

Review article

An update on the diagnosis and treatment of sinusitis and nasal polyposis

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Introduction

Terminology

Sinusitis (more properly known as rhinosinusitis due to the regular involvement of the nasal cavity) is a condition with a high and clearly increasing prevalence. According to figures from IMS Health, acute sinusitis was diagnosed 6.3 million times and chronic sinusitis 2.6 million times in a country like Germany over the course of one year (July 2000–June 2001), resulting in 8.5 million and 3.4 million prescriptions, respectively. The number of diagnoses of “nasal polyposis” was approximately 221 000 (according to IMS Health 2001). Even though no reliable epidemiological studies of the incidence of sinusitis exist, these figures do indicate that sinusitis represents a considerable socioeconomic problem. Alongside allergic and viral conditions of the upper airways, sinusitis therefore constitutes one of the most common respiratory tract conditions in humans.

Similar data are reported from the USA: in 1997, sinusitis was prevalent in approximately 15% of the population. In the last decade, the frequency of diagnosis

in the USA rose by around 18%. The economic significance of sinusitis is huge: for 1992, the total cost, including costs resulting from loss of work, was estimated at over 6 billion dollars for the USA. In the period from 1985 to 1992, the number of antibiotic prescriptions for sinusitis rose from 7.2 million to 13 million (1, 2).

Sinusitis is an inflammatory process involving the mucous membranes of one or more sinuses. Generally speaking, the mucous lining of the nose is also involved. Even in the presence of a viral cold, a CT scan will reveal the involvement of the paranasal sinuses in 87% of cases, which is why we speak of rhinosinusitis (3). Bacterial rhinosinusitis (acute sinusitis) is generally preceded by a virus-induced inflammation of the sinuses; approximately 5–10% of childhood upper airway infections develop into acute sinusitis (4). The swelling and “immunological weakness” of the mucous membrane and the blockage of the ostia by the viral infection are today believed to cause bacterial infection of the intrinsically sterile paranasal sinuses by local microorganisms. This gives rise to acute sinusitis, with severe inflammatory infiltration of

Table 1. Classification of sinusitis in adults and children (modified from Lund and Kennedy (5))

	Adults	Children
Acute sinusitis	Symptoms < 8 weeks or < 4 episodes/year	Symptoms < 12 weeks or < 6 episode/year
Acute recurrent sinusitis	> 4 episodes/year with complete resolution of the symptoms	Recurrent episodes with complete resolution of the symptoms
Chronic sinusitis	Symptoms > 8 weeks or > 4 episodes/year with residual symptoms	Symptoms > 12 weeks or > 6 episodes/year

Table 2. Classification of nasal polyps

Antrochoanal polyps
Unilateral polyps
Bilateral (eosinophil) polyposis, possibly with asthma and aspirin sensitivity
Polyposis with underlying condition (cystic fibrosis, ciliary dyskinesia, mycosis)

the mucous membranes and corresponding clinical symptoms.

Chronic sinusitis is suspected of being caused by impaired paranasal sinus ventilation and drainage disorders due to a blockage of the ostiomeatal complex in the middle nasal meatus (6); however, the significance of the bacterial infection is doubtful (7). Besides the physical pathological mechanisms, inflammatory changes in the mucous linings of the nose and paranasal sinuses (that may play a considerable part in the pathogenesis of chronic sinusitis) have been increasingly described in the last few years (8). Underlying conditions such as cystic fibrosis, immunodeficiency, ciliary dyskinesia, and others may also play a causal role.

The pathogenesis of nasal polyposis is so far largely unknown, although associations exist with other respiratory tract conditions, such as aspirin sensitivity and asthma. More recent studies show that nasal polyps are not an allergic condition, as was often suspected. Rather, nasal polyps are characterized predominantly by inflammation caused by eosinophil granulocytes, whose regulation has been partly explained in the last decade. Very different pathogenic principles (e.g. aspirin sensitivity, cystic fibrosis) underlie the various forms of nasal polyp.

In clinical terms, a distinction is made between acute, acute recurrent, and chronic sinusitis (Table 1). Establishing this distinction involves a clinical diagnosis that has to be supplemented by a CT scan only in the case of chronic sinusitis. Chronic sinusitis can be subdivided into forms that are more neutrophilic or eosinophilic, with the eosinophilic form being primarily involved in polyp formation (Table 2).

Sinusitis and nasal polyposis can be accompanied by troublesome or agonizing symptoms that markedly impair one's quality of life (9, 10); they even carry serious risks (e.g. orbital or cerebral complications). Furthermore, sinusitis is associated with considerable socioeconomic consequences.

Efficient and specific diagnosis and treatment based on the latest findings are therefore desirable, and corresponding evidence-based guidelines are essential. This is particularly true for the surgical and medicinal treatment of the various forms of sinusitis. The guidelines should help to make the most of the limited resources of the health system.

"Evidence-based medicine (EBM) is the conscious, express, comprehensible use of the best evidence in decisions about the care of individual patients" (11).

Pathophysiology

Pathophysiology of acute and chronic neutrophilic sinusitis

While acute sinusitis is understood to be an inflammatory process in which paranasal sinus drainage and ventilation are impaired as a result of a nasal infection, chronic sinusitis is acknowledged to be due to a gradual obstruction caused by increased tissue formation in the ostiomeatal complex. According to the studies conducted so far, blockage of the ostiomeatal complex in the middle nasal meatus leads in turn to impaired ventilation and drainage (12). The significance of physical obstructions caused by morphological/anatomical variations in the paranasal sinus system and nasal septum is a subject of controversy. Although some 40% of patients exhibit these variations, they are observed in equal numbers in healthy people (13, 14).

