
<td>6</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>No difference in nasal symptom score</td>
<td>Reduction in total endoscopic score *</td>
<td>Yes *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
</tbody>
</table>

4.1.9. Cromolyn sodium - an intranasal mast cell stabilizer

4.1.9.1. Background

Allergic rhinitis is a common condition, affecting 10 – 20% of the population in the USA\textsuperscript{51-54}. The overall prevalence of subjects with clinically confirmable AR in Europe amounts to 23% \textsuperscript{55}. It has been reported in 58% of patients evaluated for CRS \textsuperscript{704}. The therapy of AR is important to improve symptoms like sneezing, itching, rhinorrhea or nasal congestion, which also affect the QoL by causing fatigue, headache, insomnia and poor concentration. Although the exact mechanism of action is unclear, it has been hypothesised that cromolyn inhibits the release of histamine and other inflammatory mediators by stabilising mast cells. In allergen challenge studies of patients with AR, cromolyn sodium has proven efficacy in preventing both the early- and late-phase allergic reactions \textsuperscript{705}. It has been shown to be effective in the treatment of seasonal and perennial AR \textsuperscript{706,707}. Cromolyn sodium seems to be more helpful against sneezing, nasal hypersecretion and nasal itching, than nasal congestion \textsuperscript{708}. It does not relieve ocular symptoms. Inhibition of the release of histamine and other inflammatory mediators by stabilising mast cells could explain a certain effect of cromolyns in the treatment of CRS often associated with allergic findings.

4.1.9.2. Potential Therapeutic Actions

Cromolyn sodium is classified as an anti-allergic compound due to its inhibitory action against immunological degranulation of sensitised mast cells, thereby blocking the release of inflammatory mediators that would trigger inflammation and the allergic response \textsuperscript{485}. It does not interfere with either the binding of IgE to the high-affinity IgE receptor of mast cells or with binding of the allergen to its specific IgE \textsuperscript{485}. It has also no discernible antihistaminic, anticholinergic, antileukotriene, antibradykinin, antiserotonin, adrenergic or corticosteroid-like actions \textsuperscript{54}. Cromolyn shows inhibition of both, early and late phases of the allergic reaction \textsuperscript{709}. Thus, cromolyn interrupts the physiological response to nasal allergens and, when used prophylactically, can prevent the onset of symptoms as well as improve nasal allergy symptoms once they occur \textsuperscript{707}. 
Despite the recognition of the action of cromolyn on lung mast cells, it is not certain that its clinical benefit in AR relates to similar effects in the nasal mucosa. Ultrastructure studies suggest that nasal metachromatic cells resemble blood basophils more than tissue mast cells, and cromolyn sodium does not inhibit basophil degranulation. However, cromolyn sodium has been shown to influence granulocyte chemotaxis and cell activation in vitro, and reduces mucosal eosinophils in the nose and upper airway. The inhibition of macrophages, eosinophils, monocytes and platelets may modulate local cytokine release and play an anti-inflammatory role, a possible pathway useful in the treatment of CRS with and without NPs.

4.1.9.3. Topical Intranasal Cromolyn (Table XXVII)

Chronic rhinosinusitis without NPs

Two studies (randomized, cross-over, double-blind, placebo controlled) have evaluated the efficacy of endonasal application of cromones in patients with CRS / NANIPER. Disodium cromoglycate was applied intranasal during 4 – 8 weeks with a daily dose ranging from 21 – 40 mg. Sneezing and rhinorrhea decreased significantly (p < 0.05). No significant reduction of nasal congestion could be demonstrated. Histological examinations have detected a resolution of inflammatory mucosal infiltration and mucosal reparation in the cromolyn treated group (no statistical comparison). Although not stated, both studies might have included patients with allergies.

In another two studies (randomised, double-blind, placebo controlled), only patients suffering from CRS / NANIPER (no allergic history and negative allergic skin test) were included for an intranasal treatment with cromones. The treatment duration was 8 – 13 weeks. No significant difference between cromones and placebo was shown in both trials.

Chronic rhinosinusitis with NPs

Only one prospective, case controlled trial was found, dealing with the intranasal use of cromones in the treatment of NPs. Thirty-four patients with NPs were treated with intranasal disodium cromoglycate powder (40 mg/day) for 4 weeks. Sneezing was the only nasal symptom which has decreased significantly after the treatment (p < 0.01). Polyp size has not changed.
In conclusion, it seems that intranasal cromolyn is of no benefit in the treatment of patients with non-allergic CRS with and without NPs. The two trials with perennial rhinitis showing significant symptomatic improvement after the use of intranasal cromolyn may have probably included a high percentage of patients with AR. The benefit may be explained by the predominant mode of action of cromolyn, the inhibition of mediators’ release from mast cells in the nasal mucosa of allergic patients.

4.1.9.4. Cromolyn after Surgery
There were no data available of treatment with intranasal cromones after ESS in patients suffering from CRS with and without NPs.

4.1.9.5. Side Effects
An unpublished meta-analysis of Block (2001) showed only 3 serious adverse events in 3000 patients treated with cromones. No death was reported. Descriptions of allergic reactions, anaphylaxis, and angioedema exist. Postmarketing surveillance found only 31 serious adverse effects, with more than 17 million prescriptions. In this study, all the adverse events were subsequently determined to be unrelated to the use of cromolyn. No drug interactions are known.

Minor adverse effects reported with cromolyn sodium appear in less than 10% of the treated individuals. Most commonly, they include sneezing, nasal irritation and an unpleasant taste. Cromolyn is poorly absorbed systemically (less than 7%) explaining the excellent safety record. Tolerance to the clinical effects of cromolyn has not been described. Nasal rebound or ciliary damage has not been demonstrated.
Table XXVII. Topical cromolyn in CRS without and with NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fagerberg and Zetterström (1975)</td>
<td>CRS / NANIPER (allergic perennial rhinitis?)</td>
<td>23</td>
<td>Disodium cromoglycate vs. lactose</td>
<td>Dry powder, 40 mg</td>
<td>4 weeks</td>
<td>Randomized, cross-over, double-blind, placebo controlled</td>
<td>Sneezing *, rhinorrhea *, obstruction</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Liern Caballero et al (1978)</td>
<td>CRS / NANIPER (allergic perennial rhinitis?)</td>
<td>30</td>
<td>Sodium cromoglycate 2% vs. placebo (preservative)</td>
<td>Spray, 21 mg</td>
<td>8 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Decrease of total nasal score, obstruction, rhinorrhea, and sneezing</td>
<td>Amelioration of histological changes in nasal mucosa</td>
<td>Ib (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Löfkvist et al (1977) 71333</td>
<td>CRS / NANIPER</td>
<td>49</td>
<td>Sodium cromoglycate vs. lactose</td>
<td>Dry powder, 40 mg</td>
<td>13 weeks</td>
<td>Randomized, cross-over, double-blind, placebo controlled</td>
<td>No significant difference in nasal symptoms</td>
<td>-</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Nelson et al (1982) 71432</td>
<td>CRS / NANIPER</td>
<td>23</td>
<td>Cromolyn sodium 4% vs. placebo (preservative)</td>
<td>Spray, 62.4 mg</td>
<td>8 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>No significant difference in nasal symptoms</td>
<td>-</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Donovan and Kapadia (1972) 71634</td>
<td>NP</td>
<td>34</td>
<td>Disodium cromoglycate</td>
<td>Dry powder, 40 mg</td>
<td>4 weeks</td>
<td>Prospective, case controlled</td>
<td>Sneezing *, rhinorrhea, obstruction</td>
<td>No changes in polyp size and serum IgE levels</td>
<td>III</td>
<td>Negative</td>
</tr>
</tbody>
</table>
4.1.10. Decongestants – topical and systemic

4.1.10.1. Background
Clinical experience in the field of rhinology suggests that there is a rational for the use of decongestants in all rhinopathies where nasal resistance is increased. The decongestion of nasal mucosa and, in particular, of OMC and paranasal sinuses, is the fundamental treatment for restoration of their physiology. Nasal decongestants are applied in the treatment of acute rhinosinusitis in order to decrease congestion and in the hope of improving sinus ventilation and drainage. A decrease of OMC congestion may prevent sinus blockage inducing sinusitis. The decongestive action in the nose has been proven in several studies through the application of objective, repeatable and standardised methods, such as active anterior rhinomanometry, and acoustic rhinometry, before and after administration of intranasal and systemic decongestants. Experimental studies in patients with CRS with and without NPs seeking for an effect of decongestants on CT-scan, MRI and maxillary sinus endoscopy have confirmed marked effect on the mucosal thickness of inferior and middle turbinates, infundibular mucosa and the maxillary ostium, but no effect on ethmoid and maxillary sinus mucosa, and on NP size. In CRS, decongestants may be used for symptomatic improvement of nasal blockage.

4.1.10.2. Potential Therapeutic Actions
Decongestants or the so called vasoconstrictors exist in both intranasal and oral form. Sympathomimetics represent the most important category in this drug class. Topically applied sympathomimetic agents belong to the catecholamine (e.g., phenylephrine) or imidazoline family (e.g., oxymetazoline, xylometazoline, nafazoline), whereas oral decongestants are primarily catecholamines (e.g., pseudoephedrine, phenylpropanolamine). These agents work through the \( \alpha_1 \) and \( \alpha_2 \) adrenoreceptors present on nasal capacitance vessels, which are responsible for mucosal swelling and associated nasal congestion. Sympathomimetic amines are \( \alpha_1 \)-selective agonists and, therefore, carry on their activity mostly on capacitance vessels. Imidazoline derivatives are \( \alpha_2 \)-specific agonists and as such, acting on capacitance and also on resistance vessels. The sympathomimetic action causes vasoconstriction leading to a reduction in blood flow of the nasal vasculature and, consequently, to an improvement of the nasal patency after 5 - 10 minutes to topical decongestants or after 30 minutes to systemic oral vasoconstrictors.
Sympathomimetic amines and imidazoline derivatives are very different from a pharmacological viewpoint in terms of latency and duration of action: the two groups have almost the same latency time (10 – 20 minutes), whereas the duration of action, is considerably different: short for sympathomimetic amines: 20 minutes – 4 hours; long for imidazolines: 2 – 12 hours. This more prolonged effect may be due to the vasoconstrictor activity on the capacitance, but also on the resistance vessels, leading to a reduction of the blood flow in the nasal mucosa, resulting in a delayed elimination of the drug.

Traditionally, it has been thought that pseudoephedrine could only ameliorate the nasal congestion via the above mentioned mechanisms. However, a recent study comparing once-daily pseudoephedrine to montelukast showed a reduction in AR symptoms other than only nasal obstruction in both groups. These additional effects might possibly be due to the halo effect, in which improvement in one particular symptom, such as nasal obstruction, leads to a more global sense of well-being and, thus, less perceived severity of associated nasal symptoms. However, a recent experimental study has suggested beneficial anti-inflammatory effects of xylometazoline and oxymetazoline by increasing and maintaining of the newly discovered anti-inflammatory and pro-resolving dual-function mediator lipoxin A4, which may accelerate the termination of (acute) rhinitis-related inflammation and thus, may contribute significantly to shortening the duration of the disease.

4.1.10.3. Topical Intranasal Decongestants (Table XXVIII)

Chronic rhinosinusitis without NPs

Intranasal decongestants (xylometazoline nose drops) combined with amoxicillin for 10 days with or without sinus drainage did not prove to be superior to intranasal saline application in the treatment of 141 children with chronic maxillary sinusitis in terms of subjective and radiologic improvement in a randomised, case controlled study. This trial did not evaluate the use of intranasal decongestants alone.

One randomised, double-blind, placebo controlled study evaluated the efficacy of endonasal application of oxymetazoline hydrochloride with benzalkonium chloride versus oxymetazoline hydrochloride without benzalkonium chloride (0.3 mg/day) in 35 patients with CRS / NANIPER during 10 days. No reduction of nasal congestion was seen. The group of nasal decongestants with benzalkonium chloride showed statistically significant reduction in histamine sensitivity.
Chronic rhinosinusitis with NPs
There were no trials available on intranasal decongestants in the treatment of NPs.

In conclusion, intranasal vasoconstrictors do not improve nasal symptoms or radiologic signs of the paranasal sinuses in CRS without NPs. This treatment modality has not been evaluated in the management of NPs.

4.1.10.4. Systemic Decongestants (Table XXIX)

Chronic rhinosinusitis without NPs
One randomised, double-blind, placebo controlled study compared the efficacy of different doses of a systemic oral decongestant (phenylpropanolamine chloride) with placebo (100 mg/day vs. 200 mg/day vs. placebo) in 70 patients with CRS / NANIPER for the duration of 4 days \(^{731}\). There was a statistically significant better nasal decongestion in the 200 mg-group than in the 100 mg- and placebo-group, respectively (\(p < 0.05\)). The decrease in nasal secretion in both active treatment-groups was not statistically significant when compared with the placebo-group.

A similar, double-blind, placebo controlled, cross-over trial evaluated the efficacy of oral phenylpropanolamine vs. phenylpropanolamine with an antihistamine vs. placebo in 19 patients with CRS / NANIPER for the duration of 10 days \(^{732}\). Obstruction, secretion and sneezing improved significantly in both active treatment groups (\(p < 0.05\)) when compared to the placebo group. No statistical difference was found between the two active treatment groups.

Chronic rhinosinusitis with NPs
There were no trials available on systemic decongestants in the treatment of NPs.

In summary, systemic phenylpropanolamine improves evidentially nasal congestion, secretion and sneezing, but any long-term trials (\(> 1\) month) do not exist. No data are available in patients with NPs.

4.1.10.5. Decongestants after Surgery
There were no data available of intranasal or oral decongestant use after endonasal surgery to prevent disease recurrences in patients suffering from CRS with and without NPs.
4.1.10.6. Side Effects

In the few studies of intranasal decongestants used for 4 – 10 days in patients with CRS with and without NPs, no adverse events were mentioned \(^{723,730,731}\). Nasal decongestants produce a marked arteriolar vasoconstriction, resulting in local ischemia of the nasal mucosa. This local ischemia may be responsible for local side effects which result in serious alterations of mucosal trophism \(^{724}\). The adverse effects of topical nasal decongestants include nasal burning, stinging, dryness, edema, but also increased rhinorrhea and, less commonly, mucosal ulcerations. Far more relevant are tachyphylaxis to the drug and rebound congestion, which can occur when these agents are used for longer than 1 – 2 weeks. Shorter duration of decongestion and rebound effect result in increased need of the daily decongestant dose \(^{730}\), which can culminate in mucociliary clearance alterations, severe damage of nasal mucosa trophism resulting in rhinitis medicamentosa \(^{724}\). According to some studies where nasal decongestants were used for a long period, imidazoline derivatives (short latency and long acting) seem to be most safely, but the authors recommended the topical intranasal administration for no longer than 10 – 15 days \(^{724}\). There are virtually no systemic side effects caused by intranasal vasoconstrictors at the recommended doses, however, it is important to be aware of the clinical problems associated with topical decongestants because of the vasoconstrictor action. It has been shown that the use of topical intranasal \(\alpha\)-agonists (phenylephrine) in patients under general anesthesia could cause an idiosyncratic hypertension that, if treated with \(\beta\)-blockers, may result in a rebound refractory bradycardia and vasodilatory pulmonary edema with severe morbid or fatal outcomes (New York State Anesthesia Guidelines) \(^{733}\). In case of prolonged use or overdose of intranasal decongestants, events that stimulate the cardiovascular system or the central nervous system may occur: increase of arterial pressure and tachycardia, headache, hyperreactivity of cerebral activity resulting in insomnia, hallucinations, anxiety and seizures, nervousness and tremors, increase of vesical sphincter tone resulting in inhibition of micturition, increase of thyroid function, hyperglycemia, and increase of intraocular pressure; and individual reports of stroke, myocardial infarction, chest pain, seizures, nausea and vomiting, fatigue, and dizziness exist \(^{724}\). The risk of developing the above mentioned adverse events seems to be increased in patients with cardiovascular diseases \(^{734-737}\). Nevertheless, these major adverse effects are more related to oral decongestants \(^{485,732}\). The awareness of these local
and systemic side effects suggests a more moderate and rational, short-term use of nasal decongestants, whose efficacy in the rapid relief of nasal congestion has been proven.
### Table XXVIII. Topical decongestants in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otten (1997)</td>
<td>CRS (maxillary sinusitis) in children</td>
<td>141</td>
<td>Xylometazoline nose drops with amoxicillin vs. placebo (isotone saline) vs. drainage and irrigation vs. combination of drainage / irrigation and active treatment</td>
<td>Unknown</td>
<td>10 days</td>
<td>Prospective, case controlled</td>
<td>No significant difference between the 4 treatment groups</td>
<td>No significant difference on radiology between the 4 treatment groups</td>
<td>III</td>
<td>Negative</td>
</tr>
<tr>
<td>Graf et al (2009)</td>
<td>CRS / NANIPER</td>
<td>35</td>
<td>Oxymetazoline hydrochloride with benzalkonium chloride vs. oxymetazoline hydrochloride without benzalkonium chloride</td>
<td>Spray, 0.3 mg/day</td>
<td>10 days</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>No difference in obstruction before and after treatment</td>
<td>Reduction of histamine sensitivity * in oxymetazoline with benzalkonium</td>
<td>Ib</td>
<td>Negative</td>
</tr>
</tbody>
</table>

### Table XXIX. Systemic decongestants in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renvall and Lindqvist (1979)</td>
<td>CRS / NANIPER</td>
<td>70</td>
<td>Phenylpropanolamine chloride vs. placebo</td>
<td>Orally, 100 mg vs. 200 mg vs. placebo</td>
<td>4 days</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>200 mg &gt; 100 mg and placebo: obstruction *, 200 mg &gt; 100 mg: secretion *</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Broms and Malm (1982)</td>
<td>CRS / NANIPER</td>
<td>19</td>
<td>Phenylpropanolamine chloride vs. Phenylpropanolamine chloride + antihistamine vs. placebo</td>
<td>Orally, 100 mg + antihistamine vs. 200 mg vs. placebo</td>
<td>10 days</td>
<td>Randomized, cross-over, double-blind, placebo controlled</td>
<td>Improvement in obstruction *, secretion *, sneezing *</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
</tbody>
</table>
4.1.11. Furosemide – a topical diuretic agent

4.1.11.1. Background

The concept, that the development of oedema secondary to increased plasma and water absorption into the lamina propria and a de novo inflammatory growth of the mucosa of the lateral wall of the nose at the level of the OMC and ethmoid sinuses, resulting in the release of inflammatory mediators preceding the genesis of NPs, has been proposed $^{429,738}$. Bernstein and co-workers (1994 and 1997) $^{739,740}$ used the nasal mucosa of children affected by cystic fibrosis as a model for their studies. In these patients, NPs have been found in a percentage variable from 30 - 50%, and they were linked to the alteration of an ATPase-dependent membrane protein (CFTR) whose task is chloride secretion. The most frequent alteration of this protein in cystic fibrosis leads to the impossibility of linking ATP, and it is only ATP that activates chloride channels. The entry of sodium in the cells of the normal nasal epithelium through the basolateral surface in contact with the blood vessels is combined with the entry of chloride due to a non-ATPase-dependent form of clearance. There is also an ATPase-dependent pump on the basolateral surface, which accounts for the removal of sodium and the influx of potassium. Furthermore, sodium penetrates right into the cells from the surface of the mucosa through a selective channel following its electrochemical gradient. A similar channel is used by chloride to leave the cell itself: this channel is altered in patients suffering from cystic fibrosis. Finally, ions and water may pass through the tight connections going from the surface of the mucosa to the interstitium, and vice versa (Figure 19). So the penetration of sodium that brings about the intracellular clearance of water depends mainly on co-clearance together with chloride. The alteration of the chloride channel, as it occurs in patients with cystic fibrosis, leads to non-secretion of chloride outside of the cell, and to an increase of sodium absorption and consequently to an alteration of the flow of intra- and extracellular water and the formation of small oedematous areas. The genesis of NPs may be due to alterations of ionic flows and the main cause of these events could be mediators of inflammation: the damage caused by these mediators (first of all the major basic protein (MBP)) leads to an altered regeneration of the epithelial cells with an incorrect synthesis of the membrane protein CFTR $^{739-741}$.

According to this hypothesis, the genesis of NPs may be the result of alterations of sodium chloride net flux. Furthermore, the imbalanced sodium chloride...
transmembrane net flux probably leads to a dysregulation of calcium homeostasis, with its concomitant effect on interstitial and intracellular second-membrane messengers. The depletion of calcium would result in a destabilisation of the cells populating the nasal mucosa of patients prone to having polyps. A result of the movement of these electrolytes is the development of inflammatory mediators, such as TNF-α, IL-1 and chemokines responsible for increased and persistent eosinophilic immigration in the NPs. The primary inflammatory mediator released by eosinophils is MBP. There is some evidence that MBP has a damaging effect on the epithelial architecture and that it leads to an alteration of the flux of sodium chloride at the apical surface of the respiratory cell, resulting in increased sodium influx and the resultant increased water absorption in the cell and lamina propria. This leads to a vicious cycle in the development of NPs.

Furosemide, a diuretic of ansa, inhibits the sodium chloride co-transporter channel at the basolateral surface of the respiratory epithelial cell and blocks the influx of sodium and chloride. This leads to an effect on water movement into and out of nasal mucosa. Furosemide has also been shown to reduce arachidonic acid-stimulated production of PGs in human epithelial cell cultures from NPs and to block in vitro proliferation of fibroblasts. These mechanisms make intranasal furosemide a candidate for treatment of oedema formation, inflammation and tissue growth in patients with NPs.

4.11.2. Potential Therapeutic Actions
Furosemide is an inhibitor of the sodium chloride co-transporter channel (NCCC) at the basolateral surface of the respiratory epithelial cell, which is the important cellular protein supposed to offset osmotically induced cell shrinkage by mediating the net influx of osmotically active ions. This loop diuretic blocks the cellular influx of chloride, sodium and water, with a consequent increase of the concentration of such ions in the interstitium (Figure 19). This leads to the formation of a chemical gradient between the interstitium and the epithelial surface, leading to the appearance of an ionic flow of sodium / chloride and water, which leaves the interstitium through the tight connections, to reach the surface of the mucosa. This would effectively dehydrate the surface of the respiratory epithelial cells which explains the antioedematous effect of furosemide.
Although NCCC inhibition may hypothetically have direct impact on NP size and growth, other immunomodulatory and anti-inflammatory effects of furosemide, demonstrated in vitro and in vivo, suggest some other possible modes of action. Furosemide has also been shown to reduce arachidonic acid-stimulated production of PGs in human epithelial cell cultures from NPs in vitro. It also decreases the following inflammatory mediators: cytokines IL-6, IL-8, and TNF-α. This mechanism may be owing to immunosuppressive activity on monocytes as well as direct cellular cytotoxic effects at high furosemide concentrations. This anti-inflammatory activity is comparable with that found of hydrocortisone. In vitro studies on inflammatory cells have confirmed that furosemide had stabilising activity, which may explain protective effect in airway hyperreactivity in asthmatic patients. Furosemide, a potent NCCC inhibitor, may also affect NP growth by the inhibition of fibroblasts. Inhibition of NCCC significantly decreased lung fibroblast numbers in vitro by decreasing their proliferation. Nasal polyp fibroblasts’ products, like GM-CSF, prolong eosinophil survival in vitro. As there is in vitro evidence that NCCC controls the extracellular signal regulated kinase / mitogen-activated protein kinase

Figure 19.
Scheme of ionic changes of the nasal mucosa and the site and therapeutically action of furosemide (modified from 746).
signal transduction pathway in fibroblast and lymphocyte cultures, which supports its role in the control of normal cell proliferation, it can be hypothesised that NCCC inhibition by furosemide may block the proliferation of NP fibroblasts\textsuperscript{744}. However, there are no \textit{in vivo} data to support this hypothesis.

4.1.11.3 Topical Intranasal Furosemide

\textbf{Chronic rhinosinusitis without NPs (Table XXX)}

Only one trial of intranasal furosemide application in patients with CRS without NPs was available. In this prospective, placebo controlled, cross-over study, the short-term effect of intranasal \textbf{furosemide} was compared with isotonic saline solution (0.9\%) in 12 patients\textsuperscript{752}. Anterior rhinomanometry measurements have been done for 3 hours after a single dose of intranasal furosemide (2 mg) or saline spray. A statistically significant decrease of nasal resistance was observed when treated with furosemide (p < 0.001), but not with saline solution. Values at 180 minutes were still lower than the initial resistances. After topical furosemide, the subjective relief of nasal obstruction lasted more than 12 hours in 75\% of all studied subjects.

\textbf{Chronic rhinosinusitis with NPs (Table XXXI)}

One randomised controlled study has evaluated the efficacy of intranasal \textbf{furosemide} inhalation (max. 20 mg/day, 6.6 mmol/l) by comparing with oral methylprednisolone (1 mg/kg/day) for the duration of 1 week previous to ESS in 40 patients suffering from CRS with NPs\textsuperscript{185}. Both treatment regimen were effective and showed significant improvement in nasal symptoms including olfactory dysfunction (p < 0.001) and polyp size (p < 0.001), without any statistically significant difference between the two groups. Histomorphometric analysis has revealed significant reduction in eosinophil count in the steroid group, with no significant effect on mastocyte count and oedema. Furosemide did not affect inflammatory cell count, but it has shown significantly reduced oedema in the previously not operated patients.

In conclusion, short-term intranasal application of furosemide decreases NP size and reduces nasal symptoms including smell disorders associated with CRS with and without NPs similar to systemic steroids. The \textit{in vitro} demonstrated anti-inflammatory effect of furosemide could not be confirmed. The clinical relevance of these very short-term trials is unclear.
4.1.11.4. Furosemide after Surgery (Table XXXII)

One prospective, case controlled study has evaluated the efficacy of long-term treatment with **furosemide aerosol** in 14 patients with recurrent NPs after ESS. Aerosol with 10 mg furosemide was done once a day for 3 months (2x/year), during 3 years. The rhinometry measured nasal volume increased statistically significant (p < 0.001) after 1 month of treatment and did not change further during the whole study. The persistent increased nasal volume was considered as a sign for absence of NP recurrences.

