T. Metin Önerci
Berrylin J. Ferguson
Editors

Nasal Polyposis

Pathogenesis, Medical and Surgical Treatment

Springer

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Foreword

Having been asked to write a foreword for a book entitled “Nasal Polyposis” the first question that comes up is: Is it really necessary to have a new book on nasal polyposis? The answer is of equal spontaneity: Yes.

More than 30 years ago, Rhinologists became for the first time happier treating nasal polyposis as the topical steroids made the conservative treatment easier, and the new Hopkins rod lens system, with its great visualization facilities, aided new consolidated findings in regard to early diagnosis. In addition, when compared to the classic, radical procedures, which are more than 100 years old, surgical treatment could include many more functional considerations thus avoiding mutilating side effects and late complications, such as mucoceles. Our generation did not like the classic procedures as we knew that most of these patients will come back. Due to the improved clinical diagnostics in particular, a tremendous progress in imaging the indication for surgery was made, aiding a clear diagnosis.

Due to these factors the therapeutic results improved dramatically and Rhinology became a rising star in Otorhinolaryngology.

On the other hand, the only achievement of our therapy is a symptomatic improvement in the patient with polyposis disease as the therapy shrinks polyps and improves the drainage of the sinuses, opening a better way for medicinal treatment. So far an effective causal therapy for nasal polyposis has not been established.

The knowledge about epidemiology, etiology, pathogenesis, and pathophysiology of nasal polyposis has increased in many aspects but a comprehensive summary of the present status has been missing.

We have to thank both the editors for having put together a harmonic team of authors who are basically scientists, experienced clinicians, and surgeons, and the list of these authors reads like a who is who in Rhinology. Globalization and international cooperation have facilitated the sharing of basic research and comparing of therapeutic results across the globe and this has increased the chances of finding the deficits of the treatment and reducing them.

Everything about why polyps develop and how to treat them can be found in this book. Another great advantage of this book is that controversial issues such as fungal-induced inflammation and Staphylococcus aureus-derived Superantigens in nasal polyp disease or functional endoscopic sinus surgery and nasalization are also discussed.

Of specific importance is the last chapter dealing with the evaluation of surgical treatments leading us further to solid evidence-based judgment of what we are doing.

I am sure this great compilation of knowledge will be welcomed and appreciated by the interested reader and will work as a basis of future progress in this fascinating field of Otorhinolaryngology.

Hannover, March 2010 Wolfgang Draf

Preface

We are pleased to present the First edition of *Nasal Polyposis* compiled of contributions from world renowned international experts on a myriad of etiologic and therapeutic aspects of this complex disorder. While nasal polyposis (NP) represents the most apparent manifestation of CRS and it is standard to categorize CRS regarding presence or absence of NP, NP is a diverse disorder with multiple causes and triggers.

We have organized this book in the first section to reflect the history, epidemiology, and inflammatory characteristics, followed by tools for diagnosis – pathology and radiology. While some purposed CRS causes such as biofilms, fungi, and superantigens are not confined to NP, they nevertheless may contribute to inflammation in NP and these and other etiologic topics are addressed by experts in the field in the following section. Fungal cause of CRS inflammation is controversial and we present two chapters on this reflecting two points of view.

Other disorders are known for their association with NP and include association with asthma and lower airway disorders, systemic vasculitis syndromes, and cystic fibrosis. A chapter is also devoted to the differential diagnosis of NP in children and preceeds special aspects of NP evaluation including olfaction and nitric oxide assessment.

The second half of this book is devoted to therapeutic approaches to NP. The medical therapies of steroids, antibiotics, antifungals, and aspirin desensitization are each addressed in their own chapter. The treatment of NP has been referred to as sandwich therapy by my friend and a contributor, Wytske Fokkens MD, PhD. This reflects the need for medical therapy before and after the surgical therapy which is sandwiched between.

From the first chapter of this book we know that surgical therapy for NP dates back at least to the fifth century BCE, and Hippocrates. The last section of this book returns to surgical methods, including endoscopic sinus surgery, nasalization, aggressive sinus marsupialization, and the modified Lothrop procedure.

Despite medical interventions and the most brilliant surgery, every rhinologist and every expert has patients with recalcitrant or rapidly recurrent disease. There is still much to understand in the management of this complex and diverse disorder. We hope this book will allow you to be the best practioner possible in the care of your patient with NP.

This book would not have been possible without our outstanding contributors. Our two associate editors Harshita Pant MD, PhD now in Adelaide, Australia and Brad Otto, now at Ohio State University, USA were tireless in editing and smoothing

translations across these many chapters. This book would not have been possible without them and we thank them wholeheartedly.

Around the globe we pursue a common goal – better care and understanding of our patients' nasal polyposis. We may have different opinions on cause and management, but that is true in any field in which causes and best management are still not known. I hope you find the multiple viewpoints a stimulant to questioning and continuing research as well as a guide and help in investigation, categorization, and treatment of nasal polyposis.

21 June 2010

T. Metin Önerci
Berrylin J. Ferguson

Contents

History of Nasal Polyposis

1

Janaki Emani and Fuad M. Baroody

Core Messages

- Polyps were first reported about 4,000 years ago.
- Reported across several civilizations.
- Diagnosis and treatment revolutionized at the end of the twentieth century with the development of computerized tomography scans and endoscopy.
- Corticosteroids are the most commonly used agents for treatment.

1.1 Introduction

Nasal polyps were first recorded approximately 4,000 years ago. Over the years, there have been significant advances in the understanding of the incidence, epidemiology, and pathophysiology of polyps. The means of diagnosis and medical and surgical treatments have also undergone a major revolution. This chapter reviews the chronological history of nasal polyps, their diagnosis and pathophysiological associations, and the historical milestones that shaped the management of polyps as it is practiced today.

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1.2 The History of Rhinology and Nasal Polyps

The earliest record of nasal polyps is found in Egyptian literature of approximately 2,000 years BCE [23]. Rhinologic procedures dating to 700 BCE are depicted in the ancient Hindu and Egyptian medical texts. One of the great Hindu surgeons, Susruta, who practiced in the fifth century, was the founder of modern day rhinoplasty and nasal reconstructive flaps. In 1500 BCE, the ancient Egyptians were known for their familiarity of and dexterity in the nasal cavity as they routinely removed the cranial contents through the nose to prevent facial disfiguration during the mummification process. Though Susruta undertook advanced nasal surgical procedures, Hippocrates (460–370 BCE) is better known as the father of rhinology and medicine, due to his influence during the apex of Greek civilization, in approximately the fifth century BCE. In addition to establishing the Hippocratic oath, Hippocrates also observed and documented medical afflictions related to otolaryngology, including coryza, pharyngitis, intubation, uvulotomy, tonsillectomy, nasal fractures, epistaxis, sinusitis, and nasal polyps [16].

Hippocrates referred to the "nasal growths" as "polypus" due to their resemblance to the sea-polyp, and this name has persisted to this day [23]. Hippocrates and other renowned physicians including Claudius Galen, Paulus Aegineta, and Fabricius Hildanus were known to have treated nasal polyps in their time.

1.3 Etiology and Pathophysiology

Polyps were initially thought to be due to a state of thickened or viscous bodily humors. In the early first century AD, Celsus and others noted that nasal polyps

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were affected by moist weather and warm seasons [16]. The theory that these nasal masses were a manifestation of systemic disease prevailed until the early seventeenth century, when local trauma was hypothesized to contribute to the condition. Boerhaave, in 1744, was among the first to surmise that these growths resulted from elongation of the linings of the sinus membranes [23]. About the same time, Manne and Heister suggested that polyps occurred secondary to obstruction of the ducts of mucous glands.

The nineteenth century was also fraught with controversies regarding the etiology of nasal polyps. Virchow [20] and his pupils thought that these masses were primary tumors including myxomas and fibromas. Eggston and Wolff [9] viewed them as passive edema of mucosa, while others believed in an infectious etiology including sinusitis or osteitis [22]. In 1843, Frerichs and Billroth proposed that polyps were truly a hypertrophy of normal sinonasal mucosa, as the epithelium covering the polyp was similar to the mucosa of the originating sinus [23].

A systematic investigation of etiological associations began in the early twentieth century. In 1933, Kern and Shenck proposed a relationship between allergy and nasal polyps [13]. They found that the incidence of nasal polyps was 25.9% in patients with allergic rhinitis compared with 3.9% in a nonallergic population. They also noted that the ethmoid air cell system was the most common target for the inflammatory response and that polyps frequently originated from this site. Eggston's [9] concept of the etiology of polyps is that they arise due to basic vascular changes in the nasal mucosa induced by repeated attacks of sinusitis, periphlebitis, and obstruction of return flow of interstitial tissue fluid leading to passive congestion and edema. Advances in immunohistochemistry and immunobiology in the 1940s led to the first description of the predominance of eosinophil and lymphocyte populations in polyps. Anderson and Bing have shown the polyp stroma to be proteinaceous exudate, while Weisskopf and Burn [21] considered that it has acid mucopolysaccharides. Berdal [3] states that accumulation of reagins and ample edema in polyps is due to allergic inflammation. On the other hand, Tandon et al. [17] observed no difference in the histological appearance of allergic and infective polyps.

Kern and Schenck's initial report of the strong relationship between allergies and nasal polyps has been questioned by more recent investigations. Capllin et al. examined 3,000 patients with evidence of atopy and found that only 0.5% had nasal polyps [7]. Following their findings, Bunnag et al., reported an incidence of 4.5% of nasal polyps when 300 patients with allergic rhinitis were examined [5]. These, and other, studies have led most allergists and rhinologists to the conclusion that allergic rhinitis may not be a primary causative factor in nasal polyps. Furthermore, Bonfils and colleagues have shown that the presence of allergy does not modify symptoms of nasal polyposis or their response to medical treatment [4]. Several other theories about the etiology of nasal polyps are under investigation today: bacterial infections, mucosal inflammation from bacterial superantigens, fungal inflammation, genetic factors (cystic fibrosis, primary ciliary dyskinesia), and aspirin hypersensitivity [5, 6, 8]. The association between cystic fibrosis and polyps was first noted in 1959 by Lurie, and soon thereafter, Schwamann described its relationship with sinusitis [10].

The medicinal properties of acetylsalicylic acid (ASA) have been known for over 3,500 years. Ancient Chinese, Indian, and Egyptian healers prescribed ASA, as extracts from tree bark and leaves, for a variety of symptoms including fever, pain, and labor. In 1880, Felix Hoffman, an employee of a dye manufacturing company owned by Friedrich Bayer, used waste components of the factory to synthesize a stable form of salicylic acid powder. Over the course of 1 year, Hoffmann purified the substance until he produced a pure form of ASA. Soon after its introduction in 1899, aspirin sensitivity was reported by Hirshberg, a German physician. As early as 1929, reports of bronchospasm were noted in aspirin-sensitive patients undergoing polypectomy. Samter and Beer in 1969 reported the triad of aspirin sensitivity, nasal polyps, and asthma [24].

1.4 Diagnosis of Nasal Polyps

Contrary to one's expectation, historical description of polyp diagnosis was not limited to those that protruded through the nares or those that caused physical nasal deformity. In Egyptian literature, Samuel noted that "a polyp shows itself by a bad smell of the nose." Hippocrates describes polyps as "sacs of phlegm that cause nasal obstruction and derange the sense of smell." Celsus likened polyps to "the nipples of a woman's breast" and wrote in his case reports that "large polyps dangled into the pharynx" and "on cold and damp days strangulate a man," depicting large polyps that obstructed the choanae and oropharynx [23].

Visualization of the anterior nasal cavity was enhanced with the development of the nasal speculum. While cauterizing patients for epistaxis, Hippocrates used a crude tubular speculum. A similar prototype of tubular speculum was also used by Hindu Ayurvedic doctors in 500 BCE [16] and by Haly Abbas (940–980), a prominent figure in Islamic medicine. These early speculums were modifications of instruments used for gynecological and rectal examinations. Fabricius Hildanus (1560–1634) constructed an aural speculum, which closely resembles the modern day nasal speculum. This instrument was molded to its current specifications in the eighteenth century by Peret and Kramer [22].

Sir Morell Mackenzie, who was responsible for establishing Otolaryngology as a unique subspecialty, wrote that Levert, a French obstetrician, used a speculum of polished metal that reflected sunlight to view polyps and tumors of the ears, throat, and nostrils [2]. Until the sixteenth century, candlelight was primarily used to examine the anterior nares. In the 1570s, Aranzii used a glass flask filled with water and candles to intensify the light directed into the patient's nose. In 1829, a young physician named Benjamin Guy Babington presented a series of flat and angled handheld mirrors at the Hunterian Medical Society and demonstrated the ability to reflect sunlight to the back of the pharynx. He also used a tongue retractor to obtain an unobstructed view. Although Babington did not publish the success of his instrument in viewing the structures of the larynx, other authors over the mid-1800s did mention this device and his techniques [22].

Alfred Kirstein (1863–1922) was responsible for the introduction of artificial light to the field [15]. The instrument consisted of a flat spatula illuminated by a urologic hand lamp. Subsequently, Kirstein developed the first headlight that remarkably resembles those that are in use today (Fig. 1.1). Perhaps of greatest significance was the advent of both flexible and rigid fiberoptic endoscopes in the late 1900s, which have revolutionalized the examination of the upper aerodigestive tract in otolaryngology.

The development of X-ray techniques in the nineteenth century also influenced the diagnostic algorithm of polyps. The Caldwell, Waters', and submentovertex views became essential in identifying the opacification of the sinuses and bony abnormalities. Computerized axial tomography (CAT) that was developed by Hounsfield in 1970 surpassed conventional radiographs and provided superior imaging of the sinuses. Although CT scans are not essential for the diagnosis of most nasal polyps, they are important in determining the extent of sinonasal disease and planning surgical treatment.

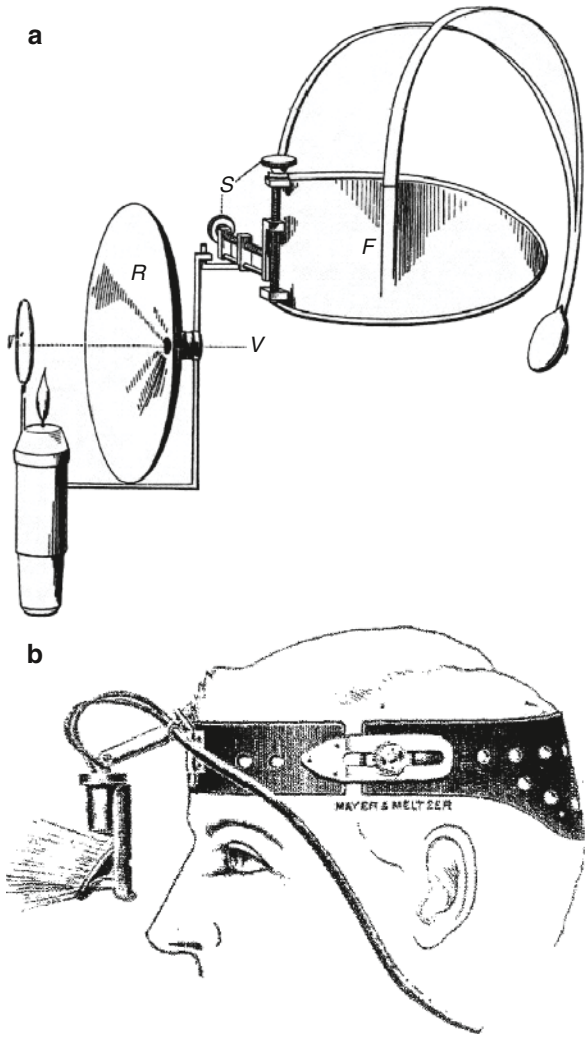

Fig. 1.1 Early urologic head lamp which led to the design of the laryngoscope (**a**). Kirstein subsequently designed the first head lamp which incorporates the design of the urologic lamp but utilizes artificial light (**b**). *S* screws by which the reflector can be made to move, *R* reflector, *V* line of vision. (Adapted from Bailey [2] and Weir)

1.5 Treatment of Nasal polyps

The recurrent nature of nasal polyps was known since the Hippocratic era. Hippocrates wrote about patients who required multiple treatments and recognized that even after performing a directed excision, additional

therapy was needed to prevent redevelopment of polyps. Thus throughout, till today, polyps are treated both medically and surgically.

1.5.1 Medical Treatment

Hippocrates used nasal packs and tampons coated with honey and copper salts in an attempt to curtail the recurrence of polyps; however, the effects of this treatment are unknown. A Roman physician, Claudius Galen, treated polyps primarily medically with oily applications, goose fat, calf tallow, and irritating medications like turpentine [23]. No further significant descriptions of the medical management of polyps were found until the twentieth century [19].

Kern and Schenk's description of the relationship between allergies and polyps paralleled the discovery that histamine caused allergic reactions. Italian pharmacologist Daniel Bovet synthesized antihistamines during much of the 1930s, and in 1944, the first nontoxic antihistamine became available to the public. Thus, antihistamines were used as a primary and postsurgical treatment for polyps. Evidence for a helpful role of antihistamines in nasal polyposis is lacking and they are now primarily used to treat concomitant allergic rhinitis, if present. The current mainstay of medical therapy is corticosteroids.

The discovery of steroids represented a new era of treatment. Anabolic steroids were first isolated and chemically characterized during the 1930s and topical and systemic steroids were used for the management of nasal polyps since the 1970s [14, 18]. Van Camp was one of the first to describe the use of preoperative oral steroids to shrink the polypoid tissue and facilitate removal [18]. Intranasal steroids are very frequently used in the treatment of nasal polyposis and have been shown to reduce the size of polyps, delay recurrences, and decrease the need for repeat surgery [1].

1.5.2 Surgical Treatment

The history of the surgical treatment of polyps is most intriguing and gruesome. In the Treatises, Hippocrates delineated several methods he used to remove polyps. One method involved using a soft sponge, large enough to fill the nasal cavity that was fastened to several pieces of string. Then a forked flexible metal probe was passed through the nostrils and into the pharynx with the strings tied to the forked end of the probe. The sponge was then pulled through the oral cavity, pushing the polyps out [23]. The sponge method was used to remove polyps until the 1880s. For larger polyps, Hippocrates used a crude snare by fashioning a loop of sinew around the base of the polyps and passing one end through the pharynx, which effectively avulsed the polyps (Fig. 1.2). He also used a hot iron passed through the nostrils to cauterize polyps. After these treatments, Hippocrates placed stents smeared with oil, honey, and copper powder in the nasal cavities [23].

Roman medicine was dominated by Aulus Cornelius Celsus, also known as the Roman Hippocrates, who wrote the book series "De Medicina." Celsus frequently treated polyps with caustic agents, but also used a sharp spatula-like instrument to separate the polyp from the bone and removed it with a hook-like instrument from the nose [16]. The "knotted-string method" was utilized in the sixth and seventh centuries by Paulus Aegineta, who wrote: "taking a thread of moderate thickness, like a cord, and having tied knots upon it at a distance of two or three finger breadths, we introduce it into the nose via a double headed speculum upward to the ethmoid openings, then drawing it with both hands, we saw away … at the fleshy bodies." In the pre-Renaissance period (1000–1200s), Rolando, a famed Italian physician, also used the knotted string and the spatula methods to remove polyps [16].

Not much changed in the surgical methods until the 1600 and 1700s, when snares and forceps were developed. Though Fallopius (1523–1562) was credited for developing the snare, medical specialists from Japan and India were using snares even prior to that. Fallopius wrote, "I take a silver tube which is neither too narrow nor too broad and … brass wire, sufficiently thick, preferably the wire with which harpsichords are made. This doubled I place in the tube so that from this wire a loop is made at one end of the tube, by which, used in the nares, I remove the polyp. When the polyp is engaged in the loop, I push the tube to the root of the polyp, and then pull on the metal threads and thus I constrict the roots of the polyp and extract it …" [23]. The forceps, introduced first by Fabricius in the mid-1600s, were actually scissors curved at the end. John Van Horne (1621–1770) added teeth at the point of the instrument to provide a better grip on the polyps. Benjamin Bell,

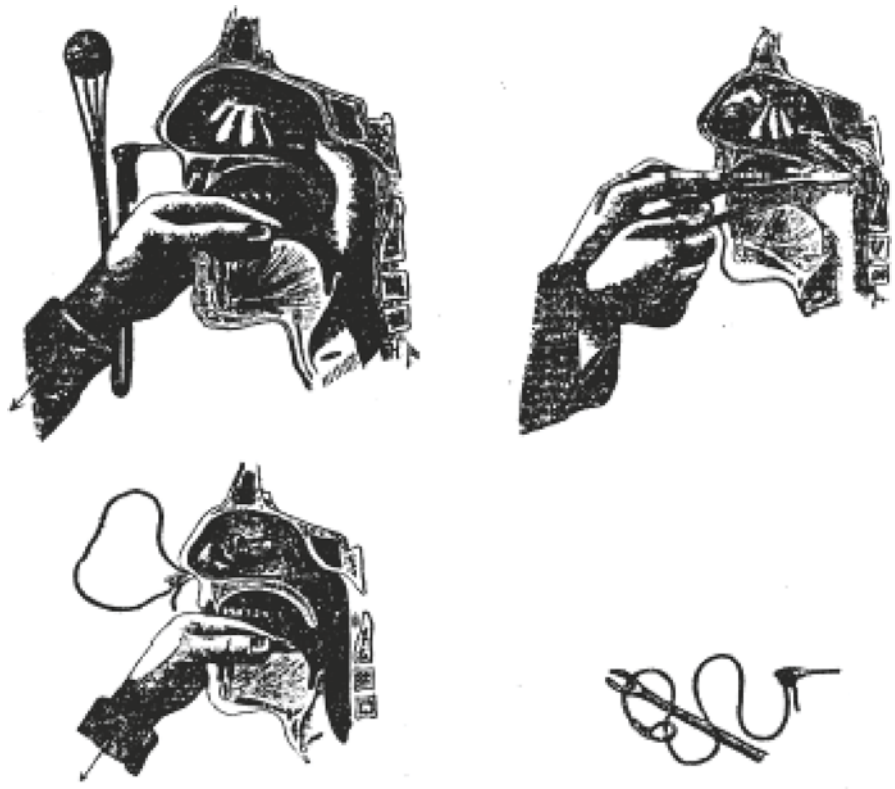

Fig. 1.2 The Hippocratic method of excision of nasal polyps. The loop is inserted intranasally, the polyps are avulsed from their base, and then removed from the pharynx. (Adapted from Stevenson and Guthrie [16])

the eighteenth century prominent Scottish surgeon, published in a System of Surgery (1791) a range of snares and forceps to remove polyps [16, 23]. Many modifications of the forceps ensued over the following years (Fig. 1.3). For larger polyps, surgeons described splitting the nasal alae and sometimes even the soft palate. The advocates of these procedures maintained that these open approaches offered better visualization, and thus, more complete excisions of the polyps [16, 22].

Throughout the eighteenth and nineteenth centuries, the struggle in treating primary and recurrent nasal polyposis continued. Until the use of endoscopy became popular, more extensive intranasal procedures such as Caldwell-Luc radical antrostomy, intranasal ethmoidectomy, and external frontoethmoidectomy were also utilized. These procedures stripped mucosa and altered the nasal and paranasal sinus landmarks [11]. Even with such extensive intervention and medical therapy, polyp recurrence was still a problem.

Significant changes in sinonasal surgery were brought about with the development of endoscopic

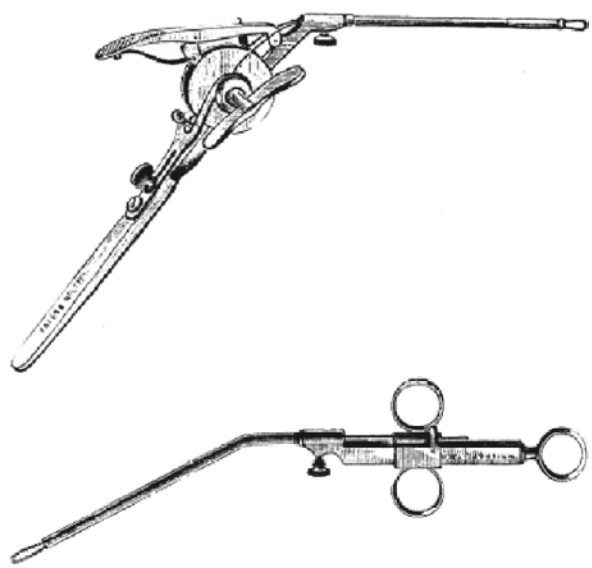

Fig. 1.3 The general design and function of modern day snares closely resemble those illustrated here. The McKenzie (*top*) and Krause (*bottom*) snares were developed in the late 1700s. (Adapted from Lack)

sinus surgery (ESS). Although the term "endoscopy" was coined by a French urologist Antonin Jean Desormeaux (1815–1894), it was a German physician, Phillip Bozzini, who developed the first endoscope, known as the "Lichtleiter," in 1805 [2]. The instrument consisted of an eyepiece and a container for a candle-light that was reflected by a mirror through a tube. Bozzini used his rudimentary endoscope to examine the bladder, rectum, and pharynx. Another German urologist, Max Nitze, modified the "Lichtleiter" by creating a metal tube with a series of lenses within. Several water-cooled platinum wires were threaded through the tubes and used as the light source. In 1950, Storz introduced the first fiberoptic endoscope that bears resemblance to those used today [2]. Hirshmann, in 1901, first applied endoscopy to sinonasal disease. He modified a cystoscope and used it to view the maxillary sinus and middle meatus through an enlarged dental alveolus. Despite the technological advancements, it was not until the1960s that the endoscope gained popularity in the diagnosis and surgical treatment of sinonasal diseases. This newfound interest was due in part to the increasing popularity of minimally invasive intervention in all surgical specialties and in part to the works of Walter Messerklinger of Graz, Austria. His work involved the anatomical and physiological study of the nose and paranasal sinuses and their mucosal blanket. Most importantly, he noted the patterns of mucus clearance of different areas of the nose and sinuses through various ostia and into the infundibulum and that disruption of the mucocilliary transport or obstruction of normal flow led to disease. With Messerklinger's discoveries, functional endoscopic sinus surgery (FESS) was introduced in the late 1960s in Germany, and David Kennedy is credited for introducing FESS in the United States in 1985 [12].

1.6 Conclusions

Nasal polyps have been recognized for a long time.

Although many theories about their cause have evolved over the years, we are still left with controversy and uncertainty about the etiology. The diagnosis and treatment strategies have undergone a colorful evolution. Today, we have overcome most of the difficulties in the diagnosis and significantly improved the technical aspects of surgical treatment. Nevertheless, we still face recurrent disease and the need for repeat surgical procedures. Thus, to this day, the quest for the cure of nasal polyps remains an important goal.

Take Home Pearls

- Polyps first reported several centuries ago.
- Relationship between nasal polyps and allergy put in doubt recently.
- Mainstay of medical therapy is systemic and intranasal steroids.
- Mainstay of surgical therapy is endoscopic, intranasal removal of polyps with functional sinus surgery.

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Epidemiology of Nasal Polyps

2

Aaron N. Pearlman, Rakesh K. Chandra,
David B. Conley, and Robert C. Kern

Core Messages

- The prevalence of nasal polyps (NP) in the population has been grossly estimated as 1–4%.
- An association between NP and allergic rhinitis (AR) is weak, with NP prevalence in patients with AR estimated between 1.5 and 1.7% and this incidence approaches that of the general population.
- Large cohort studies have revealed a strong association between asthma and NP.
- The incidence of NP increases with age and is likely the greatest between 40 and 60 years of age.
- If NP are found in a child, a workup for cystic fibrosis should be conducted.
- Genetic inheritance has been proposed as a possible etiology of NP but remains unclear.
- Up to 50% of aspirin insensitive patients have NP and up to 36% of patients with NP may have some form of analgesic insensitivity.
- Allergic fungal rhinosinusitis is a known underlying pathophysiologic etiology in a subset of CRS patients and is strongly associated with NP.
- Ethnic and geographic variation has emerged as a potential modifier in NP pathophysiology.

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2.1 Introduction

Mounting evidence suggests that nasal polyposis (NP) is a clinical manifestation of multiple possibly coexisting immunologic pathways, and because this entity likely reflects an array of disease states, the epidemiology is difficult to characterize. Phenotypically, chronic rhinosinusitis (CRS) can be classified as either CRS without NP or CRS with NP. CRS without NP, in general, reflects TH1-mediated inflammation [45]. Idiopathic CRSwNP comprises the vast majority of cases of NP, and this term typically implies a clinical picture of *diffuse* sinonasal polyposis dominated by TH2-mediated (eosinophilic) responses, at least in western patients. In rare cases, a distinct genetic, immunologic, or metabolic defect has been associated with the development of diffuse NP, and these cases will be discussed below. Furthermore, CRS with NP must be differentiated from antrochoanal polyps, which account for only 5% of polyp cases [24]. Antrochoanal polyps are usually unilateral and solitary and most often arise from the maxillary sinus. This is a distinct disease process that often presents at a younger age compared to CRSwNP. In contrast to CRSwNP, antrochoanal polyps reveal lesser degrees

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of eosinophilia with a more normal appearing mucosal surface and basement membrane [31].

The prevalence of NP in the population has been grossly estimated as 1–4%, though supporting evidence for this finding is scarce [24]. Older reports have suggested a prevalence ranging from 0.2 [12] to 2.2% [16], and autopsy studies have reported an incidence of bilateral NP at 1.5 [43] to 2% [25]. Various comorbidities such as allergic rhinitis (AR), generalized atopic status, and asthma have all been proposed as factors in the genesis of NP. Yet the data for these associations have been the subject of on-going investigations and conflicting reports can be identified. Variations in prevalence have also been reported as a function of demographic factors, including age and gender. In addition, hereditary factors and ethnic variations exist and must be considered. The present chapter is dedicated to elucidating the epidemiology of CRS with NP in general, as well as in the context of comorbid disease states and known underlying pathophysiologic processes.

2.2 Allergy and Asthma

Classic teaching has implied that NP formation is a product of an allergic response (atopy) to inhalant allergens. Although this relationship seems intuitive, current data suggest that this association is weak. NP prevalence in patients with AR is estimated to be between 1.5 [40] and 1.7% [14], and this incidence approaches that of the general population as previously described.

Large cohort studies have revealed a strong association between asthma and NP while consistently challenging the relationship between atopy and NP. In one investigation of over 2,000 patients, Settipane reported that NP were more common in nonallergic asthmatics vs. allergic asthmatics (13 vs. 5%, $p<0.01$) [39]. These data were corroborated by Grigoeras et al. who analyzed 3,817 Greek patients with chronic rhinitis and asthma. Overall, the incidence of NP in this population was 4.2% and NP prevalence was the greatest in nonallergic asthmatics vs. allergic asthmatics (13 vs. 2.4%). There was an association between NP and perennial allergy as opposed to seasonal [14].

Other studies have examined as to how factors such as NP and atopy may correlate with CRS severity, as measured by CT scan. In a group of 193 CRS patients treated at a tertiary care center, statistical analysis revealed that atopy was significantly more prevalent in the CRS without NP subgroup (32.3%) compared to those with CRS with NP (27.5%). Although the mean Lund–Mackay score was slightly greater in atopics vs. nonatopics (14.2 vs. 12.3, $p=0.05$), significance was lost when the cohort was separated into those with and without NP. In contrast, increased radiologic severity was observed in the CRS with NP group. Overall, these data suggest that the presence of NP is unrelated to atopy and is a better predictor of advancing radiologic disease [35].

A similar study examined 106 patients from a tertiary care center of which 49% were atopic by skin endpoint titration. Overall, atopics and nonatopics exhibited no difference in the prevalence of NP (38 vs. 37%). Presence of asthma, however, was an independent predictor for the existence of NP, which was observed in 57.6% of asthmatics vs. 25% of nonasthmatics ($p=0.0015$). As with previous reports, Lund–Mackay score was the greatest in *nonatopic* asthmatics, followed by atopic asthmatics, and then nonasthmatics. As expected, the Lund–Mackay score was the greatest in the polyp group, but it is important to note that this association was found to be independent of atopic status. In summary, these data indicated that asthmatic patients are more likely to have polyps than nonasthmatics [32]. Furthermore, the presence of asthma and polyps were each significant predictors of disease severity as measured by Lund–Mackay score. In contrast, atopy appears unrelated (or perhaps weakly related) to either polyp growth or advancing severity of radiologic disease.

The pathophysiology of CRS with NP and asthma may reflect a similar chronic inflammatory response in the upper and lower airways, at least in a subset of patients. An abundance of eosinophils is typically seen in the polyp tissue of patients with CRS with NP, while this is not consistently observed in patients with CRS without NP [17]. The inflammatory cellular infiltrate in asthmatics is also composed of eosinophils, mast cells, and CD4+ T lymphocytes [42]. Bachert et al. has theorized that the relationship between severe CRS and asthma may be due to the production of inflammatory cytokines in airways which induce the upregulation of eosinophils, mast cells, and basophils by the bone marrow upregulation. These inflammatory cells then migrate to the airway mucosa resulting in a reactive inflammatory response leading to NP formation [6].

2.3 Gender and Age

It has been suggested that the incidence of NP increases with age [14, 39]. Settipane reported that NP frequency reaches a peak in patients who are 50 years and over [39]. Furthermore, he reports that asthmatics over 40 years of age are four times more likely to have NP than those under 40 (12.4 vs. 3.1%, $p<0.01$) [39]. Larsen et al. reported similar results in a uniform population of Danish patients. Of 252 patients, they observed NP most commonly in patients who were 40–60 years old. Additionally, patients over 80 years of age were unlikely to have NP. The mean age of diagnosis of NP was 51 in males and 49 in females. In sharp contrast, unilateral antrochoanal polyps were diagnosed at a much younger age: males 27 years, females 22 years [24].

The discovery of NP in children is extremely rare. The estimated incidence of NP in patients less than 16 years of age is 0.1 [39] to 0.216% [24]. In a study of 1,051 pediatric allergic patients, only one had NP [40]. If NP are found in a child, a workup for cystic fibrosis (CF) should be conducted.

As with age, the literature varies in relation to the impact of gender on the development of NP. In Settipane's review of 211 NP patients, there was an equal distribution of males and females, 50.2 vs. 49.8% respectively [40]. Data published more recently using the Danish National Health Care insurance system to identify patients treated for NP differ with this prior observation. In fact, this cohort exhibited an increased incidence of NP in males over 20 years as compared to age-matched females. The male:female ratio of patients with NP was 2.9 in ages 40–50 and maximal at 6.0 for patients between 80–89 years of age [24]. The incidence was the greatest in both males and females in the age range of 40–69 years. In this group, NP was present in 1.68 male and 0.82 female patients per thousand annually. It is important to note that data from this Danish initiated study represent a homogenous population of 252 NP patients culled from 5 years of retrospective data.

2.4 Genetics

Genetic inheritance has been proposed as a possible etiology of NP. Studies have suggested that up to 14% of patients with NP have a family history of NP [13]. Attempts to delineate a hereditary pathway using monozygotic twin studies have yielded mixed results. In a report of twins with steroid-dependent asthma, only one had bronchospastic aspirin intolerance and NP while the other did not manifest these phenotypic traits [38]. Further attempts have been made to show an association of NP in families. In a cohort of 174 NP patients, 25% had a first degree relative with polyps (parent, sibling, or child) [10]. Forty-four patients manifested Samter's triad (aspirin intolerance, asthma, and NP) and 36% of these patients had a first degree relative with NP. Furthermore, 32% (57) of the polyp patients had both NP and asthma of which 30% had a first degree relative with polyps. Though a genetic predisposition to form NP is likely a significant factor, there is no clear Mendelian inheritance pattern in the vast majority of NP cases, and a gene–environment interaction is likely at work.

There are various disorders that are genetically inherited in which the formation of NP is a disease characteristic. CF is an autosomal recessive disorder caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. The gene product of CFTR is a chloride ion channel primarily in the exocrine glands of the lungs, liver, pancreas, and intestines. Approximately, 20% of patients with CF have NP [39]. A diagnostic work-up for CF should be conducted in any patient under the age of 16 who presents with NP.

Primary ciliary dyskinesia (PCD), also known as Kartagener's syndrome, is characterized by CRS, bronchiectasis, and situs inversus (reversal of internal organs). Defects in the dynein arms of cilia are primarily responsible for the immotility seen on mucosal biopsy; however, radial spoke defects and microtubular transposition anomalies have been identified [41]. Ultimately, the frequency of ciliary beat is abnormal and uncoordinated. PCD has been seen in both men and women leading investigators to conclude that this is an autosomal recessive disorder. However, recent observations of a nonconsanguineous family with retinitis pigmentosa (RP) and PCD have suggested an X-linked inheritance pattern [29]. It is likely that there may be more than one mode of inheritance pattern for PCD as investigation into left-right axis deviations in vertebrates has shown an autosomal dominant, recessive, and X-linked pattern [9].

When initiating medical treatment for CRS in patients with either CF or PCD, culture-directed

therapy should be considered. CF patients have a high likelihood of *Pseudomonas aeruginosa* infection and antibiotic therapy should be tailored to this pathogen. CF patients are often treated with maintenance antibiotics directed against *P. aeruginosa* consisting of macrolides or fluoroquinolones. Therapy may be aerosolized to increase the concentration delivered to the tissues with a low toxicity profile [44].

Young's syndrome is another disorder characterized by recurrent sinopulmonary disease, obstructive azoospermia, and NP [15]. This disease differs from CF and PCD in that sweat chloride tests are normal, as is ciliary function demonstrated by normal sperm tails and tracheal biopsies. Spermatogenesis is normal and the azoospermia results from an excess of inspissated secretions in the epididymis [15, 37]. The prevalence of Young's syndrome remains unclear, but it has been suggested to be responsible for up to 7.4% of male infertility [39].

A systemic vasculitic disorder, Churg–Strauss syndrome (CSS) commonly presents with upper airway symptoms. Originally felt to be comprised of four hallmark characteristics, bronchial asthma, CRS, eosinophilic vasculitis, and granulomas [30], there is likely phenotypic variation to this syndrome. The American College of Rheumatology accepts six primary characteristics of CSS: asthma, eosinophilia >10%, neuropathy, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. To qualify for a diagnosis of CSS, four of the six criteria should be present, yielding a sensitivity of 85% and a specificity of 99.7% [27]. CSS is a systemic vasculitis of small to medium-sized vessels and is associated with AR and/or CRS with or without NP [2, 3]. The exact mechanism of CSS is unknown, but eosinophil activation likely plays a major role [2]. Otolaryngologic manifestations may consist of AR, CRS with or without NP, nasal crusting, otitis media, and rarely, sensorineural hearing loss and unilateral facial palsy [2]. NP is present in up to 60% of patients with CSS and is likely an indicator of early disease [3]. Corticosteroids are highly effective in treating patients with NP associated with CSS [3].

2.5 Aspirin Intolerance

NP are frequently observed in patients who are insensitive to aspirin (acetylsalicylic acid) or nonsteroidal antiinflammatory drugs. In this subset of patients, these medications induce an acute asthmatic response within 30–90 min of ingestion [36]. This "triad" of symptoms, (bronchial asthma, CRS with NP, and aspirin insensitivity) is often referred to as Samter's triad or ASA-triad. In a majority of affected patients, aspirin challenges produce an acute bronchial response with rhinorrhea and nasal obstruction [33]. Aspirin insensitivity that causes urticaria without bronchospasm has not been associated with NP. It has been estimated that up to 50% of aspirin insensitive patients have NP and that 36% of patients with NP may have some form of analgesic insensitivity [39]. However, while considering all the patients undergoing endoscopic sinus surgery (ESS), including CRS with and without NP, approximately 4.6% had ASA-triad [19].

The development of a fully realized ASA-triad likely occurs over time. Initially, patients may present with chronic rhinitis. Within 5–10 years, aspirin-induced asthma will become apparent. Shortly thereafter, NP becomes prominent [34]. Nonallergic rhinitis with eosinophilia syndrome (NARES) has been proposed as a precursor in the pathway leading to ASA-triad [28]. It has been shown that NP epithelial cells from ASA-triad patients have abnormalities in basal and aspirin-induced generation of eicosanoids (products derived from arachidonic acid metabolism including prostaglandins, thromboxanes, and leukotrienes), ultimately leading to aspirin sensitivity [21].

NP of ASA-triad patients likely represent a unique phenotype of severe inflammation, which is more recalcitrant to both medical and surgical intervention. The NP of ASA-triad patients demonstrate increased edema and inflammatory infiltrate compared to the NP of aspirin tolerant patients [7]. Additionally, ASA-triad patients' response to surgery is universally poor, undergoing approximately ten times as many ESS procedures as that of ASA tolerant patients [19]. Furthermore, ASA-triad patients have a significantly higher rate of symptom recurrence (nasal obstruction, facial pain, postnasal drip, and anosmia), regrowth of NP at 6-month follow up [7, 19], and lack of statistical improvement in FEV1 [7].

2.6 Allergic Fungal Rhinosinusitis

Allergic fungal rhinosinusitis (AFRS) is a known underlying pathophysiologic etiology in a subset of CRS patients and is strongly associated with NP. Classically, a diagnosis

of AFRS is made when the following five hallmark characteristics are present: a type I hypersensitivity to *dematiaceous* fungi, NP, paranasal CT scan findings of inspissated mucus with calcification, eosinophilic mucus containing Charcot-Leyden crystals without fungal invasion into the surrounding sinus mucosa, and positive fungal stains from sinus contents [8, 22]. Intraoperatively, the eosinophilic mucus is inspissated, tan colored with a thick sticky consistency. Rarely does a patient with suspected AFRS satisfy all five of these criteria. However, the diagnosis can be made based on clinical suspicion and intraoperative observations of eosinophilic mucus and NP. Staining for fungal elements in intraoperative biopsies has proven to be inconsistent even in patients who are strongly suspected of having AFRS.

The incidence of AFRS has not been well established, but patient characteristics likely influence disease manifestation. Approximately 5–10% of CRS with NP patients have AFRS [8, 11]. This is typically a disease of younger adults, with a mean age of diagnosis between 22 [26] and 28 years of age [46], which is significantly lesser than that observed in non-AFRS patients. Studies have suggested that there is an increased prevalence of AFRS in southern, more humid climates. Recent reports have suggested that lower socioeconomic status may also play a role. In patients treated at a tertiary medical center in South Carolina, a significant proportion of the AFRS patients (24.1%) were uninsured or Medicaid recipients as opposed to 5.2% of the non-AFRS CRS with NP group. Furthermore, a significant portion of the AFRS group was African American (61.1%) who resided in counties with a greater African American population and more advanced poverty status [46]. These data raise the point that although AFRS may be more prevalent in various ethnic groups, socioeconomic status may also be a factor in that African Americans accounted for a significant portion of the un- or underinsured. It may be possible that lower socioeconomic status and thus, lack of access to health care, may have allowed for disease progression in this series.

2.7 Ethnicity and Geography

As the exact mechanism of NP formation remains a topic of investigation, ethnic and geographic variation has emerged as a potential modifier in the pathophysiology. In a Caucasian population, NP have been shown to have a strong eosinophilic component, likely due to the upregulation of interleukin (IL)-5 [4]. In addition to increased IL-5, eotaxin and eosinophilic cationic protein (ECP) are significantly elevated in NP homogenates and indicate amplified eosinophilic inflammation [45]. Additionally, transforming growth factor (TGF) β1, a cytokine known to stimulate the extracellular matrix and inhibit IL-5 synthesis [1], is downregulated in NP [45]. Therefore, a cytokine cascade culminating in the overproduction of IL-5, with downregulation of TGF-β1, may potentiate the eosinophilic response and have deleterious effects on the extracellular matrix simultaneously [45]. Of note, these results originate from a population of Caucasian patients from the country of Belgium.

Interestingly, this increase in eosinophils in NP is not consistent across various ethnicities. NP in Asian countries show a neutrophilic pattern rather than the previously discussed eosinophilic [18]. Yet, the clinical manifestation of NP remains similar between Asians and Caucasians. Zhang et al. attempted to further characterize the variations seen in Asian polyps. Polyp tissue samples from 27 Chinese patients from the Guangdong province of China were harvested. As with similarly affected Caucasian patients, most of the Asian patients had been treated with nasal steroids and antibiotics. Some had received Chinese herbal medicines. The samples were compared to a group of matched Caucasian Belgian patients, where Chinese polyps had a significantly lower incidence of eosinophils ($p < 0.01$) [47]. A Korean cohort has shown a similar preponderance of noneosinophilic NP [20]. In this study of 30 NP patients, not only were 66.7% noneosinophilic, but the basement membrane thickness of the polyps was found to be significantly thinner in the noneosinophilic vs. eosinophilic group (8.2 ± 3.5 vs. 13.9 ± 4.5 μm) [20].