The pathological mechanisms that cause sinusitis to become chronic have hitherto been attributed to mucociliary dysfunction, mucostasis, consecutive hypoxia and the discharge of microbial products (15–19). While *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* are among the microorganisms found in 75% of cases of acute sinusitis, *Staphylococcus aureus*, coagulase-negative Staphylococci, *Pseudomonas aeruginosa* and anaerobic bacteria, alone or a mixed infection with facultative anaerobic and aerobic pathogens, are the main agents in chronic sinusitis (20–25). However, the significance of bacterial and viral infections in the onset of chronic sinusitis is unclear, because the pathogenicity of these pathogens in chronic sinusitis is largely unknown (26, 27). The prevalence of anaerobic infections ranges in the literature from 80 to 100% (21) and in other studies from 0 to 25% (22, 24). The value of

the results of cultures, taken by aspiration or swab from the middle meatus, is limited because of contamination with bacteria from the nasal cavity (25). Generally speaking, results of cultures from specimens taken intraoperatively are considered more valid (28–30).

In recent years, not only physical considerations but also the inflammatory mechanisms taking place in the mucous linings of the nose and paranasal sinuses have been ascribed a significant role in the pathophysiological understanding of the condition (8).

The fluid obtained by irrigation from the sinuses of people with chronic sinusitis has been found to contain mainly neutrophil granulocytes, but also a few eosinophils, mast cells and basophils (31, 32). High concentrations of histamine, leukotrienes and prostaglandin D₂ indicate the involvement of these cells in the chronic inflammation.

Studies to identify proinflammatory cytokines in chronic and acute sinusitis have so far demonstrated the role of nonspecific cytokines such as interleukin(IL)-1 β , IL-6 and IL-8. Today, little is known about the interaction between the microorganisms and the mucous lining of the paranasal sinuses in terms of neutrophilic chemotaxis induction. In healthy people, more neutrophil granulocytes were found in nasal irrigation fluid (35%) than in the tissue itself (26, 33, 34). The continuous influx of neutrophil granulocytes is attributed to the chemotactic effect of IL-8, which is constitutively synthesized by epithelial cells, glandular cells and leukocytes (31, 35–38). Besides the IL-8-triggered migration of neutrophil granulocytes into inflamed tissue (which clearly plays a role in chronic sinusitis), IL-3 is also believed to be important. IL-3 is synthesized predominantly by activated T-cells (39) and leads to the stimulation, differentiation and activation of macrophages, neutrophils and mast cells, as well as eosinophils. Through the release of various mediators from the above cell populations, IL-3 may contribute to the local immunological response and presumably also to the development of a thickened mucous membrane in the sense of an exaggerated repair mechanism (8, 40).

Pathophysiology of chronic eosinophilic sinusitis (nasal polyposis)

Clinically, the term nasal polyposis comprises all types of nasal polyps, which emerge as blue-gray protuberances in the area of the ethmoid bone, middle meatus nose, and middle turbinate. Larsen (41) and Stammberger (42) identified the mucous membrane of the middle turbinate and middle meatus as the origin, while the inferior turbinate does not tend to form polyps; the reasons for this are unknown.

In clinical terms, nasal polyposis, characterized by eosinophil inflammation, is accompanied by acetylsalicylic intolerance in up to 25% of cases. Up to 40% of cases of nasal polyposis are associated with intrinsic asthma. Nasal polyposis associated with corticosteroid-

sensitive bronchial asthma and aspirin sensitivity is known as Samter's syndrome. Confirmed associations have also been described between eosinophilic nasal polyposis and Churg–Strauss syndrome, a form of eosinophilic immunovascularitis (43).

The predisposing role of an allergy to inhaled allergens in the development of nasal polyposis is questioned because of the low frequency of nasal polyps in allergic patients. Generally speaking, nasal polyps are cited as prevalent in less than 5% of allergic people, while allergy is prevalent in 15% of the general population. A study of 3000 atopic patients found a prevalence of 0.5% for nasal polyps, while the study in 300 nonallergic patients showed a prevalence of 4.5% (43, 44). The example of allergic paranasal sinus mycosis demonstrates that specific IgE and IgG antibodies may be formed jointly and appear to express a locally circumscribed allergic eosinophilic immune response in the paranasal sinuses (45–47).

In histological terms, nasal polyps are characterized by edema and/or fibrosis, reduced vascularization, and a reduced number of glands and nerve endings in the presence of often damaged epithelium (41, 48). Histological evaluations of polyps generally make a rough distinction between eosinophilic polyps, which correspond to approximately 65–90% of total cases, and neutrophilic polyps (49). Pathogenically, the increased tissue eosinophilia is explained by increased transendothelial migration and the inhibition of programmed cell death of eosinophils (50, 51).

RANTES protein (regulated on activation, T-cell expressed and secreted) is a member of the C–C chemokine family that induces eosinophil chemotaxis, transendothelial migration, the production of reactive oxygen radicals, and the release of eosinophil cationic proteins (ECP) *in vitro* (52, 53). Besides RANTES, eotaxin plays the main role in the selective migration of eosinophil granulocytes *in vivo* and *in vitro* (54, 55). In fact, it has been possible to demonstrate in the context of nasal polyps that RANTES might be responsible for the localization of the cells (56), and eotaxin for the accumulation of eosinophils, especially in IL-5-rich tissue (57).