A second, similar (prospective, case controlled, comparison) study has examined the efficacy of long-term intranasal **furosemide** versus no treatment after ESS in 104 patients with NP. One month after surgery, 64 patients were assigned to the furosemide-group: they started the therapy with furosemide 2 puffs per nostril a day (each puff corresponding to 50 μg) of furosemide diluted in physiological solution for 30 days. This therapy should be taken for 1 month and then interrupted for 2 months and so on for the first 2 years; then re-taken for 1 month and interrupted for a further 4 months during the third, fourth and fifth year of treatment. After 5 years of treatment, furosemide had to be administered for 1 month and interrupted for 6 months. No treatment was administered to the control group (40 patients). The result of this study showed that in a mean follow-up of 3.8 years, 93% of the patients treated with furosemide did not have relapses. These data seem to be particularly satisfactory if compared with the results obtained in the control group where the percentage of failure was 30% (p = 0.013). A follow-up study with a range of 1 – 9 year-outcome showed similar results.

In conclusion, long-term intranasal furosemide after ESS in patients with NPs seems to prolong the time to recurrences significantly, but no randomized, placebo controlled study is available confirming a positive furosemide effect and not an anti-inflammatory effect of the physiologic solution used for dilution.

4.1.11.5. Side Effects

Trials on inhaled furosemide treatment in CRS with and without NPs are few and none of those reported drug-related side effects. Besides side effects attributed to its diuretic action when taken systemically (hypokalemia, hypotension), furosemide is well-known to cause allergic reactions due to its incorporated sulfa
moiety, and it has been reported to cause ototoxicity with high-dose rapid intravenous infusions\textsuperscript{747}. However, the review of clinical trials of inhaled furosemide in acute and chronic asthma indicates that this type of administration does not induce significant local nor systemic side effects, and no diuretic effects have been reported\textsuperscript{747}. Although the resorption rate of furosemide by inhalation has not been measured in any trial, daily observations of blood pressure, blood parameters, total urine volume, creatinine clearance and potassium did not show alterations\textsuperscript{741,747,753}. These trials in asthmatic patients were performed on long-term courses with inhalation of 40 mg furosemide\textsuperscript{753,754}, even twice a day\textsuperscript{753}, which did not cause any significant systemic side effects. It may be similar for nasal sprays or aerosols.
### Table XXX. Topical furosemide in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masieri et al</td>
<td>CRS</td>
<td>12</td>
<td>Furosemide vs. isotonic saline (0.9%)</td>
<td>Spray, 1 puff/day, 2mg</td>
<td>1 day</td>
<td>Randomized, placebo controlled, cross-over</td>
<td>Obstruction decreased still after 12 hours in 75%</td>
<td>Anterior rhinomanometry * (3 hours)</td>
<td>Ib</td>
<td>Positive (1 day experimental study)</td>
</tr>
<tr>
<td>Kroflic et al</td>
<td>NP</td>
<td>40</td>
<td>Furosemide vs. methylprednisolone</td>
<td>Furosemide aerosol: 20 mg/day Methylprednisolone orally: 1 mg/kg/day</td>
<td>1 week</td>
<td>Randomized, controlled</td>
<td>Obstruction *, secretion *, olfaction *</td>
<td>Endoscopy: polyps *, edema * (furosemide), inflammatory cells * (steroid)</td>
<td>Ib</td>
<td>Positive</td>
</tr>
</tbody>
</table>

### Table XXXI. Topical furosemide in CRS with NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passàli et al</td>
<td>NP recurrences</td>
<td>14</td>
<td>Furosemide</td>
<td>Aerosol, 10 mg/day (2 x 3 mths./year)</td>
<td>3 years</td>
<td>Prospective, case controlled</td>
<td>-</td>
<td>Acoustic rhinometry (NP recurrences) *</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Passàli et al</td>
<td>NP</td>
<td>104</td>
<td>Furosemide vs. No treatment</td>
<td>Spray, 200μg/day (6 mths./year → 2 mths./year)</td>
<td>2 – 6 years</td>
<td>Prospective, case controlled</td>
<td>-</td>
<td>Endoscopy (NP recurrences) *</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

### Table XXXII. Topical furosemide in CRS after surgery to prevent NP recurrences

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passàli et al</td>
<td>NP</td>
<td>14</td>
<td>Furosemide</td>
<td>Aerosol, 10 mg/day (2 x 3 mths./year)</td>
<td>3 years</td>
<td>Prospective, case controlled</td>
<td>-</td>
<td>Acoustic rhinometry (NP recurrences) *</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Passàli et al</td>
<td>NP</td>
<td>104</td>
<td>Furosemide vs. No treatment</td>
<td>Spray, 200μg/day (6 mths./year → 2 mths./year)</td>
<td>2 – 6 years</td>
<td>Prospective, case controlled</td>
<td>-</td>
<td>Endoscopy (NP recurrences) *</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>
4.1.12. Gastroesophageal Reflux Therapy

4.1.12.1. Background and Potential Therapeutic Actions

In 1950, Holmes et al. proposed an association between sinonasal diseases and gastric hypersecretion \(^{755}\). Since then, numerous trials mentioned that gastroesophageal reflux (GER) may cause airway diseases, and beneficial effects of reflux therapy were proposed. Most studies evaluating this association were retrospective and a scientifically valid proof remains elusive. In the association between GER and CRS, three criteria should be met: 1) patients with CRS should have a higher prevalence of GER than patients without CRS, 2) the pathophysiological mechanisms between GER and CRS should help to explain how the disease processes interact, and 3) if GER is truly a contributing factor to CRS, then GER treatment should improve or resolve CRS in most patients.

With regard to the first criterion, DiBaise et al. (1998 and 2002) demonstrated a high prevalence of GER in patients with CRS \(^{89,236}\). They found proven GER in 78 - 82% of patients with CRS. Ulualp et al. (1999) also demonstrated a significantly higher prevalence of GER in patients with CRS unresponsive to conventional therapy compared with normal controls (p < 0.05) \(^{756}\). Furthermore, results from a large case-controlled epidemiologic study demonstrated that adults with complicated GER were more likely to have sinusitis (odds ratio = 1.60; 95%, CI = 1.51–1.70) than were controls \(^{757}\). Chambers et al. (1997) found that the presence of GER was a predictor for poor symptomatic outcome after sinus surgery in adults \(^{758}\). Most recently, DelGaudio (2005) showed for the first time the presence of nasopharyngeal reflux episodes in adult patients with refractory CRS. This prospective study reported a statistically significant difference (p < 0.04) in the frequency of nasopharyngeal reflux events below pH 4 - 5 in adult patients with refractory CRS compared with those patients without CRS recurrences after ESS and control patients without a history of CRS \(^{759}\). Several investigators have suggested a relationship between GER and CRS in children \(^{88,760-763}\). Subsequent studies, both prospective and retrospective, have demonstrated a high prevalence of GER (especially pharyngeal reflux) in children with CRS, providing further evidence of the relationship \(^{88,761,762}\).

The pathophysiological mechanisms by which GER may affect the sinonasal cavity remain unclear, but three mechanisms have been proposed: 1) the refluxate (acid and pepsin) provokes a direct inflammation of the mucosa, 2) a vagal mediated neurogenic mechanism involving dysfunction of the autonomic nervous system,
resulting in mucosal oedema and secondary ostia obstruction, and 3) the presence of *Helicobacter pylori*, playing a large role in stomach ulcers and gastritis, and found also in human dental plaque, oral lesions, saliva, and recently, in the nasal mucosa of patients with CRS. However, it remains unknown whether *Helicobacter pylori* is a causative agent for CRS or its result.

With regard to the third criterion, the outcome of GER therapy in children with CRS is more convincing than in adults. Two retrospective studies analysed 28 children and 12 adults with GER and refractory CRS and showed an improvement of the CRS symptoms in up to 68% of the patients treated medically or surgically for reflux. Complete symptom resolution occurred infrequently. These data suggest a contribution of GER in the multifactorial aetiology of CRS.

4.1.12.2. Reflux Therapy

Reflux therapy in CRS without NPs (Table XXXIII)
The first trial evaluated the role of GER and reflux therapy (cisapride, proton pump inhibitor, and diet modifications) for 2 months in children with CRS. Nineteen children with demonstrated oesophageal reflux were treated with a reflux therapy (prospective, case controlled). Fifteen (79%) of these 19 individuals improved their CRS symptoms.

In a similar (prospective, case controlled) study, 11 adults with CRS and GER underwent a reflux therapy with a proton pump inhibitor (*omeprazole*, 40 mg/day) for 3 months. Sinus symptoms and global satisfaction were of moderate improvement in 25% - 89% and 91% of the patients, respectively. Resolution of symptoms occurred infrequently.

Reflux therapy in CRS with NPs (Table XXXIV)
Seven patients with NPs associated to AERD were treated with 20 mg/day of *omeprazole* for 1 month (prospective, case controlled). Seventy-one percent of the treated individuals showed respiratory improvement at the end of the treatment course.

Another prospective, case controlled trial studied a reflux therapy for the duration of 1 month in 25 patients suffering from NPs and GER. They were treated with *omeprazole, lansoprazole or rabeprazole*, 40 mg/day, 30 mg/day and
20 mg/day, respectively. Only 15 patients could finally be analyzed. Ninety-three percent of them showed some sinus symptom improvement.

In conclusion, these very small, prospective, case controlled studies demonstrated a high percentage of patients (mean. 88%; range 79 – 93%) with only moderate improvement of the CRS associated symptoms and QoL after reflux therapy for CRS associated with proven GER. In a small study, omeprazole treatment showed improvement in 71% of NP patients associated with AERD without proven GER. Unfortunately, no placebo controlled study has been done, and thus evidence and clinical relevance of this treatment modality remain unclear.

4.1.12.3. Reflux Therapy after Surgery
There were no data available of reflux therapy after ESS in patients with GER suffering from CRS with and without NP.

4.1.12.4. Side Effects
Proton pump inhibitors, which are the mainstay of medical treatment of GERD, represent a very effective class of drugs, widely prescribed in all age populations, often to patients with co-morbid conditions (and therefore polymedicated), and in some instances, for prolonged periods of time. All these factors may challenge their safety profile. However, the tolerability of proton pump inhibitors in both short- and long-term use is remarkably good. The safety profile is similar across the various prescribed proton pump inhibitors. The most common adverse events are diarrhea, headache, rhinitis, nausea, pharyngitis and abdominal pain. Several changes in laboratory parameters have also been reported and are represented by elevation of hepatic enzymes, low sodium levels, alterations in white blood cell counts and γ-glutamyl transferase values. Long-term findings indicate a tolerability profile similar to that found in short-term trials. The risk of drug interactions with other medications is rather low. Finally, proton pump inhibitors’ safety seems to be high also in pregnant women and in children, although further studies in these populations are required to corroborate this evidence.
### Table XXXIII. Gastroesophageal reflux therapy in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phipps et al (2000)</td>
<td>CRS (in children with proven GER)</td>
<td>19</td>
<td>Cisapride, histamine H2 blocker or proton pump inhibitor, and appropriate diet modifications</td>
<td>Orally, 0.8 – 1.5 mg/kg</td>
<td>2 months</td>
<td>Prospective, case controlled</td>
<td>Improvement in 79%</td>
<td>-</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>DiBaise et al (2002)</td>
<td>CRS</td>
<td>11</td>
<td>Omeprazole</td>
<td>Orally, 40 mg</td>
<td>3 months</td>
<td>Prospective, case controlled</td>
<td>Modest improvement in nasal symptoms and global satisfaction in 25 – 89% and 91%, respectively</td>
<td>Endoscopically improvement in 27 %</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

### Table XXXIV. Gastroesophageal reflux therapy in CRS with NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serra et al (1998)</td>
<td>AERD / NP</td>
<td>7</td>
<td>Omeprazole</td>
<td>Orally, 20 mg</td>
<td>1 month</td>
<td>Prospective case controlled</td>
<td>Improvement in 71%</td>
<td>-</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Pincus et al (2006)</td>
<td>CRS / NP</td>
<td>25</td>
<td>Omeprazole, lansoprazole or rabeprazole</td>
<td>Orally, 40 mg, 30 mg or 20 mg, respectively</td>
<td>1 month</td>
<td>Prospective, case controlled</td>
<td>At least some improvement in 93%</td>
<td>-</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
</tbody>
</table>
**4.1.13. Immunotherapy - systemic**

### 4.1.13.1. Background

Twenty years ago, a constellation of allergic mucin, NPs and the presence of extramucosal fungi was noted for its similarity to “allergic bronchopulmonary aspergillosis” ⁷⁷⁵. Since then, the so called allergic fungal rhinosinusitis (AFRS), probably a subgroup of NPs has been the subject of numerous reports and studies. Its exact pathophysiology, criteria for diagnosis and ultimate treatment regimen remain a source of controversy. Several studies showed high levels of allergen-specific IgE and IgG for several fungal antigens in patients with AFRS ⁷⁷⁶-⁷⁸¹. The surgical removal of allergic mucin and maintenance of adequate paranasal sinus drainage is the initial step of therapy. However, surgery alone is associated with a high rate of recurrence. Nasal irrigation, INSs, topical and systemic antifungal medication, systemic steroids, immunotherapy, and other medical regimens have been used in this topic ⁷⁸². Despite aggressive treatment, the recurrence rate of NPs and eosinophilic mucus is very high. A retrospective analysis of 60 patients with diagnosis of AFRS showed promising results of immunotherapy, reporting reoperation rates of 33% in patients not receiving immunotherapy (n = 24) compared with 11.1% in those receiving immunotherapy (n = 36) ⁷⁸³. Hence, there is a clear need for a better understanding of this disease and for the development of effective therapies.

Another hypothesis of the aetiology of CRS with and without NPs is the development from acute rhinosinusitis. Chronic rhinosinusitis patients demonstrated a presence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* in the nose and paranasal sinuses. These microorganisms have frequently been cultured in CRS patients without improvement after both, antibiotic therapy and ESS. The contribution of the different microorganisms to the pathology remains unclear. Another intriguing finding is the presence of IgE antibodies against SAEs in 60 – 80% of patients with NPs and asthma ⁴². The SAEs are superantigens that interact with T cells directly, bypassing the antigen-presenting cells, thereby increasing the frequency of immune response. Patients with NPs who have IgE to SAEs in the nasal mucosa also have more severe eosinophilic inflammation and are more likely to have asthma and AS-sensitivity ⁴³. Long-term intracellular persistence and infections of *Staphylococcus aureus* in nasal and paranasal sinus mucosa was demonstrated recently and
seemed to be involved in the bad outcome and high recurrence rates of CRS with NPs.\(^{49,50}\)

Allergic rhinitis may contribute to the development of recurring or CRS. A most recent study showed a correlation of allergy and outcomes after ESS in patients with CRS. The presence of allergy (total serum IgE) demonstrated a negative effect on subjective and objective outcomes at 1 year follow-up after ESS, especially in cases with NP.\(^{784}\) In a study of 114 patients with a history of allergic rhinitis, recurring sinusitis, and radiographic evidence of rhinosinusitis; the patients receiving conventional aeroallergen immunotherapy for at least 1 year reported a 61% improvement in sinus pain, 50% improvement in nasal purulent mucus, and a 49% improvement in nasal congestion. Furthermore, there was a 54% reduction in nasal/sinus surgical procedures and 74% fewer days lost from work or school.\(^{785}\)

Immunotherapies directed against microorganisms and other «allergic» antigens potentially responsible in the development of recurring and CRS have been used, and have shown promising results.

### 4.1.13.2. Potential Therapeutic Actions

Allergic rhinitis may predispose patients with CRS with and without NPs. While traditional immunotherapy is clearly efficient in AR, there have not been well-performed trials on its usefulness in CRS / AFRS. Surgical removal of allergic mucin and NPs decreases the large and constant antigenic exposure, thus, the specific immunotherapy with fungal, non-fungal or staphylococcal antigens to which sensitivity had been demonstrated, applied postoperatively, might achieve sufficient immunomodulation to have a positive effect on the clinical course.

Fungal antigens in current testing and treatment protocols are showed in Table XXXV.

**Table XXXV. Fungal antigens in current testing and treatment protocols**\(^{786}\)

<table>
<thead>
<tr>
<th>Helminthosporium</th>
<th>Fusarium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternaria</td>
<td>Mucor</td>
</tr>
<tr>
<td>Stemphyllium</td>
<td>Pullularia</td>
</tr>
<tr>
<td>Curvularia</td>
<td>Cladosporium</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>Penicillium</td>
</tr>
<tr>
<td>Epicoccum</td>
<td></td>
</tr>
</tbody>
</table>

186
Clinical trials are under way investigating methods of making immunotherapy safer and more effective. By attaching immunostimulatory products, such as endotoxin or bacterial DNA sequences, antigens can be made much more immunogenic without increasing their allergenicity. Mice given CpG oligodeoxynucleotides (bacterial DNA sequences) during ova albumin sensitisation, had decreased eosinophilic inflammation and symptoms of rhinosinusitis.\(^{787}\)

Despite gaining experience in this area, one still has no certain knowledge about the mechanism of action of the immunotherapy with fungal, non-fungal, and staphylococcal antigens. Studies in AFRS have reported changes in allergen-specific IgE and IgG. However, a decrease in the level of specific IgE could not be demonstrated despite clinical response. No consistent pattern to IgG levels has been observed. In a study using staphylococcal antigens for immunotherapy in CRS in children, an increase of serum IgA and IgG was reported.\(^{788}\) The treatment may also affect T cells, immune complexes or other antiallergic mechanisms.

4.1.13.3. Immunotherapy (Table XXXVI)

**Chronic rhinosinusitis without NPs**
A prospective, case controlled study evaluated the outcome after subcutaneous injection of an **antigenic extract of bacterial vaccine (Staphylococcus aureus)** (2x/week) for 8 months in 50 children with CRS.\(^{788}\) During the observation period of 6 months after the treatment regimen, 82% of the children showed improved symptoms and 76% an increase of serum IgA and IgG.

**Chronic rhinosinusitis / allergic fungal rhinosinusitis with NPs preceded by surgical removal of allergic mucin**
A prospective, case controlled study evaluated the outcome after subcutaneous injection of an **immunotherapy directed against specific fungal and non-fungal antigens** (1x/week) after skin testing and preceded by surgery for an average of 8.6 months in 9 patients with AFRS.\(^{789}\) Although no control group existed, they observed that immunotherapy resulted in less crust formation and allergic mucin within the sinuses, and no adverse effects of the treatment were noted.

A follow-up study of the above mentioned prospective, case controlled trial including 23 patients with immunotherapy for an average time of 28 months showed
positive effect in preventing recurrence of AFRS after surgery without adverse effects.

To determine the effect of immunotherapy with fungal and non-fungal antigens on clinical outcome in patients with AFRS, a prospective, case controlled, comparison study has been performed. Twenty-two patients were evaluated after a mean treatment period of 33 months. All received similar treatment consisting of ESS, corticosteroids and antibiotics as needed for complicating purulent sinusitis. Eleven patients received postoperative immunotherapy with fungal and non-fungal antigens (1x/week) to which sensitivity had been demonstrated, while the remaining 11 patients received no additional therapy. The effect of immunotherapy showed significant improvement in patients’ outcome as assessed objectively by an endoscopic mucosal staging score (p < 0.001) and a sinusitis-specific QoL scale, the Chronic Sinusitis Survey (p < 0.002). In addition, immunotherapy showed a reduction of systemic (p < 0.001) and intranasal corticosteroid need (p = 0.043) during the observed period.

In conclusion, it has been shown recently that patients with allergies have worse outcome after ESS when compared with those without allergies. Allergy may also be a contributing factor in the development of recurring and CRS. Bacterial immunotherapy seems to improve nasal symptoms in children suffering from CRS. One study could even demonstrate a statistically significant improvement of QoL after the immunotherapy. The postoperatively use of immunotherapy with fungal and non-fungal antigens to which sensitivity has been proven showed better outcomes in patients with AFRS when compared with patients who did not undergo immunotherapy. The fact that no randomised, double-blind placebo controlled trial has been performed, statistical comparisons are almost lacking, and drug preparation and treatment protocols are not easily understandable, the usefulness of this treatment modality in CRS with and without NP is actually uncertain, and further investigations should be done to demonstrate that allergen-specific immunotherapies may decrease or avoid the development of CRS.

4.1.13.4. Side Effects
In the above discussed studies, adverse events were not mentioned. Anaphylactic reactions may exist.
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez et al</td>
<td>CRS (children)</td>
<td>50</td>
<td>Bacterial vaccine (Staph. aureus)</td>
<td>2 x 0.5 ml/week s.c.</td>
<td>8 months</td>
<td>Prospective, case controlled</td>
<td>Nasal symptoms improved in 82%</td>
<td>Increase of IgA and IgG in 76%</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Mabry et al</td>
<td>AFRS after surgery</td>
<td>9</td>
<td>Immunotherapy</td>
<td>Weekly, s.c. 0.05 ml</td>
<td>Average of 8.6 months</td>
<td>Prospective case controlled</td>
<td>Decrease in nasal and sinus crusting</td>
<td>Decrease in NP recurrences, decrease in CS</td>
<td>III (no statistics)</td>
<td>?</td>
</tr>
<tr>
<td>Mabry et al</td>
<td>AFRS after surgery</td>
<td>23</td>
<td>Immunotherapy</td>
<td>Weekly, s.c. 0.05 ml</td>
<td>Average of 28 months</td>
<td>Prospective case controlled</td>
<td>Decrease in nasal and sinus crusting</td>
<td>Decrease in NP recurrences, decrease in CS, stabilization or increase of serum IgE and IgG</td>
<td>III (no statistics)</td>
<td>?</td>
</tr>
<tr>
<td>Folker et al</td>
<td>AFRS after surgery</td>
<td>22</td>
<td>Immunotherapy vs. no immunotherapy</td>
<td>Weekly, s.c. 0.05 ml</td>
<td>Average of 33 months</td>
<td>Prospective, case controlled</td>
<td>Improvement of sinusitis-specific QoL *</td>
<td>Decrease in NP recurrences *, decrease in topical and systemic CS *</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

CS: corticosteroids; QoL: quality of life; s.c.: subcutaneous

4.1.14.1. Background
The mucosa of the nose is capable of swelling and shrinking, which changes nasal resistance. A dense network of venous sinusoids, whose filling is controlled by specialized « cushion veins », is typical for the nasal mucosa. The longitudinally arranged muscle walls of these cushions have a sympathetic and parasympathetic nerve supply. An increased sympathetic action leads to dilatation of the cushion veins, emptying of the venous sinusoids, and thus nasal mucosal vasoconstriction with a decrease in nasal resistance, which means nasal decongestion. A decreased sympathetic nerve action or an increase of parasympathetic drive has the opposite effect, constricting the cushion veins, filling the venous sinusoids, and leading to nasal mucosal swelling and nasal congestion\(^\text{485,790}\). The autonomic nervous system exerts its effect by secreting neurotransmitters like noradrenalin and acetylcholine by sympathetic and parasympathetic nerve endings, respectively. The nose vessels contain predominantly \(\alpha\)-adrenergic receptors, whose stimulation leads to a vasoconstriction. Any decrease or interruption of nasal sympathetic nerve supply causes nasal congestion; electrical stimulation causes decongestion\(^\text{791}\). Certain antihypertensive drugs with sympathetic blockade can cause a similar clinical picture like a vasomotor rhinitis, a subgroup of NANIPER\(^\text{792}\).

The nasal glands, however, are innervated only by the parasympathetic nerve supply\(^\text{793}\). An increase in parasympathetic action leads to an important secretion from these serous and sero-mucous glands. This effect has been demonstrated by the observation that nasal secretion can be reduced to basal levels by cutting the vidian nerve, which is the nasal parasympathetic nerve\(^\text{794}\).

An imbalance of the autonomic nervous system in the nasal mucosa may be responsible for the hyperreactivity of the nasal mucosa in patients with NANIPER. Non-allergic, non-infectious perennial rhinitis may appear as one or more of the following symptoms, such as sneezing, watery hypersecretion or nasal obstruction, and the treatment will be directed to diminish the predominant symptoms. Topically and systemically applied sympathomimetics are effective in the short-term outcome, but there is a risk of developing a rhinitis medicamentosa and tachyphylaxis\(^\text{792,795}\). In addition, vasoconstrictors have no effect on the secreting mucosal glands, and important adverse events (hypertension, urinary retention, behavioural disturbances, night terrors, etc.) have been reported\(^\text{796}\). Therapies with tricyclic antidepressant
agents having anticholinergic and sympathomimetic actions have been studied, but the long-term outcome was disappointing. Topical corticosteroids were used and showed a dramatic amelioration of the symptoms in patients with NANIPER. They have few side effects, with the exception of pain, burning and mild epistaxis.

Ipratropium bromide (IB), an anticholinergic agent with good intranasal activity, has shown efficacy in perennial AR, and seems also to demonstrate benefits in the treatment of different rhinitis subgroups of NANIPER, including gustatory rhinitis and vasomotor rhinitis in children and adults.

4.1.14.2. Potential Therapeutic Actions

Ipratropium bromide is a synthetic quaternary ammonium congener of atropine, but unlike atropine, it is poorly absorbed. It has anticholinergic actions by antagonizing the effects of acetylcholine at parasympathetic, postganglionic, effector-cell junctions by competing with acetylcholine for receptor sites. Ipratropium bromide, intranasal administered, inhibits parasympathetic function within the nasal mucosa, thus diminishing the secretory output from serous and sero-mucous glands.

Tolerance to the therapeutic effects of IB has not yet been described. Although IB primarily works at controlling watery anterior rhinorrhea, several short and long-term studies found that it might reduce also nasal obstruction, maybe by blocking an increased parasympathetic drive which led to nasal mucosa congestion.