Though the predominant inflammatory cellular infiltrate differs between Caucasians and Asians, commonalities are also apparent. Zhang et al. [47] reported that ten of the Asian polyps contained IgE against *Staphylococcus aureus* enterotoxins (SAE), which is consistent with the previously reported data that one-third of Caucasians with NP and asthma have IgE to SAE [5]. As in white subjects, tissue IgE and sIL-2R are elevated in Asian polyps. Eosinophilic infiltrate is decreased in Asian polyps as measured by ECP and IL-5/eotaxin levels compared to the tissue from

Caucasians. Total IgE was elevated in allergic NP compared with nonallergics, but ECP was not increased. Thus allergic disease likely has a negligible impact on ECP levels and eosinophil recruitment. Similar findings have been made in Caucasian polyps [5, 32, 35]. TGF-β1 was significantly downregulated in Asian polyps compared with inferior turbinate controls. Furthermore, TGF-β1 was extremely low in the NP groups with IgE to SAE suggesting a modulatory effect of staphylococcal enterotoxins. This finding has previously been observed in Caucasians. Of the Asian group, only two had asthma and nine were allergics. There was no difference between the allergics and nonallergics in relation to eosinophilic infiltrate.

It is clear that variation in the physiology of NP differs amongst Asians and Caucasians, yet there have been only limited investigations into other ethnic and racial backgrounds. A collaboration between three otolaryngology departments from various continents, Eritrea (Africa), China (Asia), and Switzerland (Europe) attempted to better characterize the racial variation of NP [23]. In this report, the African and Chinese participants did not receive preoperative steroids or antibiotics whereas the Caucasians were treated preoperatively with prednisolone 1 mg/kg/day for 5 days as well as trimethoprim/sulfamethoxazole for 10 days. Compared to Chinese and Caucasians, Africans presented with more progressive disease in which NP extended into the nasal cavity and were ulcerated. Eosinophil density was also greater in African polyps ($p<0.001$) compared to Chinese and Caucasian NP. There was no difference in the amount of eosinophils between Chinese and Caucasian NP. Plasmocytes and lymphocytes were abundant in Chinese and Caucasian NP and rare in African NP. No difference was observed in the number of mast cells in any group. Unfortunately, the patients included in these analyses were not standardized in relation to preoperative treatment. The Caucasian cohort had been treated with preoperative steroids which would likely suppress the presence of inflammatory mediators in the polyp biopsies. Both the Chinese and African cohorts received no preoperative treatment. The root cause of these discrepancies is likely due to socioeconomic disparities among the study countries resulting in a significant variation in the patients' access to health care and likely affected the molecular data. Just as NP of Caucasians and Asians can exhibit significant cellular and molecular differences, it is possible that polyps from African patients also show significant variation in cellular and molecular profile.

Take Home Pearls

- NP is a phenotypic manifestation of multiple possible immunologic processes.
- The significant association between NP and asthma suggests similar underlying pathophysiology that is independent of atopy.
- Although some CRS with NP cases are associated with established genetic syndromes, most patients likely have multiple, subtle, and as yet unknown genetic variations that combine with environmental factors resulting in polyp formation.
- Further study is necessary to elucidate the key factors that account for the variability in polyp epidemiology.

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Pathology of Nasal Polyps

3

Raja R. Seethala and Harshita Pant

Core Messages

- The most common polyps found in the nose and paranasal sinuses are those associated with chronic rhinosinusitis (CRS).
- Histologic subclassification of CRS polyps is mainly descriptive and is not specific for any particular entity.
- The presence of eosinophilic mucin should not be ignored, since this places the disease in the EMCRS/AFS category.
- Unilateral or unusual appearance necessitates the need to biopsy a polyp to exclude other possible lesions.
- Other lesions that present as polypoid masses include Schneiderian papillomas and mesenchymal neoplasms.

3.1 Introduction

The term polyp refers to the macroscopic appearance of a pedicled tissue arising from a mucosal surface and projecting into a lumen or cavity. The histopathology of polypoid tissue affecting the nose and paranasal sinuses is diverse, ranging from inflammatory nasal polyps to benign and malignant epithelial, mesenchymal, and hematolymphoid neoplasms (Table 3.1). In the context of chronic rhinosinusitis (CRS), "polyp" refers to benign nongranulomatous inflammatory tissue projection with an epithelial lining within the sinonasal cavity. There are several histopathological features that differentiate CRS nasal polyps from other types of polypoid lesions occurring in the nose and paranasal sinuses. Furthermore, nasal polyps may have some unique characteristics that are distinguishable from the surrounding nonpolypoid CRS mucosa.

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3.2 Normal Sinonasal Histology

The normal sinonasal histology is characterized by structural components including the epithelium, basement membrane, and submucosal tissue, and nonstructural components including resident and nonresident cells from the lymphoid and myeloid lineage.

3.2.1 Structural Component

Epithelium and basement membrane: The anterior 2 cm of the nasal cavity is lined by skin, composed of an epidermis with keratinizing stratified squamous epithelium, a fibrocollagenous dermis, and adnexal glands. The rest of the nasal cavity is lined by respiratory-type mucosa that is derived from ectoderm, also known as the Schneiderian membrane. Normal sinonasal mucosa is depicted in Fig. 3.1. The respiratory epithelium consists of four major cell types: ciliated columnar or cuboidal cells interspersed with goblet cells, nonciliated columnar cells with microvilli, and basal cells. The ratio of

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Table 3.1 Mesenchymal lesions that may mimic sinonasal polyps

Differential diagnostic consideration	Distinguishing clinical features and morphology	Immunophenotype
Nasopharyngeal angiofibroma	Size, cellular stroma with thick muscular arteries, young adolescent males	Beta-catenin +, androgen receptor +
Solitary fibrous tumor	Size, cellular with dense "ropey" collagen and "staghorn" pericytomatous vasculature	CD34 +, bcl-2 +, CD99 +
Inflammatory myofibroblastic tumor	Size, cellular myxoid stroma arranged in fasicles with inflammatory background	Smooth muscle actin +, anaplastic lymphoma kinase (ALK) ±
Neuroglial heterotopia	Fibrillary matrix, ± ganglion cells	Glial fibrillary acidic protein +, synaptophysin +, neurofilament ±

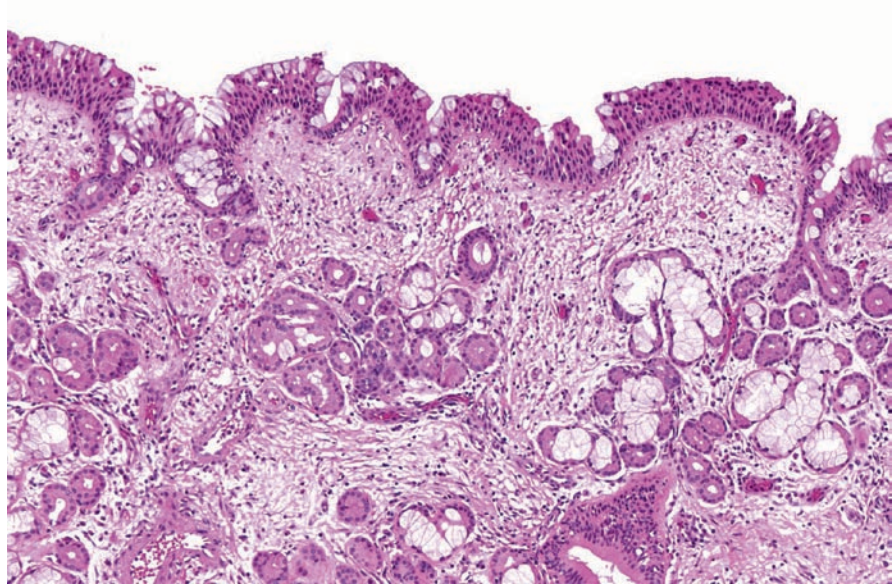

Fig. 3.1 Normal sinonasal mucosa (H&E, 100×). The surface is lined by ciliated pseudostratified columnar epithelium with goblet cells resting on a delicate basement membrane. The submucosa consists of delicate connective tissue with lobules of mucoserous glands and sparse lymphocytes representing NALT

columnar cells to goblet cells is approximately 5:1 and this ratio may vary depending on the site [21]. The normal respiratory-type epithelium often shows scattered areas of metaplastic squamous or cuboidal epithelium, and this is especially seen in the inferior turbinates [3]. The cells contain tight junctions and rest on a basement membrane composed principally of collagen fibers (types I, III, IV, V, VI, and VII) and other constituents that include heparan sulfate proteoglycan, laminin, and nidogen [1]. The basement membrane is delicate; however, in the inferior turbinate, a thick basement membrane may be seen. Compared with the nasal cavity, the paranasal sinuses have a thinner, less specialized surface epithelium and lamina propria [22]. These differences in the structural and cellular components between the sinus and nasal mucosa may reflect their different embryological origins and functional differences [2, 17].

The superior turbinate, superior nasal septum, roof of the nasal cavity and superior and medial portion of the middle turbinate are lined by olfactory epithelium also known as neuroepithelium [16]. This is also a cilated pseudostratified columnar epithelium, which consists of a basal cells, bipolar ciliated olfactory cells, microvillar cells, and supporting or "sustentacular" cells. The central axonal process of olfactory cells passes though the cribriform plate to synapse with neurons present in the olfactory bulbs. With increased age, and following injury and infections, olfactory epithelium shows patchy loss and subsequent replacement with respiratory epithelium. The epithelial surface is covered by mucus produced by goblet cells, submucous glands, and ciliated cells. Mucus is actively propelled by the cilia toward the openings of the sinuses, enabling its drainage into the nasal cavity.

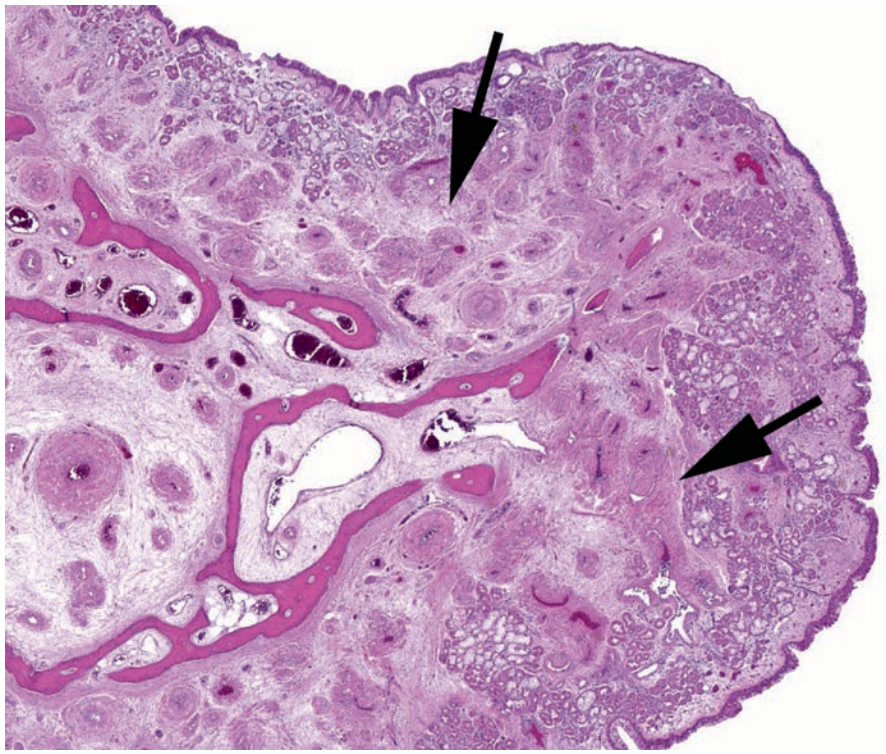

Fig. 3.2 Normal turbinate (H&E, 20×). Similar to other regions the surface is lined by respiratory-type mucosa with underlying mucoserous glands. Unique features of turbinate, however, are the thick prominent muscular arteries (*arrows*) seen below the mucoserous glands and between bony trabeculae

Submucosa: Beneath the basement membrane, the submucosa overlying the cartilage and bony sinonasal framework contains loose fibrovascular connective tissue, stromal cells including numerous seromucinous and minor salivary glands, blood vessels, nerves, and myeloid and lymphoid cells. Multiple seromucinous glands are present in superficial and deep layers and are separated by large venous sinusoids. The lobular units of the glands have a peripheral clustering of serous (~10%) and mucous (~90%) acini that secrete mucins, immunoglobulins, and enzymes that drain sequentially into the intercalated, striated, excretory, and ultimately, the main ducts. The main duct communicates with the epithelial surface. Over the age of 60, these mucoserous glands may show oncocytic change, a senescent phenomenon characterized by the abnormal accumulation of mitochondria in the cytoplasm imparting a granular densely eosinophilic appearance by light microscopy. The underlying vasculature consists of subepithelial capillaries, periglandular microvessels, and numerous arterial and venous anastomoses. The capillaries have specialized fenestrations that facilitate transport of fluid and high-molecular weight compounds. These networks communicate with venous erectile vessels that are irregularly shaped with multiple smooth muscle layers and are most prominent in the submucosa of the nasal turbinates (Fig. 3.2). Here, the prominence and irregularity of these veins may simulate an arteriovenous malformation or cavernous hemangioma to those who are unfamiliar with the regional histology. Glands are usually more abundant in the normal middle turbinate, whereas veins are more prominent in normal inferior turbinate [8].

3.2.2 Nonstructural Components

The lymphoid compartment in the sinonasal mucosa is comprised of single lymphocytes scattered among the epithelial cells and lamina propria, and the nasal-associated lymphoid tissue (NALT) [13]. The NALT are discrete unencapsulated aggregates of lymphoid cells, akin to that in the mucosa-associated lymphoid tissue in the gut (Peyer's patches). However, NALT are not as well formed in the sinonasal mucosa, but may become more pronounced in chronic inflammation. The lymphocyte population is composed of T cells, B cells and

plasma cells, natural killer (NK) cells, and natural killer T (NKT) cells, and the myeloid cells include monocytes, macrophages, dendritic cells, granulocytes (including neutrophils and eosinophils), and mast cells. These cells form an integral component in the adaptive and innate mucosal immune responses.

3.3 Nasal Polyp Histopathology

3.3.1 Chronic Rhinosinusitis with Nasal Polyps

Approximately 20% of CRS patients have nasal polyps [9]. Presence of polyps may signify a distinct type of CRS with recalcitrant disease. Clinical conditions often associated with nasal polyps include asthma, asthma and aspirin sensitivity (Samter's triad), eosinophilic mucus chronic rhinosinusitis (EMCRS, including allergic fungal sinusitis), cystic fibrosis, Churg–Strauss disease, Kartagener's syndrome, and Young's syndrome. Histologically, polyps have been classified into several groups, based on the proposed etiology, predominant inflammatory cell infiltrate, and stromal appearance. This classification is purely descriptive and not specific to an underlying associated disorder or pathology.

3.3.1.1 Macroscopic Pathology

Macroscopically, most polyps have an edematous, smooth and shiny appearance with a soft consistency compared with the surrounding nonpolypoid mucosa. The cut surface is usually pale, edematous with a translucent appearance (Fig. 3.3). Biopsies from long-standing disease may be firm and solid white suggesting extensive fibrosis. Polyps are generally mobile and often attached via a stalk to the underlying mucosa. The surrounding CRS mucosa and middle turbinate is generally more erythematous and is firm to palpation. The CRS mucosa, depending on the degree of edema, may appear polypoid, but does not have a discrete stalk. Polyps commonly arise from the middle meatus and the sphenoethmoidal recess and are often bilateral. However, unilateral polyps are not uncommon. Polyps vary in size, and in severe cases, may completely fill the nasal cavity. In long-standing polyps, the sinonasal bones may remodel and cause broadening of the nasal dorsum.

The mucosa of the middle turbinate, inferior turbinate, uncinate process, and septum may also have broad-based polyps. A large polyp originating from the inferior turbinate is unusual [4]. Polypoid mucosa in the posterior portion of the inferior turbinate is not uncommon, referred to as a "mulberry" turbinate [10], and is usually not associated with CRS. Contrary

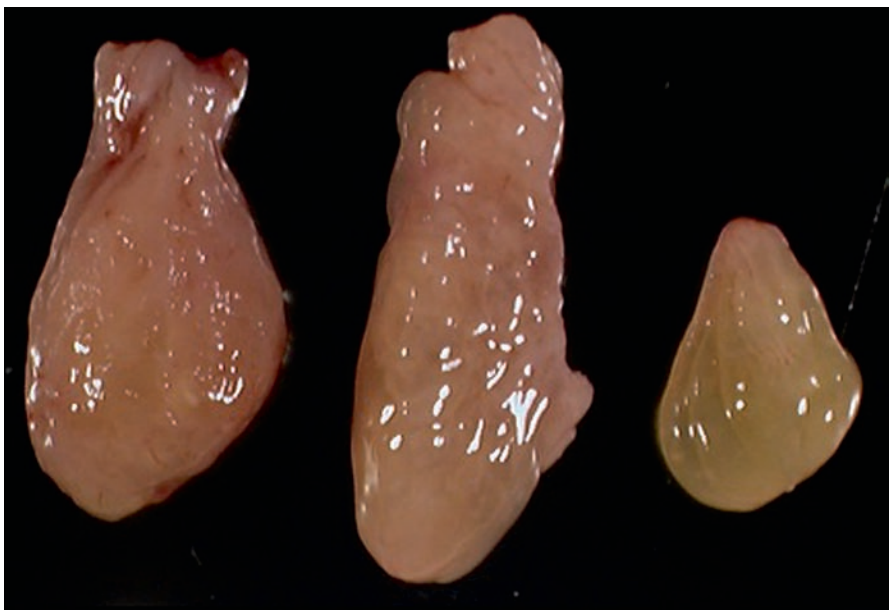

Fig. 3.3 Macroscopic appearance of a serially sectioned edematous polyp showing a delicate glistening *yellow* cut surface

to the middle and superior turbinates, the anterior portion of the inferior turbinate is rarely polypoid and this may be due to the presence of squamous epithelium and the aerodynamics in the region. A polyp arising from the maxillary sinus and into the nasal cavity is characteristic of antrochoanal polyp and is generally unilateral [25]. Nasal polyps associated with CRS do not usually have macroscopic surface ulceration, and the presence of such may indicate other pathologies. A more lobulated or "bunch of grapes" may signify other pathologies such as a sinonasal papilloma; however, based on the appearance alone, the underlying pathology is not always possible to determine. Therefore, all polyps, especially unilateral ones, need a histopathological examination at some point.

A proportion of CRS with nasal polyps also has characteristic thick, dark, and tenacious mucus, termed eosinophilic mucus. This mucus is typically seen in allergic fungal sinusitis but is also present in patients with severe and recalcitrant polypoid CRS including cystic fibrosis and Sampter's triad and in the lungs of allergic bronchopulmonary aspergillosis. In many cases, the pathology of allergic fungal sinusitis may have been missed because the mucus was not examined for fungal elements.

3.3.1.2 Microscopic Pathology

The major histological characteristics of nasal polyps and CRS mucosa compared with normal mucosa include (1) structural changes involving the epithelium, submucosa, and sometimes underlying bone; and (2) the nature and degree of inflammatory cell infiltrate. Nasal polyps are typically lined by respiratory epithelium and have a basement membrane with variable thickness and an underlying stroma with a range of structural changes and inflammatory cells. Polyps have historically been classified based on their histological structural appearance and the nature of predominant inflammatory cell population into (1) edematous, eosinophilic, or "allergic" polyps, (2) chronic inflammatory polyps, and (3) seromucinous, glandular polyps. The description eosinophilic vs. noneosinophilic polyps is often used in the literature. But this classification is not specific to any associated or underlying pathology.

Edematous and eosinophilic polyps are the most common type and are also known as "allergic" nasal polyps. However, only a small proportion of CRS with NP have coexisting allergy and the controversy involving an allergic etiology is discussed elsewhere. These polyps are lined with respiratory epithelium with a range of mucosal alterations that include ulceration, granulation tissue, acute mucositis, epithelial and goblet cell hyperplasia, and squamous metaplasia. The basement membrane is often thickened, and there is abundant submucosal edema (Fig. 3.4). Mucus retention cysts are common and varying amounts of mixed inflammatory cell infiltrates contain mostly eosinophils, plasma cells, and scattered lymphocytes. The mucoserous glands are often incorporated within the edematous polyps. The edematous and eosinophilic polyps are seen in the whole spectrum of associated disorders including, EMCRS, allergic fungal sinusitis, Sampter's triad, cystic fibrosis, and Churg–Strauss syndrome. Classically, nasal polyps associated with cystic fibrosis have delicate rather than thickened basement membranes and less stromal eosinophilia, and more neutrophils, hence termed neutrophilic polyps. Also characteristic is the presence of dense, deeply eosinophilic inspissated mucus secretions.

Chronic inflammatory polyp, also known as fibroinflammatory polyp, is less common, forming less than 10% of inflammatory nasal polyps [14]. These may represent a spectrum of edematous polyps, where occasionally, when a polyp is traumatized, the stroma may undergo secondary inflammatory change resulting in a myofibroblastic proliferation that may mimic a soft tissue neoplasm. The main histological features are the presence of submucosal fibrosis and an often prominent mixed inflammatory infiltrate with a lymphoid predominance often with germinal centers. Similar to other sinonasal polyps, mucoserous glands are still present within the polyp, unlike true mesenchymal lesions that tend to displace mucoserous glands. The surface epithelium is likely to show squamous metaplasia as a marker of chronicity (Fig. 3.5). Polyps with hyperplasia of seromucinous glands are less common. Lesions in this category are relatively new and somewhat controversial as to their relationship with true epithelial neoplasms, and include respiratory epithelial adenomatoid hamartoma and seromucinous hamartoma [23, 24].

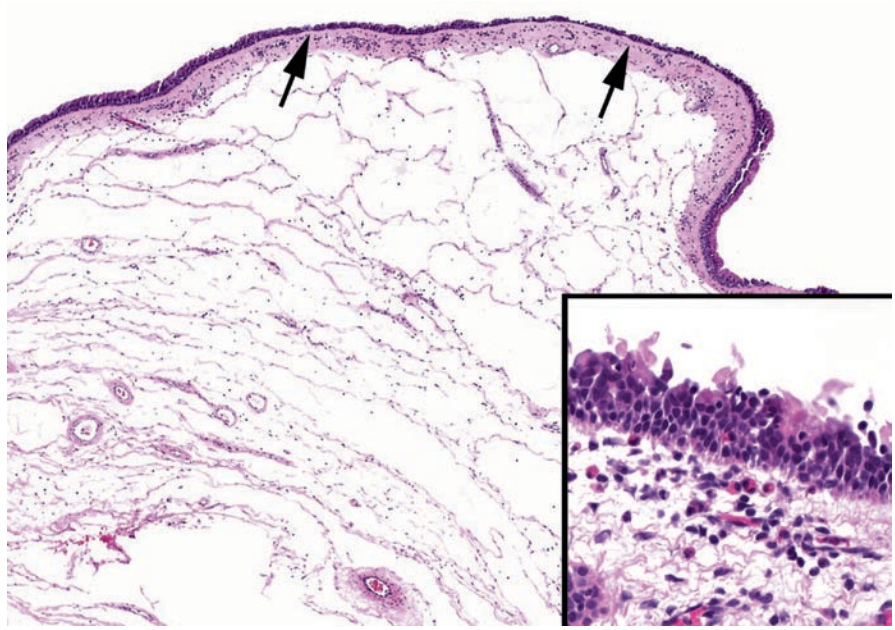

Fig. 3.4 Edematous polyp (H&E, 20×). This polyp shows slightly thickened basement membranes (*arrows*) and marked submucosal edema resulting in extensive clear space between submucosal connective tissue fibers. Inset (H&E, 400×) – scattered throughout are mixed inflammatory infiltrates including eosinophils and plasma cells

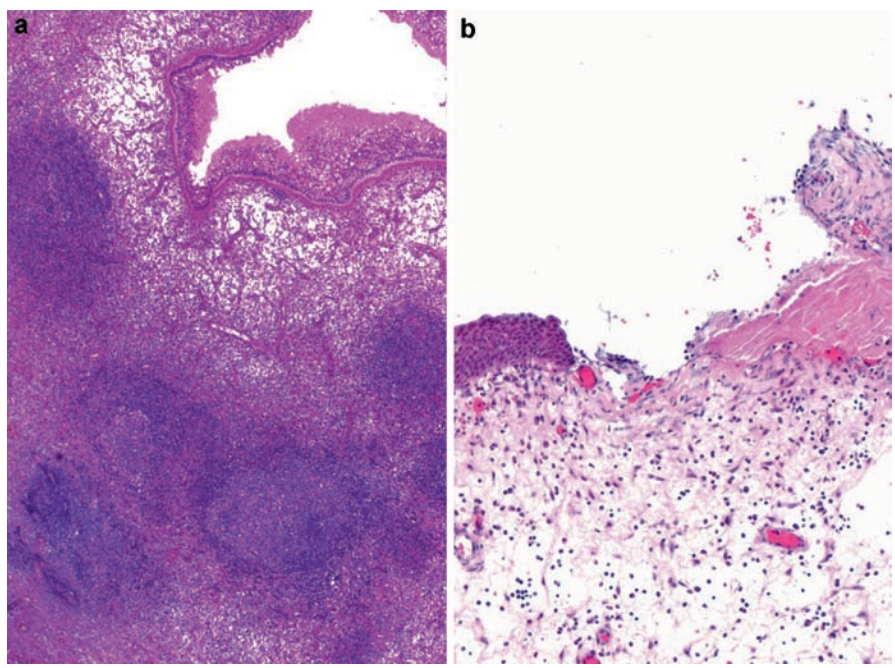

Fig. 3.5 Chronic inflammatory changes in polyps. (**a**) (H&E, 20×). This polyp shows an exuberant lymphoid hyperplasia with reactive germinal centers. (**b**) (H&E, 100×). This polyp shows mucosal ulceration (*right*) and squamous metaplasia (*left*)

3.3.2 Bone Changes

Underlying bone may show remodeling particularly in fibroinflammatory polyps.

3.3.3 Mucus Histopathology, Including "Eosinophilic Mucus"

The secretions associated with CRS with and without polyps have a range of consistencies and contain numerous inflammatory cells that reflect the infiltrate found in the mucosa and polyps. Secretions from CRS with polyps generally contain more eosinophils than those without polyps, regardless of consistency of the mucus. In the clinical group, EMCRS, the secretions are typically thick, almost solid. Formalin-fixed H&E stained sections of this mucus typically show clusters of eosinophils, eosinophil breakdown products (Charcot–Leyden crystals), and other inflammatory and epithelial cells (Fig. 3.6). Fungal elements can be detected in up to 100% of these samples, (silver stains). This mucus, termed eosinophilic mucus, is the diagnostic criteria for EMCRS and allergic fungal sinusitis.

3.3.4 Antrochoanal Polyps

Antrochoanal polyps are the most common type of choanal polyp (most common source). Other sites of origin may be sphenoid, ethmoid, rarely septum, and inferior turbinate. These are all histologically similar. Antrochoanal polyps represent 4–6% of all polyps, and in the pediatric population, up to 33% (REF). As suggested by their designation, they have an antral and choanal component. These typically arise from the posterior wall of maxillary antrum and often have a thin "neck" that passes through the maxillary sinus ostium (or accessory ostium) [5]. They are often unilateral, but may be bilateral on rare occasions. Macroscopically, these range from erythematous to cystic with the latter often seen in the antral portion. The nasal and choanal portions are usually solid.

Microscopically, these polyps are lined by ciliated pseudostratified epithelium that is usually intact, with a thin basement membrane. Stroma may exhibit myxoid change and stromal giant cells, but usually lacks a significant inflammatory component. Rarely, degenerative changes including cholesterol granulomas and angiomatous change may be found [8, 20].

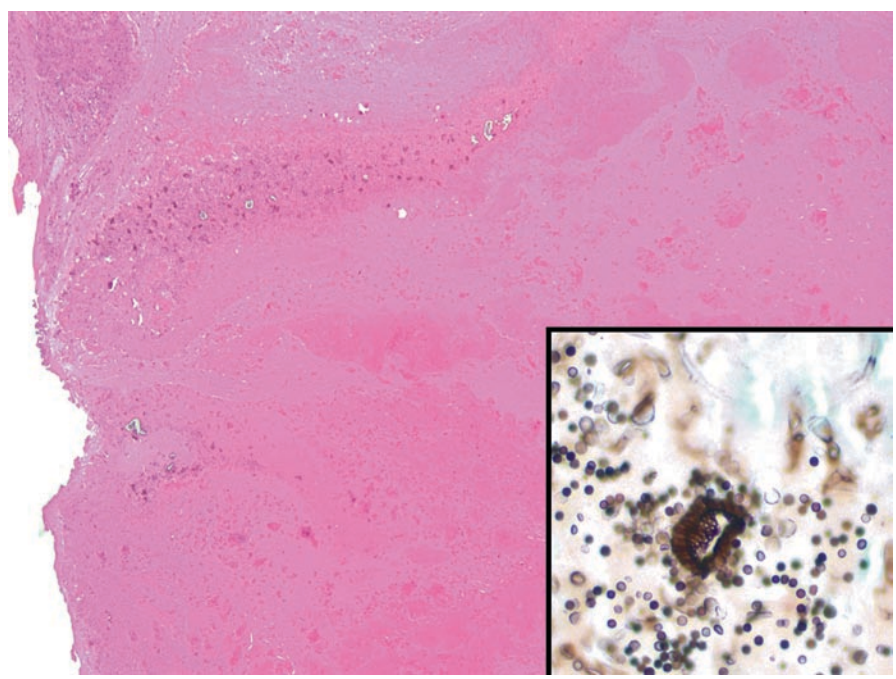

Fig. 3.6 Allergic or "eosinophilic" mucus (H&E, 40×). This consists of granular intensely eosinophilic mucus imparting a *bright pink* appearance. Inset (Grocott stain, 600×). A careful search will almost always yield fungal organisms. In this particular case, in addition to hyphae, conidiophores with condia were seen compatible with *Aspergillus niger* and confirmed by fungal culture

3.3.5 Noninflammatory Polypoid Lesions

Polyps may occasionally resemble neoplasms, both epithelial and mesenchymal. The main epithelial differential diagnostic considerations are the Schneiderian papillomas. These consist of three types, exophytic, inverted, and oncocytic (rare). Nasal polyps with extensive squamous metaplasia or basal cell hyperplasia are the most likely mimics of Schneiderian papillomas. Grossly, these are distinguished from nasal polyps by their relative opacity. Exophytic Schneiderian papillomas arise invariably on the nasal septum and have a lower propensity for local aggressiveness and malignant transformation than inverted papillomas that typically occur on the lateral nasal wall. Histologically, all Schneiderian papillomas consist of a more complex epithelial proliferation, with the inverted type showing endophytic growth of epithelial nests (Fig. 3.7). Exophytic and inverted Schneiderian papillomas are lined by a mixture of squamous, respiratory, and "transitional" epithelium that is several layers thick. Unlike nasal polyps, the basement membranes in Schneiderian papillomas are characteristically delicate. The epithelium shows scattered mucus cells and "transmigration" neutrophils. Oncocytic papillomas are lined by oncocytic columnar epithelium with numerous epithelial microabscesses. It is important to note that both nasal polyps and Schneiderian papillomas often coexist in patients, and thus, familiarity with the distinguishing characteristics is important [6].

Nasal polyps may mimic a variety of stromal neoplasms as well. This occurs when there is fibrous change or prominent vascularization of a polyp. Basically, any mesenchymal neoplasm of the sinonasal tract may present as a "nasal polyp." However, a few lesions may also show histologic overlap with nasal polyps. Hemangiomas may mimic a vascularized nasal polyp. They are most commonly located in the anterior nasal septum and turbinates. In the nasal cavity they are either of the capillary or cavernous type. These are distinguished from vascular nasal polyps by their lobular arrangement. On the other hand, lesions such as solitary fibrous tumor, nasopharyngeal angiofibroma, and inflammatory myofibroblastic tumor may mimic a fibrous nasal polyp. Clinically, these true neoplasms tend to be larger than inflammatory nasal polyps. While nasopharyngeal angiofibromas may present in the nasal cavity, they typically arise from the nasopharynx and are invariably found in young to adolescent males. Additionally, these tend to show androgen receptor positivity and beta catenin nuclear reactivity [11, 18]. Solitary fibrous tumors and inflammatory myofibroblastic tumors have a characteristic morphology, and immunophenotype [15, 16] (see Table 3.1).

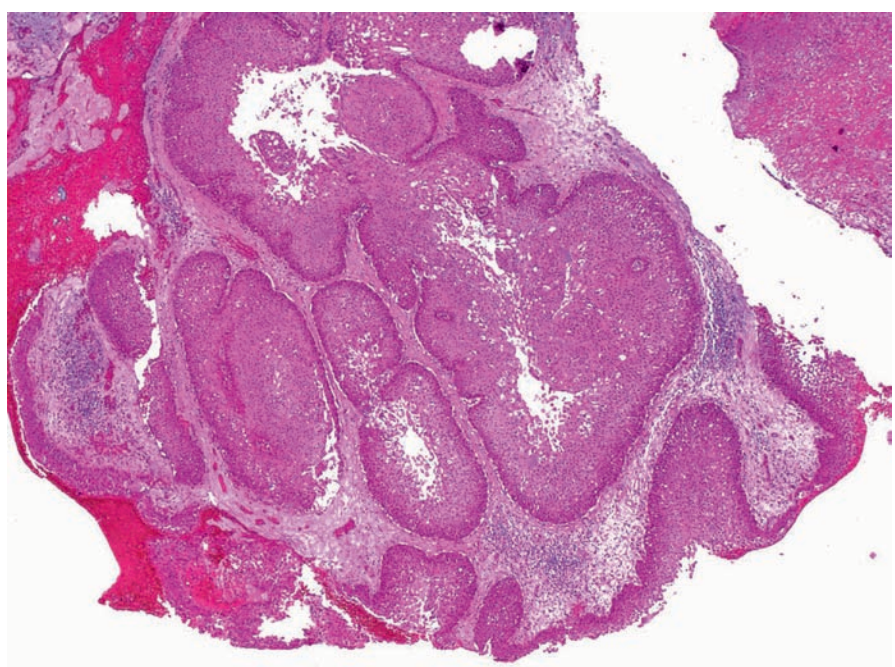

Fig. 3.7 Schneiderian papilloma, inverted type (H&E, 40×). This is a complex nested proliferation of transitional type epithelium with an endophytic growth. The nests are surrounded by delicate basement membrane

Both have a more prominent proliferation of stromal cells. In contrast, fibrous change in a sinonasal polyp is localized and not very prominent. Finally, very rarely neuroglial heterotopias may present as nasal polyps. The fibrillary glial tissue may be subtle and blend in with surrounding soft tissue edema. Immunostains directed toward synaptophysin, neurofilament, and/or glial fibrillary acidic protein may be useful to make this distinction [19].

3.4 Conclusions

Polyps associated with CRS are the most common cause of polypoid sinonasal lesions. The histological features of CRS with nasal polyps are similar among most associated disorders, and therefore cannot reliably discriminate pathologies. Pathologic evaluation is important to differentiate from other polypoid sinonasal lesions, especially in unilateral cases to differentiate from benign tumors. The presence of mucin should be reported and evaluated as polyps with this belonging to the clinicopathologic spectrum of EMCRS/AFS.

Take Home Pearls

- The most sinonasal polyps are associated with chronic rhinosinusitis (CRS) and have a broad histopathologic spectrum.
- Sinonasal polyps may be seen in the setting of EMCRS/AFS and may then be associated with eosinophilic mucin.
- Schneiderian papillomas and mesenchymal neoplasms may present as polypoid masses, and thus, unilateral or unusual appearing polyps should be biopsied.

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The Inflammatory Process in Nasal Polyposis: Genetics, Molecular Biology, and Electrophysiology

4

Joel M. Bernstein

Core Messages

- Nasal polyposis is the ultimate manifestation of chronic inflammation in the lateral wall of the nose.
- At least two factors that may lead to the development of inflammation in the lateral wall of the nose are (1) genetic polymorphism of inflammatory genes, particular the A allele at position −308 in the promotor region of the TNF-α gene and (2) the production of exotoxins by *Staphylococcus aureus* and their ability to upregulate the variable β (V_β) region of the TCR of lymphocytes.
- Cytokines in nasal polyps drive the inflammatory response.
- TNF-α can upregulate VCAM-1 (vascular cell adhesion molecule-1), which is a major counterreceptor for the integrins on the surface of both lymphocytes and eosinophils.
- TNF-α can also be released by eosinophils, resulting in an autocrine upregulation of eosinophils into the nasal polyp.
- Eosinophils release major basic protein, a granular protein that is capable of increasing net sodium flux across the apical surface of the nasal polyp epithelium, resulting in increased water absorption and the ultimate development of edema, a major histopathological feature of polyposis.
- The increased number of open sodium channels, known to exist in both CF epithelium and non-CF polyp epithelium, can be abrogated by the use of topical diuretics such as amiloride and furosemide.

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4.1 The Nasal Polyp Represents an End-Stage of Chronic Inflammation

The histopathology of the nasal polyp is not simple edema of the mucus membrane of the lateral wall of the nose. Rather, it is a de novo inflammatory growth of the mucosa of the lateral wall of the nose in the area of the uncinate process or bullar mucosa. The characteristic histopathological features include metaplasia of parts of the epithelium characterized by basal cell hyperplasia, goblet cell hyperplasia, or more rarely, squamous metaplasia. The lamina propria of the noncystic fibrosis nasal polyp is characterized by four classical findings: edema, extensive lymphocytosis, eosinophilia, and degenerated cystic glands filled with mucus. These glands are entirely different thanthe typical seromucinous glands found in the turbinate mucosa. This chapter is devoted to an overview of the inflammatory process in the nasal polyp in noncystic fibrosis adult patients.

The molecular biologic events that occur in the development of nasal polyps are now becoming unraveled [1]. Inasmuch as lymphocytosis and eosinophilia represent the major inflammatory process and edema of the lamina propria and alterations of the mucus membrane occur as mentioned above, these events need to be explained.

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Furthermore, new information is now available on the genetic predisposition to the formation of chronic hyperplastic sinusitis with nasal polyposis (CHSwNP) [8]. Thus, the odds ratio and relative risk of developing nasal polyposis may be linked to the small arm of chromosome 6 on which the HLA antigens, complement, heat shock protein, some complement proteins, and most importantly, a major proinflammatory gene, TNF-α, are situated [21]. The HLA genes, also called the immune response genes, are in genetic disequilibrium with the above mentioned proinflammatory genes, and therefore, are transferred from parent to offspring together.

4.2 Genetic Predisposition and Staphylococcal Enterotoxins as Two Predisposing Factors in the Development of Chronic Hyperplastic Sinusitis with Nasal Polyposis

Several recent studies have suggested that *Staphylococcus aureus* secrete exotoxins that may act as superantigens and upregulate the V_β region of lymphocytes in CHSwNP [4, 6, 23]. In various disease entities in which *S. aureus* is present such as acute allergic rhinitis, perennial allergic rhinitis, atopic dermatitis, and asthma, a specific allergic reaction to these exotoxins may occur and results in specific IgE directed against these exotoxins [18]. Thus, at least two distinct mechanisms, one genetic and the other immunologic, may coexist in the lateral wall of the nose and become additive in the development and maintenance of inflammation in the lateral wall of the nose that leads to the pathogenesis of nasal polyposis. Our laboratory first demonstrated that in CHSwNP, patients have a T cell receptor V_β clonal expansion and that a specific exotoxin correlated with the appropriate V_β region of the T cell receptor (TCR) in the lateral wall of the nose [4]. Furthermore, we have demonstrated that not only is the staphylococcal organism producing an exotoxin, but there is in vivo presence of the exotoxin in the mucus, adjacent to nasal polyps. Although fungus, particularly Alternaria, has been suggested by a limited group of investigators as a major cause of nasal polyposis, our laboratory has been unable to verify the presence of fungus in the great majority of patients with CHSwNP.

Although allergic fungal sinusitis is a definite entity, particularly in the southwest, the concept of nonallergic eosinophilic chronic rhinosinusitis associated with fungus is still controversial.

However, *S. aureus* exotoxins acting as superantigens and specific IgE directed against these exotoxins appear to be two independent immunological mechanisms that can upregulate lymphocytes and inflammatory mediators in the lateral wall of the nose. In summary, a genetic predisposition and an immunological mechanism (exotoxins of *S. aureus* acting as superantigens) acting together may be the triggers that are required to alter the mucosa of the lateral wall of the nose to develop nasal polyposis.

Recent work in our laboratory has demonstrated that the A allele in a single nucleotide polymorphism (SNP) located in TNF-α (rs1800629) is significantly different in patients with nasal polyposis vs. controls without nasal polyposis, 18.6 and 11.5%, respectively, with an individuals' odds of susceptibility to nasal polyps increasing almost twofold (OR = 1.86) (CI 1.14, 3.09) given at least one copy of the A allele at the SNP located at the −308 position of the promoter region of the TNF-α gene on chromosome 6. All other cytokine gene polymorphisms of inflammatory, anti-inflammatory, and chemokine genes that we studied were not significantly different between the polyp and control groups. Our conclusion was that TNF-α −308, a SNP in the promoter region of the cytokine gene, is associated with increased odds of developing massive nasal polyposis. Finally, the A allele in this position of the TNF-α gene is associated with increased transcription of the protein TNF-α.

TNF-α is a potent immunomediator and proinflammatory cytokine that has been implicated in the pathogenesis of the large number of human diseases, including periodontitis, inflammatory bowel disease, cancer, sepsis, migraine without aura, and multiorgan failure [9].

4.3 Cytokines in the Nasal Polyp Mucosa

Our laboratory has demonstrated that TNF-α, IL1-β, VCAM-1, RANTES, and eotaxin are present in most nasal polyps, for instance, in the epithelium,

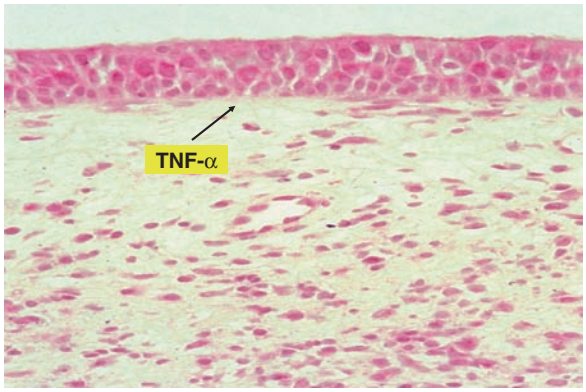

Fig. 4.1 High power photomicrograph (peroxidase–antiperoxidase ×400) of the surface epithelium of the nasal polyp. The *arrow* points to basal cells that have the product of tumor necrosis factor (TNF-α). The entire epithelium has the product of TNF-α that is also found in eosinophils in the lamina propria

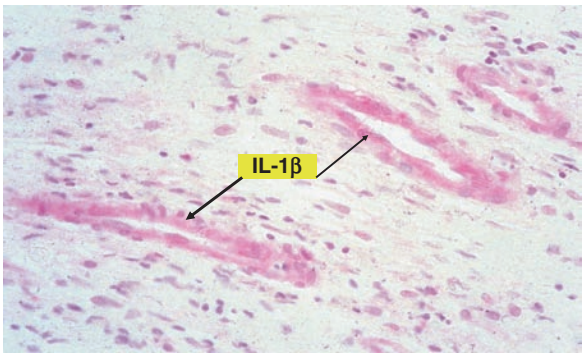

Fig. 4.2 High power photomicrograph (peroxidase–antiperoxidase ×600) of the lamina propria of the nasal polyp showing presence of interleukin-1β in the endothelial cells *arrows* of small venules

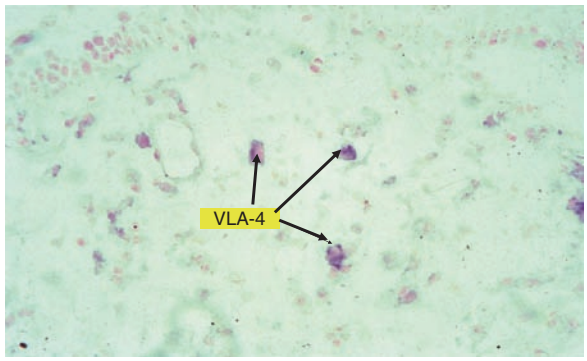

Fig. 4.3 High power photomicrograph (peroxidase–antiperoxidase ×800) of very late antigen 4 or α4-β7 on the surface of eosinophils in the lamina propria of eosinophils

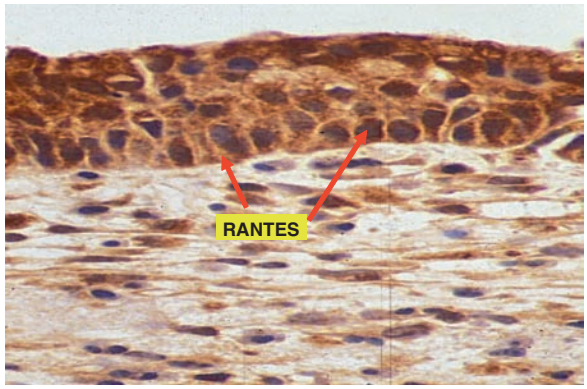

Fig. 4.4 High power photomicrograph (peroxidase–antiperoxidase ×400) demonstrating RANTES in the epithelium and also in eosinophils in the lamina propria

endothelium, fibroblasts, macrophage, lymphocytes, and most importantly, eosinophils [1]. Not only is the mRNA present, but the product is present as noted in Figs. 4.1–4.4. Recent advances in our knowledge of the molecular biology of cytokines have elucidated the mechanism by which these inflammatory mediators give rise to the classical histopathological findings in the lamina propria of nasal polyposis, mainly, lymphocytosis, eosinophilia, and edema. The remainder of this chapter gives an in-depth explanation of the mechanism by which the increased odds ratio of having increased levels of TNF-α in patients with CHSwNP, and the additional trigger of staphylococcal exotoxin acting as a local superantigen gives rise to the series of events resulting in the major histopathological findings in this chronic inflammatory disease.