Cytokines such as IL-3, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon (IFN)- γ increase the vitality of eosinophil granulocytes by inhibiting programmed cell death (apoptosis). In-vitro studies of the apoptotic behavior of eosinophils in bilateral nasal polyps show reduced eosinophil apoptosis, which appears to be regulated by the cytokine IL-5. IL-5 is presumably also synthesized and released by eosinophils, setting in motion an autocrine inflammatory mechanism that is responsible for the persistent eosinophilia (50, 51). The extravasation and storage of plasma proteins (albumin) has been identified as a link between eosinophilic inflammation and polyp growth (57).

In acetylsalicylic acid intolerance, there is a shift in the arachidonic acid metabolism (cyclooxygenase inhibition)

with increased leukotriene production in the presence of a reduced tissue prostaglandin level (58–61).

Colonization with enterotoxin-forming *Staphylococci*, whose products act as super-antigens and cause local polyclonal IgE formation, has recently been described as a possible pathological mechanism in bilateral eosinophilic nasal polyposis with associated asthma and aspirin sensitivity (62). The presence of enterotoxin-specific IgE antibodies in the tissue is accompanied by relatively severe eosinophil inflammation. The significance of these enterotoxins for the clinical severity of the condition needs to be established in more extensive studies.

In endemic (in some cases, allergic) paranasal sinus mycosis, the causal importance of fungal infections has been confirmed. The majority of all of the conditions that affect the paranasal sinuses have also recently been attributed to fungal infections, although neither the causal linkage of pathophysiological mechanisms, nor the positive effect of antimycotic treatment, has yet been demonstrated (63, 64).

Neutrophil granulocytes are associated with the development of nasal polyps in cystic fibrosis, and in Young's and Kartagener's syndrome. "Neutrophil-dominated polyps" are found in 15–20% of cases by histology. In cystic fibrosis, a genetic defect interferes with the sodium chloride ion pump in the epithelial cells of various organ systems, such as the bronchial mucosa, nasal mucosa and pancreas. The increased secretion of sodium ions and the reduced discharge of chloride ions causes thickening of the nasal secretion as a result of dehydration. The clinical picture of this condition is characterized essentially by recurrent infections with problem microorganisms such as *Pseudomonas aeruginosa* and *Staphylococci*. Kartagener's syndrome is a form of ciliary dyskinesia with an estimated incidence of 1 : 20 000. The ciliary immotility affects not only the respiratory epithelium, but also sperm motility. Besides bronchiectasis and nasal polyps, situs inversus is also observed in 50% of cases.

Young's syndrome is another condition caused by bronchiectasis, recurrent respiratory infection, and nasal polyposis, whose prevalence is estimated to be higher than that of cystic fibrosis and Kartagener's syndrome. In this condition, ciliary motility is not affected; rather, azoospermia is caused by a change in the ductus epididymidis that is ultimately responsible for 7.4% of cases of male infertility (43).

Clinical picture of sinusitis

The typical symptoms of acute sinusitis, the episodes of acute recurrent sinusitis or chronic sinusitis, differ quantitatively more than qualitatively, and according to time factors. In acute forms, the condition has a clear onset in time, and the symptoms are nasal obstruction, purulent rhinorrhoea, postnasal secretion, severe headache that typically projects into the paranasal sinuses,

and uncharacteristic headache, cough, a general lack of vitality, and depression. In children, vomiting may also be present, particularly in association with coughing episodes. In chronic sinusitis, the symptoms are often less severe, characterized mainly by obstruction and nonspecific headache (65). Although these symptoms are sensitive markers of sinusitis, only fever, facial flushing, and maxillary pain are specific to and therefore evidential of acute sinusitis (66). A purulent secretion from the nose is relatively typical of sinusitis and also has a high incidence (67), but patients with viral rhinitis can also have a purulent secretion, and patients with purulent sinusitis are free from rhinorrhoea when the ostia are blocked. Therefore, purulent secretion has a sensitivity of 72%, but only a specificity of 52% (68).

Whereas the above mentioned symptoms are regularly found in acute or recurrent-acute sinusitis, chronic sinusitis is clinically defined above all from the duration of the symptoms. Depending on the author and study group, a symptom duration of 8 weeks (69) to 12 weeks (65) is required for this definition to apply. However, since hardly anyone experiences completely consistent symptoms throughout the 2–3-month period, and since therapeutic interventions bring about symptomatic improvements, it is becoming increasingly common to define chronic sinusitis from the number of episodes per year (more than four, each lasting for 10 days) (5).

Besides nasal obstruction and discharge, an important symptom of nasal polyposis is impairment of the sense of smell. In patients with nasal polyps, hyposmia or anosmia were found preoperatively in 76% of patients (70), while only 58% with chronic sinusitis showed an impaired sense of smell (71).

Diagnosis of sinusitis

The diagnosis of sinusitis is based on the case history, clinical examination, and additional techniques such as imaging, allergy testing, and inflammatory parameters.

When taking the history, the typical symptoms of the patient should be recorded during spontaneous conversation and, if necessary, followed by questions on the most important individual symptoms. In a condition such as sinusitis, which follows a complicated time-course, a talk with the doctor can be supplemented—not replaced—by questionnaires. In one study, the symptoms of depression, disturbed sleep, nasal secretion, nasal obstruction, and hyposmia were recognized to be predictive of sinusitis (72, 73). The relative risks of sinusitis for a positive response to the following symptoms are: maxillary pain 2.9; no improvement on antihistamines or decongestants 2.4; purulent secretion according to the patient 2.2; and purulent secretion at rhinoscopy 2.9. These results (68) show that although adequate diagnostic certainty cannot be obtained by taking the history alone, some symptoms are nevertheless indicative. The