4.1.14.3. Topical Intranasal Ipratropium bromide (Table XXXVII)

Chronic rhinosinusitis / NANIPER without NPs

There are 16 randomised, double-blind, placebo controlled studies assessing the clinical efficacy of intranasal IB in NANIPER. They evaluated endonasal application of IB (84 μg/day - 1600μg/day) during 2 - 8 weeks. Rhinorrhea improved statistically significant in all of these trials (p < 0.05). However, IB did not show any significant effect on nasal obstruction and sneezing. Three of these trials studied the effect of different IB treatment doses on the symptoms of NANIPER. The daily doses ranged from 84 - 1600 μg for duration of 2 - 5 weeks. There was a statistically significant improvement of rhinorrhea with all treatment doses, with an additional slight but statistically significant reduction (p < 0.05) in the high-dose IB-group (1600 μg). One of these trials
evaluated the combination of intranasal IB and beclomethasone dipropionate and showed a statistically significant better improvement of rhinorrhea, nasal obstruction and sneezing when compared with either active agent alone (p < 0.05)\textsuperscript{241}.

A prospective, case controlled study compared intranasal IB with budesonide spray in the treatment of NANIPER in 14 patients during 10 days\textsuperscript{810}. Budesonide, but not IB, showed statistically significant improvement in all nasal symptoms (p < 0.01). Budesonide was superior to IB regarding all nasal symptoms.

Three prospective, case controlled and one randomised, double-blind, placebo controlled trials have studied the efficacy and side effects of intranasal IB in a long-term treatment course of 6 months to 4 years\textsuperscript{186,239,806,811}. Daily intranasal doses of 252 - 320 µg IB were applied. Despite a reduction of the dosage over the time according to the patients’ perceived need, the efficacy did not appear to diminish. All of these trials showed an improvement of rhinorrhea. The data indicate that long-term use of IB may also contribute to a certain control of congestion, postnasal drip and sneezing. Unfortunately, three of these studies did not show any statistical comparisons.

**Chronic rhinosinusitis with NPs**

There are no studies or data available to determine the potential usefulness of intranasal IB in the treatment of NPs.

In summary, intranasal IB improves evidentially watery rhinorrhea in patients with NANIPER. One prospective, case controlled, long-term study (months to years) found that IB might improve also other nasal symptoms, such as nasal obstruction, postnasal drip and rhinosinusitis-associated QoL. Statistically non significant improvement of smell dysfunction has been observed in one single study. Nevertheless, intranasal corticosteroids (budesonide) or the combination of IB with an INS (beclomethasone dipropionate) showed statistically significant better symptom release than IB and either agent alone. Long-term treatment with topical IB seems to be efficient, despite a reduction of the dosage over the time. Unfortunately, no study has yet been done correlating the subjective symptoms improvements with objectively demonstrated changes of the sinus mucosa by a CT-scan. Ipratropium bromides should be used alone or even better, in combination with an INS in cases where the initial INS therapy for CRS/NANIPER failed.
4.1.14.4. Ipratropium bromide after Surgery
No trials were found providing data about intranasal application of IB after ESS in patients suffering from CRS with or without NPs.

4.1.14.5. Side Effects
The side effects of IB when administered parenteral are similar to those of atropine, with the exception that central nervous system effects are much less likely, and that at higher blood levels, antinicotinic effects such as ganglion blockade and curariform neuromuscular blockade appear. Because of its low systemic absorption, the intranasal administration is relatively free of side effects usually accompanying the oral administration of anticholinergic drugs (oral and skin dryness), unless higher doses than recommended were given. Ipratropium bromide has been evaluated in both short- and long-term studies. Kaila et al. (1990) examined the effects of IB in healthy control subjects and in 10 patients who had severe NANIPER. They applied a total single dose of 360 μg of IB in the nose, which is approximately nine times the single dose recommended for this nasal pathology. Ipratropium bromide was rapidly absorbed from the nasal mucosa and achieved a mean peak concentration within 10 minutes after application of the total dose. The mean plasma concentrations were approximately 50% higher in patients with NANIPER, but were negligible and less than 400 pg/ml in both groups. Thus the increased systemic absorption in the patients with NANIPER is unremarkable. A small decrease in heart rate (8 beats/min) was noted in both groups, probably because of bed rest and a supine position during the experiment. A 10% decrease in salivary secretion was observed in both, control subjects and patients, related to the antisecretory action of the high dose of IB. Wood et al. (1995) showed that IB pharmacokinetics in patients with perennial rhinitis were comparable to those in healthy volunteers. Approximately 10% of the intranasal drug was absorbed in these patients, as measured by 24-hour urine excretion. Plasma IB concentrations did not exceed 0.5 ng/ml in any of the patients, and the drug was rapidly eliminated (within 2 hours). These patients had used IB nasal spray three times a day for at least 1 year, and there was no evidence, therefore, of long-term accumulation with chronic administration of the drug.

Any interference with the mucociliary transport in the nose is expected when an agent with desiccating potential is given. The effect of IB on MCT time has been
evaluated in several studies and no effect has been seen after the administration of doses up to 1600 μg/daily when compared with baseline and placebo applications \(^805,813\). In short-term trials (2 – 8 weeks), 2 - 61% of the patients treated with daily IB doses of 84 – 320 μg reported any adverse event \(^186,192,238,240-243,802-805,807,809\). These are usually limited to local side effects, which occur in a dose-dependent manner. The most common nasal adverse events reported by patients were epistaxis (2 - 9.4%), irritation (8 - 26%) and dryness (1 - 61%). The most common non-nasal adverse events were headache (3 - 16.9%), upper respiratory infections including pharyngitis (2.5 - 8.7%) and mouth dryness (8 - 42%). Patients treated with a IB high-dose regimen (1600 μg/daily) for 2 weeks showed statistically significant more complaints of nasal dryness (49.6% vs. 31.2%), mouth dryness (50% vs. 23.2%) and dysuria (14.1% vs. 5%) when compared with a normal-dose therapy (320 μg/daily) \(^805\). This demonstrates that systemic side effects of anticholinergic agents are typically dose related. The side effects were all mild and no serious adverse event was described.

The long-term safety of IB was studied in 4 prospective trials with an intranasal treatment for 6 months to 4 years in patients with NANIPER \(^186,239,806,811\). They showed any side effects in up to 84% of the patients. Most of the nasal side effects were dryness (3.5 - 33%), epistaxis (2.5 - 18%) and irritation (3.5 - 15\%) \(^239,806,811\). Non-nasal adverse events were upper respiratory infections including pharyngitis (4.5 - 25%), headache (5 - 10%) and anticholinergic side effects such as dry mouth or throat (33\%) \(^239,806,811\). All these described side effects were mild in nature and resolved during the studies as the patients adjusted the dosage according to individual severity of symptoms. Nasal endoscopy did not show any specific changes or abnormalities in the nasal mucosa. No serious adverse, drug-related event was described in these long-term studies. It seems that the treatment with the newer aqueous IB nasal spray has a lower frequency of nasal and systemic anticholinergic side effects than with the metered dose aerosol, at even similar applied doses \(^814\).

In summary, mild local and systemic anticholinergic side effects such as dry nose, dry mouth / throat and headache are common in short and long-term therapies, and are dose dependent. No serious adverse, drug-related event was described.
### Table XXXVII. Topical ipratropium bromide in CRS / NANIPER without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signific. *)</th>
<th>Objective (stat. signific. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borum et al (1979)</td>
<td>CRS / NANIPER</td>
<td>20</td>
<td>IB vs. placebo</td>
<td>Spray, 320 μg/day</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea *, obstruction, sneezing</td>
<td>Smell</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Bok et al (1983)</td>
<td>CRS / NANIPER</td>
<td>21</td>
<td>IB vs. placebo</td>
<td>Spray, 320 μg/day</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea (paper tissue used) *</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Malmberg et al (1983)</td>
<td>CRS / NANIPER</td>
<td>34</td>
<td>IB vs. placebo</td>
<td>Spray, 320 μg/day</td>
<td>3 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea *, sneezing, obstruction, itching</td>
<td>Metacholine provocation *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Von Haacke et al (1983)</td>
<td>CRS / NANIPER</td>
<td>20</td>
<td>IB vs. placebo</td>
<td>Spray, 320 μg/day</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea *, obstruction, sneezing</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Sjögren and Juhasz (1984)</td>
<td>CRS / NANIPER</td>
<td>13</td>
<td>IB vs. placebo</td>
<td>Spray, 320 μg/day</td>
<td>3 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea * (paper tissue used), sneezing, obstruction</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Bende and Rundcrantz (1985)</td>
<td>CRS / NANIPER</td>
<td>14</td>
<td>IB vs. budesonide</td>
<td>Spray, 320 μg/day</td>
<td>10 days</td>
<td>Prospective, case controlled</td>
<td>Nasal symptoms * (budesonide &gt; IB)</td>
<td>-</td>
<td>III</td>
<td>Negative</td>
</tr>
<tr>
<td>Knight et al (1986)</td>
<td>CRS / NANIPER</td>
<td>30</td>
<td>IB vs. placebo</td>
<td>Spray, 320 μg/day</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea * (paper tissue used), obstruction</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Kirkegaard et al (1987)</td>
<td>CRS / NANIPER</td>
<td>36</td>
<td>IB 20 μg vs. IB 100 μg vs. placebo</td>
<td>Spray, 320 resp. 1600 μg/day</td>
<td>5 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea *, sneezing Mucociliary transport</td>
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</tr>
<tr>
<td>Dolovich et al (1985)</td>
<td>CRS / NANIPER</td>
<td>25</td>
<td>IB vs. placebo</td>
<td>Spray, 320 μg/day</td>
<td>3 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea * (paper tissue used), obstruction</td>
<td>-</td>
<td>Ib</td>
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<td>O'Dwyer et al (1988)</td>
<td>CRS / NANIPER</td>
<td>61</td>
<td>IB vs. placebo</td>
<td>Spray, 320 μg/day</td>
<td>6 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea *, obstruction, sneezing</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Dolovich et al (1989)</td>
<td>CRS / NANIPER</td>
<td>23</td>
<td>IB 40 μg vs. IB 80 μg vs. placebo</td>
<td>Spray, 160 μg vs. IB 320 μg</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea * (no difference between the 2 IB groups), obstruction</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Druce et al (1992)</td>
<td>CRS / NANIPER</td>
<td>147</td>
<td>IB 21 μg vs. IB 42 μg vs. placebo</td>
<td>Spray, 84 resp. 168 μg/day</td>
<td>4 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Rhinorrhea * (no difference between IB-groups), obstruction, sneezing, postnasal drip, QoL</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Author</td>
<td>Indication</td>
<td>N</td>
<td>Drug name</td>
<td>Daily dose</td>
<td>Duration</td>
<td>Study design</td>
<td>Symptoms (stat. signif. *)</td>
<td>Objective (stat. signif. *)</td>
<td>Level of evidence</td>
<td>Outcome</td>
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<tr>
<td>Georgitis et al</td>
<td>CRS / NANIPIER</td>
<td>174</td>
<td>IB vs. placebo</td>
<td>Spray, 252 µg/day</td>
<td>8 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Rhinorrhea *, obstruction, sneezing, QoL: mood *</td>
<td>Endoscopy, nasal cytology</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Bronsky et al</td>
<td>CRS / NANIPIER</td>
<td>233</td>
<td>IB vs. placebo</td>
<td>Spray, 252 µg/day</td>
<td>8 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Rhinorrhea *, QoL: physical activities and mood *</td>
<td>Endoscopy, nasal cytology</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Meltzer et al</td>
<td>CRS / NANIPIER in children</td>
<td>40</td>
<td>IB vs. placebo</td>
<td>Spray, 252 µg/day</td>
<td>4 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Rhinorrhea *, improvement of QoL</td>
<td>Nasal cytology</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Finn et al</td>
<td>CRS / NANIPIER</td>
<td>91</td>
<td>IB + terfenadine vs. placebo + terfenadine IB + BMD vs. IB vs. BMD vs. placebo</td>
<td>Spray, 252 µg/day</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea *, obstruction, sneezing</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
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<tr>
<td>Dockhorn et al</td>
<td>CRS / NANIPIER</td>
<td>274</td>
<td>IB vs. BMD vs. IB vs. placebo</td>
<td>Spray, 252 µg/day, BMD: 336 µg/day</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>IB + BMD: Rhinorrhea *, obstruction *, sneezing *, QOL improved more than IB alone</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
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<tr>
<td>Borum et al</td>
<td>CRS / NANIPIER</td>
<td>20</td>
<td>IB</td>
<td>Spray, 320 µg/day</td>
<td>1 – 4 years</td>
<td>Prospective, case controlled</td>
<td>Rhinorrhea *</td>
<td>Metacholine provocation *</td>
<td>III</td>
<td>Positive</td>
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<tr>
<td>Dolovich et al</td>
<td>CRS / NANIPIER</td>
<td>25</td>
<td>IB</td>
<td>Spray, 320 µg/day</td>
<td>6 months</td>
<td>Randomized, double-blind, placebo controlled, crossover</td>
<td>Rhinorrhea *</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
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<tr>
<td>Milford et al</td>
<td>CRS / NANIPIER</td>
<td>40</td>
<td>IB</td>
<td>Spray, 320 µg/day</td>
<td>1 year</td>
<td>Prospective, case controlled</td>
<td>Improvement of nasal symptoms</td>
<td>-</td>
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<tr>
<td>Grossman et al</td>
<td>CRS / NANIPIER</td>
<td>285</td>
<td>IB</td>
<td>Spray, 252 µg/day</td>
<td>1 year</td>
<td>Prospective, case controlled</td>
<td>Improvement of rhinorrhea, obstruction, post-nasal drip, and QoL</td>
<td>Improvement in endoscopy</td>
<td>IV (no statistics)</td>
<td>Positive</td>
</tr>
</tbody>
</table>

BMD: beclomethasone dipropionate, IB: ipratropium bromide
4.1.15. Irrigations – nose and paranasal sinuses

4.1.15.1. Background
Impaired drainage and retention of secretions in the paranasal sinuses is usually caused by one or more of the following conditions: obstruction of the ostia, reduction in the number of cilia or any dysfunction, and overproduction of secretions or a change in their viscosity. These conditions may partially be responsible in the aetiology of CRS. Nasal saline irrigation is a simple, inexpensive and often effective procedure that is used as an adjunct treatment in acute and chronic sinonasal diseases. Nasal saline irrigation is common to both modern and traditional therapy regimens. Delivered by bottle, spray, pump or nebuliser, the topical use of saline (salt water) has been included as a supplement to most treatment protocols and relieves symptoms of a variety of sinonasal diseases: acute and CRS, allergic and non-allergic rhinitis, pregnancy rhinitis, paediatric chronic sinusitis, nonspecific nasal symptoms (including postnasal drip), septal perforations, primary care recommendations and crust-forming conditions like sinonasal sarcoid, Wegener’s granulomatosis, postoperative care of surgical patients and radiotherapy.

Nasal saline irrigations may lead to reduction of other nasal medications (such as INSs, antihistamines, antibiotics, etc.), and could help minimise antibiotic resistance. Unfortunately, studies of nasal saline irrigations are often small, poorly controlled, and unsupported conclusions are sometimes drawn. No standard uniform recommendations exist for the use of nasal saline irrigations. Various nasal saline irrigation solutions (isotonic vs. hypertonic, buffered or non-buffered) and numerous types of delivery (positive-pressure: squeeze bottles, bulb syringes with or without nasal adapters; negative pressure: sniffing solution into nasal cavity; nebulisers; sprays) are available. A study, observing healthy adult volunteers, analysed these different delivery types and found that positive-pressure and negative-pressure nasal saline irrigations were more effective than nebulisers in distributing saline solution to the ethmoid and maxillary sinuses. Sphenoid and frontal sinuses received limited solution with either negative- or positive-pressure nasal saline irrigation. The nebuliser was unable to deliver any solution to the sphenoid or frontal sinuses. Only with large volumes (300 ml) can the paranasal sinuses be reached, rinsed and washed.

The procedure has been used safely for both adults and children, and has no documented serious adverse effects. Saline nasal lavage has been advocated as...
adjunct therapy for CRS because it promotes improved ciliary function and clearance by moisturising the nasal cavity, removes encrusted material and bacteria, and decreases mucosal oedema, which would improve sinus drainage. Treatment strategies often include the use of intranasal saline from once to more than four times a day. Considerable patient’s effort is often demanded. However, despite the positive and proven effects of saline irrigations, this treatment modality is frequently regarded as a homeopathic adjunct in the treatment of sinonasal diseases.

Other, more anecdotic types and solutions of sinonasal irrigations like antiseptic solutions, carboxymethylglucan, baby shampoo, sodium hypochlorite, thermal water irrigations and inhalations, nasal hyperthermia and N-chlorotaurine antral washout are mentioned and discussed.

4.1.15.2. Potential Therapeutic Actions of Sinonasal Saline Irrigations

The nature of the benefit of saline is difficult to define physiologically and remains controversial. The mechanical clearance of sticky and encrusted mucus is commonly proposed as the sole basis of the benefit from saline irrigations. Crusts associated with various sinonasal conditions and after surgery may be soften and dislocated with nasal irrigations. Thick tenacious secretions may become less viscous, further enhancing the clearance of mucus. The remove of pollen and other allergenic or irritant material from the nasal mucosa may also be helpful in the treatment of the inflammatory condition.

However, there is increasing perception that saline has a contributory anti-inflammatory action and does not just relieve symptoms for mechanical reasons. The nasal mucus contains many inflammatory mediators, such as histamine, PGs, and LTs, which may be removed by nasal irrigations. The additional removal of these inflammatory mediators may explain the decrease in mucosal oedema, which may liberate the sinus ostia and improve their drainages.

Increasing the ciliary beating frequency seems to improve mucociliary clearance. Two in vivo studies compared the effects of normal and hypertonic saline and could show that hypertonic saline was more effective in increasing mucociliary clearance compared with normal saline. In contrast, one trial reported that both isotonic and hypertonic saline decreased ciliary activity in vitro.
Evidence shows that saline lavage can remove bacteria \cite{825,826}, and that hypertonic saline solution has topical antibacterial effect, which is well established in wound dressing and washing of open wounds \cite{835,836}. Hypertonic saline shows mucolytic properties, helpful by cleaning of sticky mucus \cite{837,838}.

Other theories exist for the beneficial physiological effects of saline irrigation, like removal of antigen and biofilms, and a protective role on the sinonasal mucosa.

4.1.15.3. Sinonasal Saline Irrigations

The studies included inhere fulfil the following criteria:

- Hypertonic versus isotonic saline
- Irrigation versus ‘placebo’
- Irrigation versus no irrigation
- Standard therapy with irrigation versus standard therapy alone
- Dead sea salt solution versus hypertonic saline
- Irrigation

4.1.15.3.1 Nasal Irrigations (Table XXVIII)

A number of randomised controlled trials have tested nasal irrigation with isotonic or hypertonic saline in the treatment of CRS. Although saline is considered as a control treatment itself, patients in these randomised trials were assigned to different modalities of application of saline or hypertonic saline, or hypertonic compared to isotonic saline.

Chronic rhinosinusitis without NPs

- Hypertonic versus isotonic solutions:

One randomised, double-blind study compared the effect of nasal wash with **hypertonic saline (HS)** (3.5%) versus **normal saline (NS)** (0.9%) during 4 weeks of treatment in 34 children with CRS by comparing cough and postnasal drip score as subjective and a radiologic score as objective outcome measures \cite{839}. Hypertonic saline demonstrated statistically significant improvement for all scores, while NS improved only postnasal drip (reduction of cough score HS 56% (p < 0.05) vs. NS 6% (n.s.)); reduction of postnasal drip score HS 44% (p < 0.05) vs. NS 42% (p < 0.05); reduction of radiology score HS 67% (p < 0.05) vs. NS 3% (n.s.).
Another randomised, double-blind study compared the effect of isotonic saline (IS) (0.9%) and hypertonic Ems saline solution (ES) (1.1%) (balneotherapeutic water). Forty patients with CRS were included and applied two times daily the solutions during 1 week. There was no significant difference between symptom scores from each group. Both improved relative to baseline. The mean symptom score change was 0.6 and 0.7 for the IS and ES group, respectively (scale 1 to 6). The Student’s test p value was > 0.05. Significant improvement was seen in radiographic and endoscopic score in the ES group. No significant improvement was seen in olfactometry, rhinomanometry, and saccharine clearance time.

- Irrigation versus ‘placebo’:
  One randomised, placebo controlled study has evaluated the treatment of hypertonic saline irrigation (HS) (2.7%) delivered by different techniques (pot (1), and bulb syringe (2)) and ‘placebo’ (reflexology massage (3)) on the QoL scores (Rhinosinusitis Outcomes Measure (RSOM-31)) of 150 CRS patients. Participants used the HS in unspecified volumes daily for two weeks. All groups (pot, bulb syringe and reflexology) showed improvements on RSOM-31. The mean improvements were 25.5%, 20.4% and 35.1% in the groups 1, 2 and 3, respectively. Percentage of individuals improved were 72%, 74% and 78%, respectively. There was no significant difference between groups and control. The ‘placebo’ group was as efficacious as both saline uses.

- Irrigation versus no irrigation:
  A randomized controlled trial in 62 patients with CRS compared the outcome between nasal irrigation with hypertonic sea salt spray (SS), alkaline saline douche (AS), and standard treatment without nasal douche during 8 weeks. After 8 weeks of treatment, they confirmed that nasal washing with SS and AS produced benefit over standard treatments without nasal douching. Irrigation per se improved endoscopic appearance ($p = 0.009$), and QoL scores ($p = 0.008$). These measures did not change in the control group which received standard treatment CRS without irrigation. There was significant difference between the two irrigation types: the AS improved endoscopic appearance, but did not enhance QoL; whereas the opposite was true for the SS. There was no significant alteration in acoustic
rhinometry, diary card scores, nasal mucociliary clearance time, and ciliary beating frequency in any of the groups.

A prospective, randomised controlled study tested the benefit from daily irrigation with 150 ml hypertonic saline (HS) (2%) versus no topical treatment during 6 months in 76 patients with CRS or recurrent acute sinusitis. The used subjective score instruments were the Medical Outcomes Survey Short Form (SF-12), the Rhinosinusitis Disability Index (RSDI), and a Single-Item Sinus-Symptom Severity Assessment (SIA). Patients with HS irrigations reported fewer 2-week periods with sinus-related symptoms (p < 0.05), and used less antibiotics (p < 0.05) and rescue nasal sprays (p = 0.06). The saline group demonstrated improvement in RSDI and SIA scores compared to controls. Six-month RSDI improvement was of 24.7% and SIA of 41%. These were statistically significant and above the proposed minimally important clinical difference for the RSDI. The SF-12 did not show a statistically significant improvement.

- Standard therapy with irrigation versus standard therapy alone:
  
  Another prospective, randomised controlled study investigated the efficacy of saline irrigations added to antihistamine therapy. Fourteen patients were randomised to two groups: 7 patients received cetirizine 10 mg daily with hypertonic (> 0.9%) saline spray (4 times a day) for 4 weeks and 7 patients received cetirizine only without any topical therapy. Significant improvements were shown by the Rhinasthma questionnaire on the upper airway (92.4%, p = 0.02) and global indices (86%, p = 0.001) in the combined saline therapy group compared with the cetirizine alone.

- Dead Sea salt solution versus hypertonic saline:
  
  A recent double-blind, randomised controlled trial in 57 patients with CRS, with persistence of symptoms for at least 1 year and previously unsuccessfully treated with conventional medical regimen, compared the outcome between nasal irrigation with hypertonic Dead Sea Salt solution (DSS) (1.8%) and hypertonic saline (HS) (1.8%) during 4 weeks. Both treatment groups demonstrated statistically significant improvement in rhinosinusitis symptoms. HS in contrast to DSS (p < 0.01) did not show a difference from baseline in the rhinoconjunctivitis QoL score. DSS
compared to HS demonstrated significantly better improvements in total rhinosinusitis symptom scores ($p = 0.003$) and rhinoconjunctivitis QoL ($p < 0.001$).

Chronic rhinosinusitis with NPs

Controlled trials of nasal saline irrigations alone in CRS with NPs are not available. Nasal saline administration was used as a control treatment in placebo controlled trials.

In conclusion, the included studies in here were of moderate quality. Nasal saline irrigation shows improvement in symptoms and disease specific QoL (5 trials) compared with no treatment and when added to an oral antihistamine therapy in patients with CRS. Rabago et al. (2002) provides the strongest support for the use of nasal saline as an adjunct in the treatment of CRS $^{840}$. The effective size was likely to be moderate. Another study (placebo controlled) could not demonstrate better improvement of disease specific QoL scores in patients treated by saline irrigations compared with reflexology control $^{244}$. Sea salt solution showed better improvement in symptoms and QoL than conventional hypertonic saline solution, which may be due to an anti-inflammatory effect of magnesium and other oligominerals in the sea salt solution, demonstrated in different dermatologic conditions (allergic, atopic, and psoriatic dermatitis). The evaluation of smell by olfactometric measures in one single study did not find statistically significant improvement. The comparison between isotonic and hypertonic saline irrigations was done in two trials showing not conclusive results in favor of one of them.

4.1.15.3.2. Antral Washouts (Table XXXIX)

Antral washout has been used in the management of sinusitis for at least a century $^{841}$. In the pre-antibiotic days, the need for sinus surgery was much more frequent than today. With the advent of INSs and efficient broad spectrum antibiotics, the need for antral washout is not as well defined.

- Irrigation versus no irrigation:

A prospective, randomised controlled study compared the results of antral washout (once a day, for 12 days) with no antral washout in children with chronic maxillary sinusitis $^{842}$. Fifty patients were randomised into two groups. Patients in Group A
received antral washouts (normal saline +/- Fluimucil®). Patients in the Group B received no treatment. A standard sinus radiology was done before and 20 days after the treatment. The Group B showed slightly better results than the Group A, but no statistical comparisons were done.

- Standard therapy with irrigation versus standard therapy alone:
  A prospective, randomised controlled study examined the efficacy of a single antral washout (normal saline) through a maxillary sinus canulation on CRS without NPs. One hundred and fourteen patients were randomised into two groups: antral washout followed by systemic antibiotics and INSs, and antibiotics and INSs alone. They were followed-up for 18 months. In each group, 51.6% and 50% of patients, respectively, improved endoscopically with the treatment. The difference was not statistically significant (p = 0.86). The addition of antral washout conferred no additional benefit in the treatment of CRS without NPs compared to medical treatment alone.

In conclusion, comparison of treatment with antral washouts in the management of chronic adult and paediatric rhinosinusitis did not prove benefit from such treatment.