4.4 TNF-α and VCAM 1

TNF-α is produced primarily, but not exclusively, by macrophages and T cells [12, 13] Initially identified for its cytotoxic and antitumor activity, it is now well documented that this cytokine plays a critical role in a variety of immunological processes including inflammation, secondary lymphoid organ development, and the control of intracellular pathogens [22]. The TNF locus is located in the class 3 region of the human major histocompatibility

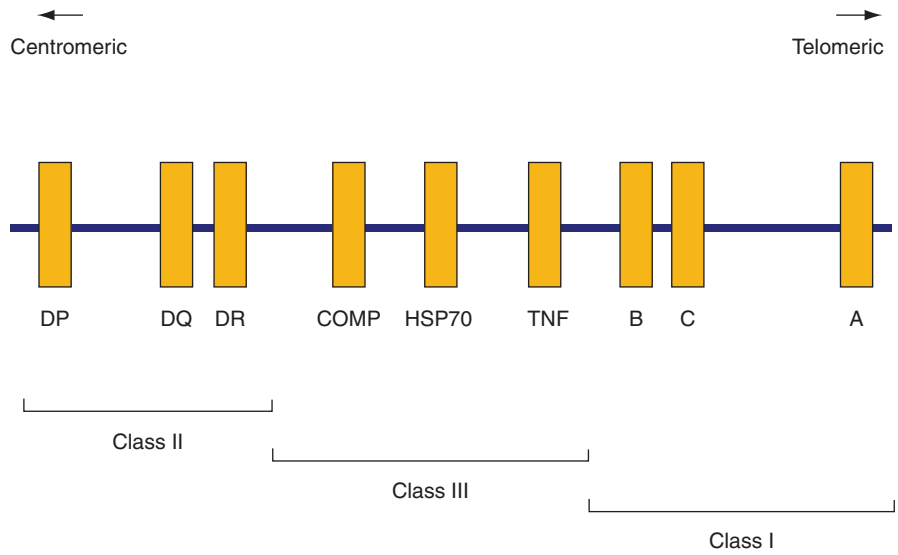

Fig. 4.5 Structure of the human major histocompatibility complex on the short arm of chromosome 6. TNF-α is found centrameric to the A, B and C HLA antigens and telomeric to the DP, DQ, DR because of the genetic disequilibrium in this area of the chromosome. These immune response genes, as well as proinflammatory genes, are transferred from generation to generation together. Thus, there is a genetic predisposition to such diseases as allergic rhinitis, asthma, and nasal polyposis

complex on the short arm of chromosome 6 (Fig. 4.5). These genes include the HLA-A, B and C, HLA DR, DQ, and DP loci, which collectively have been called immune response genes. Because these genes are close together, they are usually transmitted from generation to generation in linkage disequilibrium, i.e., they are almost always transferred from parent to child together.

Our knowledge in the trafficking of lymphocytes and eosinophils into the nasal epithelium from the bloodstream is related to the receptors on these two inflammatory cells, lymphocytes and eosinophils, and the counterreceptors on the surface of endothelial venules in the lamina propria of the lateral wall of the nose.

TNF-α upregulates VCAM-1 and NF-κβ in fibroblasts from nasal polyps [11, 16]. Nasal fibroblasts produce VCAM-1 and that production is increased by TNF-α stimulation. VCAM-1 expression in the nasal fibroblasts is induced through NF-κβ dependent pathway. These findings might provide a rationale for using NF-κβ inhibitors as a treatment for nasal inflammation.

Other investigations have also documented that VCAM-1 is upregulated in nasal polyps through the action of TNF-α [20, 24].

The receptor on the surface of lymphocytes and eosinophils that migrate to these counterreceptors and endothelial venules (VCAM-1) have also been established to be very late antigen 4, either α-4, β-1 or α-4, β-7. Our laboratory has established that both VCAM-1

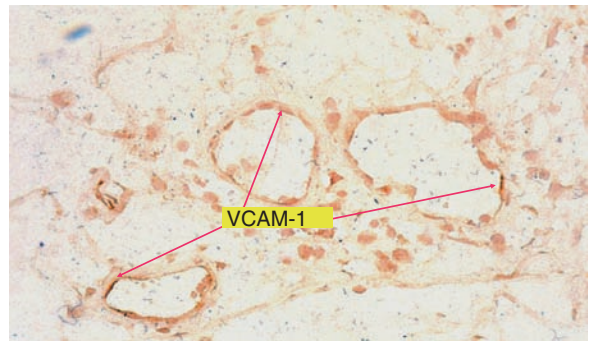

Fig. 4.6 High power photomicrograph (peroxidase–antiperoxidase ×600) of venule demonstrating the presence of VCAM-1 on the interior surface of the endothelium of a venule

in the endothelium of nasal polyps and VLA 4 on the surface of eosinophils are present in nasal polyposis (Fig. 4.6) [1].

In summary, the increased transcription of TNF-α in the cells of nasal polyps not only increases integrins on the surface of eosinophils and lymphocytes in the nasal polyp tissue, but also increase the counterreceptor VCAM-1 in the endothelium. This receptor–counterreceptor interaction drives the eosinophils and lymphocytes into the polypoid tissue. The eosinophils that have accumulated in the tissue of the polyp can also synthesize TNF-α [14]. By using Southern blot analysis after a reverse transcriptase-PCR, Finotto and

colleagues detected a signal specific for TNF-α mRNA in nasal polyp eosinophils [10]. Thus, an autocrine upregulation of eosinophils may occur in nasal polyps. Eosinophils that arrive in the nasal polyp tissue can synthesize TNF-α, which subsequently recruits more eosinophils and thus, a chronic inflammatory disorder in which eosinophils and lymphocytes predominate emerges in CHSwNP.

Finally, TNF-α can increase the secretion of chemokines that attract eosinophils into the nasal polyp mucosa. TNF-α increases not only the secretion of eotaxin but also the expression of RANTES from polyp fibroblasts [19, 25].

4.5 The Eosinophil and Alterations in the Electrophysiology of the Nasal Epithelial Cell; Sodium Channel Alterations

In our previous communications, we have suggested that mediators of inflammation that are known to be present in nasal polyps may have an effect on regulating ion transport in nasal polyp epithelia. The eosinophilic mediator, major basic protein (MBP), could have an effect on the movement of water into the cell and subsequently into the interstitial tissue, causing edema, which is one of the most prominent histopathological findings in nasal polyps [3].

MBP has a profound effect on sodium flux in the apical epithelium of the nasal mucosa [2]. Although eosinophilic cationic protein (ECP) stimulates airway mucus secretion, eosinophilic MBP inhibits airway mucus secretion [15]. Our collaborative efforts with Itzhak Choshniak's laboratory at Tel Aviv University have demonstrated that MBP significantly increases sodium flux into the interior of the epithelial cell (Fig. 4.7). Although there was a large movement of chloride in and out of the cell, there appears to be no significant net flux of chloride. The short circuit current increased significantly with MBP compared with the control.

Most interesting in terms of potential future therapeutic strategy for the treatment of edematous nasal mucosa, and more specifically nasal polyps, is the effect of Amiloride and other sodium channel blocking agents such as Furosemide on water movement into and out of nasal mucosa. Amiloride significantly decreases sodium absorption and decreases the short circuit current. This might lead to the use of Amiloride or Furosemide as topical nasal agents that could decrease sodium absorption into the cell, and thus, decrease cellular and subcellular edema [17]. To evaluate the regulatory pathways for sodium transport, specimens of nasal polyp and nasal turbinate mucosa were

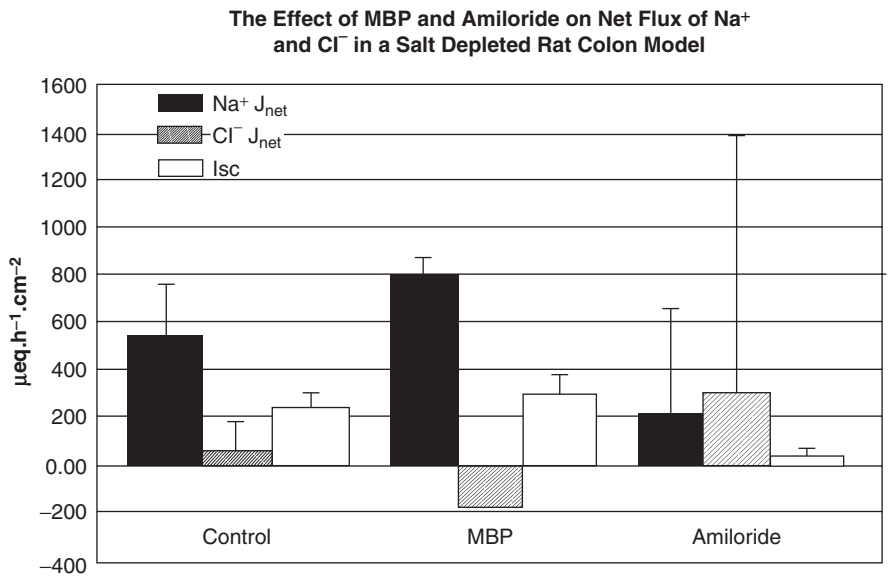

Fig. 4.7 The effect of MBP and Amiloride on the net flux of sodium$^+$ and Cl^- in the salt-depleted rat colon model (from Choshniak's laboratory). MBP has a significant effect on net sodium flux and Amiloride has a marked decreased effect on sodium flux and short circuit current

evaluated in Ussing chambers under basal conditions and during exposure to selected chemicals. The transepithelium resistance (R_t) of the turbinate cultures was lower than that of the polyp samples in CF and non-CF samples. The short circuit current in the polyp samples was decreased significantly by Amiloride and increased by Isoproterenol and ATP. Turbinate cultures have similar but smaller responses (Fig. 4.8)

The data from the bioelectric study suggest that nasal polyp epithelial cells have a normal luminal chloride channel because Isoproterenol, a drug that increases cAMP and activates protein kinase A, increases chloride permeability. Amiloride, however, caused a greater decrease in sodium absorption in nasal polyp cells than in inferior turbinate mucosa. Amiloride is a specific blocker of the apical sodium channel and decreases the basal voltage and basal short circuit current. Thus, Amiloride and Furosemide can be used as topical agents in blocking sodium channels, and in this way, they decrease water absorption and edema in the nasal polyp mucosa.

Finally, in normal adult pseudostratified human nasal surface epithelium, the cystic fibrosis transmembrane regulator protein (CFTR) is localized to the apical domain of the ciliated cells, whereas in cystic fibrosis, the mutated ΔF 508 CFTR gene causes an abnormal cytoplasmic localization of the CFTR protein. Airway epithelial damage in CF or non-CF patients may induce a remodeling of the surface epithelium characterized by a change in the morphologic structure from normal columnar pseudostratified epithelium to either basal cell hyperplasia, mucus cell hyperplasia, or squamous metaplasia [5, 7]. These histological findings are found in human polyp epithelium in the non-CF patient. Thus, abnormally low expression of the CFTR protein may be caused not only by the CFTR gene mutation in CF, but also may be associated with airway surface epithelial differentiation and remodeling as occurs in nasal polyps from non-CF patients.

In conclusion, polyp epithelia have increased sodium absorption, most likely because of increased number of open sodium channels. These results are consistent with the hypothesis that increased epithelial fluid absorption contributes to the development of nasal polyps.

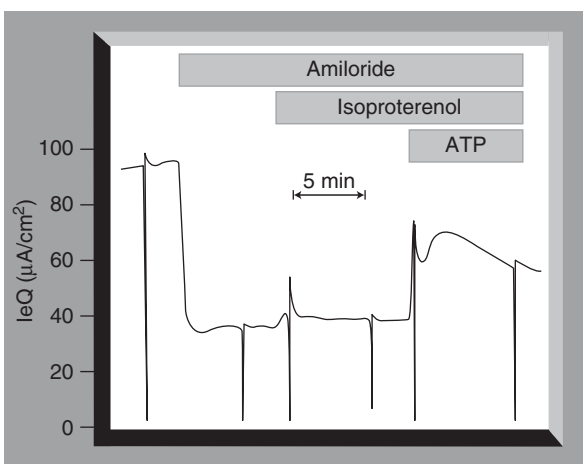

Fig. 4.8 Typical short circuit current recording of a noncystic fibrosis-cultured nasal polyp sample during exposure to amiloride hydrochloride (10^{-4} mol/L, mucosal), Isoproterenol (10^{-5} mol/L, mucosal), and adenosin triphosphate (ATP) 10^{-4} mol/L, mucosal). The current spikes reflect brief open circuit conditions, during which transepithelial potential difference was measured. IeQ indicates equivalent short circuit current. The figure demonstrates the marked inhibition of amiloride hydrochloride on the short circuit current indicating marked inhibition of sodium transport

4.6 Summary

This chapter has reviewed some basic molecular biological concepts that may lead to the development of lymphocytosis, eosinophilia, and increased edema in the lamina propria of the lateral wall of the nose that leads to the formation of nasal polyposis. The following hypotheses are suggested based on the evidence that is accumulated over the years from our laboratory.

The two basic mechanisms in the initial pathogenesis of nasal polyposis are related to the genetic polymorphism of the −308 location in the promoter region of the TNF-α gene on chromosome 6. Patients who have either the homozygous adenine or the heterozygous A/G genotype have an increased translation of the TNF-α protein. The presence of increased amount of this inflammatory mediator leads to the upregulation of integrins on both lymphocytes and eosinophils and their counterreceptors on the venules of the lateral wall of the nose, specifically VCAM-1. The interaction of the integrins of these inflammatory cells with VCAM-1 leads to their rolling and adherence to the endothelial venule surface. RANTES and eotaxin, two chemokines known to be present in all nasal polyps, lead to the migration of eosinophils into the lamina propria. The increased release of MBP by these eosinophils will then cause increased sodium absorption and edema.

The second finding, corroborated by other laboratories as well, is the presence of *S. aureus* in as high as 50–60% of cases of CHSwNP. The presence of exotoxin in the bacterial organism as well as in the mucus adjacent to the epithelium may lead to an upregulation of lymphocytes through the V_β region of the TCR of the lymphocyte. This, in turn, increases the number of lymphocytes in the lateral wall of the nose and their capacity to secrete cytokines that are also inflammatory. Other chapters in this volume will focus on the function of both eosinophils and lymphocytes. This chapter emphasizes the mechanism by which these cells are capable of migrating into the lamina propria of the lateral wall of the nose to cause their various inflammatory effects. However, it is emphasized that in addition to the inflammatory effect of cytokines released by lymphocytes and eosinophils, one of the most important results of increased eosinophils of the lamina propria of the nasal polyp is the release of MBP. Major basic protein can increase sodium absorption. As a result, water follows the sodium into the cell. This may then lead to increased edema, which is one of the hallmarks of the pathology of nasal polyposis.

Finally, because there is evidence that there are increased number of open sodium channels in nasal polyp epithelia resulting in increased transepithelial voltage and increased short circuit current across the polyp epithelium, topical diuretics that can block sodium absorption are a realistic and rational method of treating patients with small nasal polyps, and in particular, treating with topical diuretics after surgical removal of massive nasal polyposis.

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Eosinophil

5

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Core Messages

- Chronic rhinosinusitis (CRS) is characterized by distinct patterns of inflammation, mucous gland hyperplasia, and remodeling that result in various clinical subtypes.
- CRS with nasal polyps (NP) is characterized by increased populations of eosinophils, Th2-like lymphocytes, fibroblasts, goblet cells, and mast cells.
- The pathology of CRS with NP is similar to asthma and is frequently diagnosed in association with asthma.
- This chapter examines the potential role the eosinophil plays in the pathophysiology of these diseases with focus on eosinophil development, production of inflammatory mediators, and upregulation of adhesion molecules that are important in cell trafficking.

5.1 Introduction

The diagnosis and management of nasal polyps (NP) have been challenging and often unsatisfactory. No one specific etiology has been defined, and it is more likely that NP represents multiple different diseases with various stages of severity. Recognition of this has led to an increased appreciation of the importance of categorizing the unique presentations of NP, with the expectation that this will lead to improved, disease-specific therapeutic interventions. Among these categories, three diseases in particular have prominent tissue eosinophil infiltration, chronic hyperplastic eosinophilic sinusitis (CHES), allergic fungal sinusitis (AFS), and aspirin-exacerbated respiratory disease (AERD). This chapter focuses on the role that the eosinophil plays in the pathophysiology of these inflammatory disorders, including the development of NP, and the potential for novel treatment options aimed at reducing damage by these cells.

5.2 Pathogenesis: The Role of the Eosinophil

5.2.1 Development of Eosinophils

Eosinophils develop from pluripotent hematopoietic stem cells in the bone marrow. These cells initially differentiate into the eosinophil/basophil progenitors or colony forming units (Eo/B CFU). Eo/B CFU are mononuclear cells that express CD34, CD35, and interleukin (IL)-5 receptors that are capable of responding to appropriate cytokine signals to differentiate into mature basophils and eosinophils [2, 7]. Eo/B CFU are increased in numbers in both the blood and bone marrow of allergic patients, and further increases in their number are observed following

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allergen exposure [7]. These progenitors are also observed in NP tissue [21]. Several transcription factors including GATA-1, PU.1, and C/EBP are induced in response to appropriate cytokine signals and become involved in the production of the eosinophil lineage and eosinophil-associated genes [28, 33, 34]. In vitro eosinophil differentiation experiments have demonstrated that GATA-1 is the primary transcription factor responsible for this eosinophil lineage specification [19]. Deletion of the high-affinity GATA-binding site in the GATA-1 promoter results in the loss of the eosinophil lineage in mice [54].

Three cytokines, IL-3, IL-5, and granulocyte macrophage colony-stimulating factor (GM-CSF) play the most important roles in the regulation of eosinophil development. The function of IL-3 is the broadest as it leads to the expansion of a variety of cell types including monocytes, megakaryocytes, erythrocytes, basophils, neutrophils, and eosinophils [2]. GM-CSF acts in a similar fashion albeit with more mature precursor cells and induces the formation of macrophages, neutrophils, and eosinophils [36]. In contrast, IL-5 is responsible for selective terminal differentiation of eosinophils [42] and stimulates the release of eosinophils from the bone marrow into the peripheral circulation [4]. Genetic murine studies have confirmed the critical role of IL-5 in eosinophil development as IL-5 overproduction in transgenic mice results in severe eosinophilia [8, 26, 30, 51], and IL-5 gene deletion results in a marked reduction of eosinophils in the blood and lungs following allergen challenge [12]. As discussed elsewhere, anti-IL-5 administration can significantly reduce the numbers of tissue eosinophils in the bronchial mucosa of asthmatics, but not completely deplete them [11]. This is due in part to the shedding of the IL-5 receptor alpha chain from eosinophils when they enter tissue [27]. GM-CSF, IL-3, and the chemokine, CCL11 (eotaxin), are also involved in eosinophil homeostasis and may play a more important role upon arrival of the eosinophil to a tissue location. Inhibition of these cytokines in addition to IL-5 blockade is therefore associated with more robust eosinophil depletion from bronchial mucosa [13, 37].

5.3 Trafficking of Eosinophils

5.3.1 Recruitment

Eosinophil recruitment to the tissue involves a number of cytokines, chemokines, and other inflammatory mediators. *Platelet activating factor* (PAF) is one of the most potent chemoattractants for eosinophils and selectively induces the migration of eosinophils over neutrophils in atopic individuals. It is produced by a variety of cell types including mast cells, endothelial cells, macrophages, neutrophils and eosinophils. In addition to promoting maturation, the T cell products, *IL-5*, *IL-3,* and *GM-CSF,* play a role in potentiating eosinophil chemotaxis, though by themselves they are only weak stimulators of cell migration. Several members of the *CC chemokine subfamily* play important roles in eosinophil chemotaxis including CCL3 (MIP-1α), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL11, CCL13 (MCP-4), CCL22 (MDC), and CCL24 (eotaxin-2) [16, 35]. Of particular importance to sinus disease is the finding that CCL5 is expressed by infiltrating T cells and CCL11 is produced by epithelial cells at sites of allergic inflammation. The selectivity of the eosinophil response to these particular chemokines is due to their chemokine-receptor profile. Eosinophils predominately express CCR3, and to a lesser extent, CCR1 to which the above chemokines bind. Synergy exists between IL-5 and many chemokines in inducing transendothelial cell migration, thereby allowing the weak signal of each to be amplified [44]. *Leukotrienes* also exhibit chemotactic effects for eosinophils. These include LTB_4, which is chemotactic for eosinophils and neutrophils, and the cysteinyl leukotrienes $LTD_{4,}$ LTC_4, and LTE_4, which are preferentially chemotactic for eosinophils [14, 46]. Both the LTB_4 (BLT1 and BLT2) and cysteinyl leukotriene (CysLT1 and CysLT2) receptors are expressed on the surface of eosinophils and allow response to the leukotrienes. Many cytokines involved in Th1 and Th2 inflammation are able to increase expression of these receptors, thereby permitting a response at lower leukotriene concentrations [9]. Of the receptors, CysLT1 has been shown to be involved in bone marrow migration of the CD34+ Eo/B CFU cells, and as a result, may influence eosinophil maturation [1].

5.3.2 Adhesion

The majority of eosinophils reside in tissues where epithelial surfaces are exposed to the external environment, such as gut, lung, and nasal mucosa. It is estimated that the human tissue eosinophil/blood ratio is about 100:1 [15]. After circulating in peripheral

blood, eosinophils migrate into peripheral tissues at endothelial intercellular junctions and this process is influenced by a variety of cytokines and adhesion molecules (Table 5.1).

Selectins, a family of cell-surface adhesion molecules that bind to sugar moieties on specific glycoproteins with mucin-like features, are involved in the initial steps of eosinophil migration. Eosinophils express L-selectin that is shed upon cellular activation and P-selectin glycoprotein-1 (PSGL-1) [29]. This interaction causes the cells to lightly tether on counterreceptors expressed on the inflamed endothelium and roll along the endothelial surface until a second signal is received by the eosinophil. This second signal is provided by a chemokine binding to the endothelial surface. The counterreceptor for PSGL-1 is P-selectin, and for L-selectin, is CD34 or an immunoglobulin superfamily member (MAdCAM-1, GlyCAM-1). In contrast to neutrophils, eosinophils are unable to interact with E-selectin to promote rolling interactions [47].

Integrins consist of heterodimeric cell-surface proteins that are involved in cell–cell and cell–matrix interactions. Human eosinophils express seven integrin heterodimers: α_4/β_1 (CD49d/CD29), α_6/β_1 (CD49f/CD29), α_L/β_2 (CD11a/CD18), α_M/β_2 (CD11b/CD18), α_X/β_2 (CD11c/CD18), α_D/β_2 (CD11d/CD18), and α_4/β_7 (CD49d/β_7) [50]. These integrins form contacts with immunoglobulins on the endothelial surface during cell migration at the stage of rolling migration and lead to firm adhesion. In particular, eosinophils can bind to the immunoglobulins ICAM-1 and VCAM-1; VCAM-1 is relatively unique to eosinophils as the interactions are mediated by α_4/β_1, α_D/β_2, and α_4/β_7 that are primarily expressed on eosinophils and not, e.g., on neutrophils. Binding to ICAM-1 occurs through interactions with α_L/β_2, α_M/β_2, and α_X/β_2, which are expressed on both eosinophils and neutrophils [17]. Circulating eosinophils express low levels of the β_1 and β_2 integrins that are in low activation conformations. Following allergen challenge or other signals, the β_1 integrins adopt an activated phenotype and there is increased expression of α_D/β_2 on the cell surface [20]. This is believed to facilitate binding to VCAM-1 in bronchial vessels or the sinus cavity. In a milieu where IL-5 is high, eosinophils have activation of the b_2 integrins and increased expression of α_M/β_2 on the cell surface producing a hyperadhesive phenotype [20].

As a countermeasure to turn off leukocyte activation, cells express a class of molecules known as the siglecs. These are sialic acid-binding Ig-like lectins that are expressed by cells of the innate immune system that contain immune receptor tyrosine-based inhibitory motif (ITIM) in their cytoplasmic tails. These motifs trigger inhibitory signaling, and thus, it is believed that these molecules dampen the immune response following cross-linking and promote resolution of inflammation [5]. Of the eight human siglecs that have been identified, eosinophils uniquely express Siglec-8 and this can be used to purify eosinophils from blood or tissue [55].

5.3.3 Activation of Eosinophils

In addition to aiding in the growth and maturation of eosinophils, IL-3, IL-5, and GM-CSF also stimulate mature eosinophil function. All prolong eosinophil survival by antagonizing programmed cell death [18, 49]. Other IL-5 activities include synergistically enhancing the chemotactic response of eosinophils toward chemokines or lipid mediators [43, 53], enhancing integrin-dependent adhesion and activating LTC_4 and superoxide generation, phagocytosis, helminthtoxic activity, and immunoglobulin-induced degranulation [22]. Both IL-3 and GM-CSF enhance eosinophil toxicity, superoxide production, phagocytosis, and degranulation.

Many other inflammatory cytokines also have effects on eosinophil function. For instance, TNF-α works by prolonging eosinophil survival [52], enhancing eosinophil synthesis of LTC_4 [41], and increasing eosinophil adhesion to endothelial cells [45]. Th2 cytokines, such as IL-4 and IL-13, also enhance eosinophil survival and induce eosinophil chemotaxis. Prostaglandin D_2, released by mast cells during an allergic response, induces cellular degranulation, chemokinesis, and rapid morphologic changes in the eosinophil that promote diapedesis.

5.3.4 Eosinophil Secretory Products

One of the most striking features of eosinophil-induced inflammation is the marked deposition of cationic granule proteins and release of biological products (Table 5.2). The granule proteins physiologically are

Table 5.1 Eosinophil cell adhesion molecules (CAMs)

Intergrins		Selectins		Immunoglobulin-like		Chemokine receptors		Other CAMs	
Surface molecule	Ligand	Surface molecule	Ligand	Surface molecule	Ligand	Surface molecule	Ligand	Surface molecule	Ligand
α_L/β_2 (CD11a/CD18)	ICAM-1, ICAM-2, ICAM-3	L-selectin (CD62L)	GlyCAM-1 CD34	PECAM-1 (CD31)	PECAM, heparan sulfate	CCR1	CCL3, CCL5	Ppg-1 (CD44)	Hyaluronic acid
α_M/β_2 (CD11b/CD18)	C3bi, ICAM-1, fibrinogen	PSGL-1 (CD162)	P-selectin	ICAM-1 (CD54)	α_L/β_2, α_M/β_2, rhinovirus	CCR3	CCL5, CCL7, CCL11, CCL13, CCL24, CCL26	Siglec-8	Sialic acid
α_X/β_2 (CD11c/CD18)	C3bi	$Lewis^X$ (CD15)	P-selectin	ICAM-3 (CD50)	α_L/β_2, α_D/β_2	CCR6	CCL20		
α_D/β_2 (CD11d/CD18)	VCAM-1	Sialyl-$Lewis^X$	E-selectin, P-selectin	LFA-3 (CD58)	CD2	CXCR1	CXCL8		
α_4/β_1 (CD49a/CD29)	VCAM-1, fibronectin	Leukosialin (CD43)	ICAM-1			CXCR2	CXCL8		
α_6/β_1 (CD49f/CD29)	Laminin					CXCR3	CXCL10		
α_4/β_7 (CD49d/β_7)	MAdCAM-1, VCAM-1, fibronectin					CXCR4	CXCL12		

Table 5.2 Biological products of eosinophils

Granule proteins	Lipid mediators	Cytokines/chemokines	Reactive oxygen species	Enzymes
Major basic protein (MBP)	Leukotriene B_4, C_4, D_4, E_4	Interleukin-1 alpha	Superoxide radical anion	Collagenase
MBP homologue (MBP-2)	Eoxin C_4	Interleukin-2	Hydrogen peroxide (H_2O_2)	92-kDa gelatinase
Eosinophil peroxidase	Lipoxin A_4	Interleukin-3	Hydroxy radicals	
Eosinophil cationic protein	5-HETE	Interleukin-4		
Eosinophil-derived neurotoxin	5,15- and 8,15-diHETE	Interleukin-5		
Charcot–Leyden crystal protein	5-Oxo-15-hydroxy-6,8,11,13-ETE	Interleukin-6		
Phospholipase A_2 (secretory PLA_2)	Prostaglands E_1 and E_2	Interleukin-10		
β-Glucuronidase	6-keto-prostaglandin F_1	Interleukin-12		
Acid phosphatase	Thromboxane B_2	Granulocyte-macrophage colony-stimulating factor		
Arylsulfatase B	Platelet activating factor	Tumor necrosis factor α Transforming growth factor α Transforming growth factor β1, 2 Platelet-derived growth factor-β Vascular endothelial growth factor Nerve growth factor CCL2 (MCP-1) CCL3 (MIP-1α) CCL5 (RANTES) CCL11, 24, 26 (eotaxin 1–3) CXCL8 (IL-8)		

toxic to numerous pathogens, especially helminthes, but can also damage and desquamate airway epithelial cells, elicit local edema, and produce airway hyperreactivity in asthma and allergic diseases. The granule contents include lysosomal hydrolases found in other granulocytes, as well as eosinophil-specific proteins such as major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN or RNAse 3). Cytokines, such as IL-5, GM-CSF, and IL-3, and chemokines, such as CCL5, enhance the ability of eosinophils to secrete these cationic proteins. In addition, eosinophil granule proteins, including MBP, stimulate eosinophils to degranulate, suggesting an autocrine mechanism of eosinophil activation [23]. Granules also contain eosinophil peroxidase (EPO), which catalyzes the production of hypochlorous or hypobromous acid that is highly toxic to pathogens but, in the case of allergic disorders and sinus disease, contributes to tissue damage. Similar to mast cells and basophils, activated eosinophils produce and release lipid mediators, including leukotrienes, PAF, and prostaglandins (Table 5.2). Finally, eosinophils are important sources of many proinflammatory cytokines. An additional, inflammatory mechanism through which eosinophils contribute to inflammation is derived from the recent recognition that within an inflammatory milieu, eosinophils evolve the capacity to function as antigen-processing and presenting cells. Eosinophils thereby further contribute to the presence and perpetuation of the predominantly Th2-like cytokine milieu present in eosinophilic disorders.

5.4 Pharmacological Approaches to Treating Eosinophilic Sinusitis

Insofar as NPs observed in patients with CHES, AERD, and AFS are defined by the accumulation of activated eosinophils, interventions designed to attenuate eosinophilic inflammation should be beneficial in this disorder. Discussion of some of these interventions is included in later chapters: anti-IgE (Chap. 22), corticosteroid treatment (Chap. 24), antifungal treatment (Chap. 25), aspirin desensitization (Chap. 27), and surgical intervention (Chaps. 30–32). Other novel treatments are considered below.

Leukotriene modifiers. NP tissue demonstrates increased presence of CysLTs and metabolic enzymes involved in LT synthesis [39, 48]. CysLTs have important proinflammatory capabilities including primarily their ability to promote eosinophilic inflammation. Other activities relevant to NP include their ability to increase vascular permeability, stimulate mucous secretion, and decrease mucociliary clearance [48]. Clinical trials of leukotriene modifiers in asthma and allergic rhinitis have shown reductions in both circulating absolute eosinophil counts and tissue eosinophilia [24, 40]. Leukotriene modifiers could therefore provide benefit in NP through direct reduction of eosinophil recruitment and activation. CysLT1 receptor antagonists (zafirlukast and montelukast) have been suggested to have efficacy in NP in uncontrolled trials [38]. Montelukast has been reported to decrease nasal itching, postnasal discharge, sneezing, and rhinorhea for 1 year in the patients with postendoscopic sphenoethmoidectomy status [32]. In the only placebo-controlled trial of an LT modifier in AERD, the 5-LO inhibitor, zileuton was shown to reduce polyp size and restore sense of smell [6]. The efficacy of zileuton is intriguing as inhibition of 5-LO has broader implications than the use of one of the CysLT1 receptor antagonists. In addition to blocking LTB_4 and the 5-oxo-ETE pathways, reduced synthesis of CysLTs will thereby block inflammation mediated through CysLT2 as well as CysLT1 receptor.

Newer biotechnology approaches. Although many cytokines are involved in eosinophil differentiation and maturation, IL-5 remains the only known molecule able to drive the increased eosinophil production that occurs in response to allergic, parasitic, or other eosinophil-associated disease processes, suggesting a uniquely useful role for targeting this cytokine. NP could be uniquely responsive to eosinophil-directed therapies, such as with humanized anti-IL-5 (mepolizumab) (discussed in greater detail in Chap. 22). Studies with this agent in asthma have been remarkably disappointing in terms of reversing bronchial hyperreactivity, preventing bronchospasm, and improving lung function [25]. This may reflect a lack of role for the eosinophil in these facets of asthma. In contrast, eosinophilic inflammation seems uniquely capable of inducing tissue fibrosis and mepolizumab was effective in reducing airway remodeling and matrix protein deposition in asthma [10]. As a disease characterized by exuberant remodeling and deposition of matrix proteins, NPs might be more responsive to eosinophilic-directed therapies than asthma. The relatively modest reported

success of this agent in CRSwNP, as with the studies of mepolizumab in hypereosinophil syndrome, might reflect inclusion of subjects with varying degrees of underlying eosinophilic (and IL-5-dependent) inflammation.

However, that significant residual tissue eosinophilia was observed in the mepolizumab asthma studies [11] suggests that single target interventions may insufficiently reduce tissue eosinophilia to produce adequate therapeutic benefit in NP. This reflects in part the complementary role of other cytokines, including especially GM-CSF, in promoting activation and differentiation of eosinophilic precursors [3]. The shared use of the same β-chain by the receptors for IL-5 and GM-CSF (as well as IL-3) suggests that this might prove to be a more inviting target for intervention.

The failure of mepolizumab in the asthma studies also reflects roles for constitutive (IL-5-independent) eosinophilopoiesis. As would be predicted, this agent largely eliminated the presence of bone marrow and circulating eosinophilia, but only reduced lung eosinophilia by ~50%. In addition to blocking the antiapoptotic and maturing influences of GM-CSF, complete attenuation of tissue eosinophilia is likely to also require interventions to abrogate tissue recruitment of eosinophils. This could include the need to attenuate expression of eosinophil-specific chemoattractants including chemokines (e.g., inhibition of CCL11 (eotaxin), CCL24, CCL26 using chemokine-receptor CCR3 antagonists) and also targeting other chemoattractants such as PAF and CysLT. Other targets of therapy include eosinophil-specific adhesion molecules (e.g., through the use of VLA-4 antagonists) [31]. Arguably no single agent is likely to be effective for NP and it will be necessary to synergistically block both the eosinophilopoietic bone marrow component of NP and local factors critical for inflammatory cell recruitment.

5.5 Conclusion

Our understanding of NP has advanced in recent years, due in part to the recognition that this is not just one disease, but many different diseases affecting the sinus tissue. Noneosinophilic NP often responds well to surgical intervention; however, NP with an eosinophilic infiltrate has proven more difficult to manage. Eosinophils can produce many factors that are involved in inflammation and remodeling of the polyp tissue. This serves to perpetuate the disease in a continual feedback loop. As our understanding of the eosinophil has progressed, we have been able to target therapy to modulate these pathways and lessen the impact of disease on the quality of life for the patient. New therapies are being developed that offer the promise of even better control of symptoms.

Take Home Pearls

- The eosinophil can contribute to the pathophysiology of many different subtypes of sinus disease including chronic hyperplastic sinusitis, aspirin exacerbated respiratory disease, and allergic fungal sinusitis.
- Eosinophils develop in the bone marrow under the influence of IL-3, IL-5, and GM-CSF. As the eosinophil matures, the dependence on IL-5 is lost and this may explain the limited success in eosinophilic diseases of therapies aimed at blocking IL-5.
- Many factors, including interleukins, chemokines, and leukotrienes, are involved in the recruitment of eosinophils to sites of inflammation. The combination and levels of these factors influence where in the tissues the eosinophils migrate.
- As an eosinophil responds to a signal, adhesion molecules are involved in the migration from the blood into the tissues. Integrins and selectins are molecules that promote the migration into the tissues, while siglecs antagonize this action.
- As part of the natural response, eosinophils can release many mediators including interleukins, chemokines, leukotrienes, reactive oxygen species, and eosinophils specific molecules that can help recruit cells of the adaptive immune system or destroy invading parasites. When uncontrolled, this can lead to the damage of the host tissue.
- Many pharmaceutical approaches have been or are being developed that target the eosinophil. It is believed that elimination of the hyperactive eosinophil will lead to decreased inflammation, hyperreactivity, and tissue remodeling.

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Radiologic Imaging of Nasal Polyposis

6

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Core Messages

- CT is the primary modality used to evaluate patients with NP, but MR does have an occasional role.
- Conventional radiographs are no longer within the standard of care for the evaluation of the paranasal sinuses.
- Modern helical multislice CT scanners can produce reconstructed images of diagnostic quality in any plane of imaging.
- Cystic fibrosis patients have preferential opacification of the paranasal sinuses, whereas non-CF patients with NP have preferential opacification of the nasal cavity.
- On MRI, fungal infection may have very low signal on T2-weighted images, and may thus mimic aerated sinuses.

6.1 Introduction

Radiology plays several crucial roles in the evaluation of chronic rhinosinusitis (CRS) patients with nasal polyposis (NP), including establishing the diagnosis, evaluating progression of disease, surgical planning, and monitoring for recurrence. Computed tomography (CT) is the primary modality used to evaluate patients with NP, but magnetic resonance (MR) does have an occasional role.

Among sinus surgeons, endoscopy is considered the primary means of evaluating sinonasal cavity. However, radiologic modalities are used more frequently among primary caregivers, and in some instances, radiology may provide a more complete analysis of the nasal cavity and sinuses [7]. This is particularly true when the nasal cavity is completely filled with tissue, as may be the case in NP. The purpose of this chapter is to discuss the radiologic appearance of sinonasal polyps and specifically describe the findings that are associated with NP.

6.2 Radiologic Appearance of Sinonasal Polyps

Polyps appear radiographically as rounded nodules of soft tissue along the mucosal surfaces of the paranasal sinuses and nasal cavity. They are usually more radiodense than the surrounding mucosal thickening or secretions, which make them appear slightly brighter on CT (Fig. 6.1). This pattern may be reversed if the secretions become inspissated (Fig. 6.2). Sometimes, a thin pedicle is visible connecting the bulk of the polyp to the mucosal surface (Fig. 6.2). This sign may be helpful when it is present, but it is not seen in the majority of polyps.

Polyps do not erode into the surrounding bone, but pressure from a polyp may produce a benign local remodeling pattern that scallops the underlying bone (Fig. 6.3). This is distinct from a mucocele, in which the entire sinus expands. This bone remodeling will occasionally thin bony septations beyond the resolution of CT, giving the appearance of bone erosion, particularly in the ethmoid septations (Fig. 6.4).

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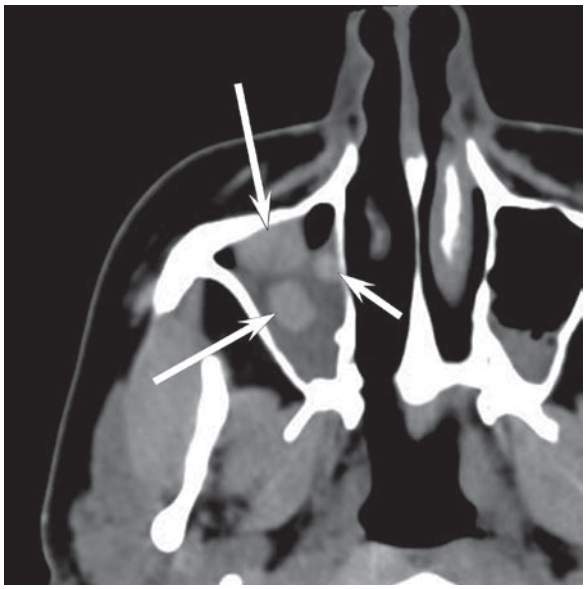

Fig. 6.1 Hyperdense sinonasal polyps. Axial CT shows polyps (*arrows*) within the maxillary sinus. The polyps are denser than the surrounding secretions

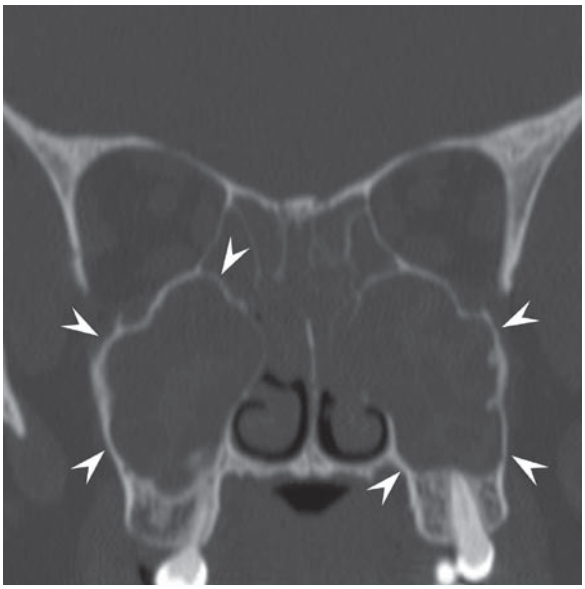

Fig. 6.3 Bony remodeling from polyps. Coronal CT shows lobular remodeling of the maxillary sinus walls (*arrowheads*) in this patient with NP. This scalloped pattern suggests a benign etiology

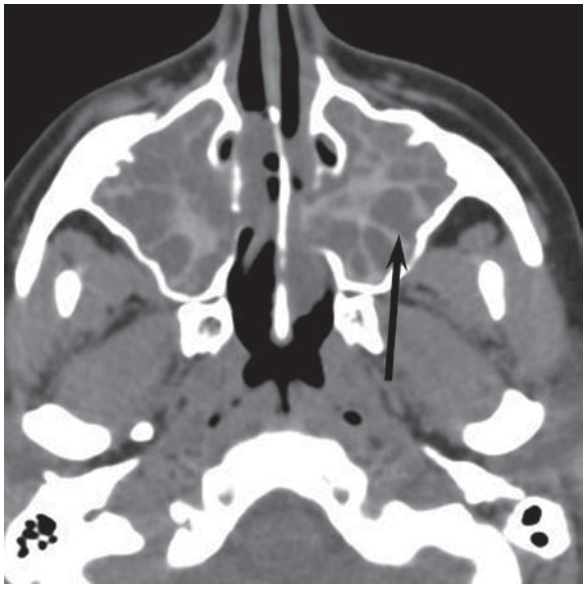

Fig. 6.2 Hyperdense secretions. Axial CT shows innumerable polyps in the maxillary sinus in a patient with NP. Some of the polyps are pedunculated (*arrow*), distinguishing them from MRC. The inspissated secretions between the polyps have increased density, which reverses the normal density pattern seen in Fig. 6.1

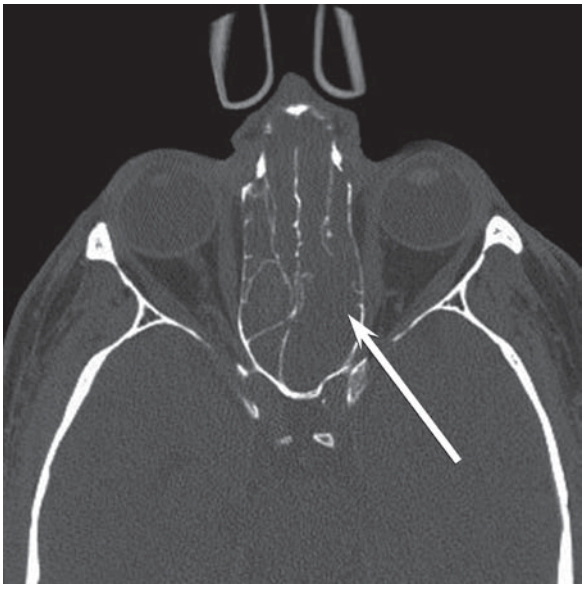

Fig. 6.4 Remodeling of the ethmoid septa. Axial CT of a patient with NP shows thinning of the posterior ethmoid septa (*arrow*) so that they are no longer visible on CT. This is still a benign pattern

Polyps themselves do not enhance with contrast administration. However, the mucosa surrounding the polyp may enhance, giving the impression of rim enhancement (Fig. 6.5). This thin, uniform rim of enhancement is usually distinguishable from the complete enhancement of nonnecrotic tumors and the irregular enhancement of necrotic tumors.