Table 3. Differential diagnosis of rhinosinusitis

Viral rhinitis
Allergic rhinitis
Seasonal
Perennial
Nonallergic rhinitis
Hyperreflexory rhinitis
Nonallergic eosinophilic rhinitis (NARES)
Rhinitis in pregnancy
Hypothyroidism
Drug-induced rhinitis
Nasal drop abuse
Cocaine abuse
β -blockers
Antihypertensive agents
Hormone preparations
Abnormalities
Ciliary dyskinesia
Cystic fibrosis
Nasal cysts
Meningocele
Meningoencephalocele
Rhinoaquorrhoea
Mechanical causes
Foreign bodies
Mucocoele
Pyocoele
Septal deviation
Concha bullosa
Polyps
Adenotonsillary hyperplasia
Benign and malignant tumors
Juvenile nasopharyngeal angiofibroma
Salivary gland tumor
Inverted papilloma
Meningeoma
Chordoma
Adenocarcinoma
Adenoidcystic carcinoma
Squamous cell carcinoma
Nasopharyngeal carcinoma
Malignant lymphoma
Aesthesioneuroblastoma
Secondary rhinitis/rhinosinusitis
Wegener's syndrome
Sarcoidosis
Immunodeficiency (inherited/acquired)
Dentogenic sinusitis
Paranasal sinus mycosis
Aspirin sensitivity
Specific infections

differential diagnosis of sinusitis also needs to be considered; important conditions are listed in Table 3.

During clinical examination, attention should be paid to any swellings and redness as well as any skin changes over the sinuses; patients are relatively frequently found to have halo eyes or discrete eyelid edema. Hypoplasia of

the bony middle part of the face also often accompanies chronic sinusitis. An inspection of the facial part of the skull should be followed by anterior rhinoscopy and posterior rhinoscopy. As a *sine qua non*, endoscopy of both nasal cavities and the nasopharynx with rigid optics is the gold standard in clinical examinations (74, 75). The patient should be given a decongestant nasal spray and a mucous membrane anaesthetic a few minutes beforehand. The examination shows all the structures of the nasal cavity (as well as the ostia of the paranasal sinuses), the structure, color and consistency of the mucous membrane can be assessed differentially, and tumoral masses can be detected at an early stage (76).

Currently the best procedure for imaging of the paranasal sinus system has proved to be CT scanning in a coronary and axial plane, or reconstruction (77). With modern generations of equipment, MRI scanning may be used as an alternative in isolated cases in the presence of inflammation (78). In individual cases, as well as for guidance purposes, and in the case of fractures and osteomas, conventional x-rays from occipitomeatal and occipitofrontal planes are indicated because of the better overall view. When interpreting the image, it should be considered that normal CT scan findings have proven to be pathological intraoperatively in up to 38% of cases (79).

However, any overinterpretation of pathological findings in the paranasal sinuses should be avoided, because these do also occur in the presence of uncomplicated viral infections (3). A variety of systems for the staging of CT findings have failed to reveal a correlation with the clinical symptoms, so at the moment they have no routine clinical significance (80).

Allergic rhinitis must be included in the diagnostic work-up because of its known incidence of up to 78%; a suitable test procedure is the prick test, with particular consideration of airborne allergens (81). The skin test can be supplemented by specific IgE determination. Microbiological studies are indicated particularly in the presence of a persistent purulent secretion when prior antibiotic treatment has proved unsuccessful. Leukocyte count and differentiation are the clinical laboratory parameters to be determined, particularly in the presence of acute events, while in chronic forms blood eosinophil levels are often elevated. In the presence of suspected Wegener's granulomatosis, the determination of antineutrophilic cytoplasmic antibody (ANCA) in combination is helpful (82). The role of nasal cytology is limited to support the diagnosis, particularly in the case of eosinophilic and neutrophilic rhinitis (83), because the method is hardly standardized. Valid standards have been achieved for the determination of nasal mediators (84); standard values for eosinophilic proteins can be given (85). To exclude ciliary dysfunction, the saccharin test is used for guidance (86), while confirmation may be provided by electron microscopy (87). Nasal biopsies are indicated in cases of suspected malignant growth, granulomatosis, and invasive fungal infections (88, 89).

Table 4. Basic and supplementary diagnostic tools

Basic diagnostic tools
Case history and clinical examination
Endoscopy of the nasal cavity and nasopharynx
CT scan in coronal and axial planes or reconstruction in chronic sinusitis or complications of acute sinusitis
x-rays in acute sinusitis only (from occipitomeatal and occipitofrontal planes)
Supplementary diagnostic tools
Allergy diagnosis
MRI scan for certain diagnoses (mycosis, extent of tumor)
Ultrasound
Microbiological studies
Leukocyte count and differentiation
Antineutrophilic cytoplasmic antibody (ANCA; if Wegener's disease suspected)
Cytology and nasal mediator determination in eosinophilic and neutrophilic rhinitis
Saccharin test, electron microscopy studies (ciliary dysfunction)
Nasal biopsies (malignant growths, granulomatosis, fungal infection)

To summarize, it can be stated that the diagnosis of sinusitis starts with the case history, is supported by the pillars of nasal endoscopy, imaging and allergy tests, and may be supplemented by additional techniques (Table 4).

Treatment

The information incorporated here is based on literature accessible through MEDLINE. The evaluations do not take account of the licensing of the medicinal products for sinusitis.