4.1.15.3.3. Nasal Irrigations after Surgery (Table XXXX)
The aim of sinus surgery in patients with CRS with and without NPs is to open narrow passages and to allow more effective drainage and airflow. Because the nasal cavity quickly becomes encrusted following surgery, frequent endoscopic nasal cleaning and suctioning by the ENT-physicians combined with saline irrigation are prescribed for 4 - 8 weeks to soften and remove the nasal crusting until the mucosal lining of the nose and sinuses has regenerated. As a result, the risks of adhesion formation and inhibition of sinonasal drainage are decreased. These benefits may be, at least in part, attributable to the effect of saline douching in reducing the nasal discharge and improving edema during the healing phase following ESS, suggesting a possible anti-inflammatory role of saline solutions.

- Irrigation versus no irrigation:
  One study has examined the efficacy of nasal spray with isotonic saline (IS) (0.9%) and hypertonic saline (HS) (3%) sprays compared to no treatment during 5 days...
after ESS in 60 patients with CRS. This study did not prove any of both treatments superior to the outcome of the no-treatment group. HS induced greater discharge during the first 5 postoperative days and showed increased pain scores, compared to IS and no-treatment. However, no objective evaluation was done in this trial and the nasal irrigation was given by spray and lasted only for 5 days postoperatively.

A similar study reviewed results of intranasal irrigation with alkaline saline solution (AS) for 3 months after ESS in patients with CRS with and without NPs. The outcome was compared with a group without additional nasal douche. Seventy-seven subjects completed the study. There were no significant differences in subjective and objective outcomes between the irrigation and non-irrigation group, but there was a tendency for patients in the irrigation group to have a better outcome.

Another study has evaluated in a single-blind, randomised controlled fashion, the efficacy of intranasal application of isotonic saline (IS) (0.9%) for 6 weeks after ESS for CRS with and without NPs. Twenty-three patients applied the IS with a 2 ml syringe via a mucosal atomisation device on only one side of the nose. At 3 weeks, saline douching significantly improved the presence of discharge ($p = 0.046$) and the presence of oedema ($p = 0.059$, not significant) with minimal difference with regard to polyps ($p = 0.32$), and no difference in adhesions or crusting. At 3 months, there was minimal difference with regard to crusting ($p = 0.18$) and oedema ($p = 0.32$), and no difference with regard to adhesion, discharge and polyps.

In conclusion, an evident benefit of saline washes frequently recommended after ESS in patients with CRS could not be demonstrated. Trials evaluating long-term courses of saline irrigation to prevent NP recurrences were not available in the literature.

4.1.15.4. Non-Saline Sinonasal Irrigations (Table XXXXI)

The studies included in the study fulfilled the following criteria:

- Irrigation versus ‘placebo’
- Irrigation versus no irrigation
- Standard therapy with irrigation versus standard therapy alone
- Irrigation
- Thermal water irrigations
- Nasal hyperthermia
4.1.15.4.1. Nasal Irrigations

- Irrigation versus ‘placebo’:
  One randomised, double-blind, cross-over, placebo controlled study has evaluated the treatment of Prorhinel®, an antiseptic agent (5m/100ml benzododecinium bromide) and ‘placebo’ (normal saline solution) on nasal symptoms and saccharine clearance time of 20 CRS patients. Participants used 10 ml of the solution 3 times a day for 1 week. There was a significant better improvement in rhinorrhea (p < 0.05) and sneezing (p = 0.05) in the group of Prorhinel® when compared with the placebo group. There was no significant difference in the saccharine clearance time measured before and after the treatment period.

One randomised, placebo controlled study compared the effect of nasal spray with carboxymethylglucan (CMG) (=lubrificant) (0.25%) versus normal saline (NS) (0.9%) during 1 month of treatment in 100 patients with CRS. All patients applied 3 times daily the nasal spray (2 puffs/nostril) during 1 month. CMG spray, but not normal saline spray, demonstrated statistically significant improvement concerning rhinorrhea, facial pain, intensity of headache, inferior turbinate hypertrophy, rhinopharyngeal exudates, nasal resistance measured by anterior rhinomanometry, mucociliary transport time, normalisation of nasal mucosa and rhinocytogram (p < 0.05). Both treatments did not affect nasal obstruction.

Dexpanthenol in sea water nasal spray is an isotonic solution. It is an analogue of pantothenic acid, which promotes wound healing. A randomised, placebo controlled trial compared the effect of dexpanthenol nasal spray with normal saline irrigation after ESS in 128 patients with CRS with and without NPs. All patients applied twice a day the nasal spray/irrigation during 1 month. Both treatments demonstrated improvement concerning total nasal symptom score, nasal secretion, crust formation and mucociliary clearance, and there was no statistically significant difference between the groups.

- Irrigation:
  A prospective, case controlled trial was done using baby shampoo (1%) in patients with recurrent CRS after ESS. Chemical surfactants can act as a mucolytic agent by reducing water surface tension and have the potential to serve as an antimicrobial
agent. In vitro testing has been performed and determined that 1% baby shampoo in normal saline was the optimal concentration for inhibition of Pseudomonas biofilm formation. Baby shampoo had no effect on the eradication of performed Pseudomonas biofilms. The intranasal irrigation of baby shampoo was done twice a day for 4 weeks. Eighteen patients with CRS with an average of 2.8 surgeries were studied after irrigation with 1% baby shampoo solution. Forty-six percent of patients experienced an overall improvement in their subjective symptoms, 60% of the patients noted improvement in specific symptoms of thickened mucus and postnasal drip, and 63.6% of the patients had an improvement in objectively tested smell.

Another prospective, case controlled study has evaluated nasal irrigation with sodium hypochlorite (NaOCl) in patients with recurrent or persistent Staphylococcus aureus associated CRS. NaOCl is a well-known bleaching and disinfecting agent that has been found to be effective against several microorganisms including Staphylococcus aureus and Pseudomonas aeruginosa. In vitro testing has been performed and determined that 0.05% NaOCl in saline solution for exposure duration of 5 minutes was less cytotoxic than a 0.5% NaOCl solution. Twenty patients known as persistent Staphylococcus aureus symptomatic carriers with unique patient-specific Staphylococcus aureus clonotypes with recurrent CRS despite classical treatment including saline lavage, INSs and several systemic antibiotics were studied. Each subject did first nasal lavage with saline alone for 3 months, followed by 0.05% NaOCl twice daily for another 3 months. The results showed a statistically significant improvement of the subjective symptoms and a decrease of the nasal resistance measured by rhinomanometry when compared with the outcome after saline irrigation (p < 0.05). No significant changes in nasal NO production was observed after treatment and bacteriological cultures of middle meatus secretions collected one month after the end of the treatment revealed the persistence of Staphylococcus aureus.

- Thermal water irrigations:
  Despite their widespread use, much mysticism and uncertainty exist about the indications and therapeutic mechanisms of nasal thermal water inhalations in treatment of CRS.
A prospective, case controlled study has evaluated a treatment with sulphurous-arsenical-ferruginous (thermal) water (SAFW) inhalations in patients with CRS. Thirty-seven patients were studied. Each subject did a 12-day course of SAFW warm vapour inhalations followed by nasal aerosols of the same thermal water. The results showed a statistically significant reduction of the nasal resistance (p < 0.01) measured by rhinomanometry and of the mucociliary transport time (p < 0.01). Nasal cytology evaluation showed a statistically significant reduction of the neutrophil count (p < 0.01). Bacterial presence was statistically reduced after the treatment (p < 0.01).

Another randomised, placebo controlled study compared a treatment with salt-bromide-iodic thermal water aerosol and nasal douche versus normal saline aerosol and nasal douche as ‘placebo’ solution during 2 weeks in 120 patients with CRS with and without NPs. Both treatment regimens showed a significant improvement of nasal obstruction, rhinorrhea, nasal mucosa congestion, nasal secretion and mucociliary transport time. The improvement variation was significantly higher in the thermal water group than in the ‘placebo’ group.

- Nasal Hyperthermia:
  Nasal hyperthermia or inhaled heated mist have been proposed for years to treat severe congestion in the common cold. Beneficial effects of such treatment regimen in CRS are unclear. Theoretically, the heated vapour may add fluid to the mucosal surface and reduce cellular mediator release. Alternatively, the heat may directly interfere with mast cell-allergen or basophil-allergen interactions, or the vapour may help stabilise the mucosal surface and reduce glandular secretions and vascular permeability.

  Controlled trials on nasal hyperthermia in CRS with and without NPs are lacking. Two randomised studies on patients with perennial AR have demonstrated promising results.

4.1.15.4.2. Antral Washouts
- Irrigation:
  A prospective, case controlled trial was done using N-chlorotaurine (1%), an endogenous oxidant with antimicrobial properties against bacteria and fungi, in 12 patients with CRS with and without NPs. The intrasinus application of N-
chlorotaurine was done 3 times a week, during 4 weeks (12 applications) using a YAMIK catheter. Subjective improvement was found in 75% and 90% of patients concerning nasal breathing and smell, respectively. However, no improvement was found on the sinus CT-scan performed before and after the treatment.

4.1.15.5. Side Effects of Nasal Saline Irrigations
Nasal saline irrigations have been shown to be safe. Minor side effects encountered are common and shown in up to 36% of patients treated for different sinonasal conditions \(^\text{244,828,856}\). Local irritation, itching, burning, epistaxis, otalgia, nausea and pooling in sinuses with subsequent drainage have been reported \(^\text{839,857}\). This pooling with delayed discharge in some head positions is most commonly seen in patients who have undergone previous sinus surgery. No major adverse events were recorded in 1659 patients from 22 trials treated with isotonic or hypertonic saline reviewed in the Cochrane analysis concerning nasal saline irrigation \(^\text{828}\).
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Solutions</th>
<th>Delivery, amount and times/day</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoseyov et al</td>
<td>CRS in children</td>
<td>34</td>
<td>HS (3.5%) vs. NS (0.9%)</td>
<td>Drops, 1 ml, 3x/day</td>
<td>4 weeks</td>
<td>Randomized, double-blind</td>
<td>HS: cough *, PND *, NS: PND *, difference * HS vs. NS in cough</td>
<td>HS: Plain x-ray *, difference * HS vs. NS in radiology score</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Taccariello et al</td>
<td>CRS</td>
<td>62</td>
<td>Hypertonic Sea Salt vs. AS vs. no treatment</td>
<td>Spray/douche, 2x/day</td>
<td>8 weeks</td>
<td>Randomized, double-blind</td>
<td>QoL *, Nasal symptoms</td>
<td>Endoscopy *, mucociliary transport, ciliary beating frequency, acoustic rhinometry.</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Bachmann et al</td>
<td>CRS</td>
<td>40</td>
<td>HS Ems (1.1%) vs. NS (0.9%)</td>
<td>Douche, 200 ml, 2x/day</td>
<td>1 week</td>
<td>Randomized, double-blind</td>
<td>Nasal symptoms improved, no difference NS vs. HS Ems saline</td>
<td>Plain x-ray *, endoscopy *, olfactometry, rhinomanometry, saccharine clearance time, no difference NS vs. HS Ems</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Heatley et al</td>
<td>CRS</td>
<td>150</td>
<td>HS (2.7%) vs. reflexology</td>
<td>Douche, ?, ml, daily</td>
<td>2 weeks</td>
<td>Randomized, placebo controlled</td>
<td>RSOM-31 *, no difference HS vs. reflexology</td>
<td>-</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Rabago et al</td>
<td>CRS</td>
<td>76</td>
<td>HS (2%) vs. no treatment</td>
<td>Douche, 300 ml, 1x/day</td>
<td>24 weeks</td>
<td>Prospective, randomized controlled</td>
<td>RSDI *, SIA *</td>
<td>Less antibiotics *, less nasal sprays *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Rogkakou et al</td>
<td>CRS</td>
<td>14</td>
<td>HS (&gt; 0.9%) +10mg cetirizine vs. cetirizine alone</td>
<td>Spray, 4x/day</td>
<td>4 weeks</td>
<td>Prospective, randomized controlled</td>
<td>Rhinasthma questionnaire *</td>
<td>Acoustic rhinometry</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Friedmann et al</td>
<td>CRS</td>
<td>57</td>
<td>HS DSS (1.8%) vs. HS (1.8%)</td>
<td>Douche, ml, 2x/day</td>
<td>4 weeks</td>
<td>Randomized, double-blind</td>
<td>Sinonasal symptom score * for HS and DSS, RQLQ score * for DSS</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Table XXXIX. Antral washouts in CRS

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication N</th>
<th>Solutions</th>
<th>Delivery, amount and times/day</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maes and Clement (1986)</td>
<td>842</td>
<td>Chronic maxillary sinusitis in children</td>
<td>Maxillary sinus catheter, 1/day, 5 – 12 days</td>
<td>20 days</td>
<td>Prospective, randomized controlled</td>
<td>-</td>
<td>Standard sinus radiology: no difference</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Pang and Willatt (1996)</td>
<td>841</td>
<td>CRS (0.9%) and systemic AB and topical steroids vs. AB and topical steroids only</td>
<td>Maxillary sinus canulation, 1 antral washout with normal saline, 10 days AB, continuous topical steroids</td>
<td>Follow-up during 18 months</td>
<td>Prospective, randomized controlled</td>
<td>-</td>
<td>No significant difference in endoscopic findings</td>
<td>Ib</td>
<td>Negative</td>
</tr>
</tbody>
</table>

AB: antibiotics, NS: normal saline

Table XXXX. Nasal saline irrigations after surgery in CRS with and without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication N</th>
<th>Solutions</th>
<th>Delivery, amount and times/day</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinto et al (2006)</td>
<td>845</td>
<td>CRS (0.9%) vs. HS saline (3%) vs. no treatment</td>
<td>Spray, 4 x 2 puffs/day</td>
<td>5 days</td>
<td>Randomized, double-blind</td>
<td>Higher discharge and pain in HS *, otherwise no difference between the groups</td>
<td>-</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Liang et al (2008)</td>
<td>846</td>
<td>CRS / NP AS vs. no treatment</td>
<td>Douche, 500 ml, 1x/day</td>
<td>3 months</td>
<td>Prospective, randomized controlled</td>
<td>No difference in symptom scores</td>
<td>No difference in endoscopic findings</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Freeman et al (2008)</td>
<td>847</td>
<td>CRS / NP NS (0.9%) vs. no treatment</td>
<td>Douche, one side, 2 ml, 3x/day</td>
<td>6 weeks</td>
<td>Randomized, single-blind</td>
<td>Less discharge *, edema, polyps, no difference of crusting/adhesion; no difference at 3 mths.</td>
<td>-</td>
<td>Ib</td>
<td>Negative</td>
</tr>
</tbody>
</table>

AS: alkaline saline, HS: hypertonic saline, NS: normal saline
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Solutions</th>
<th>Delivery, amount and times/day</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Polasek and Haudenschild (1987)</td>
<td>CRS</td>
<td>20</td>
<td>Prorhine® (5mg / 100ml benzododecinium bromide) vs. NS</td>
<td>Douche, 10 ml, 3x/day</td>
<td>1 week</td>
<td>Randomized, double-blind, cross-over, placebo controlled</td>
<td>Rhinorrhea *, sneezing *</td>
<td>Saccharine clearance time</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Neher et al (2005)</td>
<td>CRS / NP</td>
<td>12</td>
<td>N-chlorotaurine</td>
<td>YAMIK catheter, 20 ml, 3x/week</td>
<td>4 weeks</td>
<td>Prospective, case controlled</td>
<td>Obstruction (75%), smell * (90%)</td>
<td>Endoscopy (100%), CT-scan no difference</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Passali et al. (2007)</td>
<td>CRS</td>
<td>100</td>
<td>Carboxymethylglucan (0.25%) vs. NS</td>
<td>Spray, 2 puffs, 3x/day</td>
<td>1 month</td>
<td>Randomized, placebo controlled</td>
<td>Nasal symptoms *</td>
<td>Endoscopy *, nasal mucosa biopsy *, mucociliary clearance time *, rhinomanometry *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Fooanant et al. (2008)</td>
<td>CRS / NP treated with ESS</td>
<td>128</td>
<td>Dexamethasone in sea water vs. NS</td>
<td>Spray, 2 puffs, 2x/day</td>
<td>1 month</td>
<td>Randomized, placebo controlled</td>
<td>Nasal symptoms improved, no difference</td>
<td>Secretion, crust formation, and mucociliary clearance improved, no difference</td>
<td>Ib</td>
<td>Negative (Dexamethasone = NS)</td>
</tr>
<tr>
<td>Staffieri et al. (2007)</td>
<td>CRS</td>
<td>37</td>
<td>Sulphurous-arsenical-ferruginous thermal water</td>
<td>Aerosol, 20 min./day</td>
<td>12 days</td>
<td>Prospective, case controlled</td>
<td>-</td>
<td>Decrease of resistance by anterior rhinomanometry *, mucociliary transport time *, reduction of neutrophils *, reduction of bacteria *</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Passali et al (2008)</td>
<td>CRS / NP</td>
<td>120</td>
<td>Salt-bromine-iodic thermal water vs. NS</td>
<td>Aerosol and douche, 2x/day</td>
<td>2 weeks</td>
<td>Randomized, placebo controlled</td>
<td>Nasal symptoms *</td>
<td>Endoscopy *, decrease of resistance by anterior rhinomanometry *, mucociliary transport time *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Chiu et al (2008)</td>
<td>Recurrent CRS after ESS</td>
<td>18</td>
<td>Baby shampoo (1%)</td>
<td>Douche, 2x/day</td>
<td>4 weeks</td>
<td>Prospective, case controlled</td>
<td>SNOT-22 improvement (46.6% - 63%)</td>
<td>Smell improvement (63.6%)</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Raza et al (2008)</td>
<td>Recurrent CRS / NP</td>
<td>20</td>
<td>NS (0.9%) during 3 mths., then sodium hypochlorite (NaOCl) (0.05%) during 3 mths.</td>
<td>Douche, 2x/day</td>
<td>6 months</td>
<td>Prospective, case controlled</td>
<td>Nasal symptoms *</td>
<td>Endoscopy *, no significant decrease of NO, decrease * of resistance by anterior rhinomanometry</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**Table XXXXI. Non-saline nasal irrigations in CRS with and without NPs**

HS: hypertonic saline, NS: normal saline, SNOT-22: 22-item Sino-Nasal Outcome test
4.1.16. Mucoactive agents – topical and systemic

4.1.16.1. Background

Mucus in the airway is a complex mixture of water, lipids, glycoprotein, sugars and electrolytes that serves as a lubricant for the epithelium. The efficient flow of respiratory mucus is a first level of immune defence that requires an appropriate viscosity and elasticity for optimal barrier and ciliary functions. Continuous production of low-viscous mucus is important for overall health and adequate mucus clearance by ciliary movements is indispensable to keep the nasal and sinus passages sterile and working properly.

The airway mucosa responds to infection and inflammation by hyperplasia and hypertrophy of the surface mucous (goblet) cells and submucosa glands, inducing mucus hypersecretion. Inflammatory products including neutrophil-derived deoxyribonucleic acid (DNA) and filamentous actin (F-actin), defect cells, bacteria and cell debris contribute to mucus purulence. Thickening and drying of airway mucus by respiratory tract infections, allergies and medications can impair its evacuation. Tenacious sticky mucus, posterior rhinorrhea, purulent nasal discharge and nasal obstruction are annoying and frequent symptoms of CRS with and without NPs. Adequate clearance of mucus is also essential. Under normal health circumstances, secretions of mucus in the nose and sinuses are swept out to drainage pathways and then to the back of the throat, where they are swallowed. However, when inflammation narrows these passages, mucus becomes trapped and cannot drain properly, creating prime conditions for a secondary bacterial infection which may lead to a chronic inflammation. Thickened mucus can decrease the mucociliary transport and potentially damage cilia. Altered nasal mucociliary clearance can occur through a variety of conditions, including CRS, anatomic abnormalities, allergy, infections, immunodeficiency, cystic fibrosis and primary ciliary dyskinesia. Chronic rhinosinusitis and cystic fibrosis increase the viscosity of nasal mucus.

Common remedies to decrease sticky mucus include adequate hydration through water intake and nasal washes with saline solutions. Pharmacologic approaches are secondary, and may include a short course of decongestants to reduce mucosal oedema and associated nasal congestion, antihistamines to dry the excess secretions and/or mucoactive agents to alter mucus volume and tenacity. Mucoactive agents are often included as adjunct medication for sinusitis and
cough, based on clinical experience and empiric data. The use of mucoactive agents, that are meant affecting mucus properties and promoting secretion clearance, is controversial due to limited data and equivocal efficacy in available studies. Nonetheless, some patients may benefit.

4.1.16.2. Potential Therapeutic Actions

Mucus is a gel that is both viscous and elastic – properties essential for its normal optimal function. Mucociliary clearance depends on an optimal ratio of viscosity to elasticity. Increased viscosity, as may occur in CRS, can result in overextension of the cilia, thereby impeding mucus transport. Without appropriate lubrication, the cilia will not function properly.

Chronic rhinosinusitis most frequently presents with thickened and tenacious mucus. Thus, thinning secretions can enhance clearance of mucus and help to alleviate symptoms. Steam and nasal irrigations with saline solutions are commonly recommended, and a variety of available “mucoactive” agents claim to influence the clearance of abnormal respiratory secretions. Mucoactive agents may affect the volume of mucus production, its biophysical properties and clearance by the mucociliary apparatus, and its removal through expectoration. Other potential mechanisms of action may include antioxidant (N-acetylcysteine, ambroxol, carbocysteine), antibacterial and immunostimulatory activity. Mucoactive drugs are working as expectorants, mucolytics, and mucoregulatory, mucospissic and mucokinetic drugs. The mechanisms of potential therapeutic actions of the different agents are shown in Table XXXII. Although, only a few data on efficacy are available, documented use of such therapy dates back more than 3000 years.
Table XXXII. Mucoactive drugs

<table>
<thead>
<tr>
<th>Mucoactive Agent</th>
<th>Potential Mechanisms of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mucolytic thiol drugs with a free sulfhydryl group</strong></td>
<td></td>
</tr>
<tr>
<td>Cysteine and derivatives</td>
<td>Mucolytic activity, reduces mucus viscosity, possible increase of ciliary activity</td>
</tr>
<tr>
<td>Dithiothreitol (not used clinically)</td>
<td>Mucolytic activity</td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Severs disulfic bonds that link mucin oligomers, anti-oxidant and anti-inflammatory</td>
</tr>
<tr>
<td>Nacystelyn</td>
<td>Increases chloride secretion and severs disulfid bonds</td>
</tr>
<tr>
<td>Thiopronine</td>
<td>Mucolytic activity and against histamine-induced bronchoconstriction</td>
</tr>
<tr>
<td>Sodium 2-mercaptoethane sulfate (MESNA)</td>
<td>Mucolytic activity</td>
</tr>
<tr>
<td><strong>Mucokinetic drugs with a blocked thiol group</strong></td>
<td></td>
</tr>
<tr>
<td>Carbocysteine</td>
<td>Increases acid sialomucin production, reduces goblet cell hyperplasia.</td>
</tr>
<tr>
<td>Letosteine</td>
<td>Increases acid sialomucin production</td>
</tr>
<tr>
<td>Stepronine</td>
<td>Severs disulfic bonds, increases acid sialomucin production</td>
</tr>
<tr>
<td><strong>Expectorant drugs that may increase mucus secretion</strong></td>
<td></td>
</tr>
<tr>
<td>Sobrerol</td>
<td>Increases mucus secretion and volume</td>
</tr>
<tr>
<td>Bromhexine</td>
<td>Increases mucus secretion</td>
</tr>
<tr>
<td>Ambroxol</td>
<td>Increases mucus secretion</td>
</tr>
<tr>
<td>Dry powder manitol</td>
<td>Increases mucus secretion</td>
</tr>
<tr>
<td>Inorganic and organic iodides (not used clinically)</td>
<td>Increases mucus secretion</td>
</tr>
<tr>
<td>Domiodol</td>
<td>Increases mucus secretion</td>
</tr>
<tr>
<td>Gualacol and derivatives</td>
<td>Increases mucus secretion</td>
</tr>
<tr>
<td>Guaifenesin</td>
<td>Reduces mucus viscosity and increases mucus secretion, decreases surface tension of secretions</td>
</tr>
<tr>
<td>Ipecacuanha</td>
<td>Mucokinetic effect</td>
</tr>
<tr>
<td>Myrtol</td>
<td>Increases mucus secretion with mucolytic activity</td>
</tr>
<tr>
<td><strong>Peptide mucolytics</strong></td>
<td></td>
</tr>
<tr>
<td>Trypsin (not any more used clinically)</td>
<td>Degrades mucoproteins and fibrin</td>
</tr>
<tr>
<td>Geloline</td>
<td>Prevents filamentous actin polymerization</td>
</tr>
<tr>
<td>Dornase alpha</td>
<td>Hydrolyses DNA polymer and reduces DNA length</td>
</tr>
<tr>
<td>Thymosin β4</td>
<td>Depolymerizes filamentous actin</td>
</tr>
<tr>
<td><strong>Non-destructive mucolytics</strong></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>May break both hydrogen and ionic bonds</td>
</tr>
<tr>
<td><strong>Hypertonic solutions (7%)</strong></td>
<td>Increase secretion volume and perhaps hydration</td>
</tr>
<tr>
<td><strong>Water</strong></td>
<td>Systemic hydration</td>
</tr>
<tr>
<td><strong>Cough clearance promoters</strong></td>
<td>Can improve cough clearance by increasing expiratory flow</td>
</tr>
<tr>
<td>Bronchodilators</td>
<td>Decrease sputum adhesiveness</td>
</tr>
<tr>
<td>Surfactants</td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Decreases glandular secretion</td>
</tr>
<tr>
<td>Anticholinergic agents</td>
<td>Increase lacrimation and hydration of mucus</td>
</tr>
<tr>
<td>Purinergic receptor agonists</td>
<td></td>
</tr>
</tbody>
</table>

Modified from 858,865

4.1.16.3. Topical Intranasal Mucoactive agents (Table XXXIII)

Chronic rhinosinusitis without NPs

A radiologic study (prospective, case controlled) before and after 5 treatments with intranasal bromhexine nebulisation (= expectorant drug that may increase mucus secretion) in patients with chronic maxillary sinusitis showed a radiological improvement in 95% of the patients 867.