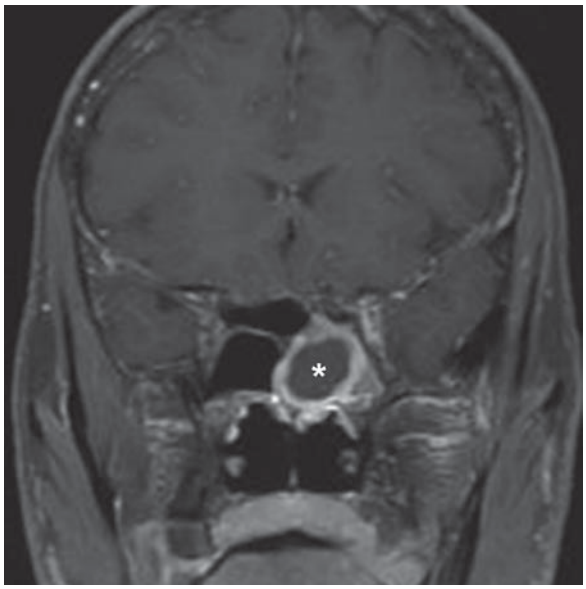

Fig. 6.5 Mucosal enhancement around a polyp. Coronal contrast-enhanced T1-weighted MR image shows a low-signal polyp (*asterisk*) surrounded by a rim of enhancement. This rim of surrounding thickened mucosa should not be mistaken for the rim enhancement of a necrotic tumor

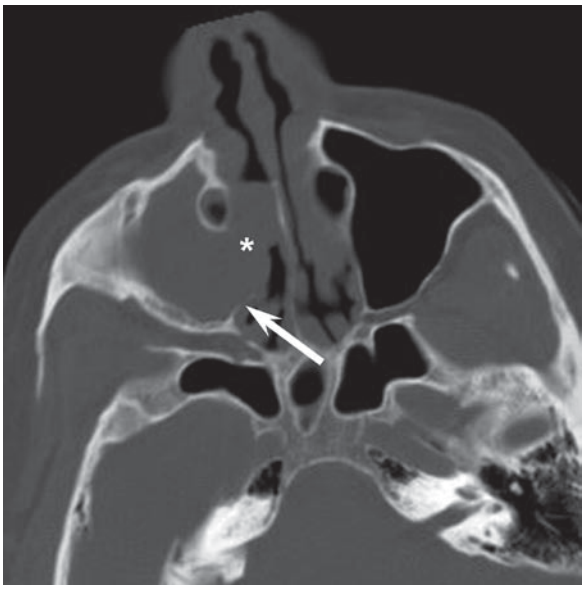

Fig. 6.6 Antronasal polyp. Axial CT shows a mass filling the right maxillary sinus and extending into the nasal cavity (*asterisk*). The medial wall of the sinus is remodeled (*arrow*), indicating a benign etiology

The location of the polyp can sometimes be predicted by the patient's symptomatology [6]. Polyps under the cribriform plate may interfere with smell or taste; polyps obstructing the frontal sinus will cause frontal headaches, and polyps near the sphenoethmoidal recess will cause deep central headaches. These guidelines are not absolute, however, because pain may be referred to (or from) other areas of the head and neck. In most primary cases of NP without surgery, facial pain is an uncommon finding.

6.3 Special Types of Sinonasal Polyps

Solitary polyps that arise within the maxillary sinus (also called the maxillary antrum) may extend into the nasal cavity by remodeling and expanding the maxillary os and infundibulum. These lesions are called antronasal polyps. Sometimes, the polyp will be narrowed as it passes through the maxillary os, resulting in a dumbbell configuration on coronal CT. The medial wall of the maxillary sinus is usually bowed into the nasal cavity (Fig. 6.6). If the middle meatus becomes obstructed, secondary opacification of the ethmoid and frontal sinuses may mask the true source of the obstruction. In this scenario, the remodeled bone of the medial maxillary wall becomes an important diagnostic sign of antronasal polyp.

If an antronasal polyp becomes so large that it extends through the nasal cavity and across the choana into the nasopharynx, it is referred to as an antrochoanal polyp [2]. The most helpful radiologic feature is the mass itself extending into the nasopharynx (Fig. 6.7). Care should be taken, however, that a polyp of the posterior aspect of the inferior turbinate that extends across the choana is not mistaken for a true antrochoanal polyp. These polyps that arise in the nasal cavity and extend into the nasopharynx are called nasochoanal polyps. While the posterior aspect of the inferior turbinate may be enlarged and edematous, it is exceedingly rare for the inferior turbinate to undergo true polypoid changes, whereas the middle turbinate in patients with NP frequently undergoes polypoid changes. Radiographically, these changes of edema and polypoid transformation are indistinguishable.

Although inflammatory NP is frequently solitary, multiple sinonasal polyps can occur outside the setting of true NP. It is important to distinguish these entities for prognostic and therapeutic reasons. Complete pansinus opacification is more suggestive of NP (Fig. 6.8) [3]. Numerous convexities

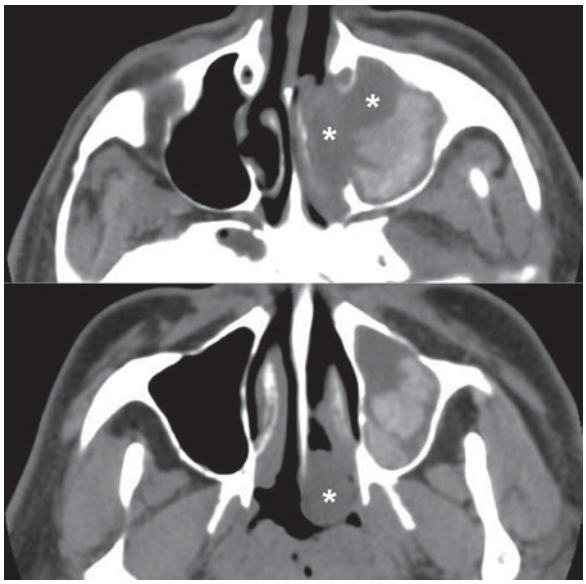

Fig. 6.7 Antrochoanal polyp. Axial CT images show a low-density polyp (*asterisk*) extending from the antrum, across the nasal cavity, through the choana, and into the nasopharynx. Fungal colonization of entrapped secretions results in high density in the remainder of the antrum

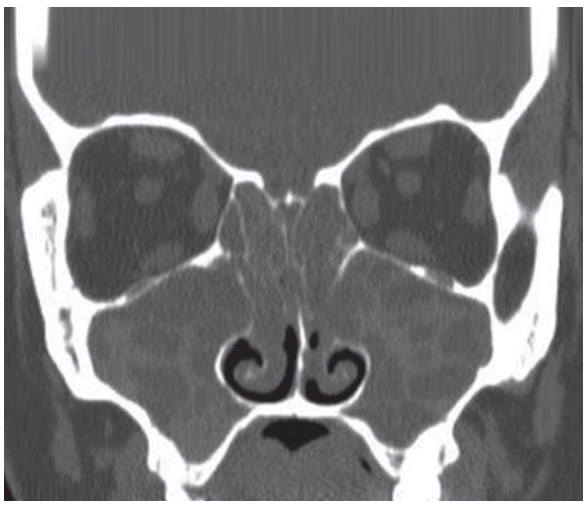

Fig. 6.8 Pansinus opacification in NP. Coronal CT shows complete opacification of the paranasal sinuses and near-complete opacification of the nasal cavity. The severity of disease suggests NP over multiple sporadic polyps

are usually visible along the inferior surface of the opacified nasal cavity in NP (Fig. 6.9). Severity of disease is also an indicator – there are usually many polyps in NP.

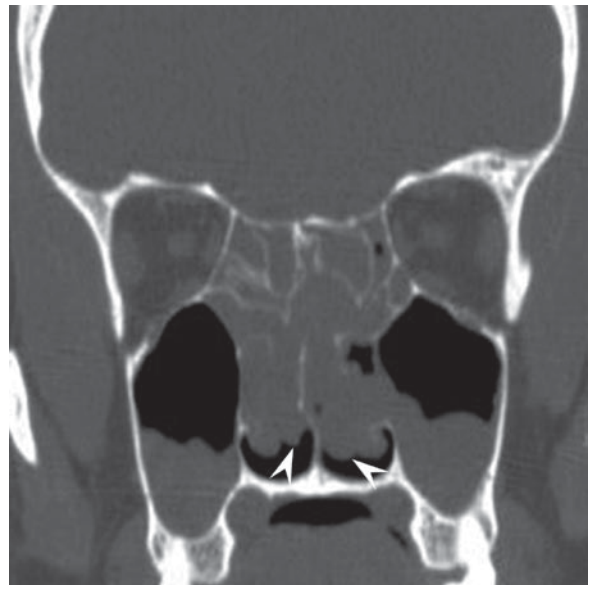

Fig. 6.9 Intranasal convexities in NP. Coronal CT shows numerous convex surfaces (*arrowheads*) along the aerated border of the nasal cavity. This finding suggests polyposis over other sinonasal diseases such as cystic fibrosis

6.4 Complications

If a sinonasal polyp arises in (or extends into) the middle meatus, it may obstruct outflow from the frontal sinus, the maxillary sinus, and the anterior ethmoid air cells. This can be referred to as a middle meatus syndrome (Fig. 6.10). Unilateral involvement of just these sinuses is highly suggestive of an obstructing mass. A chronically obstructed sinus may form a mucocele. On CT, the affected sinus enlarges and its walls become rounded outward (Fig. 6.11). This complication may be seen from NP itself, but is also commonly seen as a complication of polypectomy. An infected mucocele is called a mucopyocele, and it may be distinguished from an uninfected mucocele by MRI [1]. Sometimes, mucoceles will impinge upon surrounding structures such as the orbit (Fig. 6.12). In patients with NP, even if no mucocele is formed, the pressure from the polyps will often cause rarefaction of the ethmoid trabeculae (Fig. 6.13).

Fungal disease may coexist with NP, including a subgroup of CRS with NP termed allergic fungal sinusitis (AFS). On CT, the presence of hyperdense secretions between layers of thickened, hypodense mucosa is suggestive of AFS (Fig. 6.14). On MRI, fungi may have very low signal on T2-weighted

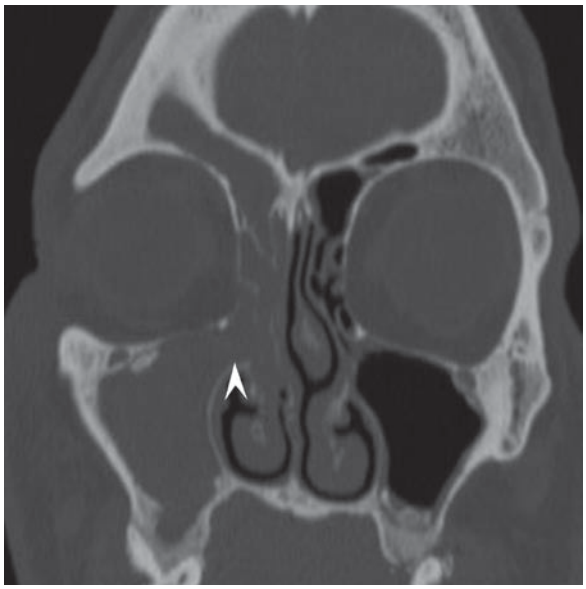

Fig. 6.10 Middle meatus syndrome. Coronal CT shows unilateral opacification of the maxillary, ethmoid, and frontal sinuses. Note the widened infundibulum (*arrowhead*) that indicates the offending antronasal polyp

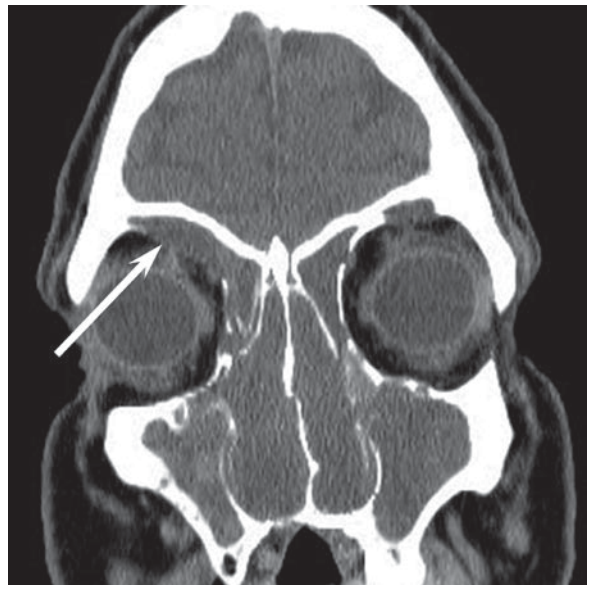

Fig. 6.12 NP with frontal mucocele causing mass effect on the orbit. Coronal CT shows complete opacification of the nasal cavity and sinuses, consistent with NP. The frontal sinus is expanding into the orbit (*arrow*). The underlying bone is thinned beyond the resolution of this CT

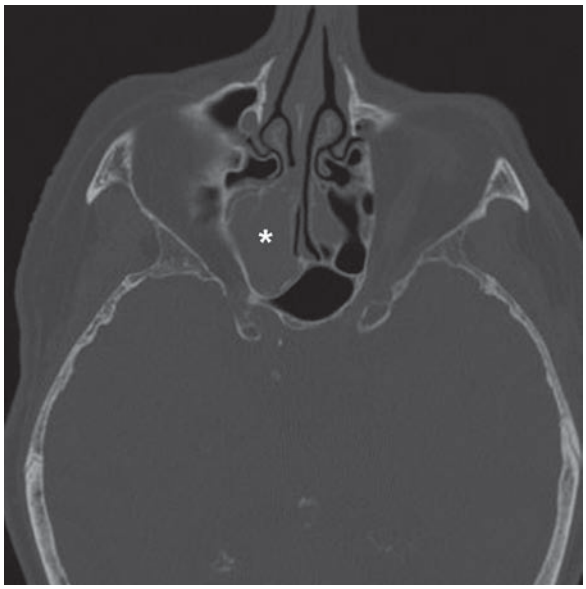

Fig. 6.11 Mucocele. Axial CT shows an enlarged, opacified posterior ethmoid air cell (*asterisk*) with rounded convex borders. The surrounding sinuses are compressed

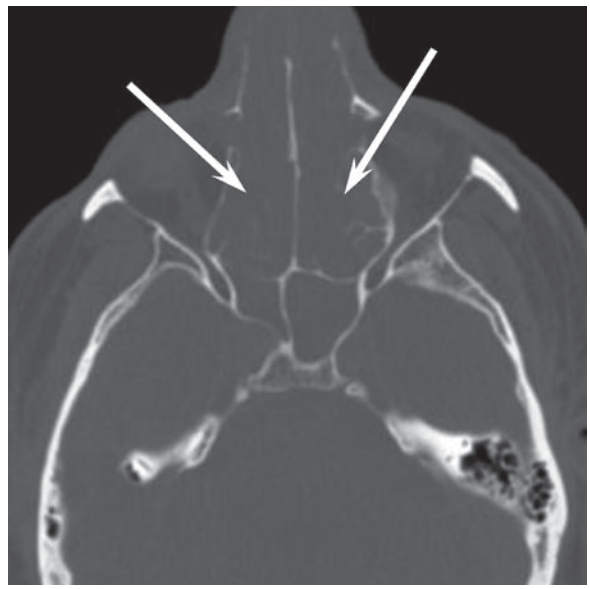

Fig. 6.13 Rarefaction of ethmoid trabeculae in NP. Axial CT shows thinning of the ethmoid septations (*arrows*) beyond the resolution of CT. Compare with Fig. 6.4

images, and may thus mimic aerated sinuses (Fig. 6.15) [1]. Correlation with other pulse sequences is critical to avoid this diagnostic error. Unfortunately, the CT and MR findings of inspissated secretions overlap with those of fungal associated inflammation, and either may be seen in patients with NP.

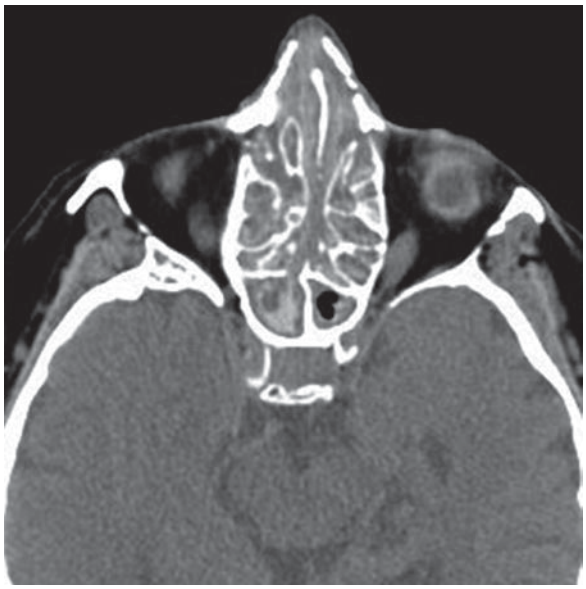

Fig. 6.14 Allergic fungal sinusitis. Axial CT shows the nasal cavity and ethmoid air cells to be filled with hyperdense secretions between layers of thickened, hypodense mucosa

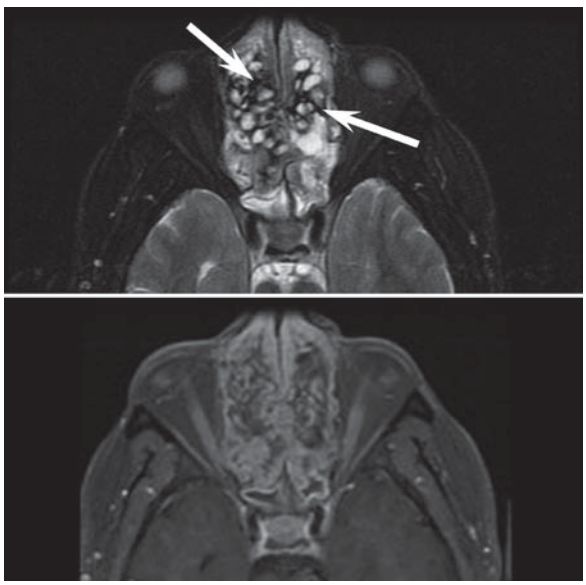

Fig. 6.15 NP complicated by allergic fungal sinusitis (AFS). On the axial T2-weighted image (**a**), areas of high signal (polyps) alternate with areas of low signal (*arrows*) indicating fungal infection. The corresponding postcontrast T1-weighted image (**b**) shows the characteristic flowing enhancement pattern of AFS

6.5 Radiologic Differential Diagnosis

6.5.1 Acute Rhinosinusitis

Acute rhinosinusitis may cause near-complete opacification of the nasal cavity and paranasal sinuses. However, rhinosinusitis lacks the multiple convexities seen in NP (Fig. 6.9). The presence of dense polypoid tissue (Fig. 6.1) is also an important distinguishing feature.

6.5.2 Mucus Retention Cyst

Mucus retention cysts (MRC) have a radiographic appearance that is almost identical to that of solitary polyps. If a pedicle is present (Fig. 6.2), the mass is more likely a polyp. If there is remodeling of underlying bone (Fig. 6.3) or expansion through the sinus osteum (Fig. 6.6), MRC is excluded. Usually, however, no distinguishing radiologic feature is present. But since solitary polyps and MRC both reflect chronic inflammation, the distinction is not usually of clinical importance. Thus, for small mucosal masses, radiologists may apply either term without fear of patient mismanagement.

6.5.3 Other Benign Masses

Inverted papillomas are often indistinguishable from polyps radiographically. Papillomas that occur in a characteristic location may be identifiable, such as inverted papillomas that arise in the medial wall of the antrum and extend both into the antrum and the nasal cavity (Fig. 6.16). A lobular ("cerebriform") configuration is also suggestive of papilloma. Bony sclerosis and osteoneogenesis are frequently present at the site of attachment of inverted papillomas.

Juvenile nasal angiofibromas are easily distinguished from other benign nasal mass by their characteristic location (centered at the sphenopalatine foramen), enhancement pattern, and remodeling of surrounding bony structures [4]. They rarely present a diagnostic dilemma. Encephaloceles and meningoceles can be surprisingly difficult to diagnose when imaged in axial

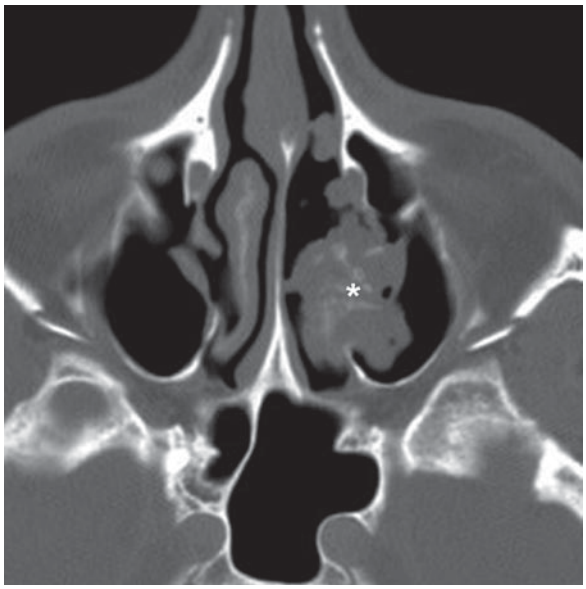

Fig. 6.16 Inverted papilloma. Axial CT shows a lobular mass (*asterisk*) centered in the lateral nasal wall, with extension into both the nasal cavity and the maxillary sinus. The location, configuration, and central calcifications are all indicative of inverted papilloma

plane. Coronal imaging is most useful to establish the communication with the cranial vault. While coronal T2-weighted MRI is useful to confirm this diagnosis and determine the amount of herniated brain tissue, the most important aspect of care is to consider the diagnosis in the first place [1].

6.5.4 Malignancy

Malignant intranasal masses that may mimic polyps include esthesioneuroblastoma, sinonasal undifferentiated carcinoma, squamous cell carcinoma, minor salivary malignancies, and malignant melanoma. These tumors will usually have an aggressive appearance, with erosion of underlying bone, rather than the benign remodeling (or no effect) seen with polyps (Fig. 6.3). Benign minor salivary tumors can arise from any mucosal surface, and may be seen in the same distribution as polyps. These tumors tend to remodel bone, but usually show pronounced focal remodeling, even when the tumor is small. Small polyps, in contrast, rarely cause remodeling.

6.5.5 Dense Secretions

Polyps, inspissated secretions, and fungal colonization can all result in material of greater-than-water density within the sinuses (Figs. 6.1, 6.2, and 6.14). Distinguishing between these entities can be difficult radiologically, even with MRI [1]. T2 signal dropout is classically associated with fungal infection, but can be seen also with inspissated secretions; it is unusual in polyps themselves. A rapid increase in the CT density of a polyp suggests fungal colonization of the polyp [4].

6.5.6 Cystic Fibrosis

There are few diseases that affect the sinuses as severely as NP. The other major contender is cystic fibrosis (CF). The clinical history of these diseases does not generally overlap, but there are also radiologic differences in the sinus manifestations (Fig. 6.17). CF tends to spare the nasal cavity, whereas NP is more likely to spare the sinuses themselves (Figs. 6.9 and 6.17). NP has more convex surfaces in the nasal cavity, whereas

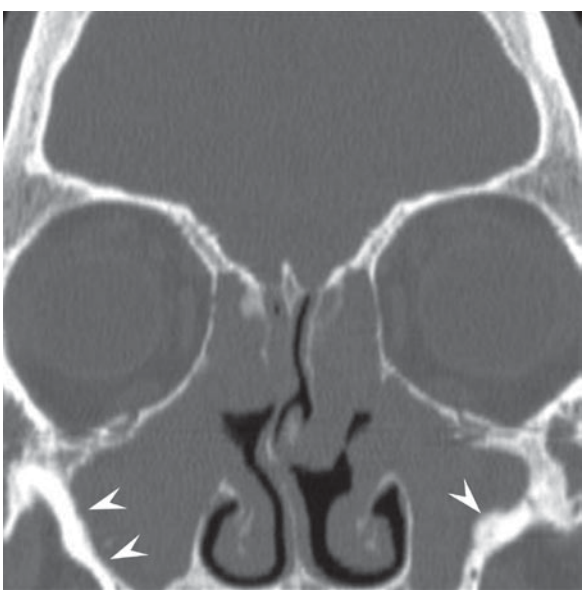

Fig. 6.17 Cystic fibrosis. Coronal CT in a patient with cystic fibrosis shows fewer convex surfaces than in patients with NP, relative sparing of the nasal cavity, and extensive osteoneogenesis (*arrowheads*). Compare with Fig. 6.9

CF produces a greater degree of osteoneogenesis in the sinus walls.

6.6 Radiologic Modalities

CT is the most frequently used radiologic modality for the assessment of NP. The detailed bony anatomy that is available on CT makes it more useful than MR, even though MR better characterizes soft tissue [1]. MR is mostly used after a mass is known, to differentiate between the mass and obstructed secretions or to limit the differential diagnosis. The multiplanar capabilities of MR are sometimes touted as an advantage over CT, which is intrinsically limited to the axial plane of imaging. However, modern helical multislice CT scanners can produce reconstructed images of diagnostic quality in any plane of imaging. Most of the diagnostic evaluation on CT is based on coronal images, but axial images are still useful to establish anatomic relationships. Multiplanar imaging with CT also allows for the use of sagittal CT images, particularly when evaluating the basal lamella of the middle turbinate or differentiating between anterior and posterior ethmoid cells. A CT scanner should have at least four data channels (preferably 16) for reconstructions to be of adequate quality.

Conventional radiographs are no longer within the standard of care for the evaluation of the paranasal sinuses. They may be used as a screening test for acute maxillary sinusitis, but evaluation of diseases such as NP requires cross-sectional imaging. Intravenous contrast is routinely used in MR imaging, but is usually not indicated with CT. Contrast is sometimes applied in the setting of a known tumor to evaluate the relationship to nearby vascular structures, or in the setting of a potential recurrence of an enhancing tumor. It is rarely useful in NP.

CT and MR are now routinely used for computer-assisted image-guided endoscopic sinus surgery for NP. CT may also have an important predictive value when preparing patients for sinonasal surgery – patients with greater opacification of the sinonasal regions on preoperative CT are at greater risk of complications during surgery [5].

Take Home Pearls

- Numerous intranasal convexities are the radiologic hallmark of NP.
- Spherical remodeling of sinus walls is the radiologic hallmark of a mucocele.
- The presence of hyperdense secretions between layers of thickened hypodense mucosa is suggestive of AFS.
- Polyps do not erode into the surrounding bone, but pressure from a polyp may produce a benign local remodeling pattern that scallops the underlying bone.
- Antronasal polyps show a dumbell configuration across the osteomeatal complex.
- Complete pansinus opacification is more suggestive of NP than of multiple sporadic polyps.

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Pathogenesis and Pathophysiology of Nasal Polyps

7

Mirko Tos, Per L. Larsen, Knud Larsen, and Per Caye-Thomasen

Core Messages

- The pathogenesis of nasal polyps explains how the polyps start and grow.
- The pathophysiology of nasal polyps explains the events and processes taking place in the outgrowth of nasal polyps.
- Histopathological studies at various stages of polyp formation, using whole-mount methods, the glands of the uncut polyps and the ordinary histological sections, allow our statements on pathogenesis of nasal polyps.
- Origin and incidence of nasal polyps on autopsies, studies on the changing epithelium and quantitative studies of the inflammatory cells of the nasal polyps, removed from the patients, allow us some statements on pathophysiology of the nasal polyps.
- In fact, only the age of the nasal polyps separates the term pathogenesis from the pathophysiology.

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7.1 Introduction

Several pathogenetic theories on the formation of nasal polyps have been published during the last 150 years that have been summarised previously [23]. These theories are based on oedema, an increase in tubulo-alveolar glands, the presence of the cysts of mucous glands and on mucous glands of NP.

7.2 Adenoma and Fibroma theory

Billroth [3] found increased number of long tubulous glands in the polyps. He interpreted them as new formations within the nasal mucosa. The NP were interpreted as adenomas that began by growing under the nasal mucosa, pushing the epithelium and the original nasal glands outwards (Fig. 7.1). Hopmann [10] did not find any glands in the NP from his study and interpreted NP as soft fibromas, protruding towards the nasal mucosa. Both the adenoma theory and the fibroma theory have been refuted in the past century.

7.3 Necrotizing Ethmoiditis Theory

This theory supposes that ethmoiditis leads to periostitis and osteitis of the ethmoid bone and causes bone necrosis (Fig. 7.2). The necrotic bone becomes surrounded by the myxomatous tissue, which projects towards the nasal mucosa, which is pressed caudally as a polyp. Hayek [9] argued strongly against this theory, based on the fact that he could not found bone necrosis in the ethmoid sinus.

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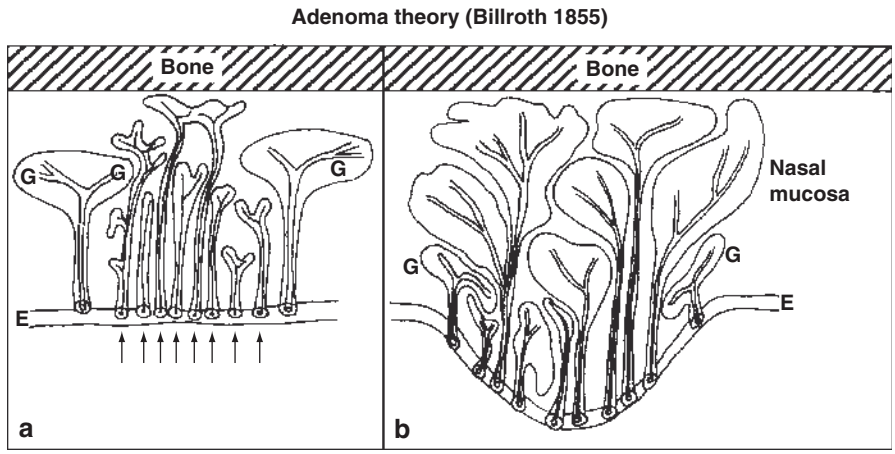

Fig. 7.1 Adenoma theory on polyp formation. (**a**) New formation of glands in nasal mucosa (*arrows*). (**b**) Newly formed glands are growing and pushing the original epithelium outwards as a polyp (*E* epithelium; *G* original tubulo-alveolar mucosal glands)

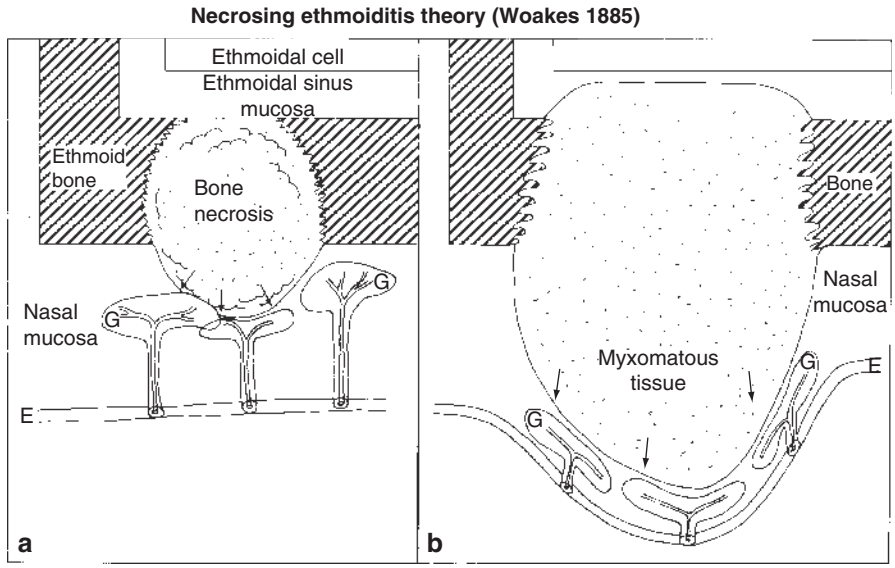

Fig. 7.2 Necrosing-ethmoiditis theory [29]. (**a**) Bone necrosis within the ethmoid bone, with myxomatous tissue protrusion toward the nasal mucosa (*arrows*). (**b**) Growth of the myxomatous tissue pressing the nasal tubulo-alveolar glands (*G*) downward as a polyp (*arrows*)

7.4 Glandular-Cyst Theory

This theory is based upon the presence of cystic glands and mucus-filled cysts in NP [8]. This is the oldest of several theories involving the mucous glands directly. It is hypothesised that oedema of the nasal mucosa causes obstruction of the ducts of basal glands, leading to the formation of cysts in the nasal mucosa (Fig. 7.3a). The cysts expand and push the nasal mucosa downwards, forming a polyp (Fig. 7.3a, b). However, Taylor [21] and our studies [22, 24, 28] have shown that cystic dilatation of the glands occurs after the polyp has been formed.

7.5 Mucosal Exudate Theory

Hayek [9] believed that the formation of NP started via an exudate localised deep in the nasal mucosa, which pressed outwards caudally (Fig. 7.4a). A vascular stalk then forms and vascular congestion increases the volume of the polyp (Fig. 7.4b). According to this theory, both layers of the tubulo-alveolar sero-mucous nasal glands should be displaced outwards and be found in the distal part of the polyp. Our studies have not found such glands in the NP [22, 24, 28]. Glands in NP develop after the polyp has been formed and attained a certain size.

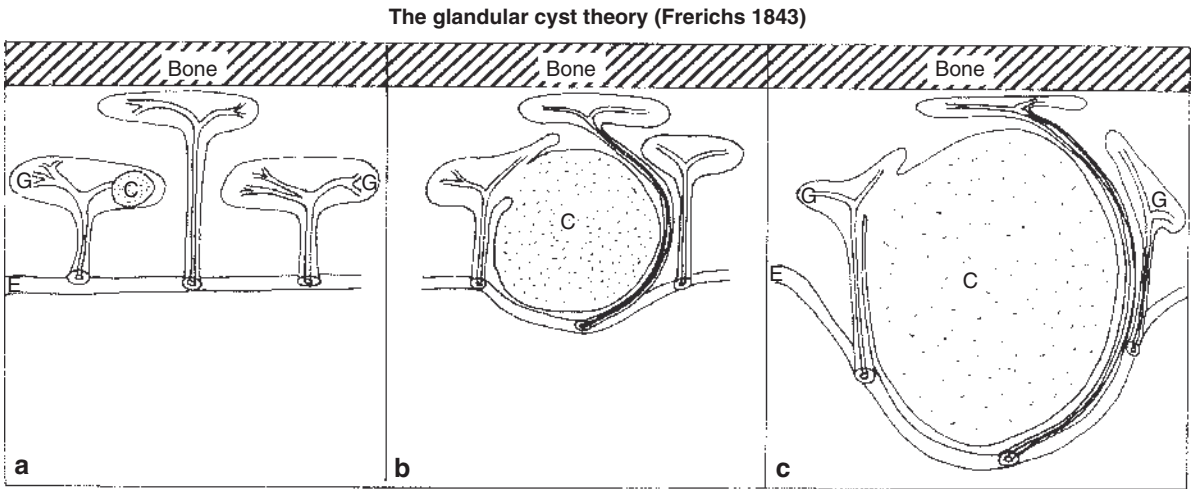

Fig. 7.3 Glandular-cyst theory. (**a**) A cyst (*C*) is formed within the nasal tubulo-alveolar gland (*G*). (**b**) The cyst (*C*) is expanding, pressing the nasal epithelium outwards. (**c**) Further expanding of the cyst (*C*) results in the nasal polyp

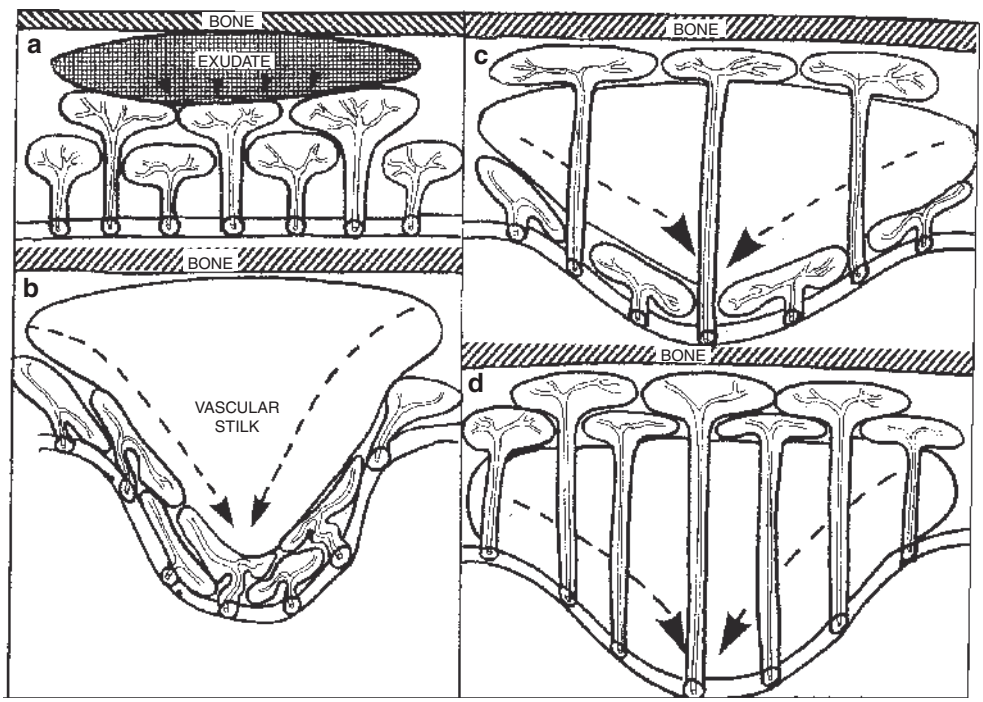

Fig. 7.4 Mucosal exudate or/and mucosal oedema theories on nasal polyp formation. (**a**) Nasal mucosa with an expanding exudate localised between the bone and the deeper layer of the tubulo-alveolar glands. (**b**) The expanding exudate has displaced both layers of the glands outwards in a nasal polyp (*arrows*). As a consequence of this theory, the tubulo-alveolar glands should be found in the distal part of the polyp, which is not the case. (**c**) In this situation exudates or oedema is predominantly between the deep and superficial glandular layers. Expansion of the oedema pushes the superficial layer outwards as a nasal polyp. As a consequence of this theory, the superficial layer of the tubulo-alveolar glands should be in the distal part of the polyp, which is not the case. (**d**) In predominantly sub-epithelial oedema

7.6 Theory on Cystic Dilatation of the Excretory Duct of Nasal Glands and Vessel Obstruction

In chronic inflammation of the nasal mucosa, excretory ducts of nasal tubulo-alveolar glands are obstructed, distended and dilatated into cystic structures [31]. The capillaries and veins (which are arranged around the excretory ducts and the gland mass) become stretched and obstructed, resulting in increased permeability, transudation and oedema. Our comment to this pathogenesis is that cystic dilatation of glands occurs among the newly formed glands only after the polyp is formed. The dilatation of tubulo-alveolar glands is seen in the nasal mucosa as a result of the hereditary gene defect of mucus transport through the duct system. This theory has been used to explain polyp formation in cystic fibrosis. We found in the NP exactly the same newly formed, long, tubulous glands in patients with and without CF [24, 28].

7.7 Blockade Theory

The theory of Jenkins [11] is based on the premise that the polyp formation is always preceded by the same degree of chronic inflammation, either infectious or allergic. The polyp itself is an accumulation of intercellular fluid dammed up in a localised tissue. The dam is usually caused by an infiltration of round cells, producing blockade of intercellular spaces and local lymph oedema. If the blockade persists, a typical polyp forms, and if the blockade covers a large area, multiple polyps may form. If the blockade of the same round cells is lifted, accumulated fluid in the polyps will be absorbed, and the polyps will disappear. This is one of the many theories of polyp formation based on oedema, but in our opinion, it does not explain why and how polyps can arise in one particular place but not in another.

7.8 Peri-Phlebitis and Peri-Lymphangitis Theory

The theory of Eggston and Wolff [6] is based upon the recurrent infections that lead to the blocking of intercellular fluid transport in the mucosa and oedema of the lamina propria. If the oedema involves major areas, the result is the prolapse of the mucosa and formation of polyps. This theory is based upon the demonstration of chronic vascular changes in the nasal mucosa, but these changes are diffuse, and the theory cannot explain how the polyp is formed in a particular place. The theory is an explanation for oedema formation rather than polyp formation.

If the oedema forms predominantly deep in the lamina propria and beneath the deepest glandular layer (Fig. 7.4a, b), this would lead to a situation already discussed by the theory of Hayek [9]. We should find displaced and prolapsed tubulo-alveolar mucous glands in the most distal part (top) of the nasal polyp, but we did not find such glands in the polyps. If the oedema arises predominantly between the deeper and the superficial layers of glands (Fig. 7.4c), the superficial layer of the tubulo-alveolar glands should be found in the distal parts of the NP, but this was not the case in our studies [24]. Furthermore, the elongated ducts of the deeper layer of the tubulo-alveoral glands should be found in the stalk of the polyp. If the oedema is localised predominantly sub-epithelially in the nasal mucosa between the epithelium and the superficial layer of glands, the epithelium will bulge out in the form of a polyp and pull out the ducts of the nasal glands (Fig. 7.4d). In such case, the stalks of the polyps would contain mainly long ducts, which we did not found.

7.9 Glandular Hyperplasia Theory

Krajina [13] found in cases of chronic infection or allergy localised infiltrates in the nasal mucosa and localised hyperplasia of nasal glands. The glands will increase in size and cause bulging of the mucosa (Fig. 7.5). Apart from the gland hyperplasia, the change of the blood vessels and the oedema in the region of the middle nasal meatus will lead to mucosal prolapses in the form of polyps. We did not find tubular-alveolar glands in polyps. In the chronic hypertrophic rhinitis, there is very little gland hyperplasia in the nasal mucosa and we did not observe localised bulging of the nasal mucosa on the inferior turbinate caused by hyperplasia of the nasal glands [22, 24, 28]. The number and density of glands were the same in patients with chronic hypertrophic rhinitis and in normal subjects [22, 25, 26].

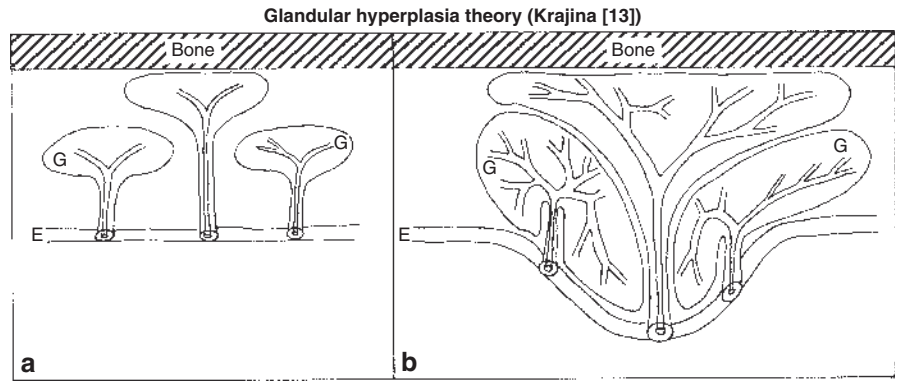

Fig. 7.5 Glandular hyperplasia theory of Krajina (1963) on nasal polyp formation. (**a**) Normal nasal tubulo-alveolar glands (*G*) arranged in two layers. (**b**) Hyperplasia of nasal glands causing protrusion of nasal mucosa, especially the nasal epithelium (*E*)

7.10 Epithelial Rupture Theory

We studied the shape, distribution, density and histologic profiles of the glands by staining NP using the whole-mount method, implicating that the polyp is not sectioned, but stained and studied in total. Based on these studies, we described a new theory for the pathogenesis of NP [27]. We postulated that in the initial stage of polyp formation, an epithelial rupture or necrosis caused by inflammation and tissue pressure from the oedematous and infiltrated lamina propria takes place (Fig. 7.6a). Lamina propria protrudes through the epithelial defect, and the adjacent epithelium tends to cover the defect by migrating from the surroundings (Fig. 7.6b). If the epithelial defect is not covered soon enough or if it is insufficiently covered, the prolapsed lamina propria continues to grow and the polyp, with its vascular stalk, is established (Fig. 7.6c). After epithelialization of the polyp, the characteristic new, long tubulous glands are formed (Fig. 7.6d, e).