Decongestant nasal drops and oral decongestants

Paranasal sinus drainage and ventilation appears to be a major therapeutic goal in both acute and chronic sinusitis. However, decongestion using nasal decongestants has been investigated only sketchily in rhinitis, and hardly at all in sinusitis. A study that used MRI to document the decongestant effect was able to show only a short-lived effect of xylometazoline on the inferior and middle turbinate, and no effect at all on the affected mucous membranes of the maxillary and ethmoidal sinuses (90). Two studies in which decongestants were used together with an antibiotic for the treatment of chronic maxillary sinusitis in children showed no difference in therapeutic success vs. placebo (91, 92). A topical treatment study in chronic purulent rhinosinusitis (defined without x-rays) compared the combination of tramazoline and dexamethasone with placebo and the additional local application of neomycin. This combination afforded an advantage over placebo treatment for both active treatment groups, whereas concomitant antibiotic treatment produced no difference. Whether this effect was attributable to the decongestant or to the corticosteroid remains unanswered (93). There have been no placebo-controlled studies of acute sinusitis. However, antibiotic treatment and/or

nasal irrigation have been shown to be superior to nasal or oral decongestant treatment alone (oxymetazoline or phenylpropanolamine, respectively) (94, 95).

Oral and topical decongestants reduce nasal obstruction and provide symptomatic relief. Clinical experience shows that targeted decongestion in the middle meatus can be effective in the short term. Overall, however, there is no evidence of their efficacy in shortening the duration of hospitalization or in reducing the paranasal sinus symptoms in acute or chronic sinusitis.

Secretolytics

In the case of mucolytics or secretolytics, a distinction must be made between chemically defined preparations, such as ambroxol or acetylcysteine, and phytotherapeutic agents.

Although the former are often used as adjuvants alongside antibiotic treatment in sinusitis, there is no evidence that the treatment is beneficial (96). There have been no studies on sinusitis, either in the acute or chronic form of this condition, that provide evidence of a therapeutic effect. The situation is different with phytotherapeutic agents. Experimental animal studies of the prosecretory effect, and a double-blind clinical trial of acute sinusitis have been carried out with a chemically undefined extract of five phytopreparations (97). These suggest that additive therapeutic effects are achieved in acute sinusitis with administration of a phytopreparation as an adjunct to basic treatment with antibiotics and decongestant nasal drops. The situation regarding studies in chronic sinusitis is inadequate. A similar mechanism of effect has been confirmed experimentally for another preparation (98), although there is no proof of an improvement in the symptoms of the condition according to scientific criteria. Open-label studies or anecdotal reports also describe positive effects for countless other phytotherapeutic agents in sinusitis, albeit without any evidence by today's standards.

Although isolated controlled studies appear to confirm the efficacy of phytotherapeutic agents, no information is available on the actual active ingredient(s) or dose–effect relationships.

Topical corticosteroids in acute and chronic sinusitis

Acute and chronic sinusitis, as well as nasal polyps, are to be regarded as inflammatory conditions of the paranasal sinuses, which is why antiinflammatory treatment of the mucous membrane is a rational approach. Although the penetration of topical, intranasally administered corticosteroids into the paranasal sinuses is not proven, a therapeutic effect may be explained by the antiinflammatory effect in the region of the ostiomeatal complex or middle meatus. Corticosteroids achieve antiedematous and strong antiinflammatory effects by reducing the synthesis and release of a series of cytokines and adhesion molecules, which are up-regulated in sinusitis. This is

Table 5. Studies of topical steroids in acute sinusitis

Study (reference)	Antibiotic	Topical steroid (treatment length)	Significant effect on
Meltzer 1993	Amoxicillin/clavulanic acid	Flunisolide 3 weeks	Obstruction, global symptom score
Barlan 1997	Amoxicillin/clavulanic acid	Budesonide vs. placebo 3 weeks	Cough, secretion
Meltzer 2000	Amoxicillin/clavulanic acid	Mometasone 3 weeks	Global symptom score, headache, obstruction, facial pain

Table 6. Studies of topical steroids in chronic sinusitis

Study (reference)	Antibiotic	Topical steroid (treatment length)	Significant effects on
Cuenant et al. 1986	Neomycin	Tixocortol vs. placebo 11 days	Obstruction
Qvarnberg et al. 1992	Erythromycin	Budesonide vs. placebo 3 months	Nasal symptoms, facial pain, cough
Lund 2002	—	Budesonide vs. placebo 5 months	Overall symptoms, PNIF, quality of life

PNIF, peak nasal inspiratory flow.

particularly true for IL-8, IL-1 β and IL-6 in acute sinusitis, and IL-3 and IL-8 in chronic sinusitis (99, 40); the release of leukotrienes and prostaglandins is also reduced. Therefore, topical corticosteroids inhibit the mostly neutrophilic inflammatory response without interfering with immunological defence mechanisms.

In acute sinusitis, there have been three controlled studies of the use of topical corticosteroids as adjuncts to an antibiotic (amoxicillin/clavulanic acid) (Table 5). Meltzer et al. (100) reported on a study which, in addition to 3 weeks of antibiotic treatment, used flunisolide (3 $\times$ 50 μ g daily) for 7 weeks *vs.* placebo. At the end of the 3-week treatment phase, nasal congestion and the total score for nasal symptoms, including headache and facial pain, was significantly lower in the corticosteroid group. Similar observations were made by Barlan et al. (101) in children from aged 1–15 years with acute sinusitis. Besides antibiotic treatment, the patients received budesonide 2 $\times$ 200 μ g daily *vs.* placebo for 21 days. After only 2 weeks, the symptoms of nasal secretion and cough were significantly reduced in the active-substance group. The largest and most comprehensive study was conducted in over 400 patients with acute sinusitis (102). Besides antibiotic treatment, which again was identical in both groups, mometasone 400 μ g administered in the morning and evening; this was compared with a placebo nasal spray over a 3-week period. The patients had to reach a minimum score of typical sinusitis symptoms and also have a pathological CT scan. After treatment, those treated with mometasone had a significantly lower total symptom score, less headache and facial pain, as well as significantly lower nasal obstruction; the scores for secretion and cough also tended to be better. The reduction in symptoms was independent of the presence of an allergy, and the side-effects were comparable in both treatment groups. Interestingly, a control CT scan at the end of treatment showed a reduction in swelling of the mucous membranes, particularly in the region of the middle meatus and infundibulum, after steroid treatment.