One randomised, double-blind, placebo controlled study has evaluated the efficacy of endonasal nebulisation of bromhexine (12 – 16 mg/day) vs. saline in 20
children with CRS associated with bronchial asthma during 2 weeks. The study did not prove bromhexine superior to saline inhalation by evaluating nasal and bronchial symptoms. The radiographic outcome of the paranasal sinuses was statistically significant better for the saline-group (p < 0.01).

**Chronic rhinosinusitis with NPs**

No trial of intranasal therapy with mucoactive agents was available in patients with NPs.

One prospective, case controlled trial suggest radiologic improvement in patients with CRS (maxillary sinus) treated with inhaled mucoactive agents (bromhexine), but no statistical comparison were done. The only randomised, double-blind, placebo controlled study comparing nebulised bromhexine with saline solution in children suffering from CRS did not show any advantages or superiority in the active treatment group. However, these studies tested the mucoactive agents only for a very short period, but trials evaluating long-term courses of inhalations with mucoactive agents are lacking.

**4.1.16.4. Systemic Mucoactive agents (Table XXXIV)**

**Chronic rhinosinusitis without NPs**

A prospective, case controlled study evaluated the systemic treatment of N-acetylcysteine (= mucolytic drug) in 40 patients with CRS. The drug was given 3 times per day for 1 month. The studied population showed clinical improvement of nasal obstruction in 70%, rhinorrhea in 72%, pain in 73% and facial pressure in 93% of the individuals, respectively. A radiological improvement was demonstrated in 76% of the patients.

Nasal mucus clearance was studied in 70 patients with chronic maxillary sinusitis in a prospective, randomised manner. Forty-five patients were treated with oral administration of bromhexine tablets (48 mg/day) (= expectorant drug that may increase mucus secretion) along with oral antibiotics and nasal decongestants. Twenty-five patients received the same treatment but without bromhexine. After 10 days of treatment, nasal mucus clearance time was significantly lowered in the bromhexine group when compared with the group without bromhexine treatment.
In a double-blind, randomised, placebo controlled, clinical trial, the safety and efficacy of 900 mg/day sobrerol granules (=expectorant drug that may increase mucus secretion) given for up to 10 days was assessed in 40 patients with CRS. Treatment with sobrerol significantly (p < 0.01) reduced frontal headache and rhinorrhea. Its efficacy has been confirmed by rhinomanometry. Patients treated with placebo also experienced a significant improvement in frontal headache (p < 0.05).

Another randomised, double-blind, placebo controlled study has compared the efficacy of systemic guaifenesin (2400 mg/day) (=expectorant drug that may increase mucus secretion) with placebo in 23 HIV+-patients with CRS for a duration of 3 weeks. There was a statistically significant better nasal decongestion and thinner postnasal discharge in the guaifenesin-group (p < 0.05).

Another prospective, case controlled trial was designed to observe the effects of standardised myrtol (Gelomyrtol forte), a secretomucolytic phytomedicine, in 22 patients with CRS. The mucociliary transport time before and after oral application of myrtol (3 x / day, 900 mg/day, 10 days) was determined using the saccharine test, and the effects of this treatment regimen on nasal patency was measured by acoustic rhinometry and active anterior rhinomanometry. Another 10 patients without medication, who had the same examinations twice with a 10-day interval, were involved as controls. Patients with treatment showed significantly improvement in mucociliary transport time, unilateral minimum cross-sectional area, the volume of 0 - 5 cm inside the nasal cavity, the unilateral nasal resistance at 75 Pa and total symptom visual analogue scale score.

Chronic rhinosinusitis with NPs
No trial of systemic therapy with mucoactive agents in patients with NPs was available.

In conclusion, several systemic mucoactive treatments evidentially suggest significant subjective and objective improvement in patients with CRS without NPs.

4.1.16.5. Mucoactive agents after Surgery
There is only one study available, evaluating aerosol with Dornase alpha, a highly purified solution of recombinant human deoxyribonuclease I (= enzyme which selectively cleaves DNA) in patients suffering of cystic fibrosis and NP. Dornase
alpha hydrolyses the DNA present in sputum / mucus of cystic fibrosis patients and reduces viscosity in the lungs, promoting improved clearance of secretions. This trial (randomised, double-blind, placebo controlled) has examined the efficacy of nasal aerosol with dornase alpha compared to hypotonic saline (placebo) after ESS in 24 cystic fibrotic children with NPs for the duration of 12 months. The dornase alpha group showed a persistent improvement in nasal symptoms (up to a mean of 32.5%) and endoscopic appearance (43.5%) by 48 weeks after surgery. The overall increase in peak expiratory nasal flow was significant (8.9%; p < 0.05) for the dornase alpha group but not for the placebo group (3.03%; p = 0.08). The efficacy of the dornase alpha treatment showed a very significant benefit (p < 0.001). No patient treated with dornase alpha showed specific adverse events. However, cystic fibrosis was a criterion of exclusion and this study does not figure under the finally analysed studies.

4.1.16.6. Side Effects
Nasal irritation and sneezing after intranasal applied mucolytic agents were described. Inhalative dithiotreitol is the most potent mucolytic thiol, but it is too irritating for clinical use. Nebulised trypsin, a proteolytic enzyme, has been abandoned due to α-1-antitrypsin deficiency, allergic reactions, hemoptysis, mucosal metaplasia and emphysematous degradation of alveolar walls.

The Cochrane meta-analysis (2006) resumed the most often occurred side effects described in large cohort studies on systemic N-acetylcysteine in patients with chronic obstructive pulmonary disease: cough, rhinitis, bronchitis and dyspnea. They were probably not drug related. Nausea and vomiting, gastrointestinal discomfort and diarrhea were also described. These large trials showed similar numbers of reported adverse events compared to the placebo group. The above mentioned meta-analysis included 26 trials and 7335 participants, respectively, and showed a significant effect in favor of N-acetylcysteine (OR 0.78, 95% CI 0.67 to 0.92, p = 0.002). However, this analysis does not include data from several large studies, and they concluded that there is no difference in the number of adverse effects compared with a placebo treatment. Inorganic and organic iodides should not be used anymore in the clinical practice because of their indisputable toxicity for induction of thyroid diseases. In the here included studies, no adverse events were observed.
### Table XXXIII. Topical mucoactive agents in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polakow (1973)</td>
<td>CRS (maxillary sinusitis)</td>
<td>44</td>
<td>Bromhexine Nebulization</td>
<td>5 ml, dose?</td>
<td>5 days</td>
<td>Prospective, case controlled</td>
<td>-</td>
<td>Maxillary sinus radiology improved</td>
<td>III (no statistics)</td>
<td>Not conclusive</td>
</tr>
<tr>
<td>Van Bever et al (1987)</td>
<td>CRS with asthma in children</td>
<td>20</td>
<td>Bromhexine Nebulization</td>
<td>12 – 16 mg</td>
<td>2 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Nasal symptoms * in both groups, no significant difference between the groups</td>
<td>Maxillary sinus radiology * only in saline group</td>
<td>Ib</td>
<td>Negative</td>
</tr>
</tbody>
</table>

### Table XXXIV. Systemic mucoactive agents in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bébéar and Darrouzet (1988)</td>
<td>CRS</td>
<td>40</td>
<td>N-acetylcysteine Oral, 3x</td>
<td>1 month</td>
<td>Prospective, case controlled</td>
<td>Improvement in obstruction (70%), rhinorrhea (72%), pain (73%), facial pressure 93%</td>
<td>Improvement in sinus x-rays (76%)</td>
<td>III (no statistics)</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Goel et al (1989)</td>
<td>CRS (maxillary sinusitis)</td>
<td>70</td>
<td>Bromhexine + amoxicillin + nasal drops of xylometazoline vs. amoxicillin + nasal drops of xylometazoline</td>
<td>Oral, 48 mg + 750 mg + 3x/day</td>
<td>10 days</td>
<td>Prospective, randomized controlled</td>
<td>-</td>
<td>Decrease in nasal mucus clearance time *</td>
<td>Ib</td>
<td>Positive (not clinical)</td>
</tr>
<tr>
<td>Bellussi et al (1990)</td>
<td>CRS</td>
<td>40</td>
<td>Sobrerol vs. placebo</td>
<td>Oral, 900 mg</td>
<td>10 days</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Improvement of frontal headache * and rhinorrhea *, no difference in global drug evaluation</td>
<td>Improvement in rhinomanometry *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Wawrose et al (1992)</td>
<td>CRS (HIV+)</td>
<td>23</td>
<td>Guaifenesin vs. placebo</td>
<td>Oral, 2400 mg</td>
<td>3 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Nasal obstruction *, postnasal drip *</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Han et al (2009)</td>
<td>CRS / NANIPER</td>
<td>22</td>
<td>Myrtol Oral, 900 mg</td>
<td>10 days</td>
<td>Prospective, case controlled</td>
<td>Improvement of nasal symptom score *</td>
<td>Improvement in MCT time*, acoustic rhinometry *, nasal resistance by AAR *, no changes in CBF</td>
<td>III</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

AAR: active anterior rhinomanometry, CBF: ciliary beating frequency, MCT: mucociliary transport
4.2. COMPLEMENTARY AND ALTERNATIVE MEDICINE

Complementary and alternative medical practices include traditional Chinese medicine (acupuncture and herbs), homeopathy, naturopathy, herbal medicine, Ayurvedic medicine, mind-body medicine, massage, and chiropractic and some forms of osteopathic manipulation. The tremendous interest of the U.S. public in complementary and alternative medicine was recognised by the medical establishment after Eisenberg et al. (1993) reported that one-third of the people in the United States used some form of unconventional medicine. The research on complementary and alternative treatments for CRS is scant. The difficulty in assessing these therapies often lies in their multimodal complexity (diet, lifestyle changes, and herbs) or in the fact that the concept of disease origin is radically different from conventional medicine (traditional Chinese medicine, homeopathy, Ayurveda). This thorough literature search revealed only a few studies on the subject.

4.2.1. Phytopreparations – topical and systemic

4.2.1.1. Background

The use of alternative therapies to treat health conditions has gained increasing attention from both patients and health-care providers. Asthma and CRS, chronic and common conditions affecting a wide age range of individuals are particularly relevant to assess the prevalence of such practices, which are also referred to as “complementary” or “unorthodox” therapies. There is also a diverse array of prescribed and over-the-counter treatment options available. Perhaps because of the limited success of conventional therapy and the nature of the condition, herbal medicines are becoming increasingly popular and are frequently used by adults with rhinosinusitis. Twenty-six percent of patients with CRS have used herbal therapy alone or as adjunct treatment for their condition.

The aim of general treatment is to establish a more normal nasal environment through moisturization and humidification, and a reduction of the viscosity of mucus and local oedema. The German Consensus Group DG-HNO considers phytomedicine such as BNO-101 (Sinupret®) to be ‘possibly efficient’ in rhinosinusitis. BNO-101 (Sinupret®) is an oral, herbal medicinal product which has been widely
employed as a ‘mucoactive’ agent in Germany for almost 70 years. Two recent systematic reviews concluded that BNO-101 (Sinupret®) provides limited evidence for a clinically symptomatic relief in patients with acute sinusitis. In the treatment of CRS, two prospective trials were found testing BNO-101 (Sinupret®, Bionorica AG, Germany), a combination of five herbs (containing Gentianae radix, Primulae flos, Rumicis herba, Sambuci flos and Verbenae herba; ratio 1:3:3:3:3). Single trials were included in here for other herbal preparations: a tea preparation (Breathe easy tea); Bi Yuan Shu, a liquid oral Chinese herbal combination (containing at least Magnolia liliiflora, Xanthium strumarium, Astragalus membranaceus, Angelica dahurica and Scutellaria baicalensis) and three intranasal Chinese herbal solutions. These studies are described below.

4.2.1.2. Potential Therapeutic Actions

The herbal formula BNO-101 (Sinupret®) has been widely employed as a ‘mucoactive’ agent for respiratory infections and diseases. Experimental studies have shown that BNO-101 (Sinupret®) has secretolytic properties. More recently, it has been shown that prophylactic administration of Sinupret may increase resistance to respiratory tract infection after intranasal application of Sendai virus (Parainfluenza viridae) in mice. It has been reported that the individual ingredients contribute to a overall pharmacological profile of a combination with secretolytic, anti-inflammatory, immunomodulating, antibacterial and antiviral effects. Based on a large epidemiological survey, the herbal medicinal product BNO-101 (Sinupret®) seems devoid of teratogenic potential in humans.

The Chinese herbal preparations might probably have similar therapeutic actions than BNO-101 (Sinupret®).

4.2.1.3. Systemic Phytopreparations (Table XXXV)

Chronic rhinosinusitis without NPs

A randomised, double-blind, placebo controlled study evaluated the efficacy of Sinupret® in 31 patients with CRS. Sixteen patients were diagnosed with chronic bilateral maxillary and frontal sinusitis; 13 with unilateral sinusitis; and the diagnosis for the other two patients were not reported. The patients were randomised into two groups to receive either Sinupret (2 tablets x 3x/day or 30 drops x 3x/day) or corresponding placebos for 7 days. The follow-up examination was performed on day
16. No baseline data are reported except that there was a significant difference between groups in the number of patients with bilateral and unilateral sinusitis. Presentation of results is unclear, but it appears that overall clinical status, probably based on radiologic and ultrasonographic findings, improved or resolved in 75% Sinupret treated patients and in 40% placebo treated ones. The statistical significance of this difference is not reported. Headache resolved in 11 of 16 Sinupret treated patients and in 3 of 11 placebo treated ones. The radiologic outcome improved in 7 of 11 Sinupret treated patients and in none of the 6 placebo treated ones. Chi$^2$ tests carried out in patient subsamples for headache ($n = 27$) ($p = 0.025$) and the radiologic outcome ($n = 17$) ($p = 0.001$) indicated a statistically significant intergroup difference favouring Sinupret.

A prospective, case controlled study evaluated the clinical outcome of a 2 week-**Sinupret**® course in 14 patients with CRS. Three times 2 tablets per day were taken during the study period. Seventy-one percent of the patients showed CRS-related symptom improvement.

A prospective, open-label pilot study evaluated any association between herbal tea consumption and CRS symptoms among African Americans. **Breathe Easy**® herbal tea was self-administered for a duration of 6 weeks in 55 patients with CRS. Of the 55 volunteers who met entrance criteria, 41 completed the study; groups were q.i.d. ($n = 27$), t.i.d. ($n = 4$), b.i.d. ($n = 5$), and non-compliant ($n = 5$). For the q.i.d. group ($n = 27$), there was a significant improvement in the Chronic Sinusitis Survey (CSS) symptom score ($p = 0.020$) and CSS total score ($p = 0.020$). Overall health status (Short Form-36) reported at baseline was very good in 35% of patients, good in 34% and fair in 17%, respectively. After 6-weeks, the q.i.d. group showed a significant change to good in 44% of patients and very good in 45%, respectively ($p = 0.001$).

**Chronic rhinosinusitis with NPs**

There were no trials available on systemic phytotherapy in the treatment of NPs.

In conclusion, there is very limited evidence of clinical benefit of oral Sinupret® treatment in patients with CRS without NPs. No long-term outcome study is available.
4.2.1.4. Systemic and topical Phytopreparations after Surgery (Table XXXXVI)

Bi Yuan Shu (BYS) oral liquid is a Chinese herbal mixture, but the exact composition is not clear. A multi-centre, prospective randomised study assessed BYS for its adjunct effect on clinical symptoms and signs in patients with CRS and NPs who had undergone ESS. A total of 340 patients were randomised to receive either orally BYS in addition to antibiotics and INSs (n = 170) or antibiotics and INSs alone (n = 170) for 20 days postoperatively. Overall therapeutic effects based on signs and symptoms were assessed on days 7, 14, 30 and 60. Significant improvements in individual symptoms that favoured BYS were seen for pain, breathing difficulty, purulent nasal discharge, hyposmia and halitosis, but not for fever and cough, which showed only a positive trend.

The influence of different nasal irrigations for postoperative treatment on the effect of ESS was explored in 192 cases with CRS and NPs. They were divided randomly into 3 groups accepting 3 different kinds of nasal irrigations and had a 3-month follow-up. The evaluation of curative effect was according to the index of HaiKou ESS-97. The curative effect of *Herba Houttuyniae* group was better than the other two irrigation solutions.

To observe the action of a Chinese herbal preparation on the recovery of nasal sinus mucosa after ESS in 78 patients with CRS and NPs, the study population was randomised into two groups. Forty patients were treated with daily nasal flushing with diluted Chinese herbal preparation while the 38 patients in the control group were untreated. Tissues of nasal mucosa taken out from patients' posterior walls of maxillary sinus at different time points, i.e. 2-3 weeks, 8-11 weeks and 13-15 weeks after ESS were examined. Significant difference was shown between the two groups observed by endoscopy at all the time points in occurrence of sticky mucus, swelling and thickened mucosa, occlusion of sinus opening, bloody secretion in sinus, and adhesions in favour to the Chinese herbal group (p < 0.05). Light microscopic examination showed significant less squamous epithelial metaplasia and fibre tissues proliferation in the herbal group (p < 0.05). An electron microscopic examination also demonstrated significant difference between the two groups with less inflammatory cell infiltration, decrease of fibres, and arrangement of disordered cells, microvilli and short cilia within the group treated with topical Chinese herbal preparation (p < 0.01).
Another randomised, prospective study investigated the effect of the irrigating solution of Sihuang (= Chinese herbal preparation) given after ESS for CRS and NPs. Sihuang was used to irrigate the operated sinus cavities for 4 weeks in 109 patients, and 0.9% saline was given in the same manner in another 109 patients after surgery. Before and 3 months after the surgery, 32 patients were selected from each group for saccharin test. The mucosa in the OMC region was examined by electron microscopy in 6 patients before, two weeks and one month after surgery. The total rate of efficacy was not significantly different between the two groups, but the postoperative morphological and functional recovery of the nasal mucosa occurred earlier in the Sihuang than in the saline group (p < 0.05). The level of serum IgA was similar between the two groups before treatment (p > 0.05), whereas after Sihuang treatment, the serum IgA level significantly increased. Mucociliary transport rate was similar between Sihuang and saline groups before the surgery (p > 0.05), but 3 months after the surgery, the mucociliary transport rate increased in the Sihuang group and in the saline group, showing significant difference in favour to the Sihuang group. Under electron microscope, the cilia of the epithelial cells were found exfoliated preoperatively, but regularly arranged after the surgery, presenting the "9+2" architecture of the microtubule.

In conclusion, oral and intranasal Chinese herbal combinations suggest clinical benefit in the postoperative care after ESS and show an earlier mucosal recovery than without the active drug administration. Unfortunately, no long-term study was done to demonstrate any preventing activity on NP recurrence.

4.2.1.5. Side effects

No serious adverse events were observed in any of the included BNO-101 (Sinupret®) studies. The remaining four Chinese herbal preparation trials reported mild to moderate adverse events with similar frequency in both test and control groups.

In the systematic review of Melzer et al. (2006), the incidence of adverse events between BNO-101 therapy and placebo was similar. This review did not report any serious adverse side effects. The incidence of spontaneously reported adverse events is about 1 per 1'000'000 patients treated (Periodic Safety Update Report 1999–2004 provided by the manufacturer). Data on routine haematology
and blood chemistry have not been reported. According to the information provided by the manufacturer, rare cases of mild cutaneous/allergic reactions, digestive side effects, episodes of dyspnea and face oedema have been reported and considered as possibly BNO-101 related. There have been isolated reports of serious adverse events (mainly cutaneous eruptions such as multiform erythema, Stevens-Johnson syndrome, and toxic epidermal necrolysis) in patients treated with BNO-101, with an approximate incidence of 1 out of 4'000'000 patients related. These eruptions, which may represent variants of the same disease process, could not be attributed with reasonable degree of certainty to BNO-101 (i.e. causal relationship not assessable) due to the pre-existing coexistence of predisposing factors, such as infections, autoimmune diseases or drug intake e.g. antibiotics, sulphonamides or NSAIDs.

Five cases of acute hepatic injuries after Chinese herbal combinations’ intake have been reported.
### Table XXXXV. Systemic phytopreparations in CRS without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richstein and Mann (1980)</td>
<td>CRS (maxillary sinusitis)</td>
<td>31</td>
<td>Sinupret vs. placebo</td>
<td>?</td>
<td>1 week</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Improvement in headache *, nasal symptom improvement in 75% Sinupret vs. 40% placebo</td>
<td>Sinus x-rays *</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Goroll and Stehle (1982)</td>
<td>CRS</td>
<td>14</td>
<td>Sinupret</td>
<td>3 x 2 drg.</td>
<td>2 weeks</td>
<td>Prospective, case controlled</td>
<td>Improvement in 71%</td>
<td></td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Hips et al (2009)</td>
<td>CRS</td>
<td>55</td>
<td>Breathe easy tea</td>
<td>4 cups/day</td>
<td>6 weeks</td>
<td>Prospective case controlled</td>
<td>Improvement in CSS *, improvement in headache *, nasal obstruction * and sleep *, QoL</td>
<td></td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>

CSS: chronic sinusitis survey

### Table XXXXVI. Topical and systemic phytopreparations after endoscopic sinus surgery in CRS with and without NPs

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liang et al (2004)</td>
<td>CRS / NP</td>
<td>340</td>
<td>Bi Yuan Shu + antibiotics + topical steroids vs. antibiotics + topical steroids</td>
<td>Orally</td>
<td>20 days</td>
<td>Randomized, prospective</td>
<td>Improvement in nasal symptoms *</td>
<td></td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Li et al (2001)</td>
<td>CRS / NP</td>
<td>192</td>
<td>3 different irrigations</td>
<td>Irrigation</td>
<td>3 months</td>
<td>Randomized, prospective</td>
<td>Nasal symptoms * in Herba Houttuyniae</td>
<td></td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Xiong et al (2005)</td>
<td>CRS / NP</td>
<td>78</td>
<td>Chinese herbal preparation vs. no treatment</td>
<td>Irrigation</td>
<td>4 months</td>
<td>Randomized, prospective</td>
<td>Endoscopic appearance *, microscopy: less squamous epithelial metaplasia *, less fiber tissue proliferation *, less inflammation *</td>
<td></td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Wu et al (2005)</td>
<td>CRS / NP</td>
<td>218</td>
<td>Sihuang mixture vs. saline (0.9%)</td>
<td>Irrigation</td>
<td>4 weeks</td>
<td>Randomized, prospective</td>
<td>Morphological and functional recovery earlier *, higher serum IgA *, increase of MCTT *</td>
<td></td>
<td>Ib</td>
<td>Positive</td>
</tr>
</tbody>
</table>

MCTT: mucociliary transport time
4.2.2. Homeopathy

4.2.2.1. Background
Homeopathy is one of the most frequently used and controversial system of complementary and alternative medicine. It is based on the 'principle of similars', whereby highly diluted preparations of substances that cause symptoms in healthy individuals are used to stimulate healing in patients who have similar symptoms when ill. Homeopathic remedies are selected according to symptoms and prepared with a special technique (repeated dilutions with "potentiation") when a single homeopathic remedy is selected based on a patient's total symptom picture, it is called 'classical' homeopathy. For Germany, the country in which classical homeopathy originated, a recent survey demonstrated that approximately 10% of men and 20% of women in the population used homeopathic medicines during the previous year. General trends show a rise in the number of individuals utilising naturopathic and homeopathic methods. The results from two large cross-sectional studies including 3126 patients with different chronic conditions showed complete satisfaction of homeopathic treatment in 44% of these individuals.

4.2.2.2. Potential Therapeutic Actions
On a scientific basis, the therapeutically action of homeopathic remedies is neither clear nor proven. Homeopathy, founded by Hahnemann at the beginning of the 1800s, relies on the principle that symptoms of a disease can be cured by the same substances that provoke them when they are ultradiluted. Homeopathic remedies are selected according to symptoms and prepared with a special technique (repeated dilutions with "potentiation") when they are ultradiluted. Homeopathy is a holistic approach to medicine, with particular attention to the homeopath-patient relationship. The scientific interest in homeopathy for treating asthma, allergies and other chronic illness is considerable, as attested by the large number of publications. There are several controlled trials of good methodological quality for homeopathy in rhinitis and asthma. Newer experimental trials showed that certain components of the homeopathic medications may have an antiviral and immunomodulating action.
4.2.2.3. Homeopathic Treatments (Table XXXXVII)

Chronic rhinosinusitis without NPs

In a controlled randomised, double-blind trial, the therapeutic efficacy of **homeopathic drug preparations** (single drug, double combination, triple combination) and placebo therapy has been investigated in 69 patients with CRS. All patients received 3 tablets daily for 4 weeks. Improvement has been found in 67% of these patients when averaged over all four groups. However, there was no remarkable difference in the therapeutic success neither among the investigated homeopathic drug combinations nor between the active drugs and placebo.

A large prospective, multicentre, observational study evaluated a **homeopathic treatment** for 2 years in 134 adults with CRS. An improvement of ≥ 50% has been demonstrated in 53.7% of all patients. Assessment of sinusitis severity score and QoL found statistically significant improvement over the 24-months study period (p < 0.001). The effects were still present after 8 years within the QoL « physical » and « mental » component scores.

Chronic rhinosinusitis with NPs

There were no trials available on homeopathic therapy in patients suffering from NPs.

In conclusion, there is very limited evidence of clinical benefit of homeopathy, and the only one randomised, double-blind, placebo controlled study did not show better outcome in the homeopathic groups than in the placebo controls. Homeopathic medical therapy, however, may play a beneficial role as adjunct treatment in the long-term care of patients with CRS.

4.2.2.4. Homeopathy after surgery

There were no trials available on homeopathic therapy after endonasal surgery to prevent CRS recurrence.