Whole-mount studies elucidated the structure and density of glands in NP and showed that their shape and distribution were completely different from normal nasal mucosal sero-mucous glands.

Our studies strongly indicate that the glands of the polyps are newly formed structures and that the polyps are not a prolapse of the original nasal mucosa. We have been able to confirm the epithelial rupture theory in experimental otitis media in rats [4]. We illustrated the early stages of polyp formation (Fig. 7.7):

1. Localised rupture of the epithelium.
2. Luminal protrusion of the lamina propria through the epithelial defect.
3. Re-epithelialization of the protruded tissue and formation of a polyp.
4. Growth of the polyp.

During these processes, the glands are formed with further growth and stretching of the polyp and become elongated and stretched. Polyp formation, including initiation by rupture of the epithelium, prolapse of the lamina propria and re-epithelialization of the protruded tissue, was also demonstrated in chronic tubal occlusion in rats (Figs. 7.8 and 7.9) [15, 17]. Polyp formation initiated by epithelial defects was also documented by Norlander et al. in experimental sinusitis in a rabbit model [18].

Histopathological examination of small, newly formed NP [14, 16] showed a low cubic or cylindrical epithelium with ciliary cells, but no or few goblet cells, compared to large (fully developed) NP, where the dominant type is the pseudostratified (respiratory) epithelium with goblet cells (Fig. 7.10a–c). A semi-quantitative analysis of epithelia in nine small polyps revealed pseudostratified in few areas, low cuboid in some more areas and low cylindric epithelium in most areas (Table 7.1).

7.11 Mucous Glands in Nasal Polyps

In most of the pathogenetic theories, the mucous glands have played a role. Therefore, our findings on these glands are presently reviewed. Billroth, in his thesis on the structure of NP, described NP glands as long tubular, new formations [3], while Zuckerkandl considered the glands as nasal glands. We [24, 28] have studied the mucous glands in NP and demonstrated that they

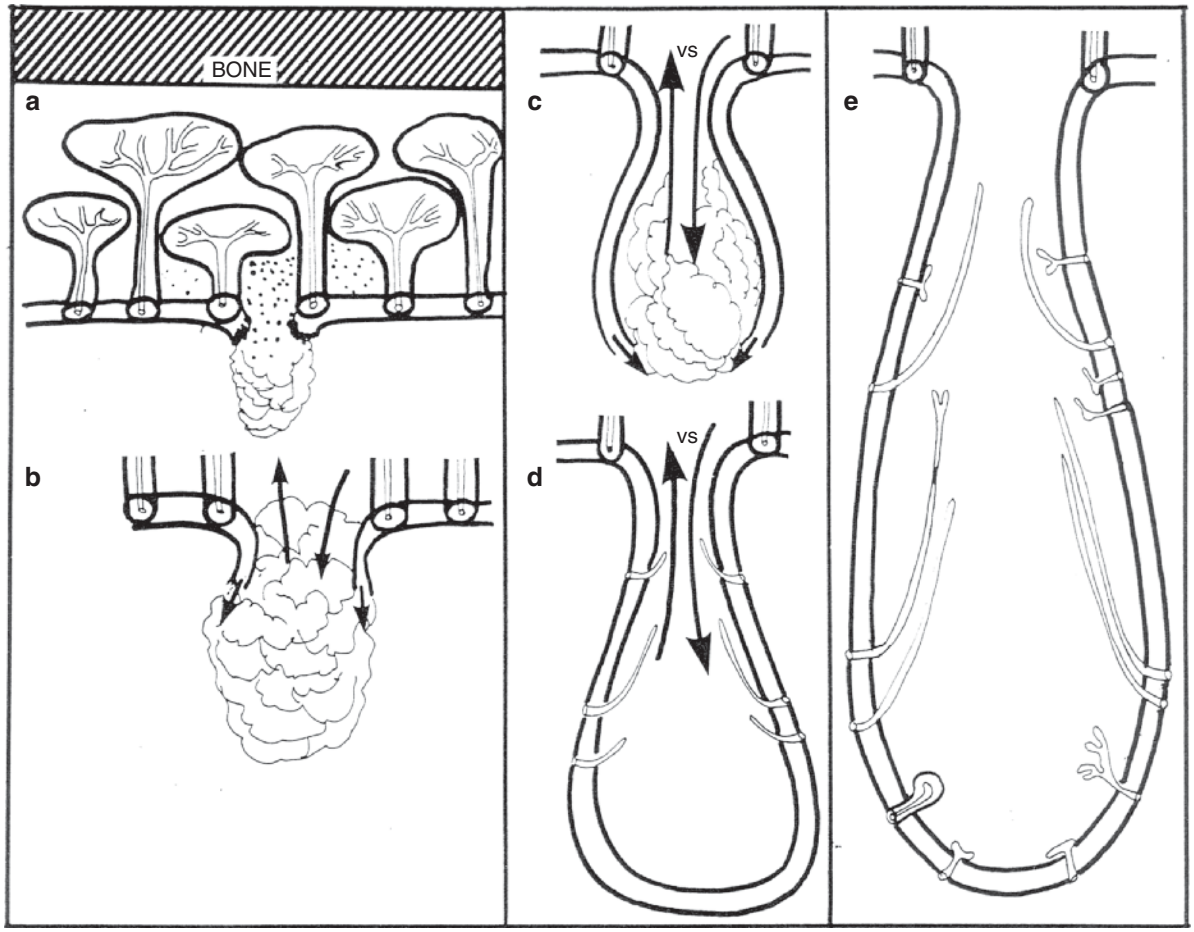

Fig. 7.6 Epithelial rupture or glandular new formation theory on nasal polyp formation. (**a**) An epithelial defect with prolapse of the underlying lamina propria. (**b**) Epithelialization of the lamina propria prolapse. (**c**) Formation of a vascular stalk. (**d**) Formation of the glands from newly formed epithelium. (**e**) A fully developed and epithelialized polyp with long tubular glands has been formed

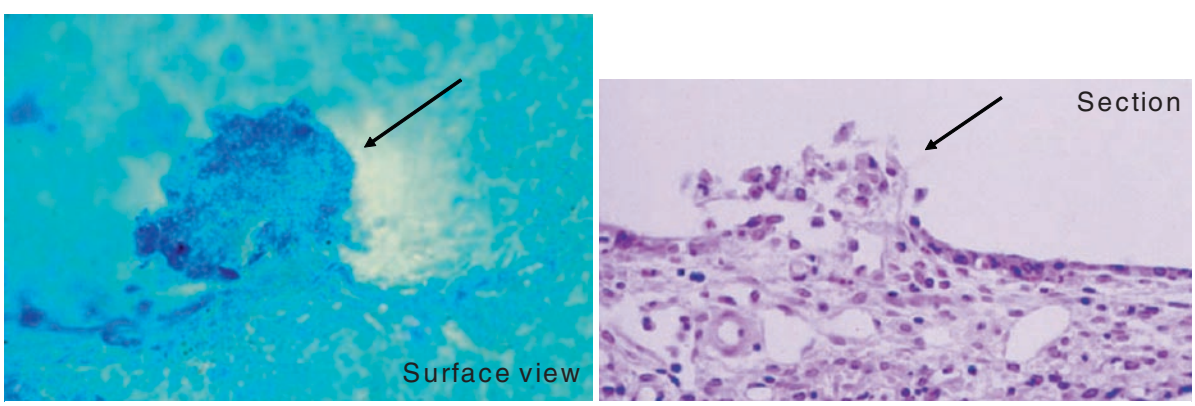

Fig. 7.7 Experimental polyp formation in the rat middle ear. (**a**) Small polypoid prominence seen on the mucosal surface 16 days after pneumococcal inoculation of the middle ear. (**b**) Section of the polyp seen in **a**, illustrating epithelial rupture, incipient prolapse of the fibrous tissue of the lamina propria and re-epithelialization

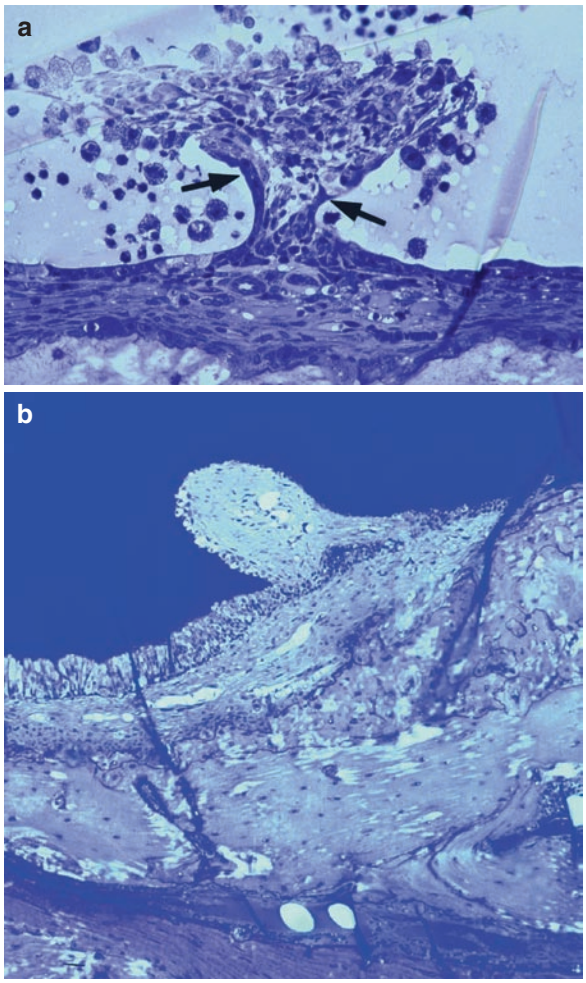

Fig. 7.8 Experimental middle ear polyp after long-term tubal occlusion in rat. (**a**) Initial, partially epithelialised polyp. *Arrow*; *epithelium.* (**b**) Fully epithelialised polyp

play an important role in understanding the pathogenesis of the polyp [23, 24, 27, 28].

The glandular orifices are irregularly distributed, as there is no particular concentration of glands in the stalk or in the most distal end of the polyp. In some polyps, less than 10 glands can be found, whereas others demonstrate more than 100. In most polyps the density is between 0.1 and 0.5 glands/mm^2 of polyp surface. The density of glands in NP is considerably lower than in the nasal mucosa [22]. In the nasal mucosa, the glands are regularly distributed throughout the mucosa and the density is around 7 glands/mm^2. Thus, the pattern is completely different from the polyp.

The polyp glands are tubular, of different shapes and sizes and differ widely from those of the nasal glands [24, 28]. They are of various types (Fig. 7.9). The most striking glands are the long tubular glands, which may be 1–8 mm of length. These glands most often arise from the middle or distal part of the polyp and grow towards the stalk. They are orientated parallel to each other and to the longitudinal axis of the polyp. Some are very simple, narrow tubes (Fig. 7.10), other have prominences of small, round, alveolar bulges on their sides (Fig. 7.11). Some glands are small, simple tubuli, without dichotomous division (Fig. 7.12), whereas others do present with a dichotomous branching.

The epithelial lining of the tubules is extremely polymorphous. Some long glands are lined with pseudostratified, columnar, ciliated epithelium with goblet cells (Fig. 7.13). Distally, these glands become thinner (one- or two-layered). Others are lined with tall, simple columnar epithelium, in which all the cells are mucous-producing.

7.12 Formation and Growth of Glands

The glands most often have their orifices in the lower halves, and the long tubules run up towards the stalk. The shape and architecture of the glands differ a great deal from those in the nasal mucosa and indicate that the glands are formed during the growth of the polyps and that none grow into the polyp from the original nasal mucosa. When the first glands form, the polyps have already attained a certain size. This is the only explanation for the shape and orientation of the long glands (Figs. 7.10 and 7.11). Presumably, the long glands are the first to form in the polyp, growing from the basal layer of the surface epithelium down towards the depth of the polyp and then becoming canalised. As the polyp continues its growth and elongates, the glands become long and stretched (Fig. 7.14). Passive stretching of the glandular ducts indicates that growth of the polyp is also passive, i.e. there is an increase in length.

7.13 Gland Degeneration

All the types of glands described above have been observed as active and as completely degenerated types. The most striking glands are the degenerated, long glands in which the entire long duct and the small

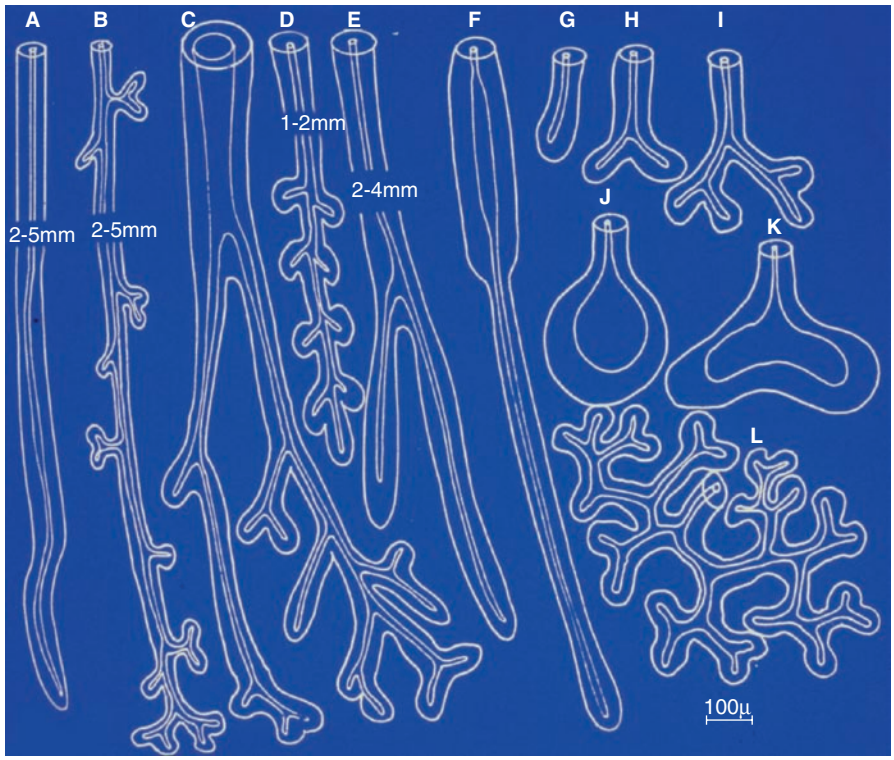

Fig. 7.9 Various types of mucous glands in nasal polyps. Long, simple tubular glands (*A, F*). Long tubular glands with some branches (*B–E*). Short, simple tubular glands (*G*). Short, branched tubular glands (*H, I*). Tubular glands with flask-shaped dilatation (*J, K*). Tubulo-alveolar glands, which are found extremely rarely (*L*)

lateral ducts are distended twofold or threefold and are filled with mucous (Fig. 7.15). The degeneration of glands starts with the stagnation of mucus within the tubulus and the duct, which then become distended. The secretory epithelium stretches, and the cells become cuboidal and flat, loose their secretory ability and gradually become entirely inactive. Such degenerated ducts in whole-mount preparations are seen as dilated; in section, they are seen as small cysts. Loss of secretory activity in the glands of NP has also been demonstrated using immunofluorescent techniques.

7.14 Cellular Infiltration in the Pathophysiology of Nasal Polyps

Eosinophilic inflammation is an important feature in the pathogenesis of chronic rhinosinositis (CRS) with nasal polyps with NP. The eosinophilic accumulation in the polyp stroma is basically caused by increased transendothelial migration and increased survival time in the tissue, where an increased concentration of interleukine 5 (IL-5) plays a major role [7], [12]. The increased amount of IL-5 is predominantly released from T-lymphocytes, independently of atopy, and the highest concentration has been found in polyps from patients with non-allergic asthma and acetylsalicylic acid (ASA) intolerance. These are the sub-groups of patients also known to exhibit the greatest accumulation of eosinophils [1, 2].

In the ASA intolerant patients, a lowered prostaglandin E2 (PGE2) production has been observed. PGE2 has a significant anti-inflammatory activity, including inhibition of eosinophils. A possible intrinsic defect in PGE2 production might, therefore, be responsible for a further increase of eosinophilic accumulation in ASA intolerant patients.

The *Staphylococcus aureus* enterotoxin (SAE)-induced T-lymphocyte production of IL-5, which activates eosinophils and prolongs their survival, is another possible factor in the inflammatory response in NP [20]. The SAE IgE antibody is found in 80% of patients with asthma and ASA intolerance (B415) and 60–80% of asthmatics [19].

In the classic allergic fungal rhinosinusitis (AFRS), specific IgE against the causative micro-organism has been detected. A high number of T-lymphocytes and a depletion of B-lymphocytes have been observed in NP. Relating to T-cellular sub-types, a slight

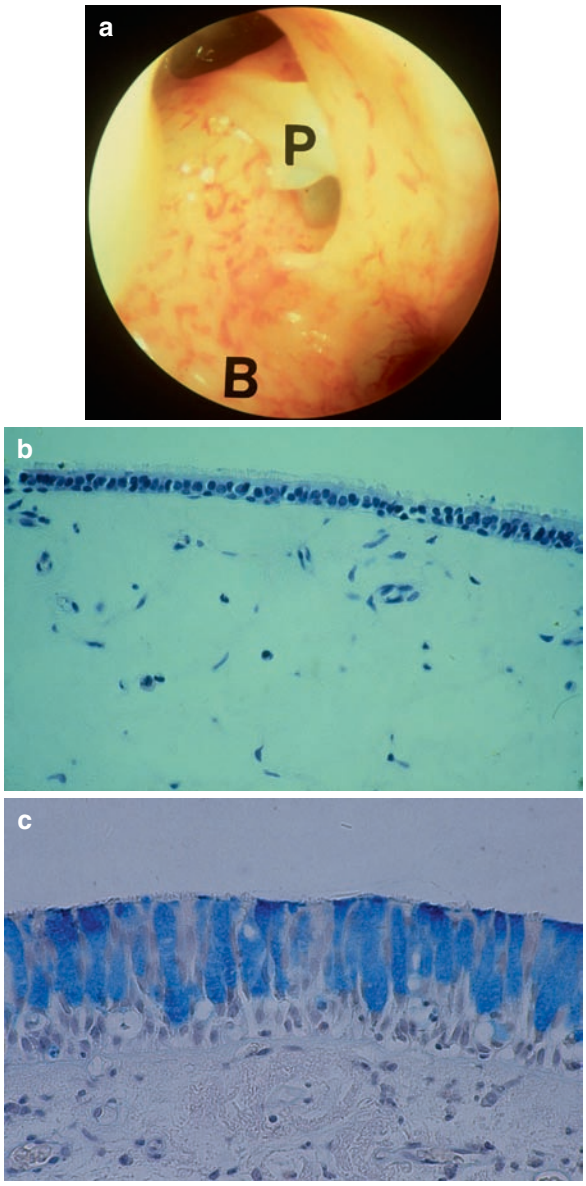

Fig. 7.10 (**a**) A small polyp found by endoscopic examination in an autopsy. The polyp originated from the mucosa of the edgy part of the frontal recess. (**b**) Cross-section of the small polyp with low, cubic two-layered epithelium with ciliary cells, but no goblet cells (H&E). (**c**) Cross-section of epithelium in a "fully developed" nasal polyp showing a higher, pseudostratified respiratory epithelium with ciliary cells and goblet cells (Pas–Alcian, H&E)

Table 7.1 Different types of epithelia in longitudinal cross-sections from nine small polyps (spread of epithelia was evaluated semiquantitatively)

Surface epithelium	
Type	Distrbution
Pseudostratified	+
Low cuboidal	++
Low cylindrical	+++

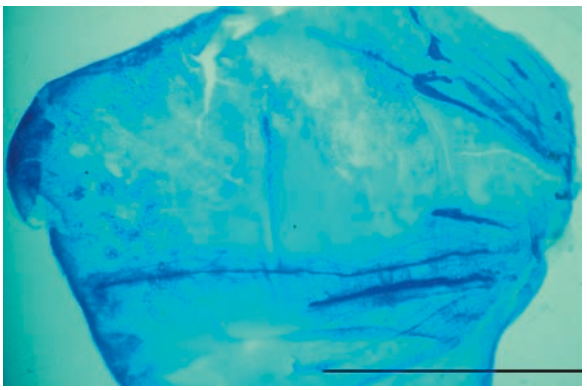

Fig. 7.11 Long, simple tubular glands in a polyp. Whole-mount, PAS-Alcian blue staining

increase in CD4+ T-lymphocytes has been reported, while others have found that CD8+ dominated over CD4+ T-lymphocytes. In a study including 140 patients and using unbiased uniform random sample technique for quantification of cellular elements in NP, the cellular infiltration was correlated to clinical findings in order to evaluate pathophysiologic aspects of the cellular infiltration in relation to clinical activity, as well as to sub-groups of patients with NP. Quantification of all inflammatory cells was performed, including eosinophils, CD3+ and CD20+ T-lymphocytes. There was a strong relationship between clinical recurrence and eosinophilic accumulation (Fig. 7.16) [14]. The T- and B-lymphocytes, as well as the total number of inflammatory cells, did not show a similar correlation. The T-lymphocytes outnumbered the B-lymphocytes by a factor around 4, with the exception of unilateral polyps, in which equal numbers were observed. The T-lymphocytes were a little more predominant in patients with ASA intolerance and those with allergy.

Based on the above findings, a classification of NP with respect to both cellular pathophysiologic findings and clinical parameters can be proposed. The eosinophilic group constitutes the largest number of patients with NP, while the neutrophilic-dominated group is much smaller, but with an overlap between the two. Within the eosinophilic group, there is a large population with clinically overt asthma and they show an increased eosinophilic infiltration, which is even more

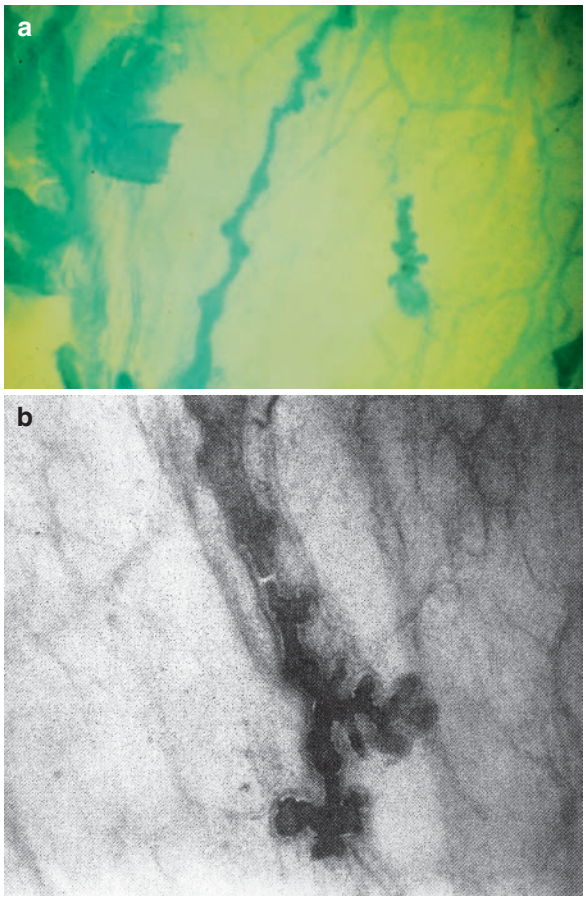

Fig. 7.12 Tubular glands with small bulges indicating dichotomous division (**a**) and a long, thin, simple gland branched at the end (**b**) Whole-mount, PAS-Alcian blue staining

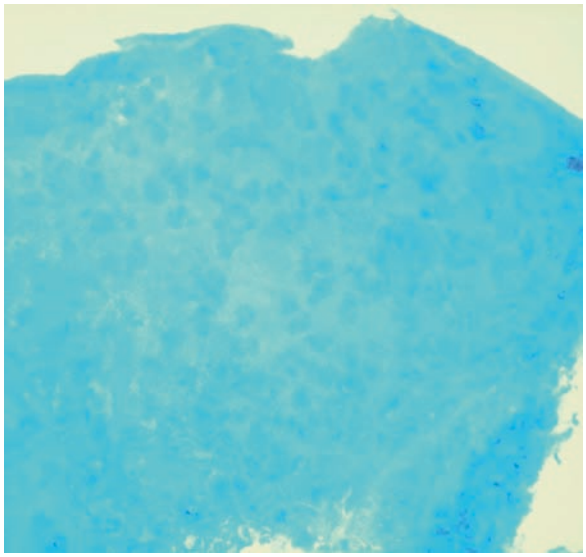

Fig. 7.13 A relatively high density of small, simple tubular glands formed in the polyp after its formation

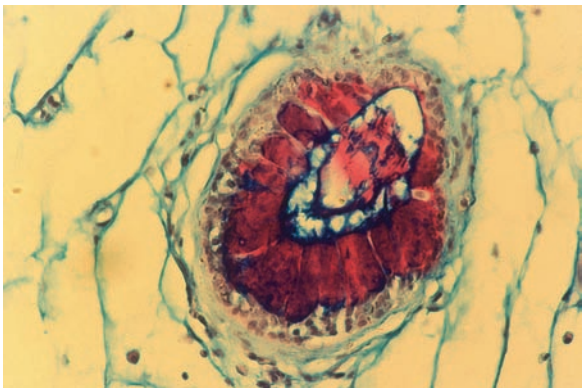

Fig. 7.14 Cross-section of a tubular gland covered with active, pseudostratified epithelium. H&E–PAS-Alcian blue staining

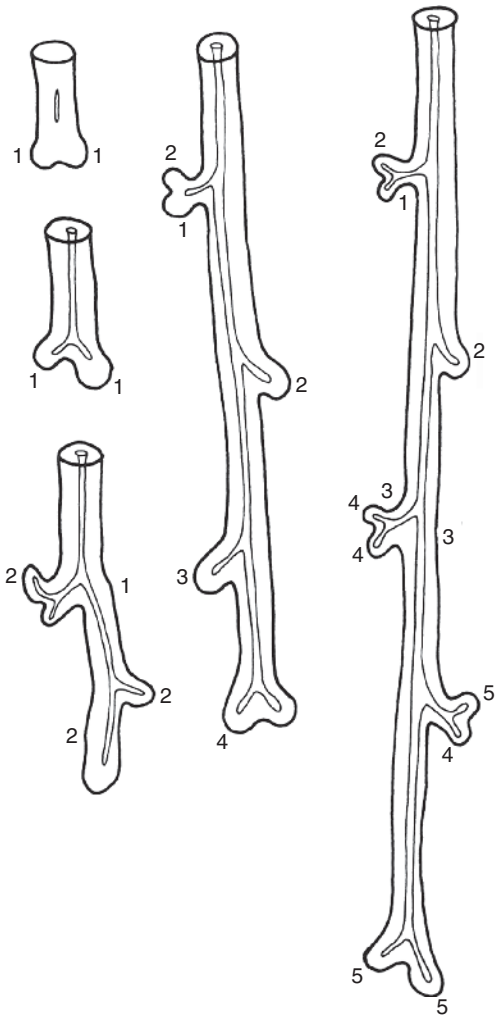

Fig. 7.15 Growth and passive stretching of long tubular glands in nasal polyps. The dichotomous divisions are numbered *1–5*; only one side of each division stretches and grows, making the glands asymmetrical

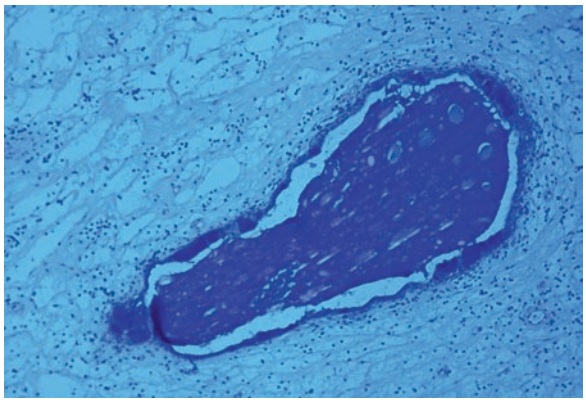

Fig. 7.16 Degeneration of glands. The lumen of a gland tubulus is completely filled with stagnated mucus. H&E–PAS-Alcian blue stained section

pronounced in patients having ASA intolerance. SAEs induce severe eosinophilia and seem related to the group with asthma and ASA intolerance. Eosinophilic mucus rhinosinusitis is described as a systemic disease caused by a dysregulation of immunologic control and has a strong relation to asthma and ASA intolerance. Classical AFRS and Churg–Straus syndrome are other eosinophilic groups. CF is a separate group within the neutrophilic type polyp, like the antro-choanal polyp, the Young's syndrome- and the Kartageners syndrome-associated polyp.

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Mucin Expression in Nasal Polyps

8

Mahmoud El-Sayed Ali

Core Messages

- As a part of the airway mucosa, nasal polyps express a wide range of mucin genes and proteins.
- Nasal polyps express the first nine mucin genes studied so far (MUCs1–4, 5AC, 5B and 6–8).
- More mucin genes are expected to be expressed in nasal polyps.
- The wide range of mucin expression patterns reflects a wide range of internal and external environmental factors involved in the development of nasal polyps.
- Mucin genes up-regulated in nasal polyps include MUC1, 2, 4, 5AC, 5B and 8.
- Sub-mucosal glands play a more important role in mucin expression than surface epithelium.
- Most of the studies on mucin expression in nasal polyps are focused on basic science.
- The role of steroids in modulating mucin gene expression in nasal polyps is still unclear.
- Further studies are needed to illustrate the role of different variables that control mucin expression in nasal polyps.
- The role of inflammatory mediators needs to be studied to help invent new treatment modalities.

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8.1 Introduction

Rhinorrhea with increased mucus secretion is one of the main symptoms related to nasal polyps. This can involve increase of quantity and/or change of quality of nasal mucus. This alteration of amount and/or physical properties of nasal mucus can have a deleterious effect on nasal mucociliary transport, which depends in part on the quantitative and qualitative properties of mucus secretion. In normal situation, the gel-like properties of airway mucus secretion depend solely on the presence of high molecular weight glycoproteins known as mucins in the mucus secretion. These are large molecules formed of sub-units joined end to end by disulphide bonds with a core protein to which hundreds of carbohydrate chains are O-linked [4]. Histochemical studies have shown that in the airway mucosa mucus-producing (goblet) cells of the surface epithelium and mucus and serous cells of the sub-mucosal glands produced different types of mucins [28].

8.2 Mucin Genes

To date 20 human mucin genes named MUC1, 2, 3A, 3B, 4, 5AC, 5B, 6–9, 11–13 and 15–20 have been identified by cDNA cloning. MUCs2, 5AC, 5B, 6, 8 and possibly 19 are secretory gel-forming mucins while MUCs1, 3A, 3B, 4, 11–13, 15–18 and 20 are membrane bound. MUC7 is a secretory, but not gel-forming mucin as it exists as a monomer. Secreted and membrane-bound forms of MUC9 have been identified. All the currently known human mucin genes, excluding MUCs 9, 11, 16 and 17, have been shown to be expressed by human airway mucosa [1]. As a part of the airway mucosa, nasal polyps are expected to express a wide spectrum of mucin genes comparable to that identified in the airway mucosa.

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8.3 Sources of Mucus Hyper-Secretion in Nasal Polyps

Increased nasal mucus secretion in the presence of nasal polyps can be due to one or more of the following reasons:

1. Sinus infection that occasionally coexists or complicates the presence of nasal polyps [1, 4, 31]. In a previous study, we found that at least three mucins, MUC2, MUC5AC and MUC5B, are expressed in sinus and mixed nasal mucus secretion of chronic sinusitis patients [2]. An inverse relation between MUC2 and MUC5AC mucin levels in sinus mucus secretion of these patients was noted. This inverse relation was significantly high only in the presence of nasal polyps [4].
2. Increased surface area of the functioning mucous membrane by polyp formation. Although there are areas of squamous metaplasia of respiratory mucosa covering the polyps, mucin expression has been identified in these squamous epithelia [3].
3. Increased number of mucus secretory elements (goblet cells and/or sub-mucosal gland). This has been reported in inflammatory airway diseases. Inflammatory mediators such as interleukin (IL)-9 and IL-13 up-regulate mucus expression by goblet cell hyperplasia in airway inflammation [25, 33, 49]. Increase of sub-mucosal gland area in inflamed sinus mucosa has also been reported [32].
4. Release of inflammatory mediators. Several inflammatory mediators can up-regulate specific mucin gene in inflamed airway mucosa. MUC2 expression is up-regulated by TNF-α [24, 40], interleukin (IL)-1β [23], IL-9 [25] and leukotriene (L) D4 [8, 42]. MUC4 expression is up-regulated by IL-1β, lipopolysaccharide [7] and IL-9 [15]. MUC5AC expression is up-regulated by neutrophil elastase [18], IL-1β [23], IL-4 [14], IL-6 [40], IL-9 [25, 33], LD4 [8] and TNF-α [40, 48]. However, the role of IL-4 on MUC5AC mRNA and MUC5AC mucin in cultured normal human nasal epithelial cells has been reported to be inhibitory rather than stimulatory [37]. MUC5B expression is up-regulated by IL-6 and TNF-α [40]. MUC8 expression is up-regulated by TNF-α and IL-1β [21, 41, 47] and prostaglandin E2 [12]. The release of one or more of these inflammatory mediators would result in increased activity (hyper-functioning) of the secretory elements of the airway mucosa. Altered quantity (mucin up-regulation) and/or quality (different mucin expression) would disturb mucociliary transport and result in the clinical manifestation of anterior and posterior rhinorrhea commonly complained of by polyp patients.

8.4 Studies of Mucin Gene Expression in Nasal Polyps

8.4.1 Techniques

Several techniques have been employed to study mucin gene expression in nasal polyps. Of these, in situ hybridization [3, 11, 27] is a sensitive qualitative technique to study mucin gene expression at the level of mRNA. Using oligonucleotide probes to the tandem repeat sequence in the mucin gene under investigation provides signal amplification and enhancement by hybridising maximum number of probes along the tandem repeat units in the same mRNA molecule. As it is applied on histological sections, in situ hybridization has the advantage of facilitating cellular localization of expressed mucin genes. However, as signal intensity does not depend on the number mucin mRNA molecules but on the number of tandem repeat units in the mRNA molecules, this technique of in situ hybridization cannot be considered as a quantitative test for mucin gene expression. It can only give semi-quantitative assessment of the level of mucin gene expression. Other techniques of mucin gene study include reverse transcriptase-polymerase chain reaction (RT-PCR) [16]. Mucin protein studying techniques include enzyme linked immunosorbent assays (ELISA) [7], Western blots [48] and immunohistochemistry [11, 27].

8.4.2 Control Mucosa for Mucin Gene Studies in Nasal Polyps

Different sources of healthy nasal mucosa have been used as a control mucosa for mucin gene expression studies in nasal polyps. Inferior turbinate mucosa is easy to harvest [10, 22, 37]. However, Mogensen and Tos [29] have reported that goblet cell density increases from anterior to posterior along the inferior turbinates. Furthermore, considering the physiological functions of the inferior turbinates, it is not clear if this mucosa can

present an ideal control model for mucin gene expression in nasal polyps. Healthy posterior ethmoid mucosa was utilised [20] as it represents a part of the mucosal lining the ethmoid sinuses from which nasal polyps usually arise and which is commonly involved in the chronic sinus infection. It is relatively easy to harvest posterior ethmoid mucosa after the removal of nasal polyps with anterior ethmoid mucosa. Due to anatomical and physiological reasons, this mucosa seems more suitable than inferior turbinate mucosa as a control for mucin gene expression study in nasal polyps. Sphenoid sinus mucosa was used as a control as it is embryologically a part of the posterior ethmoid with the advantage of being further away from anterior ethmoid sinuses, and therefore, is relatively less likely to be involved in ethmoid sinus pathology than the posterior ethmoids. The epithelium of the ethmoid and sphenoid sinus mucosa (similar to that of inferior turbinates) is typical of the respiratory epithelium (pseudostratified ciliated columnar epithelium with goblet cells). The sub-mucosal layer is usually thin with a few glandular elements.

8.4.3 Main Studies

There are three main studies that investigated the expression of a wide range of mucin genes in nasal polyps with a control nasal mucosa [3, 22, 27]. The first study used inferior turbinate mucosa as a control and the second one used sphenoid sinus mucosa. The third study did not define the source of control (normal) nasal mucosa. On the basis of the study of Reid et al. [34] on the developmental expression of mucin genes in human airways, which showed no expression of MUC3, 6 or 8 in human foetal airways, Kim et al. [22] excluded MUC3 and 6 from their study, which investigated the expression of the first nine mucin genes (MUCs1, 2, 4, 5AC, 5B, 7 and 8) in nasal polyp epithelium. They used pooled cell scrapings from normal inferior turbinate mucosa as a control epithelium employing RT-PCR and immunoblotting. They found that all the mucin genes they studied are expressed at various levels in normal inferior turbinate epithelium. Mucin expression in the sub-mucosal gland was not investigated.

We studied mucin gene expression in healthy sphenoid sinus mucosa as a control for nasal polyps. Healthy sphenoid sinus mucosa expressed MUCs1–4, 5AC and 5B, but not MUC6 or 7. The expression was mainly epithelial. Mucin gene expression in sphenoid sinus mucosa was mainly of membrane-bound mucins (MUC4 and 3), which were expressed in most of the samples [3]. In sub-mucosal gland, mucin expression was infrequent and MUCs4 and 5B expression was generally weak, while that of MUC5AC was moderate. No MUC1, 2 or 3 expression was detected in the sub-mucosal gland of healthy sphenoid sinus mucosa. Martínez-Antón et al. [27] employed in situ hybridization to study MUC2, 4, 5AC and 6 mRNA expressions in *healthy inferior turbinate mucosa* and nasal polyps. They also used immunohistochemistry to study MUC1, 2, 4–8 mucin protein expression. They found that MUC1, MUC4 and MUC5AC mucins are highly expressed in the epithelium of normal nasal mucosa. MUC8 was highly detected at both the epithelium and sub-mucosal glands while MUC5B was mainly detected in the sub-mucosal glands. MUC6 and MUC7 were scarcely expressed in normal nasal mucosa with MUC7 restricted to the sub-mucosal glands. There are other studies that investigated the expression of one or a few mucin genes in nasal polyps [8, 10, 12, 16, 20, 41].

8.5 Mucin Gene Expression in Nasal Polyps

Histologically, nasal polyps are inflammatory polyps covered by respiratory epithelium with areas of squamous metaplasia and focal thickening of sub-epithelial basement membrane. The sub-mucosal glands are occasionally dilated and lined by attenuated epithelium [3]. Sub-mucosal gland density is low in oedematous part of the polyp (fundus) and high in the neck (pedicle). Accompanying stroma is oedematous with a mononuclear cell and eosinophil infiltrate.

8.5.1 General Mucin Gene Expression Profile

Mucin expression was up-regulated in nasal polyps compared to normal inferior turbinate mucosa [10, 22, 37]. Intra-cellular mucin content in nasal polyps was 2.9 times higher than in healthy inferior turbinate mucosa [22]. All the nine mucin genes investigated so far (MUCs1–3, 4, 5AC, 5B and 6–8) have been found to be

expressed in nasal polyps [3, 22]. This is similar to mucin gene expression profiles reported for the lower and upper airway mucosa including normal and vasomotor inferior turbinates [5, 6]. Excluding MUC8 which was not included in our study, all the studied mucin genes were expressed in both epithelium and sub-mucosal glands of nasal polyps [3]. However, the expression pattern of individual mucin genes was widely variable among individual polyps and in different areas of mucin secretory elements within the same polyp. This wide variation of mucin gene expression among different polyps can be explained by the wide spectrum of local and systemic factors involved in polyp development and/or progression. Although the airway mucosa can express almost the whole set of mucin genes, in some extreme cases, the expression pattern can vary to the degree that some genes become completely down-regulated (blocked). Intra-polyp variation in mucin gene expression may be due to the differences of cell secretory stages and cell cycles at the time of tissue harvesting [5].

The predominantly expressed mucin genes in nasal polyps are MUC4, 5AC [3, 22] and MUC8 [22, 27] followed by MUC3, 1, 5B and 7. The least expressed mucin genes in the nasal polyps are MUCs2 and 6 [3]. Figure 8.1 illustrates averaged expression signals of the first eight mucin genes in nasal polyps from 20 patients based on the results in reference [3].

In situ hybridization demonstrated that there is significantly more glandular mucin gene expression in nasal polyps than in healthy sphenoid sinus mucosa. MUC1, 2 and 3 were expressed in sub-mucosal glands of nasal polyps, but not in sphenoid sinus mucosa. Average number of mucin genes expressed in the sub-mucosal glands of nasal polyps was 2.95 compared to 0.75 in sphenoid mucosa. Furthermore, averaged expression signals of mucin genes in the sub-mucosal glands were significantly more in nasal polyps than in sphenoid sinus mucosa [3]. This suggests that sub-mucosal glands play an important role in mucin gene expression in nasal polyps. Similar results have been reported in chronic sinusitis where quantitative analysis of mucin expression has demonstrated that the majority of mucin produced is of sub-mucosal gland origin [39]. This may indicate that, as a result of the inflammatory processes which resulted in the development of nasal polyps, sub-mucosal glands are exposed to more stress than the epithelium, with more mucin genes being expressed and existing genes up-regulated. Hyperplasia of sub-mucosal glands could be an additional process by which more mucin is produced. Peñia et al. [32] reported an increase in sub-mucosal gland area in sinus mucosa of children with chronic sinusitis as compared to controls.

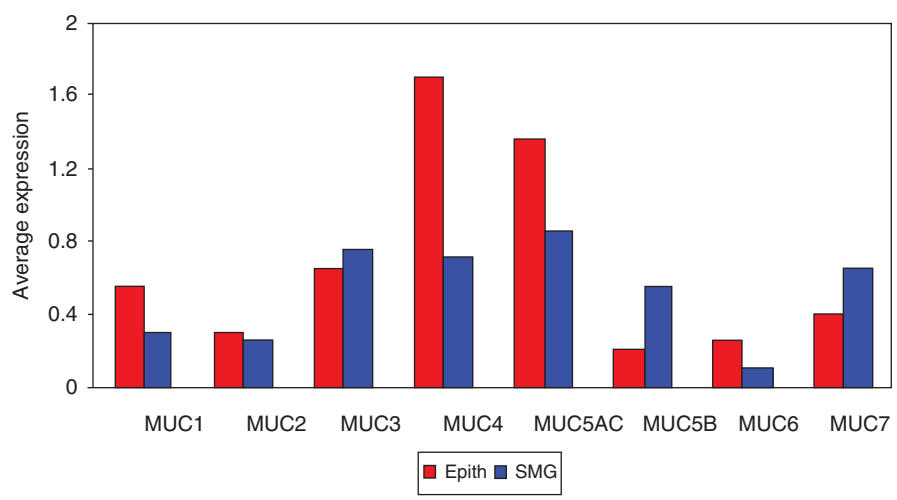

Fig. 8.1 Averaged expression signals of the first eight mucin genes in nasal polyps from 20 patients. Expression signals from 20 polyp patients were averaged for each mucin gene [in the epithelium and sub-mucosal glands separately] to show the average distribution and predominance of the different mucin genes in the epithelium and sub-mucosal glands. Weak expression signals were counted as 1, moderate signals as 2 and strong signals as 3. (Based on the results of Ali et al. [3])

8.5.2 Individual Mucin Genes

8.5.2.1 MUC1

MUC1 expression has been reported in normal inferior turbinate epithelium and nasal polyps with no significant difference in expression levels [22]. In our study, although in the majority of samples MUC1 expression was weak in both the polyp epithelium and sub-mucosal glands, epithelial MUC1 expression was more predominant in nasal polyps than in healthy sphenoid sinus mucosa. Glandular MUC1 expression was also detected in nasal polyps but not in control sphenoid sinus mucosa. Martínez-Antón et al. [27] have also reported MUC1 up-regulation in nasal polyps compared to healthy nasal mucosa. Interestingly, Aust et al. [6] noted MUC1 down-regulation in vasomotor inferior turbinates compared to normal turbinates. They speculated that decreased MUC1 expression might trigger the abnormal neurogenic signal leading to copious nasal secretion in vasomotor rhinitis.

8.5.2.2 MUC2

MUC2 encodes for a large secretory mucin which is mainly an intestinal mucin and provides a protective barrier between the intestinal epithelium and luminal contents. MUC2 up-regulation has been reported in maxillary sinus mucosa [43]. Kim et al. [22] found epithelial MUC2 up-regulation in three of six nasal polyp specimens compared to normal inferior turbinate epithelium. Their study did not include mucin gene expression in the sub-mucosal gland of nasal polyps or inferior turbinates. In our study, weak epithelial MUC2 expression was noted in nasal polyps and sphenoid sinus mucosa. However, no MUC2 expression was noted in the sub-mucosal glands of healthy sphenoid sinus mucosa while glandular MUC2 expression was detected in 20% of nasal polyps. Weak MUC2 mRNA expression in nasal polyps has also been reported by Martínez-Antón et al. [27].