In all of the studies, concomitant administration of topical corticosteroids was superior to antibiotic treatment alone, and significantly improved the typical symptoms of the condition, including nasal blockage and facial pain/headache. Therefore, the additional antiinflammatory effect of topical corticosteroid treatment, as an adjuvant to an antibiotic, can be regarded as confirmed in acute sinusitis.

There have been three controlled studies of the use of topical corticosteroids in chronic sinusitis (Table 6). An initial study compared a combination of topical steroid/topical antibiotic with a topical antibiotic alone in 60 patients with chronic sinusitis, and achieved significantly better decongestion with the combination after only 11 days of treatment (103). Qvarnberg et al. (104) studied the effect of budesonide 400 μ g daily *vs.* placebo in 40 patients with chronic sinusitis, treated at the start with a maxillary sinus puncture as well as erythromycin for 7 days. The steroid-treated group showed a significant improvement in coughing and a significant reduction in nasal symptoms and facial pain. At the same time, the radiological findings in this group were clearly, albeit not significantly, improved. A recently presented placebo-controlled study in 167 patients with chronic sinusitis confirmed a significant improvement in the symptoms, objective nasal air passage, and quality of life on nasal steroid monotherapy *vs.* placebo for 20 weeks (105).

In chronic sinusitis, there is a need for further controlled studies involving imaging techniques. The available results confirm a moderate treatment effect on the symptoms of chronic sinusitis due to the treatment with topical corticosteroids in patients who would otherwise have had to undergo surgery.

Topical corticosteroids in nasal polyposis

Nasal polyps associated with eosinophilia, in particular, are characterized by a severe inflammatory response marked by cytokines such as IL-5 and chemokines such

as eotaxin and RANTES. Corticosteroids typically exert a particularly impressive effect on eosinophil-associated inflammation, which is why the parameter of “eosinophilia” is frequently cited as an indicator for the use of this medicinal product. It has been shown that steroids induce inflammatory cell apoptosis, and the extent of the suppressive effect on IL-5 production from T-cells is believed to be a crucial parameter (99, 106).

The symptomatic treatment of nasal polyps has already been established in studies with the first topical corticosteroids (107, 108). In recent years, clinical observations have increasingly been supported by objective parameters (rhinomanometry, rhinometry, peak nasal inspiratory flow (PNIF), and MRI scans) (109–117). In some studies, the relapse rate, or time to relapse, after surgery has been significantly improved or extended, although these studies did not last longer than one year (118, 119). The dosage of topical steroid used in the studies is often above that recommended for allergic rhinitis.

The use of topical corticosteroids for several months in untreated nasal polyps, as well as in therapeutic attempts to avoid surgery and for relapse prevention after surgical treatment (6–12 months), is therefore to be recommended. Several months of postoperative steroid treatment also seems to produce improved wound-healing; controlled studies of wound-healing after sinus operations are desirable.

Systemic corticosteroids

Systemic corticosteroids in decreasing dosages have been given for the treatment of nasal polyposis, in most cases followed by several months of topical steroid treatment (90 days to 24 months) (120–122). In approximately 80% of cases, it was possible to delay operations beyond this time; however, relapses were recorded in over 50% of patients. In one study evaluated by CT, an improvement in the CT scans was noted in 72% of polyposis patients treated with oral steroids; however, most cases reverted to the baseline findings after 5 months (123). Administration of oral steroids may facilitate surgery.

Antihistamines

In medicine as practised in English-speaking countries, antihistamines are used as an adjuvant treatment in sinusitis. This usually occurs in a fixed combination with sympathomimetics, whose local decongestant effects have a positive effect on some of the symptoms of sinusitis (124). However, the first-generation products caused considerable side-effects, including sedation and dry mouth (125, 126). For the second-generation antihistamines, one methodically flawless study has been conducted, which showed the benefit of giving the antihistamine concomitantly with antibiotic treatment during acute exacerbations in allergic patients with rhinosinusitis (127). Proof of efficacy in sinusitis without

allergic rhinitis as the underlying condition has not yet been furnished.

Bacterial lysates

Prophylactic use of bacterial lysates, together with basic treatment with antibiotics, mucolytics and decongestant nasal drops, appears to reduce the renewed onset of rhinosinusitis in childhood, at least for the duration of treatment (128, 129). In a placebo-controlled, randomised study of oral bacterial lysates in infants, there was a significant reduction in the number of reinfections and the number medicinal products needed in a 6-month observation period following “subacute” sinusitis (130).

Cough and cold remedies

Cough and cold remedies have not been systematically studied in sinusitis. Therefore their use cannot be scientifically justified.

Antimycotics

Current treatment recommendations for noninvasive forms of paranasal sinus mycosis consist of a combination of functional surgery and local or (if necessary) systemic steroid treatment (64). No results are available from controlled studies on the use of antimycotic treatment in chronic sinusitis. There have only been reports of individual observations in noninvasive forms (131) and invasive mycosis in immunocompromised patients (132).