4.2.2.5. Side effects

Several authors have pointed out that homeopathy is considered as a safe treatment modality. The safety of homeopathy is regulated by European and national production regulations, and the potentiating process arguably renders these products safe to use beyond the 1:10'000 dilution set out in the EU directives. A systematic
review in the year 2000 showed a mean incidence of adverse events of 9.4 in homeopathy groups compared to 6.12 in placebo groups. A recent survey of 1025 patients receiving homeopathic treatments reported that adverse effects attributed by patients to homeopathy were experienced by 2.7% of the individuals. The results from two large cross-sectional studies including 3126 patients showed 11% of the patients reporting mild to moderate side effects. Only 1% of all patients reported any severe adverse events. Adverse events were mostly described as mild and transient, and included headaches, tiredness, skin eruptions, and dizziness, bowel dysfunction such as diarrhea or loose stools, and, more frequently, aggravations of patients’ pre-existing symptoms. The described aggravations of pre-existing symptoms are frequently encountered in homeopathic practice, and are often considered as a necessary stage of the curative process.
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiesenauer et al (1989) 38</td>
<td>CRS</td>
<td>69</td>
<td>Homeopathy (triple, double and single combination) vs. placebo</td>
<td>Orally, 3 tablets</td>
<td>4 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Improvement in 67% of all groups, no difference between groups and placebo</td>
<td>-</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Witt et al (2009) 39</td>
<td>CRS</td>
<td>134</td>
<td>Homeopathy</td>
<td>Orally</td>
<td>1 – 8 years</td>
<td>Prospective, case controlled</td>
<td>Improvement in 53.7%, improvement in nasal symptom score * and QoL *</td>
<td>-</td>
<td>III</td>
<td>Positive</td>
</tr>
</tbody>
</table>
4.2.3. Acupuncture

4.2.3.1. Background

Acupuncture is part of traditional Chinese medicine and is widely used for the treatment of chronic illnesses, including asthma. The theory behind the use of acupuncture is to restore the balance of “vital flows” by inserting needles at exact points of the body surface, where the “meridians” of these flows lie. Stimulation of the specific points can also be made with pressure or laser application. Acupuncture can be studied in a rigorous manner by using sham acupuncture as a control procedure. The efficacy of acupuncture in asthma has been evaluated in several randomised controlled trials. Few data are available for CRS. However, in an American telephone survey, 5% of the population with physician-diagnosed rhinosinusitis reported having had acupuncture treatment during the 12 months previous to the survey.

4.2.3.2. Potential Therapeutic Actions

Large randomised trials demonstrating the immediate and sustained effect of acupuncture are missing. To date, modern scientific research studies have revealed the following actions of acupuncture: inducing analgesia, protecting the body against infections and regulating various physiological functions. The therapeutic effects of acupuncture are thus brought about through its regulatory actions on various systems, so that it can be regarded as a non-specific therapy with a broad spectrum of indications, particularly helpful in functional disorders. Although it is often used as a symptomatic treatment (for pain), in many cases it actually acts on one of the pathways of a disease. These therapeutically actions may be an ascribed anti-inflammatory effect or immunosuppression. The acupuncture seems to control the release of neuropeptides from nerve endings and subsequent vasodilator and anti-inflammatory effects. Complex interactions with SP, analgesic contribution of β-endorphin, and the balance between cell-specific pro-inflammatory and anti-inflammatory cytokines, like TNF-α and IL-10, seem to play an important role in the therapeutically action of acupuncture. Although different acupuncture points and manipulations may have an effect through different actions, the most important factor that influences the direction of action is the condition of the patient. Numerous examples revealed that the regulatory action of acupuncture is bi-directional.
4.2.3.3. Chinese Acupuncture (Table XXXVIII)

Chronic rhinosinusitis without NPs

Three similar, prospective, case controlled studies evaluated the clinical outcome of Chinese acupuncture in the treatment of patients with CRS. Three hundred and twenty-nine patients underwent different types of acupuncture for about 4 weeks (10 treatments). An average of 78% (range: 63 – 90%) of the included individuals showed an improvement of their CRS symptoms. Unfortunately, any statistical comparison is missing.

In a very small, prospective, cross-over, placebo controlled study, the immediate effects of real Chinese acupuncture compared with two placebo controls (sham acupuncture and mock transcutaneous electrical nerve stimulation) have been evaluated in 13 patients with NANIPER. Each treatment type lasted for 2 weeks and a one-week-wash-out period separated the different treatments. All three treatments showed improvement in the nasal symptoms without any significant difference between the groups. Objectively, statistically significant improvement of the minimal cross-section area measured by acoustic rhinometry (p = 0.023) could be demonstrated only in the Chinese acupuncture group, however, without a significant difference between the groups. All three treatment types did not show any improvement in nasal resistance measured by posterior rhinomanometry.

Antibiotics, laser acupuncture and Chinese acupuncture upon chronic maxillary sinusitis were evaluated in 45 patients. The average number of acupuncture treatments was 6 in 3 weeks. The rate of patients with improvement was significantly better with a longer duration after Chinese acupuncture (72.2%), than after laser acupuncture (37%) and antibiotic therapy (36.8%). However, the study lacked details about patients’ selection, allocation procedure and evaluation methods.

A three-armed, single-blind, randomised controlled study compared traditional Chinese acupuncture, minimal acupuncture at non-acupoints and conventional treatment for CRS. Sixty-five patients with symptoms of sinusitis longer than 3 months and radiologic signs on CT-scan were recruited. Changes in sinus soft tissue swelling on CT, symptoms of sinusitis, and health-related QoL, using the two component summary scales of the Short Form-36 and a rating scale, were evaluated. All three groups showed improvements on nasal and sinus symptoms without a significant difference between the types of treatment. In the conventional treatment
group, sinus soft tissue swelling was reduced over 4 weeks (p = 0.04), and health related QoL improved over 12 weeks (p = 0.01 - 0.05). Pair wise comparisons of changes in total symptom scores between the groups showed signs of a difference between conventional medication and sham acupuncture over 4 weeks (p = 0.06).

**Chronic rhinosinusitis with NPs**
There were no trials available on acupuncture in the treatment of patients with NPs.

In conclusion, several trials show promising results with symptom improvement in CRS patients treated with Chinese acupuncture. The only randomised, double-blind, placebo controlled study showed, that acupuncture improved nasal symptoms similar to the medical treatment group with antibiotics, steroids, local decongestants and intranasal 0.9% saline. However, only the conventional therapy improved soft-tissue swelling over the treatment period of 4 weeks and demonstrated an increase in health-related QoL over 12 weeks in patients with CT-verified CRS, which was not the case in the traditional and sham acupuncture groups.

**4.2.2.4. Acupuncture after surgery**
There were no trials available on Chinese Acupuncture after endonasal surgery to prevent CRS recurrence.

**4.2.3.4. Side Effects**
Since the therapeutic actions of acupuncture are achieved by mobilization of the organism’s own potential, acupuncture should not produce adverse effects. On the other hand - and for the same reason – acupuncture has limitations. Even under conditions where acupuncture is indicated, it may not work if the mobilization of the individual’s potential is not adequate for recovery. In the above mentioned studies, only minor and temporary side effects were seen in up to 44% of the patients, comparable with the percentage of side effects of sham acupuncture (29%). There were bleedings around the needles, nerve pain and dizziness.
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pothman and Yeh (1982)</td>
<td>Chronic maxillary sinusitis</td>
<td>45</td>
<td>CA and laser acupuncture vs. antibiotics</td>
<td>6 treatments</td>
<td>3 weeks</td>
<td>Prospective case controlled</td>
<td>Improvement in 72.2% (CA) *, 37% (laser acupuncture), 36.8% (antibiotics)</td>
<td>-</td>
<td>III</td>
<td>Positive</td>
</tr>
<tr>
<td>Scheidhauer and Gestewitz (1989)</td>
<td>CRS / NANIPER</td>
<td>54</td>
<td>CA</td>
<td>5 – 18 treatments</td>
<td>2 – 4 weeks</td>
<td>Prospective case controlled</td>
<td>Improvement of symptoms in 83%</td>
<td>-</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Yu et al (1993)</td>
<td>CRS</td>
<td>75</td>
<td>CA</td>
<td>10 treatments</td>
<td>3 - 4 weeks</td>
<td>Prospective, case controlled</td>
<td>Improvement of symptoms in 60%</td>
<td>-</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Hu and Liu (1997)</td>
<td>CRS</td>
<td>200</td>
<td>CA</td>
<td>10 treatments</td>
<td>3 – 4 weeks</td>
<td>Prospective case controlled</td>
<td>Improvement of symptoms in 90%</td>
<td>-</td>
<td>III (no statistics)</td>
<td>Positive</td>
</tr>
<tr>
<td>Davies et al (1998)</td>
<td>CRS / NANIPER</td>
<td>13</td>
<td>CA vs. sham acupuncture vs. electric nerve stimulation</td>
<td>10 treatments</td>
<td>2 weeks</td>
<td>Prospective, cross-over, placebo controlled</td>
<td>VAS symptoms improvement in all 3 groups without significant difference</td>
<td>No improvements in nasal airway resistance in all 3 groups, improvement in acoustic rhinometry in CA *, but no difference between the groups</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Rössberg et al (2005)</td>
<td>CRS</td>
<td>65</td>
<td>Conventional medical treatment vs. CA vs. sham acupuncture</td>
<td>10 treatments</td>
<td>4 weeks</td>
<td>Randomized, prospective, placebo controlled</td>
<td>Improvement of symptom scores in all 3 groups (no significant difference), improvement * in QoL and SF-36 in conventional therapy, but not in both acupuncture groups</td>
<td>Improvement in CT scan only in the conventional treatment *</td>
<td>Ib</td>
<td>Negative</td>
</tr>
</tbody>
</table>

CA: Chinese Acupuncture, VAS: visual analogue scale
4.3. POSSIBLE FUTURE TREATMENTS – IMMUNOMODULATORY THERAPIES?

Consistent with the current knowledge on the pathophysiology of CRS and NPs, new therapeutic lines could focus on eosinophilic inflammation, eosinophil recruitment, the T cells as the orchestrating cells and IgE antibodies, as well as on tissue destruction and remodelling processes. In particular, the introduction of humanised antibodies has created new and future possibilities, however, tissue distribution, the concept of a single “key mediator” to approach, and natural antagonistic systems in place could make these approaches hazardous. Thus, small molecule approaches circumventing these hazards could offer solutions, if they demonstrate more effectiveness and better tolerability than topical corticosteroids.

4.3.1. Anti-interleukin-5 monoclonal antibody

Interleukin-5 is an eosinophil differentiating factor, which increases the sensitivity of eosinophils towards other stimuli and delays their cell death. High-affinity IL-5 receptors are exclusively expressed by eosinophils and basophils, but no other human cells. As IL-5 is increased in NP tissue and related to eosinophilic inflammation, an anti-IL-5 antibody treatment has induced eosinophil apoptosis. Therefore, neutralisation of IL-5 appeared to be an obvious approach for treating eosinophilic disorders, since no major side effects on other cells are expected. A clinical trial was done with an anti-interleukin-5 monoclonal antibody in asthmatic patients. This treatment reduced peripheral eosinophil counts and those in induced sputum but had no impact on asthma outcomes. However, biopsies of the pulmonary tissue showed that the treatment duration may not have been adequate as the eosinophil counts in the tissue were not similarly reduced.

A recent randomised, double-blind, placebo controlled study evaluated the safety and efficacy of a single intravenous administration of an anti-interleukin-5 monoclonal antibody (reslizumab, 1 mg/kg or 3 mg/kg or placebo) in 24 patients with NPs. It was demonstrated that a single injection of reslizumab up to 3 mg/kg is safe and well tolerated. Eosinophils and concentrations of ECP were reduced up to 8 weeks after the treatment in serum and nasal secretions. Individual NP scores improved only in half of the treated patients for 4 weeks. Responders had increased IL-5 concentrations in nasal
secretions at baseline compared with non-responders, and a logistic regression analysis revealed that increased nasal IL-5 levels (>40 pg/ml) predict the response to anti-IL-5 monoclonal antibody treatment. Twenty-three (95.8%) of the 24 subjects reported at least one adverse event. The most common side effect was an upper respiratory tract infection, which was reported by a total of 14 (58.3%) subjects, 5 in each of the treatment groups and 4 in the placebo group. Examination of other adverse events did not reveal any major differences.

However, major concern developed in recent years about the efficacy of such treatment. Given the key role of IL-5 in eosinophil function, soluble IL-5 receptor alpha expression pattern in NPs was investigated. Analysis of nasal tissue samples revealed that soluble IL-5 receptor alpha protein concentrations were significantly increased in NPs versus control tissue. Furthermore, the same authors recently also demonstrated the downregulation of the membrane-anchored IL-5 receptor in NP tissue in severe eosinophilic inflammation. As soluble IL-5 receptor alpha expression is increased, demonstrating antagonistic properties in vitro, and membrane-anchored IL-5 receptor expression is decreased, these studies shed new light on the mechanisms of the treatment with IL-5 monoclonal antibodies. Studies examining the cross-regulation and functional consequences of modulation of eosinophil cytokine receptor expression by IL-3, IL-5 and GM-CSF suggest a dynamic and differential regulation of eosinophil receptors for these cytokines. Incubation of eosinophils with IL-3, IL-5 or GM-CSF led to reduced expression of membrane-anchored IL-5 receptor alpha, possibly making tissue eosinophils relatively insensitive to anti-IL-5 monoclonal antibody treatment.

Nevertheless, eosinophils in the bone marrow and peripheral blood seem to respond greatly to anti-IL-5 monoclonal antibody treatment. Mepolizumab, another monoclonal antibody decreased mature eosinophil number in the bone marrow and the quantity of eosinophil myelocytes and metamyelocytes in the blood of asthmatic patients. However, it had no effect on the level of blood or bone marrow CD34+/IL-5 receptor alpha cells or eosinophil/basophil colony-forming units. There was a significant decrease in bronchial mucosal CD34+/IL-5 receptor mRNA+ cells in the mepolizumab treated group. These data suggest that anti-IL-5 monoclonal antibody therapy might induce a partial arrest of maturation of the eosinophil lineage in the bone marrow, and that only long-term treatment would sufficiently suppress eosinophils in the tissue and maybe achieve clinical efficacy.
4.3.2. Interleukin-4 and Interleukin-13 antagonists

The closely related T\textsubscript{helper} -2 cytokines IL-4 and IL-13 share biological functions that are considered important in the development of airway inflammation, including induction of the IgE isotype switch, increased expression of VCAM-1, promotion of eosinophil transmigration across the endothelium, stimulation of mucus production and T\textsubscript{helper} -2 cell differentiation, leading to release of IL-4, -5, -9, -13 and eotaxin\textsuperscript{915}. Furthermore, elevated levels of IL-4 at a site of injury could result in the development of fibrosis by enhancing fibroblast subset proliferation and collagen synthesis\textsuperscript{924}. The overlap of their functions results from the IL-4 receptor alpha chain forming an important functional signaling component of both, the IL-4 and IL-13 receptors\textsuperscript{915}. Interleukin-4 and IL-13 mRNA+ cells have been described in NPs\textsuperscript{925}, and the number of cells expressing IL-4 mRNA was shown to be increased compared with healthy mucosa samples independent of atopic status\textsuperscript{926}. It can be expected that strategies to antagonize IL-4 / -13 would also reduce inflammation in NPs, but until now no specific studies have been performed.

4.3.3. CC chemokine receptor-3 antagonists

Selective eosinophil recruitment into inflammatory sites and their subsequent activation is a characteristic of allergic diseases, such as asthma, rhinitis and atopic dermatitis. CC chemokine receptor-3 is the principal mediator of eosinophil chemotaxis and is expressed on a variety of inflammatory cells associated with allergic responses. These cells include basophils, mast cells, T\textsubscript{helper} –2 lymphocytes, and resident tissue cells such as airway epithelium cells\textsuperscript{927}. Animal studies have shown that CC chemokine receptor-3 antagonizing led to a reduction in airway inflammation. As eosinophils also have been implicated in the pathogenesis of NPs, and several CC chemokines have been identified as eosinophil chemoattractants in polyp tissue\textsuperscript{928-930}, antagonism of CC chemokine receptor-3 could have a therapeutic role in this category of CRS. Recent studies have suggested that CC chemokine receptor-3 ligands may influence epithelial cell functions\textsuperscript{931}.

Using an \textit{in vitro} migration system mimicking the airway mucosa, a pretreatment of eosinophils with anti-CC chemokine receptor-3 antibodies showed inhibition of their transmigration\textsuperscript{932}. Furthermore, these antibodies inhibited the expression of the chemokine eotaxin mRNA by cultured bronchial epithelial cells\textsuperscript{933}. 

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The development of small non-peptide molecule CC chemokine receptor-3 antagonists currently offers advantages over anti-chemokine antibodies in terms of a broader approach, affecting several chemokines and effector cells, and of a favorable pharmacokinetic profile, targeting the receptors on peripheral blood cell surfaces and being independent from tissue penetration. Studies in patients with CRS and NPs have not yet been reported.

### 4.3.4. Immunoglobulin E - Antagonism

Considering the significantly elevated concentration and marked local production of total and specific IgE antibodies in NPs, its relation to the severity of disease and to the increased number of degranulating epithelial mast cells in NPs, it appears that local IgE is functionally involved in the pathway of CRS. The increased level of IgE in NPs seems to be related to SAEs rather than atopy. Evidence accumulates that *Staphylococcus aureus* colonises NPs, and enterotoxins released by these bacteria act as superantigens and induce a locally multiclonal IgE production combined with a severe eosinophilic inflammation. Patients with NPs and associated asthma or AS-sensitivity had even higher rates of *Staphylococcus aureus* colonisation, higher IgE levels to SAEs as well as ECP, and higher total IgE in NP tissue. The immune response to superantigens leads to a modulation of the severity of eosinophilic inflammation, linking lower airway morbidity, like asthma to NPs. Basophils armed with specific IgE exposed to SAEs showed degranulation. Thus, enterotoxin-specific IgE antibodies could contribute to the disease via the degranulation of mast cells in polyp tissue. Antagonising IgE-effects by neutralising the IgE antibodies and/or inhibiting its synthesis could be a relevant therapeutic way to modulate and treat severe or recurrent NPs.

Omalizumab is a humanised, monoclonal anti-IgE antibody (mA-IgE). Treatment trials of allergic asthma and seasonal / perennial AR with this drug showed efficacy in improvement of symptoms, reduction of disease exacerbation, decreased need for other medications, and marked decrease in the level of free-circulating IgEs. It may act in the therapy of CRS with and without NPs in patients with IgE-mediated hypersensitivity due to allergy exposure. Omalizumab binds to the constant region of the IgE molecule at its IgE receptor-binding protein, thereby effectively hindering free serum IgE binding with the high-affinity IgE receptor present on mast cells, basophils and dendritic cells. Monoclonal anti-IgE antibody
binds to circulating, but not cell-bound IgE, forming stable and long-lived anti-IgE-IgE complexes. Omalizumab causes a rapid decrease in free serum IgE levels (97 – 99%), and downregulates the expression of IgE receptors (FcεR1) on mast cells, basophils and dendritic cells, which are potent antigen-presenting cells. The decrease in FcεR1 expression is proportional to the decrease in serum free IgE levels. Results of a study by Ong et al. (2005) showed a more marked effect of omalizumab treatment on allergic late-phase reactions and prevention of the repeat-dose priming effect on inflammatory cells compared with allergic early-phase skin reactions. This supports a role for omalizumab in chronic allergic conditions. By downregulating FcεR1 expression, anti-IgE might inhibit allergen presentation to T cells, possibly resulting in decreased allergen-specific T-cell activation, thus being able to block both the sensitisation and effector phases of allergen-specific immune responses. Omalizumab in vitro also inhibited allergen-induced IgE synthesis by blood mononuclear leukocytes from atopic volunteers. Figure 20 summarises the effect of omalizumab on the allergic cascade.

Figure 20.
The potential therapeutic action of omalizumab on IgE mediated responses in allergic inflammation. APC: Antigen-presenting cell; IgE: immunoglobulin E; FcεR: IgE receptors; IL: interleukins; GM-CSF: granulocyte-macrophage colony-stimulating factor.
Total serum IgE and allergen-specific serum IgE increase during treatment with omalizumab because of the formation of omalizumab-IgE complexes with a longer serum half-life than free IgE \(^945\). Chang (2000) \(^950\) has suggested that these IgE-anti-IgE complexes are in fact beneficial, because, although they can no longer bind to Fc\(\varepsilon\)R1, they can still bind to allergens and serve as competitive traps reducing the contact of the allergens with Fc\(\varepsilon\)R1-bound IgE. Omalizumab does not provoke histamine release from IgE-sensitised mast cells because it does not interact with cell-bound IgE. Finally, omalizumab will inhibit allergen-induced responses regardless of allergen specificity because omalizumab does not bind to the variable allergen-specific region of the IgE molecule \(^949\).

In allergic rhinitis, omalizumab reduced *in vitro* leukotriene release by peripheral leukocytes stimulated with allergens \(^951\). Tryptase levels (a mast cell mediator) in nasal mucus was significantly decreased in anti-IgE-treated subjects compared to placebo-treated patients \(^952\). Significantly lower blood and nasal tissue eosinophils were present in omalizumab-treated AR patients than in placebo-treated patients during pollen exposure. Significant correlation between blood and tissue eosinophil levels and serum free IgE levels \(^953\) may partly be explained by the fact that anti-IgE therapy prevents mast cell activation and the release of cytokines (e.g. IL-5), and thereby inhibits subsequent eosinophil chemotaxis \(^946\). A significant decrease in TNF-\(\alpha\) levels in nasal secretion of AR patients suggests an anti-inflammatory effect of omalizumab \(^954\). Additionally, the decrease of human serum albumin in the nasal secretion after allergen challenge in anti-IgE treated subjects indicates a probable preventing effect of increased vascular permeability due to inflammation \(^954\).

In conclusion, omalizumab counteracts the « cross-linking of IgE molecules upon allergen » contact inducing degranulation of mast cell and basophils within the airway mucosa by reducing serum levels of free IgE and plays an anti-inflammatory role in the treatment of « allergic » airway diseases. There are no prospective studies available to determine the potential usefulness of omalizumab in the treatment of CRS with and without NPs. The only study dealing with the treatment of NPs was a retrospective analysis of patients with associated atopic asthma who underwent ESS \(^955\). Four patients received omalizumab after surgery, 4 patients did not. The drug was administered by subcutaneous injection (150 mg – 375 mg) every 2 to 4 weeks for an average of 5.5 months. Both groups were evaluated by CT-scan of the
paranasal sinuses and nasal endoscopy 9 to 10 months after the anti-IgE therapy. There were no significant improvement in CT findings, but significant reduction of the polyp size \( (p = 0.03) \) in the patients treated with omalizumab.

Omalizumab is well tolerated. The incidence of acute anaphylaxis by cross-linking IgE molecules is 0.14% in omalizumab treated patients and 0.07% in control patients \(^9\). Drug-related adverse events following treatment with omalizumab were described in 9.2% - 13.7% and were generally mild-to-moderate \(^9\). No significant differences compared to placebo were found in a meta-analysis by Corren et al. (2009) \(^9\) involving more than 7500 patients with asthma, rhinitis or related conditions. The most frequent drug-related side effects were upper respiratory tract infections, headache, gastrointestinal disorders and musculoskeletal pain \(^9\). No serious adverse events were suspected to be related to omalizumab. Omalizumab exhibited a good safety profile up to 4 years \(^9,9\). Recently, there has been some interest in neoplasia and thrombocytopenia adverse events because more neoplasms and thrombocytopenia were reported in omalizumab-treated patients compared to controls. The meta-analysis of Corren et al. (2009), however, showed no causal relationship between omalizumab and cancer respectively thrombocytopenia \(^9\).

In conclusion, several studies have shown benefits in the treatment of AR with omalizumab. In NPs, evidence accumulates that SAEs act as superantigens resulting in T- and B-cell activation with massive IgE production. Currently, there is no prospective, randomised trial with omalizumab for treatment in patients with CRS available, which investigated whether high concentrations of IgE antibodies within the polyp tissue can be targeted successfully. The findings of the retrospective study show promising results of omalizumab treatment to prevent NP recurrences after surgery. Further prospective studies to substantiate the use of anti-IgE therapy in the management of CRS with and without NPs are needed, also in the absence of previous ESS.

### 4.3.5. Imatinib

**Imatinib** is a drug developed for leukaemia that has been shown to have anti-eosinophil and anti-mast cell properties through its inhibition of tyrosine kinase. It is currently being used with success for the idiopathic hypereosinophilic syndrome and for mastocytosis \(^9,9\). There are no prospective studies on its efficacy in CRS with
or without NPs. Imatinib has been used with success in an open-label trial in patients after surgery who were found to have significant eosinophilic inflammation in the nasal mucosa and in whom numerous other medical therapies have failed. Of eight patients treated with imatinib, seven had decreased peripheral eosinophil counts and four reported symptom improvement.

4.3.6. Immunosuppression

The disease management of severe and corticosteroid-resistant eosinophilic airway inflammation remains a real challenge, including severe asthma and NPs. Cyclosporine had been a mainstay of immunosuppression therapy in organ transplantation for many years. While its application clearly is efficient in the inhibition of T-cell proliferation and results in a decrease of inflammatory processes, the adverse effects associated with its long-term use, manifested most prominently through nephrotoxicity, have been a serious concern. Several new strategies have been pursued to address cyclosporine toxicity, leading to the development of novel cyclosporine analogues, and other molecules that inhibit T-cell proliferation and IL-5 production in blood mononuclear cells from asthmatics. A small but significant treatment effect of cyclosporine in terms of corticosteroid dose reduction has been shown in patients with stable asthma, but possible adverse effects have so far prevented routine use. Cyclosporine significantly inhibited the release of histamine, LTC₄, LTD₄ and thromboxane B₂ in a concentration-dependent manner in enzymatically dispersed cells from NPs. Clinical studies on CRS and NPs are lacking.

4.3.7. Interferon-gamma

Based on evidence of dysregulated interferon-gamma production and its regulatory cytokines by sinus lavage and peripheral blood mononuclear cells in patients who had treatment-resistant CRS with NPs, investigators conducted an open-label study in which 9 patients who had refractory CRS and multiple allergies to antibiotics were treated with exogenous interferon-gamma. These patients received 50μg/m² subcutaneously, 3 x/week for 3 months. The data were retrospectively analysed. Sinus symptoms were reported as better controlled in all subjects after 3 months of
therapy. Adverse reactions were limited to cutaneous reactions at the site of injection.