8.5.2.3 MUC3 and 6

MUC3 encodes for a membrane-bound mucin which is mainly intestinal, while MUC6 gene encodes for a secretory mucin which is mainly gastric. Both mucins are thought to have an important protective rule in the gastro intestinal tract. Although MUCs3 and 6 expression was not found in normal or vasomotor inferior turbinate mucosa [6], it has have been reported in allergic nasal mucosa [36]. Depending on the previous results which showed no MUC3 or 6 expression in inferior turbinate mucosa [34], Kim et al. [22], excluded MUC3 and 6 from the set of mucin genes they studied in nasal polyps. Martínez-Antón et al. [27] excluded MUC3 in their study on mucin gene expression in nasal polyps and reported weak MUC6 expression in healthy nasal mucosa. In our study, MUC3 epithelial expression was detected in both nasal polyps and healthy sphenoid sinus mucosa while glandular MUC3 expression was detected in nasal polyps only. Weak MUC6 expression was detected in both the epithelium and sub-mucosal glands of nasal polyps, while no MUC6 expression was found in the epithelium or sub-mucosal glands of healthy sphenoid sinus mucosa.

8.5.2.4 MUC4

In our study, we found that MUC4 was the most predominantly expressed mucin gene in nasal polyps. It was expressed in the epithelium and sub-mucosal glands of 80 and 60% of nasal polyps respectively. This is similar to the results reported for normal and vasomotor nasal mucosa [6]. MUC4 up-regulation has also been reported in nasal polyps compared with healthy normal nasal mucosa [27] and inferior turbinate [7]. MUC4 was expressed in the epithelium of nasal polyps in the form of diffuse signals detected in all cell types along the epithelial layer and was not confined to the goblet cells. It was also expressed in squamous epithelium in areas of polyps with squamous metaplasia. Although MUC4 encodes for a membrane-bound mucin associated with the surface epithelium, MUC4 expression was also detected in the sub-mucosal glands of nasal polyps. However, sub-mucosal gland expression was weak in 35% of polyps and moderate in only 10% (compared to 65% of polyps showing moderate to strong epithelial expression). Average expression was ~2.5× as strong as in the epithelium [3].

MUC4 mucin (encoded by MUC4 gene) is unique in that its extra-cellular 3′ segment extends far higher than other membrane-bound mucins [17]. It also contains an

extra-cellular domain called AMOP (adhesion-associated domain in MUC4 and other proteins) which has not been identified in any other mucin genes [13]. MUC4 could have a role in signalling pathways involved in epithelial cell proliferation and differentiation [30] and in nasal polyps; MUC4 could be involved in epithelial hyperplasia and/or metaplasia.

8.5.2.5 MUC5AC

This mucin gene encodes for a major airway secretory mucin known to be mainly produced by goblet cells in airway epithelium [16, 20, 27]. Various studies have been reported on MUC5AC expression in nasal polyps with conflicting results. Kim et al. [20] have found MUC5AC mRNA expression in most of the goblet cells of nasal polyps; while in the healthy posterior ethmoid mucosa MUC5AC mRNA was barely expressed. Similar results have been reported by Lü et al. [26] and Burgel et al. [11] who found more MUC5AC expression in polyp epithelium compared to normal inferior turbinate mucosa. In our study, epithelial MUC5AC expression was detected in 75% of polyps compared to 25% in normal sphenoid sinus mucosa. However, Martínez-Antón et al. [27] reported MUC5AC mucin down-regulation in nasal polyps compared to normal nasal mucosa. Although MUC5AC is known as a goblet cell mucin, glandular MUC5AC has been reported in healthy and vasomotor inferior turbinate mucosa [6]. In our study, glandular MUC5AC expression was detected in 55% of nasal polyps and average expression was ~1.5× stronger in the epithelium than in the sub-mucosal glands [3].

8.5.2.6 MUC5B and 7

MUC5B gene encodes for a major airway mucin [44] while MUC7 is a major salivary mucin [9]. Both MUC5B and 7 are known to be expressed in the airways and their expressions are mainly in the sub-mucosal glands [6, 27, 38]. In our study, both MUC5B and 7 glandular expressions were identified in 40% of polyps compared to 20 and 25% respectively for epithelial expression of the two mucin genes. The average expression of MUC5B was >2.5 fold stronger in the sub-mucosal glands than in the epithelium [3]. Similar results of MUC5B up-regulation in nasal polyps compared to healthy nasal mucosa have been reported [27]. Similar to other mucin genes, MUC5B and 7 expressions are not restricted to the sub-mucosal glands as epithelial expression was identified in our study and has been reported in other studies [32, 46].

8.5.2.7 MUC8

MUC8 is expressed in the ciliated cells of human nasal epithelium [21]. In their study of mucin gene expression in nasal polyp and normal inferior turbinate epithelium, Kim et al. [22] reported MUC8 up-regulation in nasal polyp epithelium in five of six nasal polyp specimens compared to inferior turbinates. Similar results have been reported by Seong et al. [37]. In the study of Martínez-Antón et al. [27] MUC8 was highly expressed in both the epithelium and sub-mucosal glands of nasal polyps and normal nasal mucosa; however, marked variability of expression levels was noted and there was no significant difference between MUC8 expression in nasal polyps compared to normal nasal mucosa.

8.6 Steroids and Mucin Expression in Nasal Polyps

Although local and systemic steroid remain the mainstay medication for treatment of nasal polyps, the role of glucocorticoids in mucin gene expression in nasal polyps remains unclear. Various studies have investigated the effect of systemic and topical steroids on the expression of various mucin genes in nasal polyps with variable outcomes. Budisonide and beclomethasone dipropionate have been found to reduce mucus secretion in cultured nasal mucosa [35], and intravenous glucocorticoids resulted in reduced MUC8 expression in nasal polyps [45]. Furthermore, topical nasal fluticasone propionate and in vitro triamcinolone and dexamethasone have been found to inhibit MUC4 mRNA expression in nasal polyps and cultured nasal polyp epithelium, respectively [7]. However, other studies have shown that dexamethasone has no effect on steady-state mRNA levels of MUC2, MUC5AC or MUC8 in cultured human nasal epithelial cells [19] and that although intranasal fluticasone reduced eosinophils infiltration in nasal polyps, it had no effect on MUC5AC mucin expression [11].

8.7 Discussion

The aforementioned studies show that, as a part of the airway mucosa, nasal and sinus mucosa express a wide range of mucin genes comparable to that of the airway mucosa which is known to express the majority of the currently known mucin genes. The mucin genes studied in nasal polyps so far are the first nine mucin genes out of the currently known 20 mucin genes. More mucin genes are therefore expected to be expressed in nasal polyps. This is likely to complicate the whole profile of mucin expression in nasal polyps. The wide variability of mucin gene (and subsequently mucin protein) expression patterns reflects the extremely wide range of internal and external environmental factors involved in the development of nasal polyps which can alter the type and level of individual mucin gene expression. Therefore, it would be unrealistic to expect that a single treatment modality would be able to control all mucin genes expressed in nasal polyps or to be suitable for all cases of nasal polyps.

8.8 Future Work

Mucin gene and protein expression in sub-groups of nasal polyps, classified according to different clinical (physiological and pathological) variables, needs to be studied in detail in order to understand the role of these variables in the control of mucin gene expression in nasal polyps.

Detailed histochemical and cytochemical studies of distribution, density and functions of secretory elements in nasal polyps compared to their counter parts in healthy nasal and sinus mucosa are needed to advance our understanding of the role of these elements in both mucin gene and protein expression in nasal polyps and help targeting these elements with new treatment modalities to control their increased numbers and/or functions.

The role of different inflammatory mediators needs to be studied both in vitro and in vivo in order to obtain more insight of the control mechanisms of mucin gene expression at molecular levels. This is likely to help invent new treatment modalities to control the release and/or effect of these inflammatory mediators for more effective management of this common and challenging condition.

Take Home Pearls

- Nasal polyps express at least the nine mucin genes studied so far (MUCs1–4, 5AC, 5B and 6–8).
- MUCs1, 2, 4, 5AC, 5B and 8 are up-regulated in nasal polyps, the main role played by submucosal gland.
- The multiplicity of factors controlling mucin expression in nasal polyps explains this wide range.
- The effect of steroids on mucin gene expression in nasal polyps is unclear.
- Further studies are needed for better understanding and management of nasal polyps.

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Biofilms

9

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Core Messages

- Bacterial biofilms are three-dimensional aggregates of bacteria encased in secreted exopolysaccharides (slime) and lack vulnerability to antibiotics that planktonic bacteria demonstrate.
- Biofilm-forming bacteria are common.
- Bacterial biofilms may contribute to medically recalcitrant chronic rhinosinusitis (CRS).
- Tactics developed to treat planktonic bacteria are ineffective against bacteria in a biofilm – this helps explain a portion of the persistent and recurrent infections observed in CRS.
- Understanding how biofilm infections form is fundamental to developing rational strategies for the prevention and treatment of biofilm-associated CRS.
- New investigations into therapeutic remedies aimed at eradicating biofilm infections are ongoing and hold promise for alleviating individuals' suffering from recurrent infections associated with CRS.

9.1 Introduction

Chronic rhinosinusitis (CRS) affects nearly 16% of the US population each year, with billions of dollars of annual health care expenditures dedicated to its treatment. Unfortunately, in a proportion of patients, the recalcitrant nature of CRS, which often exhibits a chronic relapsing course, significantly contributes to these health care costs. The reasons for persistent CRS are likely secondary to a number of underlying pathophysiologic mechanisms. Asthma, allergic rhinitis, gram-positive and gram-negative infections, aspirin-sensitive asthma, fungus, osteitis, nasal polyposis, superantigens, and other factors have been implicated as etiologies contributing to the development of CRS. The chronic inflammation that develops as a fundamental hallmark of the disease can both cause and be a consequence of dysfunctional mucociliary clearance. Ultimately, stasis of sinonasal secretions will lead to subsequent infection and/or persistent inflammation. In some cases, persistent and recurrent infections, despite multiple therapeutic interventions for CRS, can involve a particularly resistant form of infection known as a bacterial biofilm.

9.2 What is a Biofilm?

Certain biofilm characteristics enable bacteria to persist for extensive periods and may help explain the nature of a chronic disease process that can have acute infectious exacerbations. Bacterial biofilms are typically resistant to antibiotics due to their physical barrier and chemical characteristics. Biofilms are three-dimensional bacterial aggregates lumped together in self-produced exopolysaccharides (slime) and irreversibly affixed to a surface.

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Bacteria that embed themselves in these structures are under different transcriptional regulation and are thus phenotypically different than planktonic bacteria [12]. While recalcitrance to antibiotic interventions is one method by which these infections persist on surfaces, they are also extremely resistant to host immune defense mechanisms that can resist phagocytosis [1, 28].

A potential role of biofilms is suggested in numerous chronic diseases within the body. These include the upper respiratory tract where biofilms have been demonstrated in chronic otitis media, cholesteatoma, and chronic adenoiditis [27]. This is exceptionally demonstrated in patients who develop colonization and infection with *Pseudomonas aeruginosa*, a common pathogen in CRS, as these bacteria may become particularly resistant to antibiotic therapy and have the potential to develop chronic disease quite easily. It is well accepted that *P. aeruginosa*, in a biofilm state, plays important roles in bacterial persistence and antibiotic resistance in chronic infections, such as otitis media and cystic fibrosis lung disease [17]. If CRS develops from acute bacterial sinusitis, this progression into a chronic disease parallels other biofilm-related diseases.

9.3 Biofilms and Chronic Rhinosinusitis: What is the Evidence?

Presence of bacterial biofilms on the sinus mucosa of rabbits infected with *Pseudomonas* sinusitis and in the mucosa of CRS patients was first demonstrated by the senior author [8, 26] (Fig. 9.1). Since then, bacterial biofilms have been identified on sampled CRS sinonasal mucosa using a variety of sophisticated assessment techniques, including scanning and transmission electron microscopy, in situ FISH hybridization, and confocal laser scanning microscopy [14, 31, 33]. Bendouah et al. showed an association between culture positive *P. aeruginosa* and *Staphylococcus aureus* that form biofilms via an in vitro assay and recalcitrant CRS following endoscopic sinus surgery [4]. Furthermore, biofilm-forming bacteria can be cultured in approximately 30% of individuals with CRS undergoing endoscopic sinus surgery using a similar in vitro assay [29]. Bacterial biofilm formation has also been correlated with the persistence of postoperative symptoms and mucosal inflammation after sinus surgery for CRS [30]. Thus, biofilms may be associated in perpetuating CRS

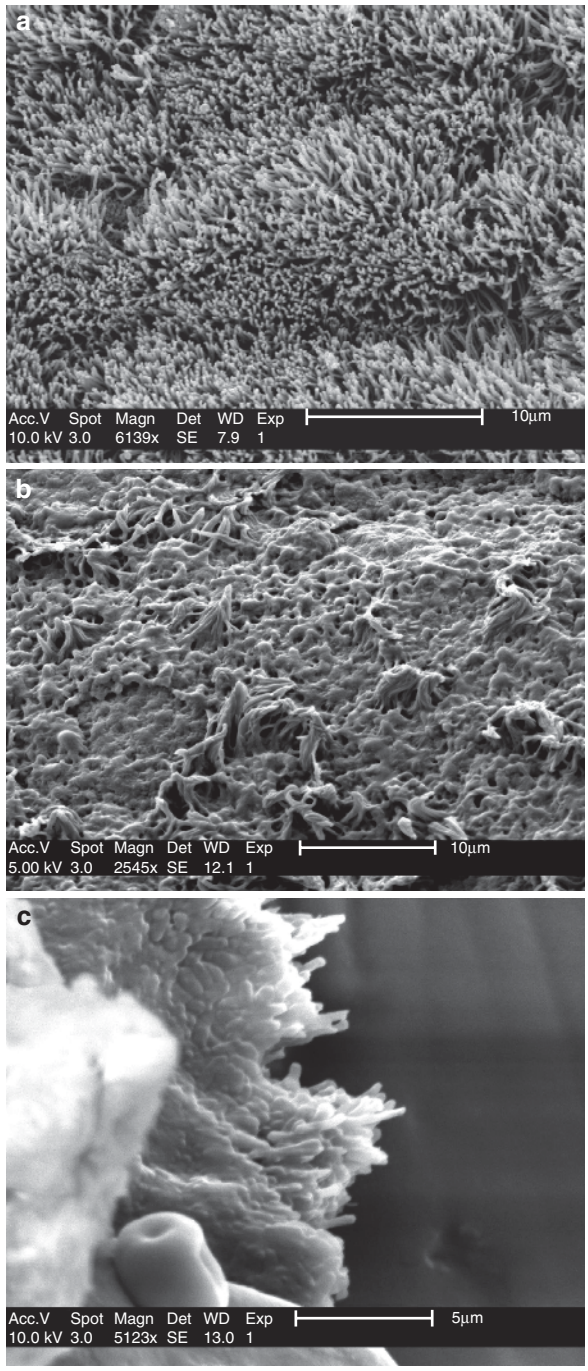

Fig. 9.1 Bacterial biofilms in sinonasal mucosa from a patient with chronic rhinosinusitis. (**a**) Demonstrates scanning electron microscopy (SEM) of normal sinonasal mucosa in which the cilia appear healthy. (**b**) Demonstrates a thick covering of sinonasal mucosa of a patient with recurrent pan-sensitive *Pseudomonas aeruginosa* chronic rhinosinusitis. There are a number of clumped cilia with the remainder of the "landscape" filled with biofilm towers. (**c**) On higher power of the specimen presented in (**b**), a biofilm tower has been "cracked open" in the preparation process revealing several rod-like structures representing the pseudomonal rod

inflammation and explain the recurrent and resistant nature of this disease. Further controlled studies are required to substantiate this and a greater understanding of biofilm-associated CRS is required to develop novel therapies directed at prevention and eradication.

9.4 Chronic Biofilm Diseases

The origin of biofilm science was in the engineering and water industries, and only recently, implications to clinical medicine have been noted [7]. Biofilms have now been implicated in many infectious processes, including otitis media, musculoskeletal infections, necrotizing fasciitis, dental caries, periodontitis, biliary tract infection, osteomyelitis, bacterial prostatitis, native valve endocarditis, and cystic fibrosis pneumonia. Furthermore, nosocomial-type infections are notoriously caused by bacterial biofilms. These include ICU pneumonia, sutures, AV shunts, scleral buckles, contact lenses, urinary catheter cystitis, endotracheal tubes, Hickman catheters, central venous catheters, and pressure equalization tubes [13, 22, 27]. In fact, biofilm-forming bacteria are so common that infectious disease researchers at the Centers for Disease Control and Prevention estimate that 65% of human bacterial infections involve biofilms and up to 99% of bacteria could assume this form of growth under certain conditions because of the survival benefits it confers [27].

9.5 Pathophysiology

Bacteria within a biofilm communicate with one another in a cooperative manner and produce a polymeric matrix, which includes mostly polysaccharides, but also nucleic acids and proteins [7]. Biofilms are first initiated when random collections of independent free-floating, planktonic bacteria attach to a surface. The bacteria next become densely adherent and start to form microcolonies. As bacterial density attains a critical number, interbacterial crosstalk triggers a phenomenon known as "quorum sensing." Quorum sensing then initiates a cascade of gene and protein expression ultimately leading to the biofilm phenotype. This phenotype is marked by formation of towers, water channels (allow diffusion of nutrients), and layers comprised of individual bacteria with functional heterogeneity in a community. Bacterially extruded exopolysaccharide matrix forms the mortar for these structures making up as much as 90% of the biofilm [36]. Single cells or small emboli of cells can dissociate from the matrix by shear forces and active molecular biofilm processes to initiate another biofilm elsewhere. This is analogous to free-floating plankton creating a coral reef (Fig. 9.2).

Biofilms have a heterogeneous morphology, because the biofilm phenotype is highly dependent on the surrounding environment. An example of this heterogeneity is demonstrated with bacterial biofilms that form on mucosal surfaces, often referred to as a *mucosal biofilm* [27]. These bacterial biofilms have unique cascades of gene expression and different microenvironments when compared to biofilms that form on inert surfaces because they form in the special environment of ciliated mucosa, an area expected to have some protection from biofilm formation. Mucosal biofilms are modified by the host inflammatory response and may incorporate some of the host proteins, waste products, and cellular debris. In addition, the pathogenicity of biofilm formation may depend on the causal bacterium.

S. aureus and *P. aeruginosa* are pathogens in both lower and upper airway disease and both organisms can produce biofilms. *S. aureus* can produce exotoxins that are active as superantigens to specific immunity. Some believe the superantigens to play a role in the development of CRS in certain individuals [3, 38]. *P. aeruginosa* is a gram-negative bacterium that is frequently associated with long-term respiratory diseases. Gram-negative bacterial CRS is particularly recalcitrant. Gram-negative sinusitis, specifically *Pseudomonas*, has been studied extensively in the past, and noted to cause an intense transmucosal injury that is far greater than experimental sinusitis using other bacteria associated with sinusitis, such as *Streptococcus pneumoniae* [5]. Inflammation and tissue destruction are particularly robust in *Pseudomonas* infections, because secreted enzymes are enhanced by the body's immune defense mechanisms (i.e., neutrophil degradation products) [32]. *P. aeruginosa* can be consistently cultured, but appropriate antibiotic therapy is often unable to eradicate the offending organism. Persistent CRS disease with either of these infectious organisms that is recalcitrant to antibiotic therapy is nicely explained by the presence of bacterial biofilms.

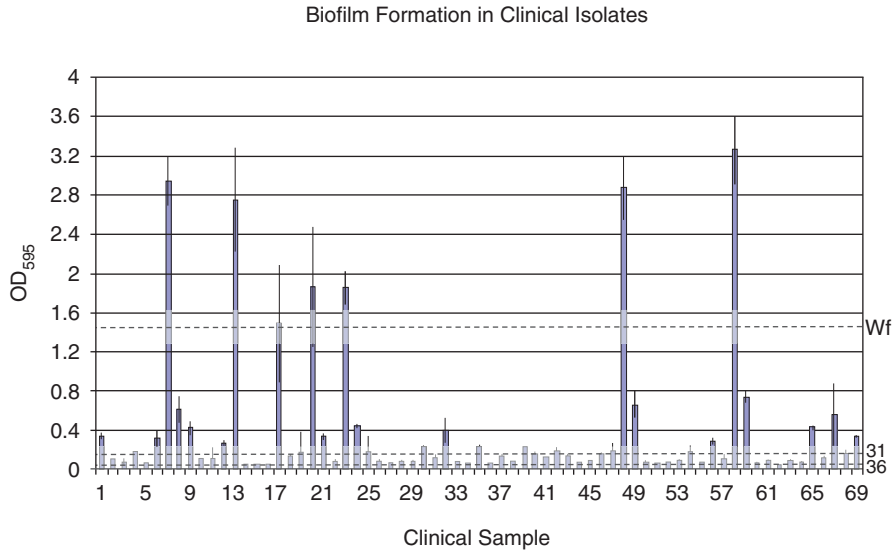

Fig. 9.2 Biofilm-forming bacteria demonstrated from endoscopically guided sinonasal cultures. Patients evaluated in the outpatient clinic or in the operating room who were found to have sinonasal mucopurulence were cultured in duplicate. While one sample was analyzed by the hospital microbiology lab for culture and sensitivity, the duplicate swab was processed for the detection of biofilm-forming capacity. In this in vitro assay, cultures are grown in 96 well plates in quadruplicate and compared to positive (PAO-1 – wild type *Pseudomonas* species) and negative controls (*Sad-31*, *Sad-36 Pseudomonas*). The *sad-36* species carries a mutation in the *flagella* gene, which is required for the attachment of the *Pseudomonas* to surfaces, thereby making this mutant unable to transition from the planktonic to the adherent phenotype. The *sad-31* species possesses a mutation in the *type IV pili* gene, responsible for auto aggregation, thereby allowing it to adhere to surfaces, but is unable to organize into microcolonies and develop into formal biofilms. Biofilm mass is detected by crystal violet staining of inverted pegs incubated in the 96 well plates with bacteria. The crystal violet staining is read at an optical density of 595 nm (OD_{595}). Severe biofilm formation is categorized by OD_{595} greater than PAO-1 (wt), moderate OD_{595} less than wt but greater than *Sad-31*, and minimal as OD_{595} greater than *Sad-31* but greater than *Sad-36*

9.6 Antibiotic Resistance

As previously mentioned, biofilms can evade host defenses and demonstrate decreased susceptibility to systemic and local antibiotic therapy [9, 36]. The biofilm coat of exopolysaccharide alginate could lead to decreased penetration of antibiotics into the biofilm. However, concentration studies showing that antibiotics can diffuse efficiently into biofilms contradict this theory [36]. Because water comprises a large portion of the biofilm mass, this allows for diffusion of antibiotics down water channels into the core regions of the biofilm. Resistance could also be conferred by deactivating or neutralizing positively charged antibiotics interacting with the negatively charged polymers of the biofilm matrix. A third theory suggests that bacteria could lie in a nongrowing state of suspended animation in the basal layers of the biofilm due to the accrual of waste products and depletion of needed substrates. This could confer relative resistance to antibiotics as most antibiotics work only on dividing bacteria. Finally, decreased diffusion of antibiotics into the bacterial cytoplasm due to fewer porins in the bacterial cell wall is another possible method of resistance. Fewer porins could develop as a stress response due to osmotic forces changing nutrient gradients. In reality, strong antibiotic resistance is probably secondary to a combination of these mechanisms.

Aminoglycoside antibiotics may potentially induce biofilm formation in some bacteria at subtherapeutic doses. Hoffman et al. demonstrated the induction of biofilm formation in *P. aeruginosa* and *Escherichia coli* when exposed to subtherapeutic concentrations of these antibiotics [19]. Certain *Pseudomonas* may have a gene named the aminoglycoside response regulator that confers this biofilm-specific aminoglycoside resistance. As topical sinus irrigations with gentamicin or tobramycin are often prescribed in patients with CRS, this could be a potential source of bacterial biofilm development, especially at subtherapeutic concentrations.

9.7 Mucociliary Clearance Effects

Normal airway mucociliary clearance is a critical host defense mechanism that clears the upper airways of inhaled pathogens. This defense mechanism is dependent on the coordinated beating of ciliated cells and the mucus production. Cilia continually sweep debris out of the respiratory system for elimination through the gastrointestinal tract. Impairment of ciliary motility is important not only in the pathogenesis of CRS, but also asthma and infertility [37, 42]. Insults such as acute viral and bacterial rhinosinusitis affect mucociliary function and could ultimately allow the bacteria to form a mucosal biofilm, and initiate a chronic, recalcitrant infection within the sinonasal passages.

We investigated a method for reliable analysis of in vitro interactions of *P. aeruginosa* bacterial biofilms and respiratory epithelium [40]. *Pseudomonas* was cocultured on intact cultured murine septal epithelium developed at an air–liquid interface [2, 39]. An examination of cultures with both SEM and CLSM demonstrated that the biofilm mass can anchor among cilia on respiratory epithelial cells and that cell death was localized to the epithelium underneath biofilm formation. This provided experimental evidence that biofilms may first anchor among cilia and ultimately gain a vital foothold by disrupting the cilia (mucociliary clearance) and the epithelium in the area underneath the biofilm mass.

9.8 Treatments

A number of techniques have been evaluated for their capability to manage and control biofilms in environmental science. Materials and coatings to help reduce initial cell adhesion to surfaces and a variety of treatments aimed at decreasing or destroying already formed biofilms, including heat, chemical treatments, antibiotics, sonication, quorum-sensing analogs, cleaning regimens, low-power laser, and lectins [18, 23–25, 34, 35]. Furthermore, new investigations into biological control agents such as bacteriophages and protozoa to reduce biofilms have shown promise [20]. However, many of these treatments are prohibitive in the treatment of human biofilm infections due to detrimental effects on host cells. Hence, the pursuit of a reliable method for the elimination of human biofilm infections is ongoing.

Although CRS may have many independent inciting factors, including bacterial infection (whether planktonic or biofilm-mediated), genetics, reactive airways, anatomic abnormality, fungal infection, and allergy, the mainstays of therapy remain the same: anti-inflammatory and antimicrobial agents combined with surgical ventilation. Surgical ventilation of infected sinuses could be the optimal therapy for combating bacterial biofilms in patients with CRS as it increases oxygen tension, assists with the host's natural defenses to clear infection, and provides access for topically designed irrigations to mechanically disrupt biofilms.

Other treatments for biofilms include novel methods of antibiotic therapy. Investigators have demonstrated that low-dose macrolide therapy at levels far below the established minimal inhibitory concentration for *Pseudomonas* can decrease biofilm formation [16, 41]. However, the underlying mechanism behind this decrease has yet to be elucidated.

Topical saline irrigations are often utilized as a mechanical debridement of the mucosal surface following sinus surgery. Another topical agent utilized in clinical practice is 1% baby shampoo solution in normal saline. Chemical surfactants are detergents that have antimicrobial activity and can break apart bacterial cell walls. Baby shampoo is an inexpensive, commercially available solution containing multiple chemical surfactants. Our prior studies demonstrated an in vitro antibiofilm effect on *Pseudomonas* biofilm formation using this solution [6]. We subsequently studied its effects in a prospective study of symptomatic postfunctional endoscopic sinus surgery (FESS) patients who irrigated twice a day for 4 weeks. Sixty percent of patients noted improvement in specific symptoms of thickened mucus and postnasal drainage with the formulation. Other surfactant-containing agents are currently under investigation including a combination of citric acid and zwitterionic surfactant. One study demonstrated significant reductions in biofilms on human chronic sinusitis mucosal specimens with hydrodynamic administration of this solution [10].

Future directions for biofilm-associated CRS include investigations into the nature of the biofilm at the molecular and cellular levels. Molecular targets of specific aspects of the biofilm lifecycle continue to show promise. Disrupting the type IV *pili* attachment phases of *Pseudomonas* is one potential target of ongoing research [15]. Disrupting quorum sensing could be the most specific and unique target for biofilm therapeutics. A variety of novel mechanisms, including the substitution of

furanones [21] and the enzymatic cleavage of acyl-homoserine lactones (one of the quorum-sensing signals), can interfere with quorum sensing. Targeting quorum-sensing signals at the molecular level is an area of continuing research and has great potential for biofilm interventions and eradication [11].

9.9 Conclusions

Over the past decade, bacterial biofilms have been discovered to propagate many chronic infectious and inflammatory diseases. Biofilms continue to evade host defenses and create persistent, medically recalcitrant infections, despite increasing knowledge and advancements in treatment for these tenacious infections. Although recent findings demonstrate bacterial biofilms in the sinonasal mucosa of patients with CRS, their contributory role to the disease is not completely understood. The pathogenesis of CRS has many underlying causes and persistence of bacterial biofilms may be only one of many contributing etiologies involved with the recalcitrant nature of the disease. As the data supporting the contribution of biofilms to the persistence of CRS build, it becomes more evident that novel antibiofilm therapies must be developed.

Take Home Pearls

- Bacterial biofilms are three-dimensional aggregates of bacteria encased in secreted exopolysaccharides that are strongly resistant to antibiotics and host immunity defense.
- Approximately 30% of the bacteria isolated from patients with CRS form biofilms.
- Possible methods for resistance of bacterial biofilms to antibiotics include.
- Deactivation or neutralization of the antibiotic.
- Quiescent bacteria in the biofilm resist antibiotics that only eradicate actively dividing bacteria.
- Decreased penetration of antibiotics into the biofilm.
- Decreased porins in the bacterial cell wall that inhibit diffusion of the antibiotic.
- The mainstays of therapy for biofilm remain antimicrobial and anti-inflammatory agents combined with surgical ventilation.
- Aminoglycosides at subtherapeutic concentrations can stimulate biofilm formation.
- Targeting the biofilm lifecycle through interruption of the attachment phase and quorum sensing are probable avenues of future therapy.
- New therapies directed at biofilm prevention and eradication are needed.

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Staphylococcus-aureus-derived Superantigens in Nasal Polyp Disease

10

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Core Messages

- *Staphylococcus aureus* (SA) secretes enterotoxins, small proteins that act as superantigens because of their potent effect on the immune system.
- The main mode of action of superantigens is the coupling of the major histocompatibility complex molecule with the T-cell receptor.
- The effect is a powerful stimulation of the adaptive immune system in a polyclonal (non-antigen-specific) way, resulting in a T-helper-2-biased inflammation.
- This superantigen mechanism is involved in the pathogenesis of nasal polyps (NP) in about 50% of the cases.
- The superantigenic effect is hallmarked by immunoglobulin changes in biopsies: high total IgE, polyclonal IgE to multiple allergens, and IgE specific to SA enterotoxins. Serum immunoglobulins coincide only partially with biopsy findings.
- Patients with this IgE pattern have an increased risk of asthma and aspirin-exacerbated respiratory disease (AERD).
- Future treatments with topical or systemic antibiotics and monoclonal antibodies to IgE and interleukin-5 (IL-5) are being studied.

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Abbreviations

AERD	Aspirin-exacerbated respiratory disease
ASNP	Aspirin-sensitive nasal polyps
ATNP	Aspirin-tolerant nasal polyps
CysLT	Cysteinyl leukotrienes
ECP	Eosinophil cationic protein
IFN-γ	Interferon-gamma
IL	Interleukin
MHC	Major histocompatibility complex
NP	Nasal polyps
SA	*Staphylococcus aureus*
SAE	*Staphylococcus aureus* enterotoxin-like toxins
SAE-IgE	IgE antibodies to SAE
SEA–SEU	Staphylococcal enterotoxin A–U
TCR	T cell receptor
TGF-β	Transforming growth factor-beta
Th	T helper
TNF-α	Tumor necrosis factor-alpha
TSST-1	Toxic shock syndrome toxin-1

10.1 Introduction

The discovery of IgE antibodies to *Staphylococcus aureus* enterotoxins (SAE) A and B in nasal polyp tissue homogenates [4] indicated for the first time that these bacterial

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products could be involved in the pathogenesis of nasal polyposis. Nasal polyposis, also referred to as chronic rhinosinusitis (CRS) with nasal polyps (NP) [19], is mostly characterized by an eosinophilic, T helper 2 type of inflammation, driven by interleukin-5 (IL-5) and eotaxin which orchestrate chemotaxis, activation, and increased survival of eosinophils [2–4, 53]. This disease can be differentiated from chronic rhinosinusitis without nasal polyps (CRSsNP), which has a T helper 1 (Th1) type of inflammation with increased levels of interferon-gamma and transforming growth factor beta 1 [60]. A subgroup of NP shows high nasal colonization rates with *Staphylococcus aureus* (SA), an increased local polyclonal IgE synthesis, correlating with the degree of eosinophilic inflammation, and has an increased prevalence of asthma and aspirin hypersensitivity [4].

There is a wealth of data to support the hypothesis of the role of SA enterotoxins in nasal polyposis. In this chapter, we summarize the current evidence of an active role of SAE in nasal polyposis and contemplate on the possible clinical implications. After introducing the superantigenic properties of the staphylococcal enterotoxins, we present evidence for an increased nasal colonization with SA in NP and a specific humoral immune response to SAE. We provide an insight into the possible mechanisms that can elicit a polyclonal, Th2 skewed, eosinophilic milieu characteristic of NP and discuss current and future therapeutic approaches directed toward these key events in the pathophysiology of NP (Fig 10.1).

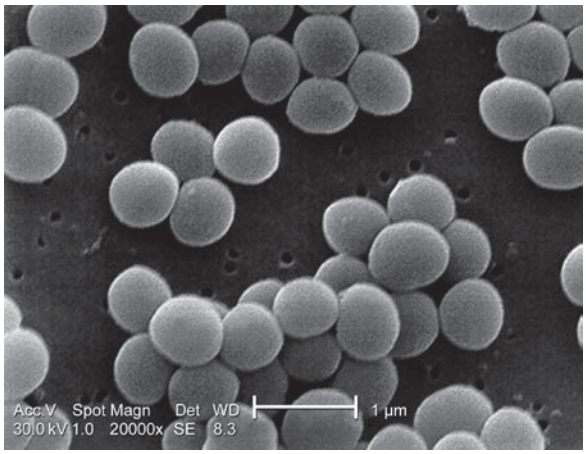

Fig. 10.1 Scanning electron micrograph of a *Staphylococcus aureus* colony under a magnification of 20,000x. (Photograph courtesy of J. Carr, Centers for Disease Control and Prevention, 2001)

10.2 Superantigenic Properties of *Staphylococcus aureus* Enterotoxins

Since its discovery in the 1880s [40], SA has been recognized as an important pathogen in human disease, including minor skin infections, food poisoning, life-threatening infections, septicemia, and toxic shock syndrome [35]. Despite its powerful pathogenic capabilities, approximately 20% of the population are persistent nasal carriers of SA, and up to 60% of individuals are colonized with SA intermittently [65]. In contrast with intermittent carriers, persistent carriers tend to be colonized with the same bacterial strain over time. The versatile virulence is determined largely by its ability to regulate the production of surface and secreted proteins by a set of more than 50 genes known as the virulon [42]. Secreted proteins include extracellular enzymes, such as catalase and coagulase, and a group of host-damaging proteins known as exotoxins. Of the latter, the enterotoxins have potent gastrointestinal effects and are the cause of staphylococcal food poisoning [55]. An increasing number of staphylococcal toxins are described. The classical members, Staphylococcal enterotoxin A to E, are designated SEA-SEE, and newer toxins have been assigned a letter in the order of discovery (SEG-SEJ). However, some toxins lack proof of emetic properties, and they are considered as enterotoxin-like toxins (SElK-SElR, SElU), together with toxic shock syndrome toxin-1 (TSST-1) [34].

The staphylococcal enterotoxin-related toxins (further referred to as SAE) share the ability to mount a massive inflammatory reaction resulting from a polyclonal activation of T and B lymphocytes that is independent of a specific adaptive immune response, a unique interaction for which they are known as superantigens, as first described by Kappler and Marrack in 1989 [38]. It has been suggested that pathogens evolved to produce superantigens, thereby evading an efficient adaptive immune response from the host, thus aiding in colonization and spread of the pathogen [52]. Superantigens from other bacteria have been described, including *Streptococcus pyogenes, Streptococcus dysgalactiae, Mycoplasma arthritidis, Yersynia pseudotuberculosis, and Peptostreptococcus magnus* [20].

Unlike conventional T-cell activation via specific recognition by the T-cell receptor (TCR) of processed antigen peptides in the major histocompatibility complex (MHC) molecule, SAE directly activate T-cells

via bridging the MHC class II molecule with the TCR directly, without being processed by an antigen presenting cell (APC). Superantigens bind to one of the domains of the MHC class II molecule on APCs in a region distant from the peptide-binding cleft, and to the Vβ-domain in the β chain of the TCR. This bypasses specific antigen recognition [20]. To date, there are only 52 Vβ gene segments described that code for the Vβ domain, and consequently, superantigen binding can result in polyclonal activation of lymphocytes. It is estimated that SAE are able to stimulate up to 20–30% of the T-cell population, compared to <0.01% by conventional antigen recognition. Staphylococcal enterotoxin-related superantigens are specific for one or more Vβ domains, linking them to specific T-cell populations and creating a superantigen-specific Vβ signature [23] (Fig 10.2).

There are several ways by which staphylococcal superantigens exert their function on immune effector cells. T-cell superantigens stimulate $CD4^+$ and $CD8^+$ T cells and can induce either a Th1-type or Th2-type $CD4^+$ T-cell activation, with subsequent release of IFN-γ, TNF-α or IL-4, IL-5, and IL-13. The latter may occur due to direct T-cell activation but also indirectly via stimulation of APCs. The type of the T-helper response (Th1 or Th2) can be influenced by the concentration of superantigens, the nature of the APC, and costimulatory molecules. Mandron et al. [36] showed that SEB activates monocyte-derived dendritic cells (DCs) to secrete IL-2 and that these activated DCs polarize naïve T cells to a Th2 type.

Despite the polyclonal T-cell expansion in acute diseases such as toxic shock syndrome, chronic stimulation by superantigens may lead to an oligoclonal T-cell pattern, presumably resulting from the concerted action with the conventional T-cell activation mechanism, where clones recognizing antigens are selected after chronic exposure [33]. Moreover, after polyclonal expansion, superantigen stimulation induces clonal deletion and anergy of remaining T-cell populations [28]. Loss of immunosuppressive effects of naturally occurring regulatory T cells ($CD4^+$ $CD25^+$) has been described in different inflammatory conditions; in atopic dermatitis, SEB has been shown to suppress their activity [43].

A polyclonal humoral immune response is evoked by SAE in a T-cell dependent way by cross-linking MHC class II molecules on B-lymphocytes and the TCR. In addition, SAE can enhance Th2 response by inducing isotype switching to IgE and augmenting the synthesis of IgE [23]. Furthermore, SEA and SED, together with Staphylococcal protein A (SpA), may act as a B-cell superantigen by directly binding to VH3 or VH4 domains of the B-cell receptor, resulting in enhanced survival of these subsets of B-cells.

The findings of both T-lymphocytes and IgE specific to SAE (SAE-IgE) indicate that SAE may also be involved as conventional antigens, in which the SAE

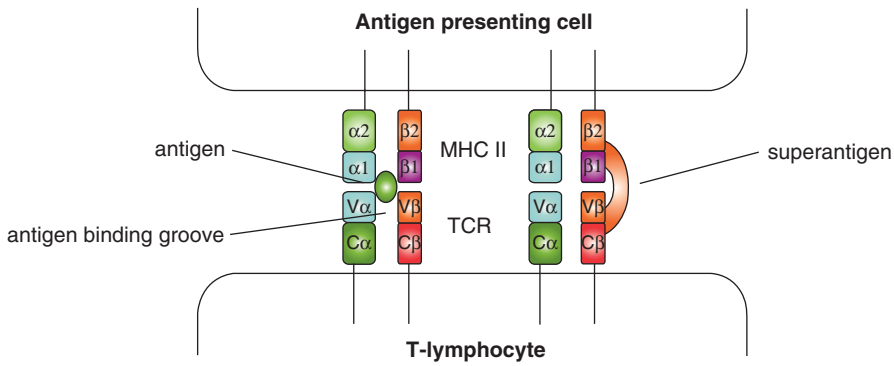

Fig. 10.2 Stimulation of a T lymphocyte by an antigen presenting cell (APC). *Left*: conventional antigens are processed by the APC and presented in the peptide binding cleft of the major histocompatibility complex (MHC) class II molecule. Upon recognition by the T cell receptor (TCR), signal is transduced to the T cell. *Right*: superantigens are not processed by an APC and activate the TCR directly by crosslinking the TCR to the MHC class II molecule, distant from the complementarity-determining regions. (Illustration courtesy of Dr. T. Van Zele, 2006)

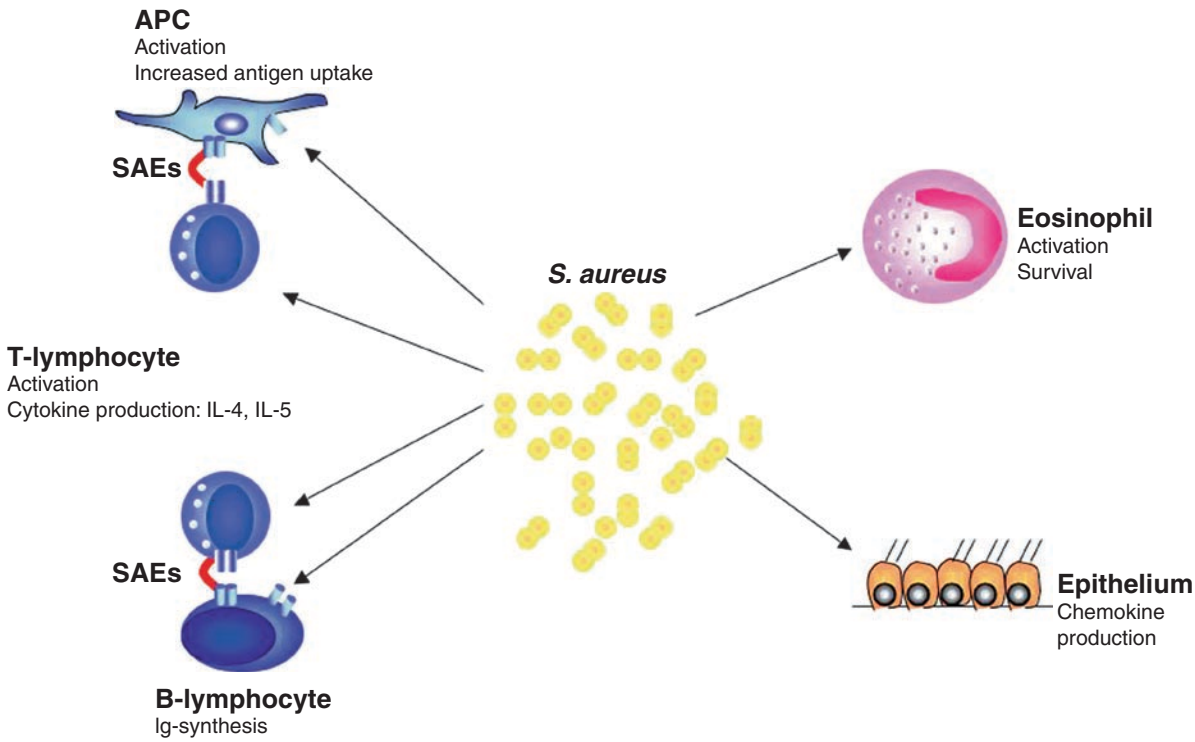

Fig. 10.3 Effects of *Staphylococcus aureus* enterotoxins on antigen presenting cells, T lymphocytes, B lymphocytes, eosinophils and epithelial cells. (Illustration courtesy of Dr. T. Van Zele, 2006)

are processed into oligopeptides and presented in the antigen-binding groove of the MHC molecule. It is hypothesized that the superantigen and the conventional response may act in concert, where polyclonal stimulation of both T- and B-lymphocytes allows for an increased specific humoral or cellular response to SAE [23]. Finally, staphylococcal superantigens may have a direct effect on proinflammatory and other cells, such as eosinophils, macrophages, epithelial cells, and fibroblasts. SpA is also able to induce degranulation of mast cells by crosslinking FcεRI molecules via binding to VH3 IgE domains, and is therefore called a superallergen [37] (Fig 10.3).

10.3 Invasion of Nasal Tissue by *Staphylococcus aureus*

SA frequently colonizes the nasal cavity, with an average persistent colonization rate in 20–30% of individuals [65]. Although SA can be isolated in acute and chronic rhinosinusitis, a disease-modifying role of SA in CRS without NP has never been proven. Microbiology studies of the middle nasal meatus in CRS present conflicting results; however, in controlled studies, SA has been isolated in comparable rates in controls and CRS patients [1, 18].