Antibiotics

Evidence-based data on the efficacy of antibiotic treatment in acute and chronic sinusitis are often based on a plethora of studies that have nonuniform designs and use nonstandardized terminology and definitions regarding the clinical picture of sinusitis; such discrepancies make it difficult to evaluate the data. Furthermore, there are still considerable gaps in our knowledge of the pathophysiology of sinusitis. Even the significance of the commensal bacteria that colonize the nose and paranasal sinuses, and their relative pathogenicity for the onset of chronic sinusitis, is not yet established (29, 30).

As viral rhinosinusitis also involves the sinuses and causes symptoms similar to acute sinusitis complaints, it is often difficult to differentiate both diseases on the basis of symptoms only (3). In primary care, the majority of community-acquired cases diagnosed as acute sinusitis may actually represent viral rhinosinusitis, and should not be treated with antibiotics to help avoid bacterial resistance. Primary antibiotic treatment is indicated, if at least one of the following symptoms or conditions is present: maxillary or frontal pain, purulent secretion at rhinoscopy, orbital or meningeal complications of sinus-

itis, sinusitis in patients at risk (immunocompromised, or intubated).

Generally speaking, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* are regarded as the trigger microorganisms in acute bacterial sinusitis. In immunocompromised patients, problem microorganisms such as *Pseudomonas aeruginosa*, coagulase-negative *Staphylococcus aureus* and anaerobic bacteria are detected more often. However, in the literature, the prevalence of anaerobic microorganisms in acute sinusitis varies from 80–100% (133) to 0–25% (24, 134). On the one hand, this situation is attributed to the collection technique and the type of transport medium; on the other hand, the spectrum of microorganisms on the mucous membrane, changed by prior antibiotic treatment, also plays a part. For example, it has been shown that the spectrum of microorganisms in sinusitis, in which *S. pneumoniae* and *M. catharrhalis* were initially detected in the aspirate, changed after antibiotic treatment to a mixed flora with *Fusobacterium*, *Porphyromonas* and *Peptostreptococcus* (135), and resistant microorganisms were produced (136).

Although some 1800 studies on the antibiotic treatment of acute sinusitis have already been published, only about 32 meet the Cochrane Board criteria for placebo control, statistical analysis, sufficient sample sizes, and the description of clinical improvements or success rates (137, 138).

The effect of penicillin or amoxicillin and lincomycin vs. placebo was confirmed in acute sinusitis in three studies (95, 139, 140) involving 456 patients. The resolution rate was statistically significantly higher for these antibiotics than for the placebo control group.

Another 10 studies ($n = 1590$ patients) compared the treatment of acute sinusitis with nonpenicillins vs. penicillin derivatives. In these studies, the nonpenicillins (cephalosporins, macrolides, minocycline) were equivalent to the penicillin derivatives in the treatment of acute sinusitis.

The effect of nonpenicillin derivatives vs. amoxicillin/clavulanic acid was investigated in 10 studies. In a population of 3957 patients, it was shown that the resolution rate in terms of the clinical picture of acute sinusitis was no different in either treatment group. Stated by way of example in a study by Sterkers et al. (141) the clinical success rate for patients treated with 1×400 mg cefibuten daily for 8 days was 83%. By comparison, no statistically significantly higher clinical success rate was recorded for the treatment group that received amoxicillin/clavulanic acid (500 mg/125 mg) $3 \times$ daily. However, the rate of side-effects in the patients treated with amoxicillin and clavulanic acid was stated to be significantly higher (142–159).

The efficacy of the antibiotic treatment of acute sinusitis can therefore be deduced using evidence-based medicine. The effect of penicillin and amoxicillin as well as nonpenicillin derivatives during a treatment period of

7–14 days is proven, with the spontaneous remission rate for acute sinusitis being cited as 48–80% (160). Owing to the bacterial resistance, cephalosporins are recommended as an alternative to amoxicillin (if necessary, with clavulanic acid) (161).

It is significantly more difficult to evaluate the efficacy of antibiotic treatment in chronic sinusitis compared to acute sinusitis, because of the conflicts in terms of terminology and definition of the clinical picture of chronic sinusitis in the literature. The duration of symptoms ranges from more than 10 days to 3 months, and the persistent rhinorrhoea that characterizes chronic sinusitis is described as ranging from mucous to purulent. In most studies, no radiological diagnosis, such as computer tomography, has been performed to confirm the diagnosis of chronic sinusitis. It is not possible to differentiate between a viral cold that might be accompanied by a secondary bacterial superinfection and a primary bacterial infection of the paranasal sinuses. For this reason, rhinorrhoea was used as the leading symptom for the diagnosis of pediatric rhinosinusitis in particular (145), and the indication for antibiotic treatment was based on this symptom. Whereas, in France, children with purulent rhinorrhoea are treated with antibiotics at an early stage, in the USA antibiotics are prescribed only when the condition has persisted for 10 days and a secondary bacterial infection is assumed. 90% of children between 2 and 6 years of age, and 70% of older children with persistent rhinorrhoea show radiological signs of sinusitis (162).

Microbiological studies of 265 adult patients with chronic sinusitis have demonstrated the presence of Gram-negative bacilli, coagulase-negative Staphylococci and *Staphylococcus aureus* as the most common microorganisms in the paranasal sinuses, compared with a healthy control population (29). Coagulase-negative Staphylococci were isolated as often in patients as in a healthy control population. Patients who take systemic steroids show an increased incidence of coagulase-negative Staphylococci.

Data is available from five studies that evaluated the efficacy of antibiotic treatment in persistent rhinorrhoea, and they describe a weak effect of antibiotic treatment in the short to medium term (126, 145, 162, 163, 165).

A recent study by Otten et al. (91) failed to demonstrate any long-term efficacy of antibiotic treatment in children with chronic sinusitis.