Due to the fact that interferon-alpha selectively downregulates in vitro IL-5 synthesis in human CD4+ cells 967, another open-label study has been performed in 4 patients with recurrent NPs by subcutaneously injecting interferon-alpha2a in a dose of 3 x 10^6 IU (3 x/week, ? months) 968. In all 4 patients, no recurrence of NPs was observed at 3 and 6 months after the initiation of interferon-alpha-therapy. Apart from the flulike symptoms in the first few days, no specific side effects were noted.

Gollob et al. (2000) found that patients with immunodeficiency involving regulatory mechanisms of interferon-gamma production may present with treatment-resistant CRS 969. Patients deficient in regulatory cytokines for interferon-gamma production are reported to have normal results in antibody production, lymphocyte phenotypes, and proliferative responses to mitogens and recall antigens, and production of reactive oxygen species. These patients, however, tend to be susceptible to bacterial, but not to fungal or viral infections 970.

Care should be taken when using interferon-gamma, as a possible complication of this therapy can be an induction of \( T_{helper}^1 \)-dominant autoimmune disorders 491. Randomised, double-blind, placebo controlled studies should be performed to establish efficacy for exogenous interferon-gamma in CRS patients who are interferon-gamma deficient and suffer from recurrent NPs.

### 4.3.8. Matrix Metalloproteinase Inhibitors

The term CRS represents a chronic inflammatory disease with numerous subclasses. Differentiation should at least be made between CRS without NPs and CRS with NPs, as these groups differ in cytokine and growth factor (TNF-\( \beta \)) profiles, but also in matrix metalloproteinase (MMP) expression, which are enzymes associated with oedema formation in NPs. Recurrence rate and postoperative healing appears to be subclass-dependent, and patients with NPs have a worse healing prognosis than patients with CRS without NPs, especially when associated with asthma and AS-intolerance 316,971. Concentrations of MMP-9 and MMP-7 protein were found to be significantly increased in NPs compared with control tissue, whereas their natural antagonising tissue inhibitor was not 915,972,973. Previous data have demonstrated that both pre- and postoperative levels of MMP-9 are significantly and independently predictive for the healing outcome 974. This was clinically linked to the diagnosis of...
CRS with NPs rather than CRS without NPs, as well as to previous surgery. Indeed, patients with high concentrations of MMP-9 (and probably other MMPs) in the preoperative and late postoperative period suffered from poor healing, indicating that MMP-9 may serve as a target for therapeutic interventions to achieve better healing quality.

MMPs are involved in the different tissue degradation and cellular functions in different stages of the disease. Moreover, MMPs have a dual role, in which low physiologic levels are needed in tissue homeostasis and protection, whereas pathologically excessive MMP activity results in destructive processes. Too strong, an inhibition may prohibit the homeostatic and defensive functions, leading to side effects, reduced efficacy or even disease progression. A weak, ‘leaky’ MMP inhibitor rather than a potent one may thus more safely modulate host response and lead to reduced tissue destruction without interfering the physiologic functions of MMPs. Such weak MMP inhibitors are tetracycline derivatives, such as doxycycline, which at a regular or sub-antimicrobial dose also exerts a systemic anti-inflammatory effect. Doxycycline has been reported to affect several critical aspects of the wound healing process, including inhibition of collagen synthesis and attenuation of angiogenesis. Doxycycline has shown MMP-decreasing activity in vitro and in vivo, and it is especially active in reducing pathologically excessive MMP activity from local mucosal fibroblasts and neutrophils. Animal models confirm the improvement in tissue repair upon doxycycline application, as in mice an improved regenerative capacity of the oral epithelium was attained after surgical incision, and in rats doxycycline attenuated neovascularisation, inhibited early fibrous-tissue formation and decreased pouch-tissue regression by inhibition of MMP activity. In murine models of asthma, the inhibition of the MMPs with recombinant tissue inhibitor metalloproteinase, synthetic MMP inhibitors or doxycycline prevented the inflammatory cell infiltration and the induction of airway hyperresponsiveness. Moreover, in patients suffering from periodontal disease, low-dose doxycycline enhanced postsurgical wound healing compared with placebo. Therefore, inhibition of MMPs may contribute to the promotion of favourable wound healing.

A randomised, double-blind, placebo controlled trial evaluated the topical application of doxycycline (= MMP-9 synthesis-suppressing agent) after ESS and frontal recess liberation (Table XXXXIX). In this perspective, a doxycycline-releasing stent delivering the MMP-9 synthesis-suppressing agent locally to the
frontal recess area has been developed, and postoperative MMP-9 levels, bacterial colonisation, healing quality and symptom scores in patients suffering from CRS with and without NPs (n = 10) who underwent functional ESS during which the doxycycline-releasing and placebo stents were placed, have been evaluated. They found that MMP-9 concentrations were significantly lower at the side of the doxycycline-releasing stent compared with the contralateral side where a placebo stent was placed (p < 0.05) at 3 months post-surgery. Doxycycline stents adequately suppressed bacterial growth compared with placebo stents. Furthermore, the visual analogue scale score for the frontal region was significantly better (p < 0.001) compared with its placebo counterpart. In conclusion, doxycycline-releasing stents significantly lowered local MMP-9 concentrations and bacterial colonisation, and improved postoperative healing quality after functional ESS, as demonstrated by visual analogue scale scores and ostia patencies. All these findings may lead to an interesting research topic, with the specific viewpoints of prognostic value of MMP levels and MMP/tissue inhibitor MP ratio before treatment, the correlation between clinical and histological improvement and MMP activity, and the differences between polypoid and non-polypoid CRS.

4.3.9. Recombinant Human Granulocyte Macrophage - Colony Stimulating Factor

In the protection of the paranasal sinuses against bacterial and fungal rhinosinusitis, neutrophils seem to play an important role. The proliferation and differentiation of neutrophils are promoted by the administration of recombinant human GM-CSF. Clinical studies in subjects who are neutropenic or have alterations in neutrophil function indicated that recombinant human GM-CSF could be beneficial as adjunct therapy for treatment of serious bacterial and opportunistic fungal infections.

A double-blind, placebo controlled, randomized study investigated the influence of filgrastim administration (300 μg s.c. daily, and then every second day) for 10 weeks on the QoL of 58 patients with refractory CRS without response to regular treatments (Table XXXIX). Quality of life scores of filgrastim treated patients suggested a better outcome than the placebo treated patients, although none of the differences were statistically significant.
<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>N</th>
<th>Drug name</th>
<th>Daily dose</th>
<th>Duration</th>
<th>Study design</th>
<th>Symptoms (stat. signif. *)</th>
<th>Objective (stat. signif. *)</th>
<th>Reduction of NP size</th>
<th>Level of evidence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gevaert et al (2006)</td>
<td>NP</td>
<td>24</td>
<td>Anti-interleukin-5 antibodies (resilizumab) vs. placebo</td>
<td>Intravenous, single dose, 1 mg/kg or 3 mg/kg</td>
<td>1x</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>No difference of nasal symptom scores when compared with placebo</td>
<td>No difference of PNIF when compared with placebo, reduction * of eosinophils and ECP in serum and nasal secretion</td>
<td>Yes</td>
<td>Ib</td>
<td>Negative</td>
</tr>
<tr>
<td>Huvenne et al (2008)</td>
<td>CRS + NP after ESS</td>
<td>10</td>
<td>Doxycycline (=matrix metalloproteinase-9 synthesis-suppressing agent) vs. placebo</td>
<td>Topical application with a stent</td>
<td>3 months</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Nasal symptom scores *</td>
<td>Lower matrix metalloproteinase-9 concentration *, bacterial suppression</td>
<td>-</td>
<td>Ib</td>
<td>Positive</td>
</tr>
<tr>
<td>Van Agthoven et al (2001)</td>
<td>Refractory CRS</td>
<td>58</td>
<td>Filgrastim (=recombinant human granulocyte colony-stimulating factor) vs. placebo</td>
<td>Subcutaneous, 300 μg</td>
<td>10 weeks</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>No difference in QoL</td>
<td>-</td>
<td>-</td>
<td>Ib</td>
<td>Negative</td>
</tr>
</tbody>
</table>

PNIF: peak nasal inspiratory flow
5. DISCUSSION

The principles involved in the treatment of CRS include identifying and treating the underlying causes. The goals include improvement of symptoms (nasal blockage, loss of smell, rhinorrhea, and facial pain or pressure) and quality of life (QoL), reduction of mucosal edema, reestablishment of sinus ventilation, eradication of infecting pathogens, and prevention of recurrences. A combination of topical and oral therapeutics is often required to achieve these objectives.

The following sections will discuss critically the available evidence of the retained treatment modalities of CRS without and with NPs, and of prevention of NP recurrence after surgery. The level of evidence is given for each analyzed treatment category [I – IV] (see Table III, p.52). A (+)-evidence level means treatment with a positive outcome; a (-)-evidence level means that there is negative outcome for this treatment category. The strength of recommendation for the available therapies is mentioned [A – D] (see Table IV, p. 52). A (-)-recommendation means (-)-evidence-based advice against the evaluated treatment. Under relevance it is indicated whether the treatment seems to be of clinical usefulness or not. Unfortunately, the CRS with its entities is not always clearly defined and distinct, making analyses of outcome and evidence of a treatment difficult and often imprecise.

The analyses are summarized in the Tables L, LI and LII at the end of this chapter.

5.1. MEDICAL TREATMENTS

5.1.1. Antibiotics – topical and systemic

The role of bacteria in the pathogenesis of CRS and NP is still controversial. While certain bacteria are commonly associated with these chronic inflammatory disorders, their presence has not definitively been demonstrated as causative. Recent theories include roles for bacterial biofilm formation, intracellular bacterial residency and bacterial enterotoxins as possible contributing factors to the inflammation of CRS and NP. Macrolide antibiotics have recently been shown to have anti-inflammatory, immunomodulatory and anti-mucous properties, in addition to their antimicrobial action.
There is clear Ib(-)-evidence that topical antibiotic nasal washes confer no benefit in the treatment of CRS with and without NPs, as demonstrated by the results from three randomized, double-blind, placebo controlled studies. Culture-directed, short-term (< 2 weeks) oral antibiotic therapy seems to be a reasonable treatment option for patients with an acute exacerbation in CRS with and without NPs, but not for the chronic inflammatory conditions [Ib(-)-evidence]. The few available prospective studies show a symptomatic improvement in 51 - 96% of patients. There is a lack of randomized, placebo-controlled studies on this matter.

Long-term antibiotic, particularly macrolide therapy is an effective treatment in CRS [Ib(+)-evidence]. *In vivo* and *in vitro* studies suggest that erythromycin, clarithromycin and roxithromycin are effective at modulating inflammation in CRS, leading to an improvement in symptoms from 71 - 80%. Macrolides also appear to decrease the NP size. However, only two prospective, case controlled trials are available [III(+)-evidence] on this CRS subclass demonstrating a decrease in neutrophilic NP sizes in Chinese patients. Improvement of QoL was statistically significant in 2 long-term macrolide studies.

Studies about antibiotic treatment after ESS to prevent NP recurrence are not available.

In summary:

- **Topical antibiotics (< 2 weeks):** Ib(-)-evidence in CRS, grade of recommendation: D, not clinically relevant; no data of NPs.
- **Systemic antibiotics (< 2 weeks):** Ib(-)-evidence, grade of recommendation: D, clinically relevant for acute exacerbation; no data of NPs.
- **Systemic antibiotics (macrolides) (> 1 month):** Ib(+)-evidence in CRS, grade of recommendation: A, clinically relevant; III(+)-evidence in NPs, grade of recommendation: C, clinically relevant in neutrophilic NP in Chinese patients.
- **Treatment after surgery to prevent NP recurrence:** no data available on antibiotic treatments.

### 5.1.2. Antifungal treatment – topical and systemic

The use of antifungal irrigations and oral antifungal treatments in patients with CRS and NPs is not justified by the majority of recent data [Ib(-)-evidence]. It has been
shown that eradication of fungi in these patients does not alleviate symptoms. Although safe to use and despite evidence of benefit in 3 uncontrolled trials, 4 subsequent placebo controlled studies failed to show clinical benefit of topical antifungal treatment in patients with CRS and NPs [Ib(-)-evidence]. Although therapeutic effects of amphotericin B are said to result from its antifungal effect, they may also result from a selective cytotoxicity and possible anti-inflammatory properties. Similar to topical antimycotics, no clear evidence exists justifying the routine use of oral antifungal agents [Ib(-)-evidence], nor the adjuvant topical and oral antifungal therapy after ESS in patients with CRS and NPs. The improvement of QoL has not been shown to be statistically significant.

Further research needs to be performed to test whether variations in topical antifungal dosage, formulation, application methods and duration of treatment, oral antifungals, and post-ESS therapy could improve clinical signs and symptoms and decrease the recurrence rate in patients with CRS and NPs.

In summary:

- **Topical antifungal agents (> 1 month):** Ib(-)-evidence in CRS and in NPs, grade of recommendation: A(-), not clinically relevant.
- **Systemic antifungal agents (> 1 month):** Ib(-)-evidence in CRS, grade of recommendation: A(-), not clinically relevant; no data of NPs.
- **Treatment after surgery to prevent NP recurrence:** no data available with antifungal treatment alone, grade of recommendation: D, unclear clinical relevance for topical antifungal treatment.

### 5.1.3. Antihistamines – topical and systemic

Because of the antagonising action of H₁-receptors, oral and intranasal antihistamines are evidentially recommended as a first-line therapy for AR. The additional anti-inflammatory action of certain antihistamines may, at least theoretically, be a pathophysiological basis for antihistamine treatment in CRS with and without NPs. The benefits of intranasal therapy for CRS with and without NPs include activity at the site of inflammation and a low incidence of systemic side effects.
Intranasal azelastine (> 2 weeks) represents an effective treatment in CRS / NAINPER and seems to be an important option for its therapy [Ib(+)-evidence]. It likewise prevents sneezing, itching and runny nose, but also improves nasal congestion. Oral antihistamines (astemizole, cetirizine, loratadine) (> 2 weeks) improve sneezing, itching and rhinorrhea of CRS / NAINPER [Ib(+)-evidence]. Oral astemizole shows similar results when compared with intranasal beclomethasone dipropionate. Antihistamines have not been extensively studied in patients with NPs. They are not the drug of choice in this CRS entity, but nasal symptoms improved when treated systemically [Ib(+)-evidence, 1 study] and intranasal [II(+)evidence]. Statistically significant improvement of QoL has been shown in 1 study about systemic antihistamines. No changes in polyp size could be demonstrated. Patients with NPs also suffering from seasonal or perennial AR have no increased risk of exacerbations of symptoms during allergen exposure. Thus, the role of allergic immune reactions and so an antihistamine treatment in these patients remains unclear.

Studies about antihistamine treatment after ESS to prevent NP recurrence are not available.

A correct diagnosis of CRS subtypes should be the basis for the choice of therapy. However, if a definitive diagnosis is missing, agents such as azelastine nasal spray, which demonstrated efficacy in both AR and non-AR, can provide symptom relief regardless of rhinitis type.

In summary:

- **Topical antihistamines (> 2 weeks):** Ib(+)-evidence in CRS/NAINPER, grade of recommendation: A, clinically relevant in NAINPER; III(+)-evidence in NPs, grade of recommendation: C, clinically relevant for rhinorrhea (not drug of first choice).
- **Systemic antihistamines (> 2 weeks):** Ib(+)-evidence in CRS/NAINPER, grade of recommendation: A, clinically relevant in NAINPER; Ib(+)-evidence in NP, grade of recommendation: A, unclear clinical relevance (only 1 single study) (not drug of first choice).
- **Treatment after surgery to prevent NP recurrence:** no data available on antihistamines.
5.1.4. Antileukotrienes - systemic

Antileukotriene therapy can be considered useful in the treatment of NPs. There are seven randomised studies on the efficacy of LT-receptor antagonists and LT-synthesis inhibitors. Data are essentially limited to NPs associated with asthma and NSAID-intolerance. Furthermore, the available data are somewhat confusing in that every study had a different design, compares different drugs, and seems to make a great deal out of minimal (probably clinically irrelevant) differences in outcome measures. Only three double-blind, randomised, placebo controlled trials have been done\textsuperscript{165,234,515}.

All studies about the treatment of NPs in AERD showed a benefit to using these drugs without surgery and also after ESS to prevent NP recurrence. The data do support clearly the use of antileukotriene agents, particularly montelukast, in the management of NPs in AERD [lb(+)-evidence]. These drugs may offer a non-steroidal oral alternative in the treatment of patients with AERD. However, the present data have demonstrated that the efficacy of antileukotriene agents was not significantly different when compared with intranasal corticosteroids in the treatment of NPs\textsuperscript{513,516,517}. Statistically significant improvement of olfaction and QoL have been shown. Antileukotriene treatment in AERD after ESS prevents or prolongs the time to NP recurrence significantly [lb(+)-evidence]. For patients who have CRS without NPs, there are no data to support the inclusion of these medications in their care.

It is not clear exactly where in therapy these drugs are indicated. Large studies comparing the efficacy of an antileukotriene agent versus an INS are needed.

In summary:

- **Systemic antileukotrienes (\textgeq 1 month):** lb(+)-evidence in AERD (NPs), grade of recommendation: A, clinically relevant (non-steroidal alternative); no data in CRS without NPs.
- **Treatment (\textgeq 1 month) after surgery to prevent NP recurrence:** lb(+)-evidence in AERD (NPs), grade of recommendation: A, clinically relevant (non-steroidal alternative).
5.1.5. Aspirin desensitization and maintenance –
topical and systemic

Many AERD patients (NPs, asthma and airway reactivity to AS and NSAIDs) can be managed successfully with conventional treatments for both, the upper and lower airway processes and with avoidance of medications that inhibit the COX-1 enzymes. As in patients with CRS with NPs due to other processes (e.g., IgE-mediated allergic sensitisation), intranasal corticosteroids can help reduce inflammation, polyp formation and symptoms, and should be used as first-line therapy in AERD. Similarly, management of asthma in patients with AERD should include inhaled corticosteroids with or without long-acting β-agonists and other therapeutic options in accordance with recently updated asthma management guidelines. For patients who have inadequately controlled rhinosinusitis and asthma despite these treatments, AS desensitisation may be an important therapeutic option. Current evidence provides strong support for the clinical efficacy of oral and intranasal AS desensitisation and daily AS maintenance in the chronic inflammatory disease of the upper and lower airway in AERD. Reduction of nasal symptoms, chest symptoms, need for surgical intervention and medication burden have been demonstrated in patients with AERD and NPs. However, there were only two randomised, double-blind, placebo controlled studies available, one in the oral AS (positive clinical outcome) [Ib(+) evidence] and one in the lysine AS regimen (negative clinical outcome) [Ib(-) evidence], respectively. However, fourteen prospective, case controlled trials exist with benefits of these treatment modalities in AERD and NPs without and after ESS [III(+)-evidence]. Three of 5 trials have shown statistically significant improvement of smell dysfunction.

In conclusion, the above mentioned trials underline the clinical benefit of AS desensitisation and maintenance; however, larger randomised, placebo controlled trials should be carried out to confirm this efficacy, in view of the low-grade evidence of the published data.

In summary:
- **Topical lysine AS desensitization and maintenance (≥ 1 month → years):**
  III(+) evidence in AERD (NPs), grade of recommendation: D, unclear clinical relevance (not treatment of first choice); no data available of CRS without NPs.
• **Systemic oral AS desensitization and maintenance (≥ 1 month → years):**
  lb(+)–evidence in AERD (NPs), grade of recommendation: A, clinically relevant (not treatment of first choice); no data available of CRS without NPs.

• **Treatment after surgery to prevent NP recurrence:** III(+)–evidence of intranasal lysine AS in AERD (NPs), grade of recommendation: C, unclear clinical relevance (not treatment of first choice); no data available of oral AS desensitization and maintenance.

### 5.1.6. Bacterial lysate preparations and other immunostimulants – systemic

Bacterial lysates are powerful inducers of a specific loco-regional immune response that significantly enhance the concentration of antibodies directed to antigenic structures of bacteria most commonly observed during infections of the upper respiratory tract. Those antibodies have the capability of opsonising living bacteria, thus allowing the engulfment and killing mediated by phagocytes. This activity is linked to the capacity of inducing a significant reduction or a complete disappearance of signs and symptoms related to primary or recurrent airway infections.\(^{995}\)

The analysed studies are encouraging and show evidentially significant decrease in CRS symptoms, and particularly, prevention of acute episodes of CRS in paediatric and adult patients treated with bacterial lysate preparations [lb(+)–evidence]. No data could be found on treatment with bacterial lysates in patients neither with NPs nor after ESS.

It would be worthwhile to build up new trials. Those new trials should include a higher number of patients selected according to the disease and its severity, patients with NPs, and patients after ESS. This could permit to get even stronger evidence of their beneficial effect on symptoms, endoscopically and radiological findings, and on prevention of recurrent infections in CRS with and without NPs.

In summary:

• **Systemic bacterial lysates (≥ 3 months):** lb(+)–evidence in CRS without NPs, grade of recommendation: A, clinically relevant for reduction of acute rhinosinusitis episodes in CRS; no data available of NPs.
• **Treatment after surgery to prevent NP recurrence:** no data available of bacterial lysates.

### 5.1.7. Capsaicin – topical

Intranasal capsaicin, a pungent compound present in red-hot peppers, can induce nasal burning, rhinorrhea and nasal congestion through stimulation of the nasal nerve C-fibres. With repeated applications of capsaicin, C-fibres are thought to become depleted of neuropeptides, leading to reduced nasal hyperreactivity.

Several studies have shown symptoms' improvement in patients with CRS with and without NPs [Ib(+)-evidence], without affecting cellular homeostasis or overall neurogenic staining up to 9 months after treatment. One single study showed that intranasal capsaicin after ESS for NPs prolongs significantly the time until recurrence (9-month observation period) [Ib(+)-evidence]. The improvement of smell dysfunction has not been shown to be statistically significant in one single study. A published practical therapeutic approach has suggested induction of topical intranasal anaesthesia, followed by 5 hourly applications of capsaicin. This treatment regimen has shown similar efficacy compared to an intermittent treatment over 2 weeks.

Intranasal capsaicin seems to be a satisfactory solution for many patients with CRS with and without NPs unresponsive to standard treatment regimens. Thus, more research is required to better define the role and long-term effects of capsaicin therapy.

In summary:

- **Topical capsaicin:** Ib(+)-evidence in CRS/NANIPER, grade of recommendation: A, clinically relevant (not treatment of first choice [painful]); Ib(+)-evidence in NPs, grade of recommendation: A, clinically relevant (not treatment of first choice [painful]).
- **Treatment after surgery to prevent NP recurrence:** Ib(+)-evidence, grade of recommendation: A, unclear clinical relevance (1 single study) (not treatment of first choice [painful]).
5.1.8. Corticosteroids – topical and systemic

Chronic rhinosinusitis and NPs are part of a complex inflammatory process of the upper respiratory tract. Steroids have a powerful anti-inflammatory effect. The clinical efficacy of steroids may be due to their abilities to reduce the recruitment of inflammatory cells (e.g. airway eosinophils) and the secretion of pro-inflammatory mediators during the late phase of the inflammatory response. Corticosteroid treatment is a medical therapy with proven efficacy on the symptoms and signs of CRS with and without NPs, and can be used topically or systemically.

There is clear evidence that topical INSs confer a benefit in CRS, as demonstrated by the results from numerous randomized, double-blind, placebo controlled studies [Ib(+)Evidence]. Intranasal steroids decrease NP size and reduce the nasal symptoms, such as nasal obstruction, rhinorrhea, sneezing, and impairment of smell [Ib(+)Evidence]. Intranasal steroids after surgical polypectomy and ESS in patients with NPs significantly prolong the time to recurrence [Ib(+)Evidence].

Short-term oral corticosteroid therapy seems to be a reasonable treatment option for patients with severe NPs and uncontrolled symptoms (such as nasal blockage and olfactory dysfunction) which persist after INS therapy. The few available prospective studies show a symptomatic improvement, and a reduction in NP size. Two trials with oral corticosteroids have been shown to improve statistically significant the QoL. There is only one randomized, double-blind, placebo controlled study on this matter [Ib(+)Evidence].

Intranasal steroids are highly effective, but local side effects have been reported: epistaxis is the most frequent one. Rarely, there may be systemic adverse events (such as effects on growth, eyes, bone and the hypothalamic-pituitary-adrenal axis). Thus, care has to be taken, especially in children, when long-term treatments are prescribed. Short-term treatments with oral corticosteroids are effective in patients suffering from CRS with NPs, but major systemic side effects have been described (insomnia, personality changes, stomach ulcers and diabetes). Oral corticosteroid treatment should only be given as a rescue medication for severe NPs and uncontrolled symptoms after INS treatment.

In conclusion, the design of topical INSs has provided a much better therapeutic ratio than oral corticosteroids. The pharmacodynamic and pharmacokinetic properties of these agents play an important role in facilitating local
anti-inflammatory activity with a low rate of side effects. The ideal combination of features would include a high degree of lipophilicity coupled with low systemic absorption and rapid clearance. It could be argued that the newer agents, fluticasone propionate, momethasone furoate, ciclesonide and fluticasone furoate come remarkably close to the pharmacokinetic and pharmacodynamic criteria for the ideal INS because they have: 1) a high degree of glucocorticosteroid receptor affinity, potency and specificity; 2) a low systemic availability; 3) a high rate of hepatic first-pass clearance and rapid systemic elimination; and 4) an once-daily dosing scheme.

In summary:

- **Topical corticosteroids (> 2 weeks):** Ib(+) - evidence in CRS with and without NPs, grade of recommendation: A, clinically relevant.
- **Systemic corticosteroids (< 2 weeks):** III(+) - evidence in CRS, grade of recommendation: C, clinically relevant only in short-course therapy; Ib(+) - evidence in NPs, grade of recommendation: A, rescue treatment in severe NPs without improvement after topical corticosteroids.
- **Treatment after surgery to prevent NP recurrence:** Ib(+) - evidence of topical corticosteroids, grade of recommendation: A, clinically relevant; no data available of systemic corticosteroids.