We reported for the first time an increased colonization rate in middle meatus nasal swabs from CRS with NP (63.7%) compared with CRS without NP (27.3%) [59]. Even higher rates were detected in NP patients with asthma (66.7%) and aspirin hypersensitivity (87.5%), whereas there was no significant difference in the colonization rate between CRS without NP and controls. Furthermore, repeated cultures over time in patients with NP indicated long-term colonization. The colonization rates in these patients were paralleled by IgE antibodies to SAE, total IgE, and eosinophil cationic protein (ECP) in nasal tissue homogenates. These findings were corroborated in a second study by our group, showing a colonization rate of 71% in CRS with NP vs. 25% in controls [21]. On the other hand, conflicting results with our above studies have been

reported [41], with detection of staphylococci in nasal lavage samples and in minced biopsies, in comparable levels between CRS with NP, CRS without NP, and controls, using conventional culture methods, PCR and FISH.

As the above studies used endoscopically guided swabs from the middle meatus, these results do not necessarily reflect the presence of SA within the nasal mucosal tissue. While SA has traditionally been regarded as an extracellular pathogen, there is increasing evidence that SA has the ability to invade and survive in nonphagocytic eukaryotic cells such as keratinocytes and respiratory epithelial cells [11]. An intracellular reservoir of SA in three patients with recurrent/chronic rhinosinusitis undergoing sinus surgery has been shown by confocal immunofluorescence microscopy in nasal epithelial cells, mucous gland cells, myofibroblasts, and CD45-positive phagocytes [11]. These findings were confirmed in a population of CRS patients undergoing sinus surgery, where intracellular SA could be demonstrated in the nasal epithelium of 17 of the 27 patients [49]. Long-term carriage of identical clonal strains in CRS suggests that intracellular invasion presents an escape mechanism for host defence or antibiotic therapy. This finding may point to the involvement of SA small colony variants (SCV), strains that show a decreased growth rate, decreased hemolytic activity, increased intracellular survival, and decreased antibiotic susceptibility; however, evidence of involvement in nasal pathology is lacking [63]. The role of biofilms in CRS is being studied extensively (reviewed in [25]), but studies explicitly involving NP are scarce [8, 39]. However, as biofilms have been shown to be related to protracted disease and antibiotic resistance, their role in the continuous immune stimulation by SA superantigens in NP is of particular interest.

We recently demonstrated intraepithelial presence of SA in a subgroup of NP using immunohistochemistry. Interestingly, SEB could be colocalized to the intracellular SA, indicating a potential local intracellular production of SA enterotoxins (Patou, unpublished). Investigating invasive SA in different CRS subgroups, we used peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) technique to stain for SA in nasal tissue samples [17]. Intramucosal presence of SA was comparable between control and CRS without NP groups. Although we did not demonstrate a significantly higher rate of intramucosal presence in NP per se, we showed for the first time that the presence of intramucosal SA is significantly augmented in aspirin-sensitive asthmatic NP patients compared to polyp patients without such comorbidities.

10.4 Augmented Immune Response to SAE in Polyps

In 2001, we presented a role for staphylococcal superantigens in NP [4]. Investigating the relationship between atopy, local IgE concentration, and parameters of eosinophilic inflammation, we demonstrated local IgE specific to staphylococcal enterotoxins (SAE-IgE) SEA and SEB in a subgroup of polyp patients with high local IgE concentrations and a multiclonal IgE pattern. This represented up to 50% of the NP patients in the study. These polyps showed higher concentrations of sCD23, ECP, IL-5, eotaxin, and cysteinyl leukotrienes (CysLT), and a higher eosinophil count compared to control tissue and to polyps with low IgE. These patients had a higher prevalence of asthma, and the inflammatory parameters and IgE concentrations in polyps were not related to atopy.

We subsequently reported a higher colonization rate of SA in NP (63.6%) which was paralleled by an increased presence of SAE-IgE (SEA, SEC, TSST-1) (in 27.8%), total IgE, and ECP; observations that further increased in subgroups with asthma and with aspirin-exacerbated respiratory disease (AERD), detecting SAE-IgE in 53.8 and 80%, respectively [59]. The colonization rates of SA always exceeded the rate of detection of SAE-IgE, indicating that colonization may not necessarily lead to the generation of a humoral immune response. Furthermore, ECP and total IgE were increased where IgE to SAE was detected, suggesting a role for SA in eosinophilic inflammation and high IgE concentrations. These results were confirmed in a further study where SAE-IgE (SEA-SEE, TSST-1) was demonstrated in 50% of NP, compared to 0% in control tissue [21]. Total IgE, the ratio of IgE to albumin concentrations, and eosinophil count was higher in the tissue of polyps that were positive for SAE-IgE. In accordance with these findings, a study from a South-Chinese hospital showed that 10/27 NP were positive for SAE-IgE vs. 0/15 controls, although those rates may be lower in other parts of China [66]. Suh et al. found IgE to SEA and SEB in one third of aspirin-sensitive nasal polyps (ASNP) compared to one

fifth in aspirin-tolerant nasal polyps (ATNP) [54]. The levels of SEA-IgE and SEB-IgE were closely correlated with total IgE, ECP, and IL-5 concentrations.

Most of the in vivo evidence of enterotoxin secretion is indirect, by demonstration of staphylococcal enterotoxins-specific IgE. A study [9] isolated enterotoxin-producing SA strains in 55% of NP patients, although it is not clear whether and to what extent these organisms secrete superantigens in vivo. Seiberling et al. [51] detected common staphylococcal toxins (SEA, SEB, SEC1-3, SED, TSST-1) using ELISA in 48% of polyp patients and in 7.7% of CRS without NP. Nine out of fifteen positive patients demonstrated more than one toxin. It is common for SA to produce more than one toxin at a time. In a Chinese study, the same superantigens were detected by ELISA in 12 of 22 NP, compared to none in CRS without NP or controls [64].

The classical superantigens (SEA through SEE and TSST-1) have been characterized and studied intensively, and most IgE responses described are directed against one or more of these proteins. Recently, the egc gene cluster, encoding SEG, SEI, SEM, SEN, and SEO was identified in SA [30]. We identified enterotoxin genes in 75% of SA strains detected in middle nasal meatus swabs, and showed an amplification of the egc gene cluster in 67.5% of strains [62]. As there are no validated tests for the measurement of specific IgE against egc cluster enterotoxins, previous data regarding specific IgE production against SAE might underestimate the impact of enterotoxins. Interestingly, there were no differences in enterotoxin genes between SA isolated from controls compared with NP patients, suggesting that the specific immunological response of the host to SAE rather than the panel of enterotoxin genes produced by the organism determines the clinical outcome.

10.5 Mechanisms Leading to Polyps

Evidence for the involvement of a response of T lymphocytes to staphylococcal superantigens has been shown in a series of studies showing proliferation of T lymphocytes bearing specific Vβ domains. Bernstein et al. [9] demonstrated significant clonal expansion of T cells with specific Vβ domains (Vβ skewing) in three NP patients. In a further study with 12 NP patients, Vβ skewing was demonstrated using flow cytometry in polyp lymphocytes of seven patients, whereas this expansion was not detectable in peripheral blood lymphocytes [57]. Subsequently, this group reported expansion of polyp lymphocytes expressing TCRs with specific Vβ domains in all of 18 polyp patients[16]. The average number of Vβ clones per CRS with NP patient was seven in polyp lymphocytes but only two in peripheral blood lymphocytes. In another study, 7 of 20 subjects exhibited skewing in Vβ domains with strong association to SAE [15]. In Chinese patients, an increased percentage of Vβ-expressing T cells was observed in toxin-positive polyps [64]. Many of the clonally expanded Vβ domains found in these studies are known to be associated with specific SAE. Moreover, the ratio of skewing of polyp lymphocytes compared with peripheral blood lymphocytes points to a local expansion of these lymphocytes (Fig 10.4).

In a recent study, we elucidated the modulatory effects of SEB and SpA exposure on NP cytokine secretion in an ex vivo setting [44]. Nasal polyp and inferior turbinate fragments were suspended in culture medium and stimulated with SEB and SpA for 30 min and 24 h. Spontaneous release of IL-5, IL-13, TNF-α, and IL-10 was greater in NP than in control tissue. Twenty-four-hour stimulation with SEB caused a significant increase of Th1 and Th2 cytokines (IFN-γ, IL-2, IL-4, IL-5, IL-10, IL-13) in inferior turbinates and to a greater extent in polyp tissue. By calculation of the ratio of increase in polyps to that in control tissue, it became apparent that the cytokine production was increased predominantly in Th2 cytokines (IL-4, IL-5) but an increase in T-regulatory cytokine production (IL-10 and TGF-β) was disfavored by SEB stimulation. This study clearly confirmed that SEB can polarize mucosal inflammation to a Th2 pattern. SEB may contribute to persistent inflammation by the suppression of T-regulatory lymphocytes, in line with our previous findings, where we showed a decreased FOXP3 and TGF-β1 expression in NP compared with CRS without NP and controls [58].

By detailed analysis of the pattern of increased IgE in NP and in serum, three groups of NP can be discerned [4, 21]: (1) no detectable specific IgE and low total IgE, (2) An “allergic” type of IgE expression characterized by increased concentrations of total IgE and selected specific IgE antibodies to aeroallergens corresponding to those found in serum and to skin

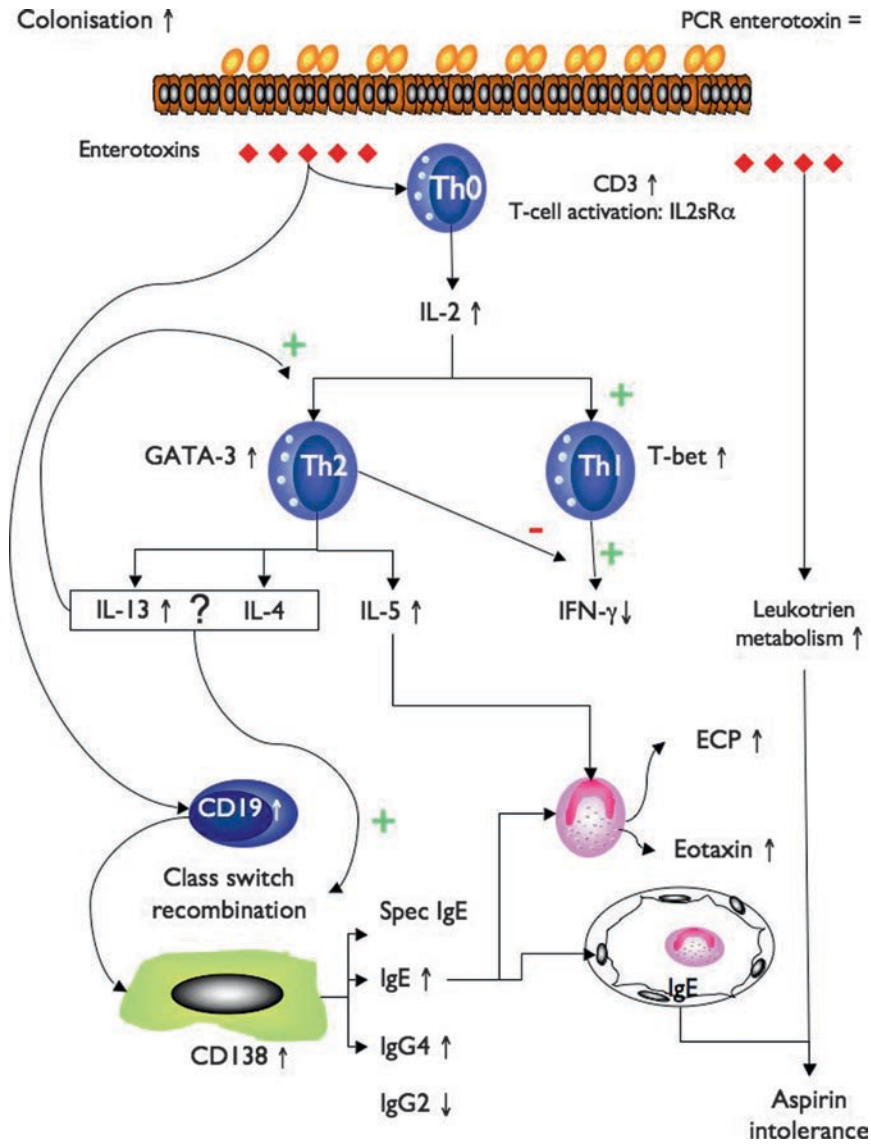

Fig. 10.4 Suggested model of SAE induced disease modulation of nasal polyps. (Illustration courtesy of Dr. T. Van Zele, 2006)

prick test positivity and (3) polyclonal pattern of IgE expression with specific IgE to a majority of allergens and increased total IgE, reflecting only partially the serum IgE response and independent of skin prick test positivity. The "allergic" type can overlap with the "polyclonal" type. The polyclonal pattern was detected in 10 of 20 NP in our first study and in 16 of 24 NP in our second study, and there were SAE-IgE in, respectively, 10 and 12 of these NP, indicating that SAE are most often involved in the polyclonal IgE response. Toxins other than the classical staphylococcal enterotoxins, or bacterial products from other organisms might have acted as superantigens in some cases.

Although extravasation of serum proteins has been shown in NP [3], there is indirect evidence for a local production of IgE rather than a local reflection of a systemic production. Total IgE and SAE-IgE concentrations were in all cases higher in NP tissue compared to serum [21]; SAE-IgE may be detected in the serum of NP patients, unrelated to atopic status, especially when asthma coexists [14, 56]. Moreover, the IgE/albumin ratios in polyp tissue and serum were dissociated, and specific IgE antibodies in polyp tissue showed only a partial relation to serum IgE antibodies, indicating that tissue IgE is rather the result of a local IgE production than of extravasation [21].

When NP were analyzed for T and B lymphocytes and for IgE by immunohistochemistry, there were lymphoid accumulations seen in all samples, and lymphoid follicular structures were seen in 25% of polyps, whereas no secondary lymphoid tissue could be shown in control samples [21]. Follicular structures stained positive for B cells (CD20) and T cells (CD3), and for IgE and CD23, whereas FcεRI was found only outside the follicles. Lymphoid accumulations stained positive for plasma cells (CD38), CD3, IgE, and FcεRI but not for CD23. We demonstrated the binding of biotinylated SEA to both follicular structures and lymphoid aggregations. These data support the hypothesis of a local organization of secondary lymphoid tissue with polyclonal activation of B cells due to the stimulation by staphylococcal enterotoxins.

Acting as B cell superantigens, there is evidence that SAE can directly alter the B cell repertoire, apart from cross-linking TCR with MHC on APC. By cross-linking MHC class II molecules on B lymphocytes with TCR on T-lymphocytes, SAE can stimulate B cells in a T cell-dependent way. SpA, a surface protein of SA, can directly induce the proliferation of B cells. Moreover, TSST-1 induces isotype switching and synthesis of IgE, depending on CD40L expression on B cells [29]. A more recent study showed a direct effect by demonstrating TSST-1-induced expression of B7.2 on B cells, enhancing the Th2 response and regulating IgE production [27]. In the mucosal tissue of atopic patients, mRNA for the ε chain of IgE was found in a significant proportion of B cells using in situ hybridization, supporting the hypothesis of a local IgE synthesis in upper airway mucosa. Coker et al. [12] showed that local clonal expansion of B cells, somatic hypermutation, and class switching occur in the nasal mucosa. A significantly biased expression of the VH5 regions of the IgE molecule [13] suggests that superantigens may modulate IgE production.

A high degree of infiltration by plasma cells in NP had been described earlier [60]. We showed increased $CD19^+$ naïve B cells and $CD138^+$ plasma cells but not $CD20^+$ mature B cells in NP compared to controls using immunohistochemistry [61], implying a differentiation of memory B cells into plasma cells. In this study, we extended our observations of increased IgE to other immunoglobulin isotypes. NP showed increased total IgA, IgG, and IgE concentrations compared to CRS without NP and controls which was not the case in the serum of these patients. Of interest, polyps with detectable SAE-IgE had significantly higher concentrations of IgE and IgG, and a larger fraction of the IgG4 subset of the IgG isotype, than SAE-IgE negative polyps. The fraction of IgG4 correlated strongly with IgE concentrations and CD138 counts. These findings were not reflected in the serum of these patients, supporting the hypothesis of the modulation by SAE of the local immunoglobulin production by plasma cells and local isotype switching toward IgG4 and IgE.

Investigating the effect of staphylococcal products on NP cytokines and effector molecules, Patou et al. [44] reported an increased secretion of histamine, CysLT, PGD_2, and IL-5 after stimulation with SpA. These results support the view that SpA may be acting not only as a B cell superantigen but may have a direct impact on mast cell and basophil activation. This activity, for which SpA is referred to as a superallergen, is mediated by the interaction of SpA with the VH3 region of IgE bound to FcεRI, the antigen-independent crosslinking of FcεRI which it causes resulting in activation of the effector cell [37].

Nasal symptoms and markers of inflammation do not increase with seasonal allergen exposure even in ragweed sensitive patients with NP, and nasal provocation is largely unsuccessful in NP patients [31]. A polyclonal IgE pattern in NP may however cause a permanent degranulation of mast cells by conventional aeroallergens and superantigens, thus maintaining polyp growth, but not acute allergic symptoms. This hypothesis needs further study, but may also explain similar mechanisms in nonatopic, but IgE-positive asthma.

10.6 Relation to Eicosanoid Metabolism and Aspirin Sensitivity

We reported increased SA colonization rates, total local IgE, specific IgE to SAE, and ECP in ASNP [59]. In Polish NP patients, we showed increased total IgE, SAE-IgE, IL-5, and ECP in ASNP compared to ATNP [45], suggesting a relation of staphylococcal superantigens to aspirin sensitivity by upregulating eosinophilic inflammation. Posthoc subgroup analysis revealed increased IL-5 and ECP in SAE-IgE-positive ATNP compared to SAE-IgE-negative ATNP, but these differences could not be shown in SAE-IgE-positive compared with SAE-IgE-negative ASNP groups, suggesting that aspirin sensitivity is linked indirectly to SAE by the severity of

inflammation rather than via direct mechanisms. Our findings have been confirmed by Suh et al. [54], reporting increased ECP, IgE, and SAE-IgE levels in Korean polyps.

Comparing eicosanoid production in CRS with NP and CRS without NP, concentrations of leukotriene C_4 synthase, 5-lipoxygenase, and CysLT were increased in different sinus disease subgroups (CRS without NP, ATNP and ASNP) in parallel and in correlation with eosinophilic inflammation severity whereas COX-2 and PGE_2 were inversely correlated [46]. These data confirmed the notion that changes of eicosanoid metabolism do occur in CRS even in the absence of clinical aspirin sensitivity and appear to be related to the severity of eosinophilic inflammation. We extended our observations by demonstrating that the production of CysLT, LTB_4, and LXA_4 is upregulated in SAE-IgE-positive NP compared to SAE-IgE-negative NP, and correlates to SAE-IgE, IL-5, and ECP levels [47]. Taken together with these results, staphylococcal enterotoxins have an amplifying role in upper airway disease with aspirin sensitivity, without evidence for a direct causal relationship of SAE with aspirin sensitivity. However, we recently isolated inferior turbinate fibroblasts and cultured the cells in the presence of different concentrations of SEB [48]. After preincubation with IFN-γ, SEB significantly downregulated PGE_2, COX-2, and EP2-receptor mRNA expression, pointing to a direct effect of staphylococcal superantigens on eicosanoid metabolism in upper airway tissue.

10.7 Clinical Implications

There is accumulating evidence that staphylococcal superantigens may have a major impact on lower airway disease such as asthma, chronic obstructive pulmonary disease, and early wheezing [6]. In a NP patient, the clinician could speculate about the activity of SAE, especially if comorbidities such as severe nonallergic asthma, aspirin sensitivity, or corticosteroid-resistant disease are present. Detection of SA by culture of swabs from the nasal middle meatus is a readily available diagnostic tool, but gives only a limited idea about an active immune response to the enterotoxins. Indeed, the colonization rates exceeded the levels of SAE-IgE, and it is the latter that correlated with the severity of inflammation [60]. Furthermore, the in vivo ability of SA to produce a superantigenic effect in the nasal tissue may vary according to the number and type of strains of the colonizing bacterium, and also depends on individual host factors, such as the genetic makeup and the inflammatory background, affecting the virulence and the interaction of enterotoxins with MHC molecules, TCR, and Igs.

The local Ig pattern may give a more specific idea about the effect of superantigens; this pattern is only partially reflected in serum. Presence of SAE-IgE indicates a former or present stimulation of the local immune system by the respective enterotoxin. A locally high total IgE and a polyclonal IgE response, directed to multiple conventional aeroallergens, which may be unrelated to serum IgE specificities, is indicative of a superantigenic effect. In asthmatic patients, the SAE-IgE level in serum is related to disease severity [5].

In contrast to the polyvalent mechanisms of action of superantigens, currently, the therapeutic armamentarium mainly consists of topical or systemic glucocorticosteroids and surgery [19]. Therapeutic failure and recurrence account for a large part of patients treated with glucocorticorsteroids, and cellular resistance to glucocorticosteroids is considered a main cause of treatment failure [50]. Staphylococcal enterotoxins may impair corticosteroid treatment possibilities, as it has been shown that superantigens may alter steroid sensitivity and expression of glucocorticosteroid receptor beta [26].

Having an established role in NP pathophysiology, eradication of SA with antibiotics seems a logical treatment option. This has not yet been studied extensively in NP, but the benefit of antibiotic and antiseptic treatment has been shown in atopic dermatitis, a disease sharing the modifying effects of staphylococcal superantigens. An eradication scheme, consisting of oral antibiotics, topical antiseptics, and nasal mupirocin ointment resulted in a significant but temporary improvement in atopic dermatitis patients who were colonized with SA [10]. Nasal mupirocin lavage might be particularly useful in eradicating nasal SA because of its potent effect on SA in biofilms [24]. Studies investigating the therapeutic benefit of antibiotic treatment in nasal polyp disease are currently underway. Further studies are needed to suggest other treatment options including long-term treatment with intracellular active antibiotics, SA vaccination, and specific enterotoxin antagonists. Based on the hypothesis of a continuous mast cell degranulation by an overwhelming polyclonal local IgE, treatment

with monoclonal antibodies to IgE could be of relevance in suppressing IgE-mediated effects in analogy to the effect in allergic disorders. A randomized double-blind placebo-controlled trial is currently performed.

In the light of the association of SAE antibodies with eosinophilic inflammation, treatment strategies antagonizing IL-5 provide an opportunity to prove the hypothesis. We recently reported a double-blind placebo-controlled randomized trial evaluating the safety and pharmacokinetics of intravenous injection of humanized anti-IL-5 antibody in NP patients [22]. We demonstrated that a single injection of anti-IL-5 is safe and well tolerated, and reduced the levels of blood eosinophilia and ECP, and IL-5Rα concentrations in both blood and nasal secretions. In half of the patients, polyp scores improved after single injection, and responders could be differentiated by increased levels of IL-5 in nasal secretions.

10.8 Summary and Perspectives

We presented evidence for a role of SA superantigens in the pathogenesis of CRS with NP by (1) showing an increased colonization rate of SAE-secreting SA strains in NP, (2) presence of superantigens in NP, (3) evidence for an immune response to SA characterized by SAE specific IgE antibodies, (4) in vitro modulation of NP cytokine pattern to a Th2 response by SEB and (5) specific T lymphocyte Vβ-skewing, characteristic of SAE. However, data supporting the superantigen hypothesis by these modalities have been shown in only 50% of NP [4, 21, 59]. Approximately 50% of NP patients do not show evidence for a superantigen effect, but share a similar eosinophilic inflammation. Currently, it remains unclear as to why only a subset of NP is showing superantigen response and why only some individuals exposed to superantigens develop NP. A genetic predisposition (expression of alleles specific to the superantigen interaction with MHC and TCR molecules) could explain part of this observation. Measurement of IgE antibodies to only the classical enterotoxins (SEA-SEE, TSST-1) could mask the possible effects of other staphylococcal superantigens or superantigens produced by different organisms. Furthermore, the observation of the variable possibility of SA to invade tissue and cells could point to the defects in mechanical or innate immunity. Genetic, epigenetic, or environmental factors are involved in epithelial antigen passage and processing, and could explain the highly variable immune response to a given staphylococcal load [32].

Of interest, we demonstrated that NP from South Chinese patients do not share the Th2-biased inflammatory pattern of polyps in European patients, as they were characterized by a neutrophilic inflammatory pattern and lacked increased IL-5, ECP, or IgE concentrations within polyp tissue [66]. Further studies revealed that Chinese polyps were characterized by a Th1/Th17 type of inflammation [67]. Those polyps may be less susceptible or may respond differently to the same exposure of SAE than European NP. Furthermore, in exploring the therapeutic role of anti-IL-5 antibodies for NP, only a subgroup of patients responded to treatment. Studying the effect of anti-IgE-antibodies on NP, it is expected to find again a subgroup of responders.

The above evidence indicates that SAEs with superantigenic activity do play an amplifying role in a subgroup of NP patients that may eventually lead to asthma comorbidity and persistent unified airway disease. The clinical identification of those patients is currently indirect, but the analysis of total and specific IgE antibodies in serum, or better in tissue biopsies, may support such diagnosis. First steps in the development of appropriate new therapeutic targets have been made, and will in the near future impact our daily clinical management [7].

Take Home Pearls

- *S. aureus* enterotoxins are involved in the pathogenesis of a subgroup of nasal polyps via the superantigen mechanism.
- These polyps have a more severe eosinophilic inflammation and a local polyclonal pattern of increased IgE.
- This subgroup is associated with asthma and aspirin exacerbated respiratory disease.
- Diagnostic and therapeutic tools for this specific group need to be studied further.

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Fungal-Induced Inflammation and Nasal Polyps

11

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Core Messages

- Fungi are present in the mucus of chronic rhinosinusitis (CRS) patients and normal healthy controls.
- Fungi (especially Alternaria) induce the production of cytokines (IL-13 and IL-5) crucial for the eosinophilic inflammation. This immune response occurred only in CRS patients but not in healthy controls.
- Fungi induce an eosinophilic tissue airway inflammation in mammals (mice), which is in contrast to a neutrophilic response to bacteria.
- Fungi can induce an eosinophilic airway inflammation and congestion in patients.
- Eosinophils, in vivo, target fungi in the mucus with CRS and nasal polyps.
- Fungal antigens with a molecular weight of 61 kilodaltons (kDa) cause activation and degranulation of human eosinophils via the beta-2 integrin on the CD11b receptor.
- Clinically, antifungal drugs can reduce nasal polyps, improve computed tomography (CT) scans, and decrease levels of interleukin-5 (IL-5) and markers of eosinophilic inflammation. However, data between different antifungal applications and different outcome measures are conflicting.

11.1 Introduction

Every patient with nasal polyps exhibits evidence of chronic inflammation of the upper airway and has chronic rhinosinusitis (CRS). This chronic inflammation is associated with heterogeneous damage of the respiratory epithelium of the nasal and sinus mucosa, and this is identical to the epithelial damage seen in asthma [23, 37]. Nasal polyps are the result and ultimate end-stage of this chronic inflammatory reaction of the upper airway. Notable exceptions include antral-choanal polyps and the hallmark polyps of cystic fibrosis. The predominant cell characterizing this chronic inflammation is the eosinophil. So what evidence exists to support the contention that fungi induce this eosinophilic response? Where are these fungi located: in the airway mucus or in the airway tissue?

11.2 Fungus Is Among Us

Fungi inducing this eosinophilic inflammation of the upper airway are located in the airway mucus, and not in the tissue. It is not a fungal infection (since an infection requires microorganisms to enter tissue) and is differentiated from other forms of fungal involvement

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in the upper airway such as fungus balls (noninvasive) and invasive fungal sinusitis (acute fulminant) seen in immunocompromised patients.

Sensitive fungal culture techniques require that adequate amounts of mucus be harvested and the disulfide bridges of mucin be chemically disrupted releasing the entrapped fungi [1, 21]. Utilizing these culture methods, fungi are found in the mucus of 96% ($n>202$) and 91.3% ($n>92$) of unselected, consecutive patients with chronic eosinophilic inflammation of the nose and paranasal sinuses, respectively [1, 21]. In addition, fungi are present in almost every healthy control. Fungi are ubiquitous. In fact, fungi are present in the mucus after birth: 20% of newborns, 72% of infants at 2 months, and 94% at 4 months [17]. Careful collection and proper staining are critical for finding fungi since Gomori's methamine silver stain (GMS) yields fungi in merely 82% ($n>101$) of patients with chronic eosinophilic airway inflammation [1, 21]. Using a chitin-based immunofluorescence staining technique, fungal elements are found in 100% of airway mucous specimens [34]. Thus, these newer fungal detection techniques demonstrate significant fungi in the mucus in almost every upper airway.

Another study confirms the existence of fungal DNA in the polypoid nasal tissue ($n>27$) of all patients (100%) with chronic eosinophilic inflammatory mucosal changes [8]. Interestingly, the patients vs. healthy controls differed in terms of the presence of Alternaria-specific DNA. It was detectable in all the patients but absent in all healthy controls. This might suggest that only patients (not healthy controls) process certain fungal DNA for antigen presentation [8].

These findings regarding the ubiquitous presence of fungi is supported by a recent study from the National Institute of Environmental Health Science exclaiming that practically everyone (including patients and normal healthy control) is exposed to Alternaria antigens in their homes [29].

Certain fungal antigens, e.g., from Alternaria sp., are only secreted by the fungal cell wall when the fungal spore is germinating, or on the growing tip of the fungal hyphae. Despite improvements in the sensitivity of culture methods, Alternaria species were only growing in 40–50% of the specimen, which means improvement over previous studies, but still lacks sensitivity compared to follow-up studies looking for Alternaria-specific DNA or Alternaria antigen [8, 25, 32].

We conclude that with the newer detection techniques, fungi, especially Alternaria species, are present in the nasal mucus secretions in almost every patient with nasal polyps and in normal healthy control subjects. Fungi are everywhere. Hence, the presence of fungi is not diagnostic of disease.

11.3 The Immune Response to Fungi

So what is the evidence that fungi can induce a chronic eosinophilic inflammatory response in patients but not in normal healthy control subjects? Why do the eosinophils exist and how do they fit into the pathology of CRS and nasal polyps? What mechanism triggers the parade of eosinophils from the bone marrow to the nasal tissue and subsequently into the nasal mucus? We will answer each of these questions.

We know that some patients with nasal polyposis produce specific immunoglobulin E (IgE) against fungi [6, 20]. Note that an IgE-mediated reaction with exposure to allergens reliably results in allergic rhinitis and not in nasal polyposis. In fact, nasal polyposis occurs independent of the presence of an IgE-mediated allergy [31]. Certain fungi, especially Alternaria, have the ability to induce symptoms of eosinophilic airway inflammation in the absence of an IgE-mediated systemic reaction [16].

Thus, patients with chronic eosinophilic inflammation of the upper airway may have IgE-mediated hypersensitivity to molds as a comorbid disease, but the underlying eosinophilic inflammation appears to be driven by a mechanism independent from an IgE-mediated one. So what is our proposed non-IgE-mediated mechanism that drives the underlying chronic eosinophilic inflammation? Additionally, how do harmless ubiquitous inert fungi participate in triggering this inflammatory process? Answering these questions requires understanding that the human immune system recognizes fungi in the airway mucus (of patients only) as foreign, thereby recruiting eosinophils from the bone marrow by the mechanism of cytokine production, which in turn regulates the eosinophilic inflammation. Cytokines activate eosinophils. Tissue-bound lymphocytes are the primary source of cytokines in patients with chronic eosinophilic upper airway inflammation (CRS with or without nasal polyps) [10]. We are using the terms chronic eosinophilic upper airway inflammation and CRS interchangeably.

In addition, the expression of vascular cell adhesion molecule-1 (VCAM-1) has been identified in the vascular endothelium of patients with chronic eosinophilic inflammation of the nose and sinuses and is necessary to induce selected adhesion to the vessel wall, as well as migration of the eosinophil into the tissue [11]. VCAM-1 specifically binds to VLA-4 (very late-appearing antigen-4) on eosinophils, thereby causing selective adhesion and migration of eosinophils from the vasculature into the tissue [11]. The cytokine that is directly associated with the expression of VCAM-1, independently from the allergy status of the patients, is IL-13 [10, 11]. Shin et al. recently demonstrated in patients with CRS that isolated peripheral blood mononuclear cells (PBMCs), which contain lymphocytes and antigen-presenting cells, are capable of producing large amounts of interleukin-13 (IL-13) when exposed to various mold extracts – especially Alternaria species. This is in contrast to the lack of IL-13 when PBMCs from healthy controls were stimulated with the same extracts [32]. IL-13 production in response to Alternaria may enhance the expression of VACM-1 by vascular endothelial cells, which in turn facilitates the "eosinophil exodus" from the vasculature into the upper airway tissues [32].

Another very important cytokine is IL-5, which is the key cytokine for eosinophil production, differentiation, and activation, and survival is present in tissue specimens from patients with chronic upper airway eosinophilic inflammation and not in normal healthy controls [4, 9, 19, 30, 33]. The majority of IL-5 staining cells are lymphocytes (68%) [9]. A direct link to fungi is provided again in the study from Shin et al. where PBMCs from patients with CRS induced IL-5 production in 89% ($n > 18$) when exposed to Alternaria antigens [32]. When Alternaria antigens were exposed to PBMCs from 15 healthy controls, none demonstrated any IL-5 production [32]. Not surprisingly, elevated levels of specific IgE for Alternaria were detected in only 28% (5 of 18) of these patients. In other words, the increased IgE levels did not correlate with increased levels of IL-5 and did not explain the presence of eosinophils in nonallergic patients [32]. The fact that this immune response was detected in peripheral blood lymphocytes is the evidence for CRS being a systemic disease.

Mean serum IgG levels specific for Alternaria were increased fivefold in the CRS patients ($n > 18$) compared to the healthy controls and also correlated with the amounts of IL-5 produced in each individual patient ($n > 15$) [32]. Since IgG levels usually indicate the amount of immunologic exposure, these results suggest a direct correlation between the exposure to Alternaria antigens and the degree of the immune response measured by the amount of IL-5 production.

Thus far, we have shown that fungal organisms are present and especially that Alternaria induces the cytokine response in CRS patients (in contrast to healthy controls), which is crucial for eosinophilic inflammation to occur.

11.4 The Destructive Power of Eosinophils

So once eosinophils are in the tissue, what happens to them? Newer studies focusing on the preservation of mucus and ensuring that this mucus stayed attached to the tissue revealed intact eosinophils in the tissue and also found striking amounts of eosinophils forming clusters in the mucus [1, 21]. Consequently, this mucus was termed eosinophilic mucus and showed that eosinophils found in the tissue are essentially migrating into the sinus lumen [1, 21]. Furthermore, histochemical studies showed that eosinophils did not degranulate in the tissue, but that the degranulation occurred in the mucus once the eosinophils reached these clusters [24]. There they released major basic protein (MBP), which is toxic to respiratory epithelium and is capable of producing the epithelial damage found in CRS (with or without polyps) [12, 13, 24, 37]. MBP levels exceeded the threshold for upper airway respiratory epithelial damage by at least 3,000-folds in each patient studied [13, 24]. These in vivo observations explain the patterns of damage seen in chronic upper airway eosinophilic inflammation where only the outer layers of tissue are damaged, suggesting that the damage is inflicted to the airway side (airway lumen) [12, 24, 37]. The epithelial damage may predispose CRS patients to secondary bacterial infection and clinically important acute exacerbations.

Eosinophilic inflammation has been observed in tissues that contain large, nonphagocytosable parasites such as helminthes [15]. Earlier reports documented the accumulation of eosinophils and their subsequent degranulation on the surfaces of these parasites. The toxic proteins in the eosinophil granule (including MBP)

damage and kill these organisms. Recent observations of eosinophil clusters in mucus from CRS patients are reminiscent of the accumulations around parasites [1, 15, 21].

11.5 An Immunologic Defense?

Imagine the hypothetical question: what would happen if the immune system determines these extramucosal fungi as foreign? Fungal organisms are large and cannot be engulfed and devastated by the mechanism of phagocytosis. So what would be the consequences in this situation? One likely answer is that the patient's immune system recognizes fungi as foreign and mounts a similar defense against fungi through:

1. Eosinophil recruitment from the vasculature by inducing IL-13 production.
2. Eosinophil activation and life prolongation by inducing IL-5 production.
3. Eosinophil migration to the fungi in the mucus.
4. Eosinophils clustering around the fungi and degranulating when in contact with the fungi, releasing toxic proteins such as MBP and thus destroying the fungi as well as causing collateral damage to the respiratory epithelium.

The above notion is further supported by immunohistochemistry, which demonstrates clusters of eosinophils surrounding the fungi within the mucus associated with intense eosinophil degranulation. This suggests that eosinophils move from tissue into the airway mucus specifically targeting fungi in vivo in CRS (Fig. 11.1).

11.6 Alternaria-Induced Eosinophil Degranulation

The next questions are whether fungi are capable of inducing eosinophil degranulation and if all fungi are equally capable of activating the eosinophils. When eosinophils were exposed to different fungal antigens, by far the most robust and consistent stimulation occurred with Alternaria extract that induced both eosinophil activation and degranulation [18]. The antigen fraction from Alternaria that induced the degranulation had a molecular weight of 61 kilodaltons (kDa), was highly heat labile, and functioned via a G protein-coupled receptor [18]. Other fungal antigens, including *Aspergillus*, *Cladosporium*, and *Candida*, did not induce eosinophil degranulation. It must be pointed out that the fungus-induced degranulation of eosinophils is an innate response occurring automatically whenever fungi and eosinophils are brought together, regardless of whether they came from CRS patients or healthy controls. However, patients with upper and lower airway inflammation released about 60% more granular proteins per eosinophil compared to healthy controls [14]. Another study identified CD11b as the receptor through which the Alternaria antigen binds to the eosinophil and induces the degranulation [35]. Blocking this receptor completely took away the ability of eosinophils to degranulate in response to Alternaria. Interestingly, it was not the entire receptor but only the beta-2 integrin that was the binding site for the Alternaria antigen. The same study visualized that eosinophils degranulate on Alternaria hyphae in vitro [35]. In contrast, when neutrophils were stimulated with Alternaria antigens, they did not respond with degranulation or activation, which suggests that the presence of a specific fungal species (Alternaria) produces a specific innate immune cell type response to certain fungi in humans [14]. Thus, both innate (degranulation and activation of eosinophil) and acquired immune responses (cytokine production by lymphocytes, independent of IgE production) to environmental fungi, such as Alternaria, provide cellular activation signals necessary for the robust eosinophilic inflammation in CRS patients with or without nasal polyps. In addition, murine models for CRS using fungal antigens have resulted in eosinophilic airway inflammation, in contrast to neutrophilic inflammation using bacteria as a stimulus [18]. The displayed evidence supporting the role of fungi in CRS with or without nasal polyps brings up the role of antifungal therapy. While some trials demonstrated clinical benefit of topical Amphotericin B, including the reduction of nasal polyposis and eosinophilic inflammation, other trials did not show any patient improvement. The trials differed in the formulations used, the concentrations of the antifungal including the toxic dissolvent (desoxycholate), the delivery device and the patient selection, and the outcome measures, making comparison between them impossible [2, 5, 22, 25, 27, 28, 36].

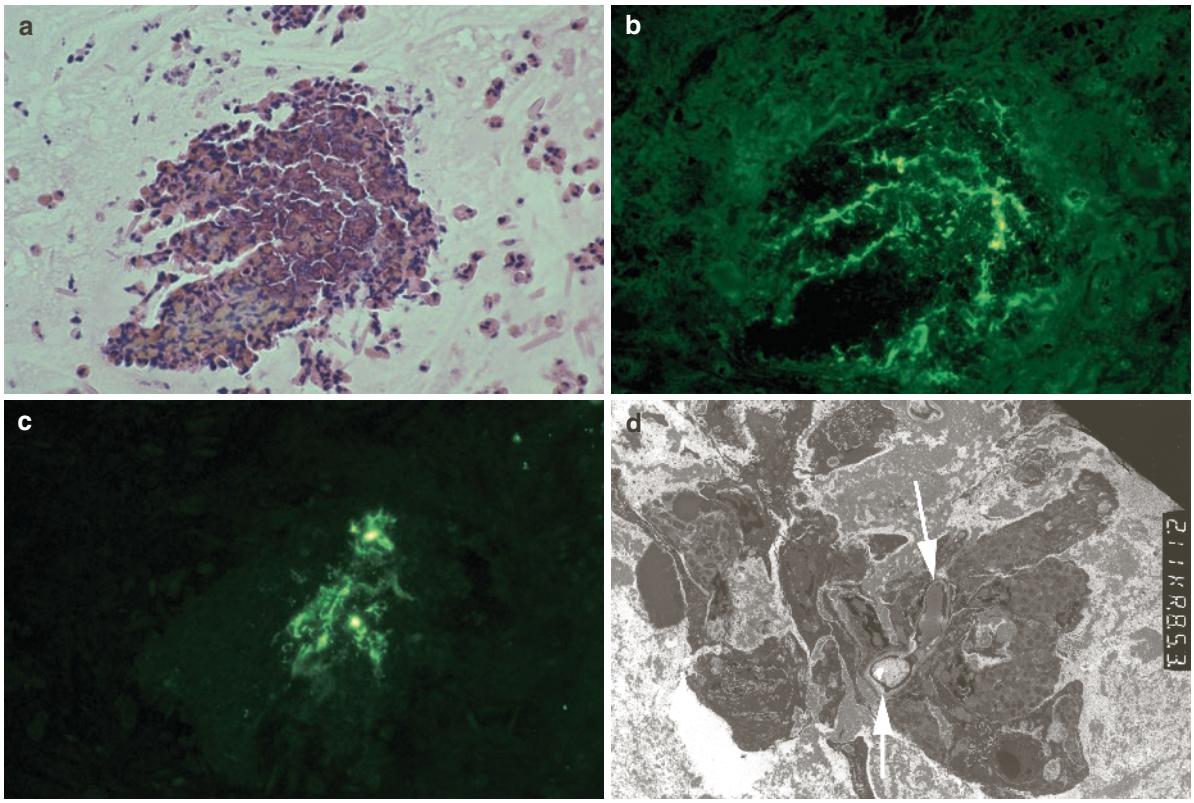

Fig. 11.1 (**a**) Mucus from a patient with CRS and nasal polyps that has been stained with hematoxylin and eosin (H&E). The image shows the typical cluster formation of eosinophils in the mucus of CRS patients (H&E, original magnification ×400). (**b**) Serial section of (**a**) is stained for eosinophilic major basic protein (eMBP). The diffuse release of eMBP demonstrates that eosinophils are degranulating. MBP release occurs only in the clusters in the mucus, not in the tissue. This suggests that the eosinophils in the tissue are in transit toward their final target in the mucus (anti-MBP immunofluorescence staining; original magnification ×400). (**c**) Serial section of (**a**) and (**b**) is stained for Alternaria antigen. The clustering of eosinophils and the release of toxic eMBP occur at the exact location of the fungal antigens, suggesting that the eosinophils are targeting the fungus (anti-Alternaria immunofluorescence staining; original magnification ×400). (**d**) Electron microscopy of mucus from a patient with CRS and nasal polyps showing a cluster of eosinophils. A fungal hyphae can be visualized in the center of the cluster of eosinophils, suggesting targeting of the fungus by the eosinophils. Note the intimate relationship of the eosinophils engulfing the fungi in preparation to release their toxic MBP (transmission electron microscopy; original magnification ×5,275)

It must be emphasized that the Amphotericin B for intranasal applications should not be formulated in glucose (lack of osmotic pressure gradient prevents diffusion into the mucin), is incompatible with saline, is toxic to respiratory mucosa (with desoxycholate as a desolvent) in concentration above 300 µg/mL, and must be applied correctly through a devise capable of delivering the drug into the obstructed nose and paranasal sinuses [7]. While intranasal Amphotericin B continues to be in clinical development, approaches with the systemic antifungal itraconazole show promises [26]. A recently published randomized-controlled-trial showed that oral itraconazole of 400 mg/day for 32 weeks in patients with severe asthma and fungal sensitization (determined by positive skin prick or positive IgE RAST to fungi) demonstrated not only significant improvement in their asthma symptoms, but also showed significant improvement in their associated rhinologic symptoms [3]. One can only wonder if the same treatment would be effective in patients who are not preselected for having an IgE-mediated allergy to fungi, but in all patients regardless of their allergy status.