In a prospective study by Legent et al. (166), 251 adult patients with chronic sinusitis were treated with ciprofloxacin vs. amoxicillin/clavulanic acid. The chronic sinusitis resolution rate was significantly higher in the patients treated with ciprofloxacin, although there was no statistical difference in the bacterial eradication rate.

To summarize, antibiotic treatment cannot currently be considered effective in chronic sinusitis in the sense of bringing about a resolution of the condition.

Table 7. Summary of the indication and extent of interventions in the paranasal sinuses

Operation	Indication
Maxillary sinus puncture	Isolated treatment-resistant maxillary sinusitis
Beck's drill	Isolated treatment-resistant frontal sinusitis
Infundibulotomy	Anterior ethmoid disease ± involvement of the maxillary and frontalsinuses
Ethmoid surgery	Ethmoid disease with involvement of the posterior ethmoid cells
Endonasal maxillary sinus surgery	Maxillary sinus cysts, severe maxillary sinusitis
Endonasal (transseptal) sphenoid sinus surgery	Sphenoidal sinusitis
Conchotomia media (lateral)	Concha bullosa media
Conchotomia inferior	Irreversible turbinate hyperplasia
Septumplasty	High septum deviations, interference with the middle meatus of the nose
Extranasal ethmoid and frontal sinus operation	Large mucocoeles, trauma, tumors
Radical procedures (Caldwell–Luc, Moure, Midface degloving)	Large and/or malignant tumors

Table 8. Therapeutic recommendations in acute and chronic sinusitis

Treatment	Acute sinusitis (evidence level)	Chronic sinusitis (evidence level)
Decongestant nasal drops	No evidence of efficacy* (symptomatic treatment of nasal obstruction effective)	No evidence of efficacy*
Secretolytics	No evidence of efficacy*	No evidence of efficacy*
Phytotherapeutic agents	Individual preparations may be helpful† as adjuvant treatment	No evidence of efficacy*
Antibiotics	Recommended‡: amoxicillin, 2nd and 3rd general cephalosporins, aminopenicillin + beta-lactamase inhibitors; alternatives: macrolides, cotrimoxazole, clindamycin, doxycycline, fluorquinolone (Ia, Ib)	No evidence of efficacy*
Antimycotics	No evidence of efficacy*	No evidence of efficacy*
Antihistamines	Recommended‡ in underlying allergic condition (Ib)	No evidence of efficacy*
Topical steroids	Recommended‡ as adjuvant treatment (Ib)	Recommended (Ib)
Miscellaneous (cough + cold remedies)	No evidence of efficacy*	No evidence of efficacy*
Analgesics	Recommended‡ for pain treatment only	Recommended for pain treatment only
Bacterial lysates	No evidence of efficacy*	May be helpful†(Ib)

Statement of evidence (category of evidence (Shekelle et al. (179)). Ia: evidence from meta-analysis of randomised controlled trials; Ib: evidence from at least one randomised controlled trial; IIa: evidence from at least one controlled study without randomization; IIb: evidence from at least one other type of quasi-experimental study; III: evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies and case-control studies; IV: evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

* No evidence of efficacy: the use of this medicinal product does not appear expedient according to the literature or clinical experience.

† May be helpful: clinical studies appear to confirm the efficacy of the medicinal product but, owing to its nondefined or nontargeted composition, clinical doubts have been raised; conclusive evaluation not possible at this time.

‡ Recommended: the efficacy of the medicinal product is sufficiently proven and appears to be clinically expedient.

Surgical interventions

Surgical treatment of sinusitis is indicated when conservative treatment has brought little or no lasting improvement in the symptoms or when the patient refuses further conservative treatment (Table 7). Absolute indications for surgery are orbital complications (167), endocranial complications (168) and suspected septic complications (169). A further absolute indication for surgery is the clinical suspicion of a malignant growth (170). In inflammatory conditions, surgical treatment is a relative indication (171).

One of the simplest and least invasive methods for the surgical treatment of sinusitis is aspiration. Probably one of the most common methods is sharp maxillary sinus puncture, indicated to relieve maxillary sinus empyema, but it is ill-suited for the treatment of chronic sinusitis

(172). Drainage is also an expedient method in acute frontal sinusitis (173).

With the development of nasal endoscopy (174) and the surgical techniques that this has made possible (175), the move away from the classical surgical techniques in the treatment of sinusitis, such as Caldwell–Luc, has begun (176). The aim of treatment is to restore the mucociliary clearance and ventilation of the paranasal sinuses (177). The approach common today is functional endoscopic sinus surgery, which essentially involves surgery to the middle meatus (42). The affected part of the mucosa is removed, the exact amount varying according to the individual, and paranasal sinus drainage and ventilation are restored once the wound has healed. The result of the operation depends on the severity of the condition (178): minor lesions heal more easily than major ones. Nasal respiration and mucociliary clearance

are improved following surgery (180), and the sense of smell can also be enhanced in this way (181). The quality of life following paranasal sinus surgery improves at a social level (182) and in relation to all of the other organ-specific symptoms (183). The complications of the technique mainly involve injuries to the orbits and dura (184). For this reason, the treatment should be performed only by experienced, well-trained surgeons in appropriately equipped centres. The techniques are currently undergoing continuous refinement, with navigated and powered surgery (185), the aim being to further minimize tissue

trauma and therefore perioperative morbidity. The use of new instruments is also bringing about an improvement in this area (186).

Therapeutic recommendations

Table 8 presents recommendations for the use of different groups of medicinal products in acute and chronic sinusitis (including an evaluation of the available literature by evidence categories).

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