### 5.1.9. Cromolyn sodium – an intranasal mast cell stabilizer

Intranasal cromolyn has proven efficacy in patients with seasonal and perennial AR. It has an excellent safety profile in the treatment of asthma and in the treatment of AR. In these conditions, intranasal cromolyn offers an alternative to treatments that have been associated with serious adverse effects, such as sedation in antihistamine treatment or corticosteroid effects. Its safety record and lack of drug interactions make intranasal cromolyn a good alternative for many patients, especially children and those taking concomitant medications for other chronic co morbidities. The mechanism of action seems to be a mast cell stabilising effect and its ability to prevent early- and late-stage inflammatory (allergic) responses.

Two studies show clinical improvement in sneezing and rhinorrhea in patients with perennial rhinitis treated with cromolyn\(^{712,713}\). The same treatment regimen in
patients with NANIPER did not demonstrate a difference between the efficacy of cromones and placebo. The good outcome in the patients with perennial rhinitis may be due to a possible bias in the inclusion criteria, where it is not mentioned, if patients with allergies participated in these trials or not. The intranasal cromolyn in patients with NPs did not demonstrate any effect on the polyp size.

In conclusion, there is no evidence of the usefulness of intranasal cromolyn in the treatment of non-allergic CRS with and without NPs.

In summary:

- **Topical cromolyn sodium (≥ 1 month):** Ib(+-)-evidence in CRS, grade of recommendation: D, not clinically relevant; III(-)-evidence in NPs, grade of recommendation: C(-), not clinically relevant.
- **Treatment after surgery to prevent NP recurrence:** no data available on cromolyn sodium treatment.

### 5.1.10. Decongestants – topical and systemic

Experimental studies in patients with CRS on the effect of topical and systemic decongestants by CT-scan, MRI and maxillary sinus endoscopy on ostia and OMC patency have confirmed marked effect on the mucosal thickness of inferior and middle turbinates, infundibular mucosa, and the maxillary ostium, but no effect on ethmoid and maxillary sinus mucosa and NP size.

Topically administered decongestants for 10 days in patients with CRS without NPs did not show any clinical improvements. Subjective decrease of nasal congestion was demonstrated in CRS patients without NPs treated with systemic decongestants in a trial for the treatment duration of 4 days. There are no data of long-term treatments and outcome available.

Overall, monotherapy with intranasal vasoconstrictors seems not to decrease nasal symptoms like nasal obstruction in patients with CRS without NPs. It has also a limited role in the treatment of a chronic sinusopathy, as that a long-term treatment would be necessary, which is not recommended because of the high incidence of tolerance phenomena, rebound effect and rhinitis medicamentosa when topically administered for longer than 10 – 15 days. Intermittent dosing with wash-out periods
of 10 – 15 days can help to avoid these side effects. The severe adverse effects of oral decongestants including central nervous system stimulation and cardiovascular events should warn against the use of these drugs in the treatment of CRS.

In conclusion, clinical trials proving the usefulness of nasal decongestants in long-term outcome are lacking and topical and systemic vasoconstrictors cannot be recommended as a monotherapy in CRS with and without NPs.

In summary:

- **Topical decongestants (< 10 days):** Ib(-)-evidence in CRS, grade of recommendation: A(-), not clinically relevant; no data available of NPs.
- **Systemic decongestants (< 10 days):** Ib(+)-evidence in CRS, grade of recommendation: A, clinically relevant only in short-course therapy; no data available of NPs.
- **Treatment after surgery to prevent NP recurrence:** no data available of topical and systemic decongestants.

### 5.1.11. Furosemide – a topical diuretic agent

The suggested anti-oedematous, anti-inflammatory and anti-proliferative actions of furosemide make its nasal application a candidate for treatment of CRS with and without NPs. Furosemide spray applied as a single puff reduced objectively for 3 and subjectively for 6 to 12 hours nasal obstruction in patients with CRS without NPs. This only trial of furosemide treatment in CRS without NPs is unfortunately a 1-day observational study, and not clinically relevant \(^{752}\) [Ib(+)-evidence]. Intranasal furosemide administered in CRS with NPs decreases polyp size and improves nasal symptoms including olfaction similar to systemic steroids \(^{185}\) [Ib(+)-evidence]. The *in vitro* demonstrated anti-inflammatory effect of furosemide could not be confirmed clinically. Long-term intranasal furosemide after ESS in patients with NPs prolongs the time to recurrences significantly \(^{741,746}\) [III(+)-evidence]. None of the published trials on intranasal furosemide treatment reported local and systemic side effects.

Topical application of furosemide, a much cheaper medication with probably less adverse effects than steroids, could be an alternative to the use of topical corticosteroids in the treatment of NPs and in the prophylaxis of NP recurrences after
ESS. Unfortunately, randomized, placebo controlled trials on a long-term treatment are lacking.

In summary:

- **Topical furosemide (≤ 1 week):** Ib(+) evidence in CRS, grade of recommendation: A, not clinically relevant (1 day experimental application); Ib(+) in NPs, grade of recommendation: A, unclear clinical relevance in short-course treatment (1 single study).

- **Treatment after surgery to prevent NP recurrence:** III(+) evidence of furosemide treatment over years, grade of recommendation: C, unclear clinical relevance (no placebo controlled trial, possible effect of saline for furosemide dilution).

### 5.1.12. Gastroesophageal reflux therapy

The published literature weakly supports a potential causal association between GER and CRS. It is possible that GER plays a role in some patients with CRS based on the increased prevalence of GER in this disease. It is likely that GER is one contributing factor to the multifactorial CRS, and that reflux treatment alone will be insufficient. On the other hand, proton pump inhibitors and other acid-suppressing medications only decrease the pH of gastric refluxate by reducing hydrochloride formation. They do not stop the reflux process due to an incompetent lower oesophageal sphincter or an ineffective oesophageal peristalsis. Therefore, some GER patients require long-term medical treatment while others, who face a lifetime of anti-reflux treatment or failed medical therapy, require fundoplication to restore the competence of the lower oesophageal sphincter. Furthermore, as proton pump inhibitors only reduce gastric acid formation, non-acid reflux would continue and this might explain, in part, the failure of such a treatment in CRS with associated GER.

The results of the retained, prospective, case controlled trials suggest at least some efficacy of an antireflux therapy in patients suffering from CRS and proven GER [III(+) evidence]. Improvement of QoL showed in one trial was not statistically significant. Unfortunately, randomised, double-blind, placebo controlled trials are lacking. Proton pump inhibitors cannot be recommended as a monotherapy in CRS with and without NPs. However, refractory CRS after intensive medical management
should be evaluated for GER and if GER is present it should be treated accordingly before ESS will be considered. More work needs to be done to solidify this relationship, especially with regard to the pathophysiology linking CRS and GER, and the reasons for a lack of therapeutic response in some patients.

In summary:

- **Gastroesophageal reflux therapy (months):** III(+-)-evidence in CRS and in NPs, both associated with GER, grade of recommendation: C, clinically relevant only in refractory CRS and NPs with proven GER.
- **Treatment after surgery to prevent NP recurrence:** no data available of gastroesophageal reflux therapy.

### 5.1.13. Immunotherapy - systemic

Despite gaining experience in the area of CRS / AFRS, the mechanism by which specific immunotherapy with fungal, non-fungal and staphylococcal antigens benefits patients with CRS / AFRS remains unknown. Studies on immunotherapy in CRS / AFRS have reported changes in allergen-specific IgE and IgG. No consistent patterns to IgG levels have been observed. In the study using staphylococcal antigens for immunotherapy in paediatric CRS, an increasing of serum IgA and IgG were reported\(^{788}\). The treatment may also affect T-cells, immune complexes and other allergic mechanisms.

There are only a few prospective, case controlled, badly designed trials available, dealing with immunotherapy in the treatment of CRS and AFRS. The only one study using staphylococcal antigens for immunotherapy in CRS in children showed a clinically long-term improvement\(^{788}\). Unfortunately, no statistical comparison was done. Three prospective, case controlled studies have evaluated an immunotherapy with fungal and non-fungal antigens in the treatment of AFRS preceded by surgical removal of allergic mucin\(^{237,786,789}\). The results were not conclusive, and only the study comparing immunotherapy versus « no immunotherapy » showed a clear, statistically significant, clinical benefit and decrease of NP recurrence in favour of long-term immunotherapy [III(+-)-evidence]\(^{237}\). Statistically significant improvement of sinusitis-specific QoL has been shown in this study.
In conclusion, there are only very few trials using immunotherapy in CRS / AFRS. The results of two of these studies are not conclusive. The outcome of the remaining two trials is encouraging, but any randomised, placebo controlled, double-blind study is lacking.

In summary:

- **Systemic immunotherapy (> 8 months):** III(+-)-evidence in CRS/AFRS, grade of recommendation: D, not clinically relevant; no data available of NPs.
- **Treatment after surgery to prevent NP recurrence:** no data of systemic immunotherapy available.

### 5.1.14. Ipratropium bromide - topical

Short- and long-term studies of intranasal IB therapy in patients with NANIPER show that it is well tolerated without evidence of rebound, mucosal and mucociliary damage, and without severe local and systemic adverse events, especially with doses within the recommended range or when patients were allowed to adjust the dosage to their perceived symptoms [Ib(+)-evidence]. They show evidential efficacy in the treatment of persistent watery rhinorrhea, and also possibly, nasal obstruction as a result of hypersecretion by the mucosal glands. The side effects were primarily related to mucosal dryness. The combination of IB with an INS showed statistically significant better symptom release than either agent alone. Only one study was evaluating the olfactory outcome, but could not prove any significant amelioration. The QoL has been studied in 6 trials, two of them showing significant improvement. Several studies showed a statistically significant reduced response to metacholine provocation after the treatment with IB ¹⁸⁶. However, the observation that IB selectively reduces the secretory response suggests that cholinergic hyperreactivity does not fully explain the pathophysiology of NANIPER. Ipratropium bromide appears to be an effective and safe addition to the treatment regimens for rhinorrhea in this subtype of CRS.

Ipratropium bromide should primarily be used in the treatment of anterior rhinorrhea as the only nasal symptom. This agent has not proved to be particularly effective in the management of sneezing, obstruction and postnasal drip. The
prescription as additional drug in the therapy of rhinorrhea not totally controlled by other agents can be recommended.

In summary:

- **Topical ipratropium bromide (≤ 2 months):** Ib(+)-evidence in NANIPER, grade of recommendation: A, clinically relevant in NANIPER (rhinorrhea); no data of NPs available.
- **Topical ipratropium bromide (> 2 months):** Ib(+)-evidence in NANIPER, grade of recommendation: A, clinically relevant in NANIPER (rhinorrhea); no data of NPs available.
- **Treatment after surgery to prevent NP recurrence:** no data of topical ipratropium bromide available.

### 5.1.15. Irrigations – nose and paranasal sinuses

Nasal saline irrigations are an important component in the management of CRS. Long-term nasal saline irrigation is an effective [Ib(+)-evidence], simple and inexpensive adjunct treatment that relieves symptoms and discomfort in patients with CRS. One clinical trial indicates that patients treated with nasal saline irrigation are less reliant on rescue medications \(^{245}\). Five studies have demonstrated statistically significant improvement of QoL, but no trial could show significant reduction of smell dysfunction. Any long-term outcome is lacking. The procedure has been used safely by both adults and children and has no documented serious adverse effects. There is evidence that sinonasal saline irrigation by pressurized nasal lavage or douche is a more effective method of delivery than the drop, spray or nebuliser modes \(^{823,996}\). The benefit of nasal saline irrigation alone in CRS with NPs is unclear because of lacking controlled trials. Nasal saline application was used as a control treatment in placebo controlled trials with topical steroids, antibiotics and antifungal solutions in CRS with and without NPs. The comparison of treatment with antral washouts in the treatment of chronic adult and paediatric rhinosinusitis did not prove benefit from such treatment \(^{841,842}\). An evidential benefit of the empirically used saline washes frequently recommended after ESS in patients with CRS could not be demonstrated, and long-term outcome trials are not available.
Several non-saline nasal irrigations are mentioned in the literature (antiseptic solutions, carboxymethylglucan, dexamethasone, baby shampoo, sodium hypochlorite, thermal water irrigations and inhalations, nasal hyperthermia, N-chlorotaurine antral washout) showing promising outcomes. Two of these trials showed significant improvement of smell dysfunction, but no significant outcome concerning QoL. These more anecdotic treatments need further evaluations by randomised, double-blind, and placebo controlled trials.

In summary:

- **Saline irrigations (< 1 month):** Ib(-)-evidence in CRS, grade of recommendation: A(-), not clinically relevant; no data of NPs available.
- **Saline irrigations (≥ 1 month):** Ib(+)-evidence in CRS, grade of recommendation: A, clinically relevant; no data of NPs available.
- **Saline antral washout:** Ib(-)-evidence in CRS, grade of recommendation: A(-), not clinically relevant; no data of NPs available.
- **Diverse non-saline irrigations:** Ib(+)/III(+)evidence, diverse single trials with different treatment modes in CRS with and without NPs, not clinically relevant.
- **Treatment after surgery to prevent NP recurrence:** Ib(-)-evidence in both, the short-term (< 1 month) and long-term (≥ 1 month) saline irrigations, grade of recommendation: A(-), not clinically relevant (but empirically used postoperatively to remove and diminish crusts and adhesions).

### 5.1.16. Mucoactive agents – topical and systemic

Mucoactive agents are extremely safe and well-tolerated drugs. Nonetheless, clinical data on their use and efficacy are limited and conflicting, reflecting a less-than-perfect understanding of the pathophysiology of mucins and mucociliary clearance, different methodologies, and lack of a standardised way to objectively measure mucus.

Mucus hypersecretion and “stickiness” is a big problem for many patients with CRS. Therapy to loosen mucus and help the patient eliminate the excess secretion which congests the nose is desirable. Despite the conflicting data available, some patients benefit from using mucoactive agents. Clinical trials proving the superiority of intranasal nebulisation of mucoactive agents to saline solution are lacking, and this
treatment regimen cannot be recommended as a monotherapy in CRS with and without NPs [Ib(-)-evidence]. Systemic administration of mucoactive agents in CRS without NPs shows evidential improvement in nasal symptoms [Ib(+)-evidence]. It can be recommended in CRS without NPs where other topical intranasal therapy failed. More data are needed to better define the clinical use of mucoactive agents in CRS with and without NPs.

In summary:

- **Topical mucoactive agents:** Ib(-)-evidence in CRS, grade of recommendation: A(-), not clinically relevant; no data available of NPs.
- **Systemic mucoactive agents (< 1 month):** Ib(+)-evidence in CRS, grade of recommendation: A, clinically relevant only in short-course therapy; no data available of NPs.
- **Treatment after surgery to prevent NP recurrence:** no data available of topical and systemic mucoactive agents.

5.2. COMPLEMENTARY AND ALTERNATIVE MEDICINE

5.2.1. Phytore preparations, homeopathies and Chinese acupuncture

Considering the popularity of herbal medicine among patients with CRS, it was disappointing to identify only one small randomised, double-blind, placebo controlled trial conducted specifically in patients with CRS. It is, however, not entirely surprising that not much research has been done for CRS. The reasons for the limited number of therapeutic trials for CRS were believed to include the lack of wide-spread acceptance of existing definitions for the disorder and the acknowledged difficulty in establishing its causes. Evidence that any herbal medicines are beneficial in the treatment of CRS is limited [III(+)-evidence]. Sinupret® may be an effective treatment in this disease [Ib(+)-evidence]. Positive results from isolated prospective, randomised studies of four Chinese herbal preparations (1 oral, 3 intranasal) applied after ESS in CRS with and without NPs require independent replication [Ib(+)-evidence]. They seem to improve the postoperative course, but did not go further to
observe if there would be an effect on NP recurrences. One of these studies showed statistically significant improvement of QoL.

Some prospective, case controlled trials let conclude that some effect of homeopathy exists. However, the only randomized, double-blind, placebo controlled study where patients suffering from CRS were treated with homeopathy [Ib(-)-evidence] showed no benefit compared with a placebo. The evidence for a specific effect of homeopathy in CRS is weak, whereas such evidence is strong with conventional (“allopathic”) treatments. One trial showed significant amelioration in QoL.

Prospective, case controlled studies concluded a benefit of acupuncture in CRS. There are only two randomized, placebo controlled studies treating patients suffering from CRS with acupuncture. These trials showed a subjectively similar and radiologically lesser benefit of acupuncture compared with the conventional medical treatment [Ib(-)-evidence]. There was no difference between Chinese and sham acupuncture. Any significant improvement of QoL could not be demonstrated. The evidence for a specific effect of acupuncture in CRS is weak.

Complementary and alternative medicine is widely practised, and many patients who use it appear to be satisfied. From a scientific viewpoint, there is no definitive or convincing proof of efficacy for most complementary and alternative medicines in CRS. In general, the methods used to study them are often inadequate (i.e., not randomised, not controlled and not blinded, without any quantitative measurements). Considering the few randomised, double-blind, placebo controlled trials, there is no clear evidence for the efficacy of complementary and alternative medicine in CRS. Some positive results were described in prospective, case controlled trials. Therefore, it is not possible to provide evidence-based recommendations for the use of alternative and complementary medicine to treat CRS, and further randomised controlled trials are needed. In addition, complementary and alternative medicines might not be devoid of side effects, and some of them might interact with other medications.

In summary:

- **Systemic phytopreparations (≥ 1 week):** III(+) - evidence in CRS, grade of recommendation: C, unclear clinical relevance; no data of NPs available.
• **Topical phytopreparations:** no data of CRS and NPs available.

• **Treatment after surgery to prevent NP recurrence:** Ib(+)-evidence in both, the topical and systemic phytopreparations, grade of recommendation: A, improvement in postoperative healing, but not clinically relevant in preventing NP recurrence.

• **Homeopathy (≥ 1 month):** Ib(-)-evidence in CRS, grade of recommendation: A(-), not clinically relevant; no data of NPs available.

• **Treatment after surgery to prevent NP recurrence:** no data available of homeopathy.

• **Acupuncture:** Ib(-)-evidence in CRS, grade of recommendation: A(-), not clinically relevant; no data of NPs available.

• **Treatment after surgery to prevent NP recurrence:** no data available of Chinese acupuncture.

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5.3. POSSIBLE FUTURE TREATMENTS – IMMUNOMODULATORY THERAPIES?

There are only few data available on clinical trials with immunomodulatory treatments and their clinical impact is low. Anti-IL-5 antibodies (reslizumab)\textsuperscript{921} show a decrease in NP size, but no difference of symptom improvement when compared with the placebo treatment [Ib(-)-evidence]. Topical doxycycline, a matrix metalloproteinase-9 synthesis-suppressing agent\textsuperscript{987} demonstrates an improvement in nasal signs and symptoms after ESS [Ib(+)-evidence]. Subcutaneous filgrastim, a recombinant human granulocyte macrophage-colony stimulating factor does not improve QoL after 10 weeks of treatment [Ib(-)-evidence]\textsuperscript{251}. Omalizumab, an IgE antagonist, interferon, and imatinib were studied in very small, retrospective, open-label trials. Their outcome shows promising results. None of these trials could show a significant improvement in QoL outcome. Clinical studies evaluating the efficacy of IL-4 and IL-13 antagonists, CC chemokine receptor-3 antagonists and immunosuppression (cyclosporine) are lacking and only hypothetic actions can be discussed.
In conclusion, immunomodulatory drugs keep promises for the future of CRS with and without NPs, but in light of their low evidence and possible side effects, they need to be better studied before being implemented in the clinical setting.

In summary:

- **Systemic immunomodulatory therapy:** Ib(-)-evidence of filgrastim in CRS, grade of recommendation: A(-), not clinically relevant; Ib(-)-evidence of reslizumab in NPs, grade of recommendation: A(-), not clinically relevant.
- **Topical immunomodulatory therapy:** no data available.
- **Treatment after surgery to prevent NP recurrence:** Ib(+)—evidence of topical immunomodulatory therapy (doxycycline), grade of recommendation: A, not clinically relevant in preventing NP recurrence, but in the postoperative healing phase (crusts, secretion).
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### Table L. Continued.

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<td>III (4+)</td>
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<td>III (2+)</td>
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I – IV: level of evidence with positive outcome, I – IV (-): level of evidence with negative outcome, A – D: strength of recommendation for the therapy, A – D (-): strength of advice against the therapy, RC: prospective, randomized, controlled trial, C: prospective, case controlled trial

- : proven clinical relevance
--- : unclear clinical relevance
---- : no clinical relevance
- : no data
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<td>1 RC</td>
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<td></td>
<td>2 RC</td>
<td>lb (2-)</td>
<td>A (-)</td>
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<td></td>
<td>4 C</td>
<td>III (4+)</td>
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I – IV: level of evidence with positive outcome, I – IV (-): level of evidence with negative outcome, A – D: strength of recommendation for the therapy, A – D (-): strength of advice against the therapy, RC: prospective, randomized, controlled trial, C: prospective, case controlled trial

- proven clinical relevance
- unclear clinical relevance
- no clinical relevance
- no data

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Table LII. Summary table of controlled clinical trials: Possible Future Treatments – Immunomodulatory Therapy

<table>
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<tr>
<th>Therapy</th>
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<th>Clinically relevant</th>
<th>Study N</th>
<th>Level of evidence</th>
<th>Strength of recommendation</th>
<th>Clinically relevant</th>
<th>Study N</th>
<th>Level of evidence</th>
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<td>-</td>
<td>Yes, only in postop. healing doxycycline</td>
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</table>

I – IV: level of evidence with positive outcome, I – IV (-): level of evidence with negative outcome, A – D: strength of recommendation for the therapy, A – D (-): strength of advice against the therapy, RC: prospective, randomized, controlled trial, C: prospective, case controlled trial

---
- : proven clinical relevance
---
---: unclear clinical relevance
---: no clinical relevance
---: no data
6. CONCLUSIONS

The often imprecise definition of CRS, complex pathogenesis and uncertainties regarding the precise role played by the involved processes of CRS and a lack of well designed trials make an analysis of the retained data difficult. The initial management of CRS is medical, with endoscopic sinus surgery reserved for complications, anatomical variations causing local obstruction, allergic fungal disease or if adequate drug treatment fails, which often needs to be maintained after surgery.

First-choice drug treatment in CRS with and without NPs comprises long-term, intranasal steroids [Ib-evidence] (grade A recommendation). Short-term, systemic corticosteroids [Ib-evidence] (grade A recommendation) are used as rescue medication in severe NPs. Intranasal steroids also are preventing NP recurrences after surgery. Long-term systemic low-dose macrolides with their anti-inflammatory, immunomodulatory, anti-mucous and less, antimicrobial actions seem to be a good alternative treatment modality in steroid non-responders [Ib-evidence] (grade A recommendation). Long-term saline irrigation’s may be used singly or may be included as an adjunct treatment for managing the symptoms of CRS and conditions producing chronic sinonasal disorders [Ib-evidence] (grade A recommendation). Antileukotriene and aspirin desensitisation / maintenance therapy can be considered for aspirin exacerbated respiratory disease (asthma, NPs, aspirin intolerance) [Ib-evidence] (grade A recommendation). Antileukotriene agents are preventing NP recurrences after their removal by endoscopic sinus surgery [Ib-evidence] (grade A recommendation). Topical capsaicin promises anti-inflammatory action in the treatment of CRS with [Ib-evidence] (grade A recommendation) and without NPs [Ib-evidence] (grade A recommendation) and the systemic bacterial lysate preparations may be helpful to reduce the frequency of acute infectious episodes in CRS [Ib-evidence] (grade A recommendation). Topical and systemic antihistamines [Ib-evidence] (grade A recommendation) and intranasal ipratropium bromide [Ib-evidence] (grade A recommendation) demonstrated improvement in the treatment of rhinorrhea and less of nasal congestion in vasomotor rhinitis, a specific subclass of non-allergic, non-infectious perennial rhinitis. Studies dealing with olfaction and QoL outcome are rare, demonstrating significant improvement in the treatment groups of AS desensitisation and topical / systemic steroids, and in the treatment groups of
long-term macrolides, antileukotrienes, systemic steroids, topical ipratropium bromide and saline irrigations, respectively. An excellent safety profile could be demonstrated for these drug categories.

Due to evidenced negative outcome in randomized trials or bad safety profile intranasal antibiotics [Ib(-)-evidence], topical and systemic antifungal agents [Ib(-)-evidence], intranasal cromolyn sodium [Ib(-)-evidence], long-term decongestants, topical mucoactive agents [Ib(-)-evidence], homeopathy [Ib(-)-evidence], and acupuncture [Ib(-)-evidence] can actually not be recommended in the medical management of CRS with or without NPs. Treatments like topical furosemide, gastroesophageal reflux therapy, systemic immunotherapy and topical / systemic phytopreparations can also not be retained as first-choice therapy options or are not clinically relevant in the conservative management of CRS due to the lack of randomized, placebo controlled studies or unclear clinical outcome,

New approaches are currently evolving, specifically targeting eosinophilic recruitment (chemokine receptor 3, eotaxin) and inflammation (interleukin-4, -5, -13), immunoglobulin E, or tissue remodelling by reducing the activity of metalloproteininases. Until now, these modern immunomodulators cannot be recommended due to the lack of randomized trials or the absence of clinical relevance.

The following table summarizes the clinical relevance of the above mentioned treatment modalities in the primary therapy of CRS without and with NP, and the adjuvant postoperative treatment to avoid NP recurrences (Table LIII).
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CRS: chronic rhinosinusitis; NP: nasal polyposis; NANIPER: non-allergic, non-infectious perennial rhinitis; - : no data available; *: some of these studies included patients with NP
Although much work has recently been done on CRS and NPs, a validation in terms of its clinical impact is necessary. The following suggestions should highlight some areas of interest for further investigations:

- the pathogenesis of CRS may be better explored with research techniques taken from the growing field of genetics

- development of means targeting biofilms, reducing Staphylococcus aureus colonisation and intracellular reservoirs, and modulating response to Staphylococcus aureus enterotoxins

- the relationship between the upper and lower respiratory tract needs further investigation and will offer further insight into pathophysiology of inflammation and therapeutic possibilities

Better uniform definitions and classifications of CRS with and without NPs and further well conducted prospective trials in clearly defined patient groups are needed to progress in the understanding and management of this chronic inflammatory disease.
Treatment of CRS with or without nasal polyps in present times.
7. REFERENCES

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