Take Home Pearls

- Fungi are present in the mucus of CRS patients and normal healthy controls.
- Fungi (especially Alternaria) induce the production of cytokines (IL-13 and IL-5) crucial for the eosinophilic inflammation. This immune response occurred only in CRS patients, but not in healthy controls.
- Fungi induce an eosinophilic tissue airway inflammation in mammals (mice), which is in contrast to a neutrophilic response to bacteria.
- Fungi can induce an eosinophilic airway inflammation and congestion in patients.
- Eosinophils, in vivo, target fungi in the mucus with CRS and nasal polyps.
- Fungal antigens with a molecular weight of 61 kDa cause activation and degranulation of human eosinophils via the beta 2 integrin on the CD11b receptor.
- Clinically, antifungal drugs can reduce nasal polyps, improve CT scans, and decrease levels of IL-5 and markers of eosinophilic inflammation. However, data between different antifungal applications and different outcome measures are conflicting.

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Categorization of Nasal Polyps

12

Berrylin J. Ferguson, Habib Rizk, Jeevan Ramakrishnan, and Harshita Pant

Core Messages

- Chronic rhinosinusitis (CRS) with nasal polyps (NP) represents a diverse group of potential etiologies, many of which may be overlapping. The clinical symptoms of NP do not differentiate between etiologies.
- Symptoms in patients with NP can be categorized by symptom scores from several instruments, although none are specific for NP and none correlate with the extent of objective disease.
- Sinus CT scans can be categorized by a variety of scoring systems; however, correlation between sinus symptoms and CT findings is generally poor; the most widely utilized is the Lund–Mackay scoring system.
- NP can be categorized endoscopically by size through several staging systems, which demonstrate intra and interrater concordance, but again without demonstrated correlation to symptoms.
- Objective verification of symptoms can be performed through nasal airway patency assessment and smell testing.
- NP can be categorized by the presence of predominant inflammatory cell population into eosinophilic, neutrophilic, and mixed types.
- Presence of coexisting pathogens such as bacteria or fungus and the inflammatory response (eosinophilic vs. noneosinophilic) can be utilized to further differentiate NP into distinct categories; the significance of categorization in this manner is under investigation.
- Categorization by severity should reflect objective disease state, medications required for control, and risks of treatment and untreated disease.
- A NP categorization system that incorporates sinonasal symptoms scores, objective evidence of disease (CT and endoscopic scores), known risk factors for recalcitrant NP disease, and extent of disease control with medical and surgical treatment over time is most likely to accurately assess the severity of NP disease, assist in the patient's treatment, and facilitate optimal study of NP.

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12.1 Symptom Scores

Disease-specific questionnaires are usually more sensitive than general quality of life questionnaires and include assessment of facial pain or pressure, nasal blockage, olfaction, and nasal discharge or post nasal discharge. It is difficult to compare one patient's subjective assessment

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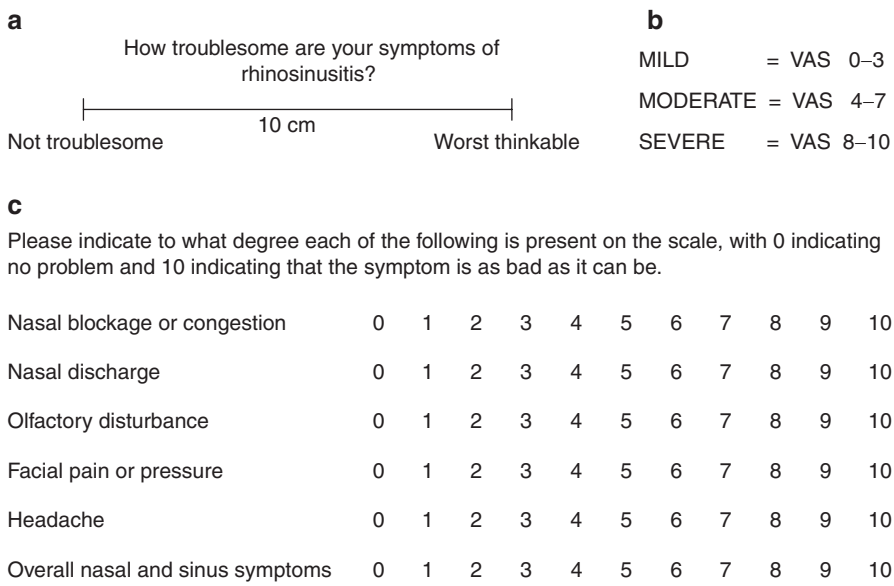

Fig. 12.1 (**a**) On the visual analogue scale the patient is asked to indicate how severe a symptom is by placing a mark on a 10-cm line, with 0 indicating no problem and 10 indicating the "worst thinkable or most troublesome." (**b**) The disease can be divided into mild, moderate, and severe as follows. (**c**) Alternatively, patients can be asked to indicate their symptoms on a 0–10 scale

to another patient. These questionnaires are generally used to assess response of a patient to an intervention over time. None of the following questionnaires was specifically designed for or validated in nasal polyp (NP) patients. The most frequent and bothersome symptoms for patients with NP are impaired olfaction and nasal blockage [1].

1. *Rhinosinusitis Outcome Measure 31 (RSOM 31)* is a validated survey of 31 questions in six domains. The patient scores each item for its severity and importance to the patient. It takes over 15 min to complete. It was originally validated on a mixed group of patients including those with allergies, NP, and sinusitis. Presence of sinus disease was not objectively verified in these patients.
   a. *Sinonasal Outcome Test 20 (SNOT 20)* is a modification of the RSOM 31, which is easy to use and has been used in numerous studies. Unfortunately, it does not include questions on nasal blockage or sense of smell. The SNOT-22 includes these questions but is unvalidated.
2. *Rhinosinusitis Disability Index* is a 30-item validated questionnaire that has similarities to the RSOM 31 and the SF-36. The patient is asked to relate nasal and sinus symptoms to specific limitations on daily functioning. It can be completed quickly and easily, but does not allow the patient to indicate their most important symptoms.
3. *The Chronic Sinusitis Survey* is a six-item duration-based assessment of specific rhinosinusitis symptoms (pain, congestion, and drainage) and medication usage. It does correlate with general quality of life surveys and patients undergoing endoscopic sinus surgery showed improvement at 1 year.
4. *Rhinitis Symptom Utility Index (RSUI)* is a ten question survey designed for cost effectiveness studies. It asks about the severity and frequency of nasal obstruction, rhinorrhea, sneezing, itching, and watery eyes. The 2-week reproducibility was weak,

Table 12.1 The sinonasal questionnaire discriminates better than SNOT 20, CT scan, or nasal endoscopic screening in determining CT evidence of sinus inflammation

	Never	1–4 Times/month	2–6 Times/week	Daily
Runny nose				
Postnasal drip				
Need to blow your nose				
Facial pain/pressure				
Nasal obstruction				

Scoring: never (0), 1–4 times/month (1), 2–6 times/week (2), and daily (3); score reported as average of five items: range of possible scores 0–3

probably reflecting the dynamic variability of rhinitis on a day-to-day basis.

5. *RhinoQol* is a sinusitis-specific instrument that measures symptom frequency, bothersomeness, and impact, and can be used for both acute and chronic RS.
6. A *visual analogue scale (VAS)* can be used for discreet symptoms and patients can mark on a line the severity of symptoms (Fig. 12.1a–c). A VAS >5 has been shown to effect quality of life [1].
7. *The sinonasal questionnaire* is a five-item questionnaire with a scale of 0–3, where a higher score indicates more frequent symptoms. It was specifically designed as a screen for chronic sinonasal disease and demonstrated superior sensitivity and specificity for detection compared to SNOT20 and RQLQ. It has yet to be validated for use in interventional studies and omits questions on smell, a frequent disability in patients with NP [2] (Table 12.1).

General health status instruments enable the comparison of patients suffering from CRS to other patient groups.

1. *Medical Outcomes Study Short Form 36 (SF36)* is the most widely used and well-validated general health status instrument in use. It has been used both preoperatively and postoperatively in CRS and includes eight domains – physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health.
2. Other general health status instruments that have been used in sinusitis studies include EuroQOL, *Short Form 12, Quality of Well-Being Scale, Glasgow Benefit Inventory, and McGill pain questionnaire*.

12.2 CT Imaging Categorization

CT scanning is the imaging modality of choice for confirming the extent of pathology and anatomy in CRS with NP. The information provided by CT complements the data collected by history and endoscopic exam to not only stage the patient's disease, but also evaluate response to treatment.

There have been several CT scoring systems developed for CRS, but none specifically developed for CRS with NP. The Lund Mackay scoring system is the most widely used and validated (Table 12.2). It consists of a score of 0–2 dependent upon the absence, partial, or complete opacification of each sinus system and of the osteomeatal complex, deriving a maximum score of 12 per side.

Table 12.2 Lund–Mackay sinus CT grading system

Sinus system	Left	Right
Maxillary (0,1,2)		
Anterior ethmoid (0,1,2)		
Posterior ethmoid (0,1,2)		
Sphenoid (0,1,2)		
Frontal (0,1,2)		
Osteomeatal complex (0 or 2 only)*		
Total		

0 = No mucosal thickening
1 = <Total opacification
2 = Total opacification
Above scoring system is applied to each individual patient
*No score of 1 is given for osteomeatal complex

The Lund–Mackay scoring system has been validated in several studies and was adopted by the Rhinosinusitis Task Force Committee of the American Academy of Otolaryngology Head and Neck Surgery in 1996. It has been used in studies to show that CT scores correlate well with endoscopic scores. However, CT scores have generally had poor correlation with symptoms scores when measured by validated disease-specific or general health questionnaires.

Zinreich modified the Lund–Mackay scale to allow more discrimination in grading the sinuses. His method is shown in Table 12.3.

Table 12.3 Zinreich modification

CT and categorization CT imaging date		
Zinreich method (Lund modification) scores each sinus 0–5, OMC 0–2		
0 = 0%, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–99%, 5 = 100%		
	Right	Left
Maxillary sinus		
Anterior ethmoid sinus		
Posterior ethmoid sinus		
Sphenoid		
Frontal		
Osteomeatal complex (0–2 scale)		
Total		

Table 12.4 Lund–Kennedy scoring system

Characteristic	Baseline and follow-up
Polyp, left (0,1,2,3)	
Polyp, right (0,1,2,3)	
Edema, left (0,1,2)	
Edema, right (0,1,2)	
Discharge, left (0,1,2)	
Discharge, right (0,1,2)	
Postoperative scores to be used for outcome assessment only	
Scarring, left (0,1,2)	
Scarring, right (0,1,2)	
Crusting, left (0,1,2)	
Crusting, right (0,1,2)	
Total points	

Polyps: *0* – absence of polyps, *1* polyps in middle meatus only, *2* polyps beyond middle meatus but not blocking the nose completely, *3* polyps completely obstructing the nose. Edema: *0* absent, *1* mild, *2* severe. Discharge: *0* no discharge, *1* clear, thin discharge, *2* thick, purulent discharge. Scarring: *0* absent, *1* mild, *2* severe. Crusting: *0* absent, *1* mild, *2* severeReprinted from Lund and Kennedy [6]), with permission from the Annals Publishing Company

12.3 Endoscopic Scoring

The Lund–Kennedy score is the most widely used endoscopic scoring system; however, it is not specific for NP (Table 12.4).

12.4 Specific Nasal Polyp Scoring

Several authors have proposed an endoscopic scoring system for NP. Johansson showed a correlation between a 0 and 3 scoring system and their own system in which they estimated the percentage projection of polyps from the lateral wall and the percentage of nasal cavity volume occupied by polyps. Symptoms did not correlate with volume occupied by NP [1]. In rhinosinusitis: developing guidance for clinical trials, a 0–4-stage polyp grading shown below was introduced; however, Hadley et al. later showed that the five-stage scoring system trended toward more discrimination; the differences, however, were not statistically significant. Difficulties in judging the grade of polyp relative to the turbinates include variability in the size of turbinates and prior surgery in which the turbinate may have been significantly reduced. Polyps can also be manipulated in size, by pulling down or pushing up. These staging systems have yet to be validated by response to intervention. NP are scored individually by side in all three systems (Fig. 12.2a, b).

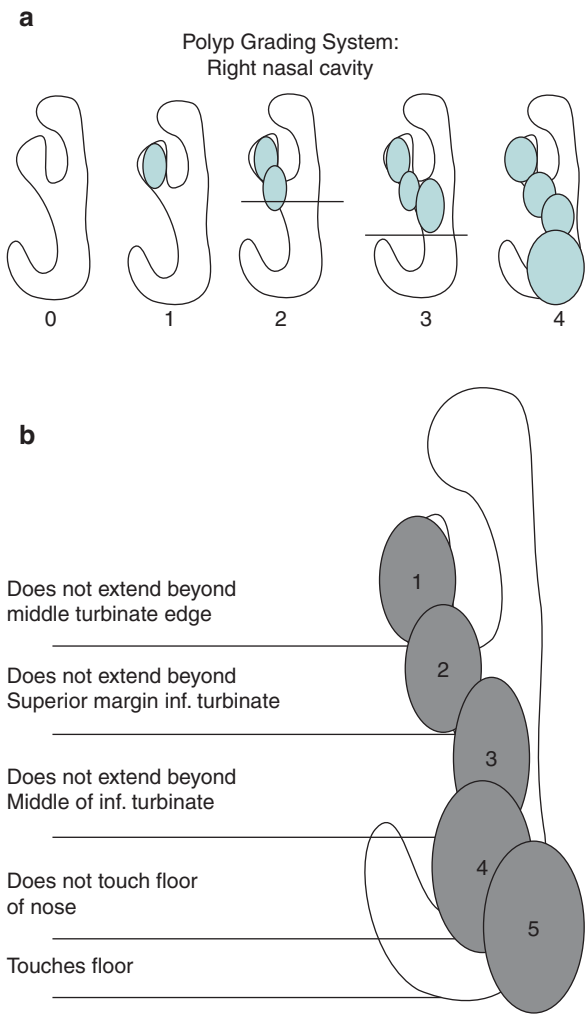

Fig. 12.2 (**a**) Four-stage polyp grading system: *0* no visible NP; *1* small amount of polypoid disease confined within the middle meatus; *2* multiple polyps occupying the middle meatus; *3* polyps extending beyond the middle meatus; *4* polyps completely obstructing the nasal cavity (reprinted from Meltzer et al. [5]. (**b**) Five-stage polyp grading system: *0* no visible NP; *1* NP proximal to middle turbinate; *2* NP distal to middle turbinate but not beyond superior margin of inferior turbinate; *3* between inferior turbinate and middle of inferior turbinate; *4* between middle of inferior turbinate but not totally obstructing; *5* touching the floor of nose

12.5 Objective Measures of Nasal Function for Categorization

Nasal airway can be assessed by acoustic rhinometry or rhinomanometry in the laboratory setting. A practical method of objectively assessing nasal airway in a clinic or patient home setting is with the peak nasal inspiratory flow meter. These are relatively inexpensive, on the range of $15 per individual subject device (Fig. 12.3).

Olfaction can be assessed by at least 20 different published methods. The two most widely used include: (1) The University of Pennsylvania Smell Identification Test (UPSIT) has a short test of 11 items or a longer test of 40 items, which the subject scratches, sniffs, and then chooses one of four multiple choice answers corresponding to the smell. Each booklet is intended for single subject usage. (2) Sniffin' Sticks that consist of reusable odor sticks and can be administered as a threshold test or a discrimination test with multiple choice answers similar to UPSIT (Fig. 12.4). The use of an alcohol pad as a fast semiquantitative method of assessing smell was popularized by Terry Davidson. Subjects with normal olfaction can smell a newly opened alcohol pad at around 12 in. from the nares, while subjects with hyposmia will only be able to smell the alcohol at distances of half this or less. The anosmic will not be able to smell the alcohol even when the alcohol pad is directly under the nares [3] (Fig. 12.5a, b).

Fig. 12.3 Peak nasal inspiratory flow meter

Fig. 12.4 Sniffin' Sticks

Fig. 12.5 (**a**) Patients with hyposmia will be able to smell alcohol at 2–4 in. from their nose. Anosmic patients will not smell the alcohol even when it is right at their nose. (**b**) Patients with normal sense of smell detect alcohol at 12 in

12.6 Histologic Categorization

The categorization of NP as eosinophilic, noneosinophilic, and neutrophilic can be important in differentiating potential etiologies and evaluating potential to respond to treatment. Eosinophilic conditions are considered more steroid responsive than noneosinophilic NP. Over 80% of NP in Western Europe are characterized by a predominate eosinophilic infiltrate. Patients with cystic fibrosis usually have polyps with a neutrophilic predominance. Geographical differences exist in the incidence of eosinophilic infiltration, and in China, eosinophilic NP are the minority. Well-defined eosinophilic disease states include allergic fungal sinusitis, nonallergic fungal sinusitis with eosinophilic mucin and NP, and nonfungal eosinophilic sinsusitis. The latter may overlap with patients with aspirin-exacerbated respiratory disease, also known as triad syndrome and Samter's triad. Presence of lymphoid aggregates may indicate potential superantigen stimulation of lymphocytes. In addition to pathologic assessment of tissue, the mucus should be examined specifically for the presence of eosinophils, fungi, and bacteria (Table 12.5).

12.7 Presence of Bacteria or Fungus

The role of bacteria and fungus in NP is evolving. Certainly, fungal presence in eosinophilic conditions may predict response to antifungal therapy in refractory cases. Cultures should be obtained, especially if polyps are associated with eosinophilic mucin or purulence. Potential categorizations relative to fungal or bacterial presence in NP include NP with eosinophilic mucus (Table 12.6).

12.8 Categorization by Disease Severity and Medication Requirements

In 2006, asthma guidelines were developed, which recognized that disease severity was affected by medical intervention [4]. While patients prior to treatment could be categorized reasonably accurately into mild, moderate, or severe disease based on their symptoms and objective airway findings, these categories would change with treatment. For instance, patients on treatment may be classified as well-controlled, but in the absence of medication, represent moderate or severe disease classification. In an attempt to categorize all patients with regard to asthma severity, including those who were medication naïve, as well as those on medication, scales of severity, degree of control, and scoring of severity relative to medication were developed. Medication in asthma is prescribed in steps, with the medication with the fewest side effects that is most likely to control disease initiated, and if control is inadequate, then additional medications are utilized that carry progressively more side effects and/or costs.

Table 12.5 Categorization by leukocyte infiltrate and pathogens

Degree	Eosinophil presence	Neutrophils presence	Lymphoid aggregates	Eosinophilic mucus	Fungi	Bacteria
Absent						
Scant						
Moderate						
Marked						

Table 12.6 Categorization by histology and allergic status

Eosinophilic mucus rhinosinusitis subtypes	Allergy to fungus	Fungal presence	Bacteria present
Allergic fungal sinusitis	+	+	Usually
Nonallergic fungal	Negative	+	Usually
Eosinophilic mucus rhinosinusitis without fungus	±	Negative	Sometimes
Aspirin-exacerbated respiratory disease	Usually not	Usually not	Maybe, also high association with IgE to staph superantigens

We have adapted this outline for asthma in NP patients. This is a preliminary proposal that awaits validation. Based on preliminary clinical data, it appears that this measure may serve to better categorize the true severity of NP, including treated patients even when they are well controlled on medications or surgery (Table 12.7).

Patients with NP and purulent secretions present for greater than 7 days should be treated with culture-directed antibiotics in step 1 (Table 12.8).

Patients with NP are managed in a stepwise fashion. Those with well-controlled disease based on Table 12.7 would begin with step 1 and work up the steps until well-controlled. Patients with severe disease based on physical findings would begin with step 4. Not all patients will achieve well-controlled status. Patient control is determined by symptoms present and medications required. Patients still poorly controlled, despite step 5 interventions, should be reevaluated with verification of NP objectively and undergo investigation for immunodeficiency, eosinophilic and granulomatous disorders, food or inhalant allergy or exacerbating exposures, and disorders.

Table 12.7 Categorization of components of severity

	Normal or in remission	Mild	Moderate	Severe
Endoscopic findings	No polyps No purulence or eosinophilic mucus	Stage 1 nasal polyps and no eosinophilic mucus	Stage 2–3 nasal polyps or scant eosinophilic mucus	Stage 4 or 5 nasal polyps or moderate to severe amounts of eosinophilic mucus
Step required for control, see Table 12.8	No therapy or step 1	Step 1 or 2	Step 3–4	Step 5

Patient's category is determined by highest level based on endoscopic findings or step required to achieve that level of endoscopic finding. If initial patient examination, initiate therapy with step corresponding to severity endoscopically and step down as control is achieved

Table 12.8 Stepwise approach for managing nasal polyps

Step1	**Step 2**	**Step 3**	**Step 4**	**Step 5**
Intranasal steroid spray once daily Hypertonic or isotonic Saline irrigation Mucolytics Purulent nasal polyposis[a]	Intranasal steroids twice daily[b]	Intranasal steroid sprays once or twice daily and any of the following: antihistamines spray or use of a leukotriene receptor antagonist such as Montelukast or Zafirlukast	Add to treatment Zileuton or omaluzumab or short steroid taper	Daily corticosteroids or antifungal agents if fungal culture is positive

Each step must be used for at least 1–2 weeks before reevaluation to assess need to step up or down

Comorbidities must be managed appropriately

In patients with allergies, environmental control is important

Upon worsening of a previously well-controlled patient r/o need for antibiotics preferably culture-directed and reevaluate to assess need for step up

For patients poorly controlled under step 4 or 5, treatment of surgery must be considered as a palliative adjunct for medical treatment

[a]For patients with purulent nasal polyposis lasting for more than 7 days, culture-directed antibiotics are considered the first step of treatment

[b]If patient fails step 2, then refer to ENT

Take Home Pearls

- CRS with NP represent diverse etiologies but may be categorized with regard to sinus CT staging, specific sino-nasal symptom surveys, general quality of life surveys, objective olfaction, histology and presence of absence of fungi or bacteria and aspirin sensitivity.
- No sinus CT staging score exists specifically for NP, but the Lund Mackay scoring system is most widely used.
- Sinus symptoms do not correlate with disease severity on sinus CT scores.
- No validated sinus symptom score exists for NP alone.
- Subjective sinus symptom scores are not comparable between patients, but have validity to show change for individual patients.
- Olfaction can be objectively measured by many tests, the easiest and least expensive is the distance to smell newly opened alcohol pad.
- Nasal patency can be objectively measured in many ways, the least expensive quantitative measurement is the peak inspiratory flow meter.
- NP can be categorized histologically relative to presence of eosinophilia, neutrophilia, allergy and fungal or bacterial presence.
- NP can be categorized by size and associated mucous in treatment naïve patients however therapy alters NP size and thus categorization of NP must also incorporate level of therapy required to control NP.

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Nasal Polyps and Lower Respiratory Tract Relationship

13

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Core Messages

- Nasal polyps (NP) are most prevalent in asthma with aspirin hypersensitivity.
- Genetic factors are implicated in neutrophilic NP diagnosed in cystic fibrosis and ciliary disorders.
- Appropriate treatment of NP may result in the improvement of asthma control.
- NP in asthmatics are more frequently resistant to therapy.

13.1 Introduction

According to recent European guidelines, chronic rhinosinusitis (CRS) with nasal polyps (NP) and CRS without NP are nowadays considered two distinct entities with different inflammatory mechanisms [20]. Prior studies focusing on link between NP and lower respiratory tract frequently did not differentiate between patients with CRS with or without NP [3, 20]. In this chapter, only papers including subjects with NP will be discussed. Most studies addressed link between NP and bronchial asthma, whereas considerably much less is known about relationship between NP and lower airways in cystic fibrosis (CF), ciliary disorders, or immunodeficiencies.

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13.2 Prevalence of Nasal Polyps in Diseases of Lower Respiratory Tract

Reporting subjective nasal symptoms, without the use of nasal endoscopy or sinus computed tomography (CT), may bias epidemiological data on NP incidence in diseases of lower airways. NP affect about 2–4% of general population, 5% atopic asthmatics, and 13% of nonatopic athmatics [20, 30, 56]. The course of NP in asthmatics is usually more severe. In a tertiary care institution, asthmatics had significantly higher prevalence of NP (47 vs. 22%), olfactory dysfunction (26 vs. 6%), and nasal congestion (85 vs. 60%) than non-asthmatics [57]. They required significantly more revision sinus procedures overall (mean: 2.9 vs. 1.5) [57]. The most severe form of asthma, aspirin-induced asthma (AIA) is characterized by the highest prevalence of NP (36–60%) [62, 63].

On the other hand, in patients with NP, asthma can be found in 26% of cases, whereas episodes of wheezing are reported in up to 42% [30]. In about 70% of asthmatics, NP are diagnosed before asthma [20]. Gender seems to predict incidence of NP in asthma. Females with NP are 1.6 times more likely to be asthmatic [12]. AIA is also more prevalent in women in their thirties [62, 63]. Genetic factors are possibly implicated in NP origin. Children of patients with AIA and NP more commonly develop NP [40].

Much less epidemiologic data are published in other types of NP. NP diagnosed in children or showing

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neutrophilic infiltrates should raise suspicion of CF or ciliary disorders. The prevalence of NP in CF reaches 20%, whereas in Kartagener syndrome, a congenital ciliary dyskinesia, it is 30% [22].

NP in middle-aged females may indicate aspirin hypersensitivity, whereas in children – CF, ciliary disorders, or immunodeficiencies.

13.3 Link Between Nasal Polyps and Lower Airways

As more data emerge, it becomes obvious that the link between CRS with NP and lower airways includes several mechanisms. Importantly, NP impair basic functions of nasal mucosa: defending against infections and conditioning the air before entering lower airways. Viral and bacterial infections are common causes of asthma exacerbations [10]. The bronchial hyperresponsiveness (BNR) observed in patients with CRS and NP has been formerly explained by the activation of pharyngobronchial reflexes [20]. However, microaspiration of postnasal drip from sinuses into bronchi is irrelevant in conscious subjects [10, 20].

The concept with the best supporting evidence involves systemic propagation of inflammation from nasal to the bronchial mucosa by mediators and inflammatory cells stimulating bone marrow ("systemic cross-talk") [3, 10, 13, 20]. This systemic inflammation in respiratory tract results in a spectrum of manifestations – NP in upper airway and asthma, CF, or bronchiectases in lower airways.

The key mechanism in NP and lower airway disorders is systemic inflammation.

13.4 Inflammatory Mechanisms of NP in Diseases Other than Bronchial Asthma

The origin of NP in CF is linked to an impaired function of the chloride channels, resulting in an increase in mucus viscosity [1]. Almost all patients have severe involvement of sinuses [22]. Higher scores at initial sinus CT were risk factors for revision sinus surgery in CF [6]. Patients with CF suffer from recurrent infections in the respiratory tract, and their lung function has an obstructive or mixed pattern due to bronchiectases and lung fibrosis [22]. Interestingly, NP in patients with CF may indicate a higher frequency of chronic colonization of *P. aeruginosa* in the lower respiratory tract [23]. It was found that respiratory comorbidities in CF were asthma alone (28%) and aspirin hypersensitivity (5%) [6].

NP in CF are noneosinophilic. Unlike as in eosinophilic NP in asthmatics, no measurable levels of IL-5 in the nasal lavage in CF could be found [23]. Distinct cytokine pattern results from recurrent infections. In nasal lavage fluid in patients with CF and NP lysozyme and IL-8 concentrations were increased in comparison with the healthy control group [23]. The mainstays of CF treatment are lavage with saline solution, intranasal corticosteroids, antibiotics, and functional sinus endoscopic surgery.

The origin of CRS and NP in primary ciliary dyskinesia has been linked to an altered function or structure of the ciliated cells, which leads to a poor clearing of mucus [11, 22]. In lungs, purulent bronchial infections and bronchiectases are hallmarks of this disease [11]. A sinus CT scan usually demonstrates invasion of ethmoidal and maxillary sinuses, together with hypoplasia of the frontal sinus [22]. Therapy consists of respiratory physiotherapy with postural drainage, antibiotics for respiratory infections, and sinus surgery in resistant NP.

13.5 Inflammatory Mechanisms in NP and Bronchial Asthma

Eosinophilic NP are nowadays considered the T-helper-2 cytokine-mediated disease, with a high production of key regulatory cytokines such as IL-5 and IL-4 and formation of immunoglobulin E [3, 20]. This is in contrast to CRS without NP characterized by T-helper-1 cytokine pattern [20]. The importance of type 2 T-helper responses in the pathogenesis of asthma is well recognized [28]. IL-5 and eotaxin induce infiltrates of eosinophils in nasal and bronchial mucosa by increasing eosinophil chemotaxis, migration, activation, and prolonged survival [3, 20]. Activation of eosinophils, basophils, and T cells leads to a further release of mediators, e.g., potent proinflammatory agents such as cysteinyl leukotrienes (cys-Lts), which sustain chronic inflammation. The stimulation of the bone marrow leads to further recruitment of cells and

mediators into the lower respiratory tract. Eosinophil progenitors may migrate to the airways [61]. The highest concentrations of IL-5 were found in polyps in nonallergic asthma and aspirin hypersensitivity [31].

13.6 The Role of Cysteinyl Leukotrienes in Nasal Polyps and Bronchial Asthma

cys-LTs are potent proinflammatory mediators that contribute to pathophysiologic features of CRS, NP, and asthma as they increase microvascular permeability and mucus secretion, impair mucociliary clearance, induce long-lasting bronchospasm, and recruit eosinophils into the nasal mucosa [48].

The levels of cys-Lts appear to correlate with the extent of NP or bronchial asthma severity. Nasal mucosa was demonstrated to be an important source of urinary cys-Lts in AIA [41]. Also in patients with aspirin-tolerant asthma (ATA), similarly to those with AIA, urinary hyperleukotrienuria was associated with a more severe asthma and CRS with NP, as well as with hypereosinophilia and anosmia [24].

AIA, representing the most severe form of CRS with NP and bronchial asthma, is characterized by much higher levels of LTs as compared to ATA or healthy controls [62, 63]. High urinary leukotriene E_4 (LTE_4) may be a marker of NP. AIA with CRS and NP had the highest levels of urinary LTE_4 as compared to AIA with isolated CRS, mild atopic asthma, and normal controls [41]. Moreover, the rate of recurrences of AIA with NP in postoperative period was significantly higher in those with lower prostaglandin E2 (PGE2) or higher leukotriene C4 (LTC4) concentrations in nasal mucosa [29].

However, only eosinophilic NP are rich in leukotrienes. The cys-LTs concentrations within noneosinophilic NP were similar to those in control tissue [59]. In the same study, the presence of cys-LTs in eosinophilic CRS was linked with increased expression of LTC_4 synthase mRNA [59].

Treatment of CRS and NP may result in significant drop in cys-Lts global burden and possibly contribute to better postoperative asthma control. There were significant decreases in the urinary LTE_4 concentrations after the sinus surgery in both the AIA and ATA groups [24].

13.7 The Role of Microorganisms in Nasal Polyps and Bronchial Asthma

Enterotoxins of *Staphylococcus aureus* have been implicated in the pathophysiology of eosinophilic NP as they may considerably enhance T-helper-2 cytokine pattern typical for NP [4]. Specific IgE antibodies to enterotoxins A or B were demonstrated in 50–90% of patients with NP and their presence was related to a more pronounced eosinophilic inflammation and higher concentrations of ECP, IL-5, and eotaxin [4]. The role of nasal *S. aureus* in pathogenesis of severe asthma was suggested [4].

Fungal colonization in patients with NP may also precipitate Th 2 responses, and thus, perpetuate chronic inflammation in respiratory tract [50]. Eosinophilic mucin rhinosinusitis, devoid of fungal hyphae, had a significantly higher association with asthma, AIA, and an increased incidence of IgG1 deficiency [19].

Nevertheless, it is not clear whether *S. aureus* or fungal colonization is a primary or rather secondary phenomenon, due to imbalance in local defense mechanisms in advanced CRS with NP.

13.8 Effect of Nasal Polyps on Bronchial Hyperreactivity

Although a large number of studies proved the link between allergic or nonallergic rhinitis and BHR, there is still limited evidence of such relationship for NP [10, 13].

BHR can be demonstrated in 35% of patients with NP without asthma [52]. Lack of bronchial symptoms does not rule out a possibility of inflammation in lower airways. Asymptomatic BHR was associated with infiltrates of eosinophilis and lymphocytes in bronchial biopsies, similarly to asthmatics [18, 33]. An increased number of IL-5 protein(+) cells in bronchial biopsies in patients with NP and asymptomatic BHR as compared to patients with NP alone was demonstrated [35]. In patients with NP and BHR, an increased expression of IL-9 mRNA in bronchial biopsies, inversely correlating with the airway responsiveness to methacholine and positively with IL-5 mRNA expression or eosinophil infiltration, was found [64].

BHR in NP may be a risk factor of resistance to pharmacotherapy and a need for subsequent sinus

surgery. A therapeutic protocol consisting of short-term oral prednisolone and intranasal beclomethasone on a daily basis (for 3 years) proved successful in 93.4% of patients with isolated NP, in 82.2% with BHR, and only in 60% with BHR and AIA [8]. Significantly more patients with BHR or AIA required sinus surgery than those without BHR [8]. A prospective study demonstrated an increase of BHR and a decrease of FEV_1 over 12 months in patients with NP not responding to intranasal corticosteroids who underwent intranasal ethmoidectomy, whereas no change was observed in the group of responders [32]. Long-term observation of NP patients confirmed steady, irreversible decrease in FEV_1 over a period of 4 years [34].

It is likely that sinus surgery may result in disappearance of BHR and possibly interferes with potential asthma development in some patients with NP [27].

13.9 Effect of Sinus Surgery on Clinical and Therapeutic Outcomes of Bronchial Asthma

Sinus surgery for NP may influence the course of bronchial asthma, which is an additional proof of the close relationship between upper and lower respiratory tract. Today, the most appropriate way of surgical approach to extensive CRS and NP is endoscopic sinus surgery (ESS), whereas simple polypectomy should be avoided, especially in AIA [20, 63]. A recent systematic review showed that symptomatic improvement following FESS in patients with NP ranged from 78 to 88% as compared with 43–84% for comparative sinus procedures [16].

Most studies show that sinus surgery in asthmatics results in better asthma control, improvement of lung function tests, decrease in BHR, and reduction of doses of steroids [2, 7, 8, 17, 20, 36, 43]. Fifty asthmatics who failed to improvement following aggressive pharmacotherapy for CRS were observed for 12 months following ESS [17]. The authors found that 20% asthmatic patients could use less corticosteroids, whereas 28% bronchodilator inhalers [17]. In those patients the number of hospitalizations for asthma also dropped significantly [17].

Usually the most dramatic improvement of asthma occurs in the first year after sinus surgery [36, 51, 55]. However, in a study assessing long-term effect of ESS about 70% of patients who responded to standardized surveys reported further improvement in their asthma beyond the first postoperative year [36]. Sinus surgery may reduce costs of asthma control. In a questionnaire-based study, ESS in asthmatics resulted in a 75% reduction in the number of hospitalizations and 81% reduction in acute care visits within the year after the surgery (Nishioka 1994). However, there were also some studies indicating deterioration of asthma following sinus surgery [20].

On the other hand, the presence of asthma, or even more importantly AIA, may adversely affect outcomes of sinus surgery. In 119 adult patients with CRS, pre and postoperative quality of life parameters were negatively affected by incidence of AIA, depression, and female sex [58]. Moreover, endoscopy scores following sinus surgery were significantly worse in patients with asthma, aspirin hypersensitivity, prior sinus surgery, and NP [58].

Even well-performed ESS does not prevent relapses of NP in asthmatics and in some cases must be repeated [67]. Within a 3-year follow-up following sinus surgery impaired sense of smell returned again in patients with asthma or AIA [67]. AIA is well known for high frequency of NP relapses and the effect of sinus surgery on lung function in AIA seems more controversial [62, 63]. Patients with AIA undergoing sinus surgery did not experience a statistical improvement in postoperative FEV_1 and nasal symptoms, as did those with ATA within at least 12 months of follow-up [5]. However, another study demonstrated a significant improvement in postoperative lung function tests [43].

ESS is currently considered the most effective therapy in massive NP. In asthma, sinus surgery results in better asthma control, improvement of lung function, decrease in BHR, and reduced need for steroids.

13.10 Effect of Pharmacotherapy of Nasal Polyps on Bronchial Asthma

13.10.1 Corticosteroids

Oral corticosteroids are nowadays considered the most effective pharmacotherapy in NP (especially with concomitant asthma). Due to their potent, systemic anti-inflammatory effect, their use allows achieving concomitant asthma control. Short-term courses of oral corticosteroids (usually 3–4 times a year) effectively reduce size of NP ("medical polypectomy"). However, the effects of oral corticosteroids in NP are

short lasting, and regrowth of polyps occurs within weeks to months. Unfortunately, there are few controlled studies assessing the effect of those drugs in NP [46]. Prednisolone (50 mg) daily for 14 days significantly improved nasal symptoms and reduced polyp size, as noted with endoscopy [25].

Intranasal steroid sprays may slightly reduce the growth of minor NP and retard relapses following sinus surgery, but they do not improve sense of smell. Therapy of concomitant allergic rhinitis may improve control of asthma [10]. Resistance of NP to intranasal corticosteroids was linked to BHR or AIA appearance [8, 32, 34].

13.10.2 Leukotriene Inhibitors

As discussed above, cys-Lts are important mediators implicated in the pathogenesis of eosinophilic NP, especially in AIA [48, 63].

Leukotriene inhibitors are either leukotriene synthesis inhibitors, which act by blocking 5-lipoxygenase activity (zileuton) or leukotriene receptor antagonists (zafirlukast, montelukast, pranlukast). Antileukotrienes exert moderate systemic anti-inflammatory effect in lower respiratory tract, which was documented in many studies including patients with atopic, nonatopic, and exertional. Antileukotrienes might seem particularly beneficial in AIA, well known for overproduction of cys-LTs [14, 39, 60]. Allergic rhinitis with concomitant asthma is one of the recognized indications for antileukotrienes [10]. Unfortunately, although there are many studies evaluating the effect of antileukotrienes on asthma, only very few studies focused on NP. The current guidelines indicate that there is a need for larger, controlled trials assessing the role of antileukotrienes in NP [20].

13.10.3 Zileuton

In a double-blind placebo-controlled crossover study, the effects of 6-week treatment with zileuton (600 mg, four times daily) in 40 patients with AIA on nasal symptoms and PNIF were evaluated [14]. There was a statistically significant reduction in the VAS scores for loss of smell and rhinorrhea [14]. The subsequent open study has demonstrated beneficial effect of zileuton in 10 patients with CRS and NP [45].

13.10.4 Leukotriene Receptor Antagonists

Open studies have demonstrated beneficial effect of leukotriene receptor antagonists for subjective symptoms in NP [53, 65]. An open study investigated the response to montelukast in NP with or without aspirin hypersensitivity [53]. Montelukast treatment resulted in significant subjective improvement in 64% ATA and 50% AIA patients; however, objective changes in peak expiratory flows occurred only in ATA group [53]. Acoustic rhinometry, nasal inspiratory peak flows, and nitric oxide levels did not change significantly in any group [53]. More recently, a prospective double-blind study compared the efficacy of montelukast with beclomethasone nasal spray in 40 patients with NP after ESS [42]. Although montelukast attenuated itching, postnasal discharge, and headache more than did intranasal corticosteroid, there was no difference in the recurrence rate between both groups [42].

13.10.5 Aspirin Desensitization

A significant improvement of asthmatic symptoms, hospitalizations due to asthma exacerbations, and decrease in doses of corticosteroids following aspirin desensitization were demonstrated [38, 49, 60]. Number of sinus infections and the need of sinus surgery for NP decreased in those patients as well [38, 49, 60].

Intranasal L-ASA administration may bypass side effects of aspirin, but its effect seems to be limited to upper airways only [44].

13.10.6 Other Agents

There are only anecdotal reports concerning the use of anti-IgE treatment or macrolides in CRS with NP.

According to current guidelines, both NP and bronchial asthma are IL-5-driven disorders characterized by elevated local IgE levels and eosinophilic infiltration [3, 20, GINA 2007 revised]. Omalizumab, an anti-IgE agent, is indicated in severe asthma (GINA 2007 revised). A pilot study assessed the efficacy of omalizumab in atopic asthmatics with NP who underwent ESS [47]. Although there was no improvement in the sinus CT scores in either treatment group, the nasal

polyp scores significantly decreased in the anti-IgE group as compared to controls [47].

In addition to their well-recognized antimicrobial activity, macrolides exert a wide range of anti-inflammatory activities in CRS, NP, asthma, or CF [21]. Those agents regulate leukocyte function, increase mucociliary clearance, decrease nasal secretions and polyp size, attenuate BHR, and improve pulmonary function [21, 37, 54]. A beneficial effect of macrolides resulting in reduced NP size was linked with decreasing the levels of IL-8 [26, 66].

Given the common pattern of inflammation seen in eosinophilic NP and asthma, patients may best benefit from a therapeutic approach covering the entire airways rather than only a part. Oral corticosteroids, aspirin desensitization, and possibly anti-IL-5 therapy or macrolides may stand for a therapeutic alternative in NP.

Conflict of Interest

We declare that we have no conflict of interest.

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Take Home Pearls

- Nasal polyps afflict 2–4% of the general population, 5% of atopic asthmatics, and 13% of nonatopic asthmatics and over 50% of patients with aspirin induced asthma (AIA).
- Even in the absence of asthma, patients with NP are more likely to have bronchial hyperresponsiveness.
- In 70% of asthmatics, NP are diagnosed before asthma.
- Nasal polyps are generally more refractory to therapy in asthmatics than nonasthmatics, especially in patients with AIA.
- Most studies show some improvement in asthma with sinus surgery, but not all patients benefit and relapse is common.

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Nasal Polyp, Analgesic Intolerance, and Bronchial Hyperreactivity

14

Gül Karakaya and A. Fuat Kalyoncu

Core Messages

- The coexistence of bronchial asthma, persistent rhinosinusitis/nasal polyp, and analgesic intolerance is called as Samter's syndrome or aspirin-induced or analgesic-induced asthma. This condition should be investigated especially if the asthma is severe and/or the polyps are recurrent.
- There seems to be no ideal curative treatment modality for nasal polyposis. Similar results are reported after medical or surgical polypectomy. Recurrence is possible and frequent with both methods.
- Aspirin desensitization can be applied as a complementary treatment option. Although some patients improve with this method, long-term results are not yet known.

14.1 Introduction

Nasal polyp (NP) is a local inflammatory condition affecting up to 4.3% of the population [13]. Since the diagnosis is not easy and needs to be done by an experienced specialist after a detailed examination, its prevalence might probably be higher. Polypoid formation in the nasal mucosa usually involves all cranial sinuses and is generally accompanied by chronic rhinosinusitis and bronchial hyperreactivity, but less frequently by asthma and analgesic intolerance (AI). However, the majority of the analgesic intolerant asthmatics have chronic rhinosinusitis and/or nasal polyposis, and the prevalence of NP is up to 70.8% in these patients, showing that the upper airway system is rarely disease free in this group of asthmatics [25]. Patients with NP tend to be nonatopic. Nasal polyposis has been reported in about 31% of aspirin (ASA: acetyl salicylic acid) intolerant individuals, and ASA intolerance has been reported in up to 52% of those with polyps, where 64.5% of patients concomitantly had asthma and NP [11, 40, 50]. Since many surveys on this topic have concentrated on ASA, general AI rate might probably be higher as its association with NP is more common. The frequency of AI in the general population is 0.6–2.5% [13, 18, 53]. There are a few field surveys reporting on this subject, which are mostly questionnaire-based depending on patient declaration. Variations in the prevalence estimates are possibly due to the different descriptions of AI. A survey performed by mailing questionnaires to 4,300 individuals in Finland, reported an ASA intolerance rate of 5.7%, with the frequency of asthmatic attacks triggered by ASA ingestion as 1.2% [13].

Bronchial asthma accompanying NP and AI is called by various names including Widal syndrome, Widal–Abrami–Lermoyez triad, ASA triad, ASA triad disease, ASA disease, analgesic-induced asthma, ASA-induced asthma (AIA), ASA asthma, ASA triad, analgesic/ASA-exacerbated respiratory disease, and ASA-intolerant asthma/rhinitis in addition to Samter's syndrome. The ASA triad syndrome was first described by Fernand Widal, Pierre Abrami and Lermoyez in

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1922; however, later in 1968, Samter and Beers reported that this condition, which seems to be a special phenotype of asthma, could be explained by a common pathogenesis [50]. It occurs mainly in females in the third or fourth decade of life. The rate of Samter's syndrome was 21% (95% confidence interval 14–29%) and 5% (95% confidence interval 0–14%) in adult and child asthmatics, respectively, in a systematic review, in which AI was confirmed by oral provocation tests [15]. Obstruction of the nose and paranasal sinuses are the dominant symptoms in the majority of the patients with Samter's syndrome, on which no reports about the racial and ethnic characteristics yet exist.

14.2 Histopathology

The etiology for the high rate of occurrence of rhinosinusitis and NP in ASA-intolerant individuals is not clear. The local multicellular inflammation of the airways appearing on a suitable genetic basis, leads to a course which mostly ends up with surgical intervention. HLA polymorphisms are reported to be one of the reasons for the high prevalence of polyposis in AIA [20, 35].

Some studies suggested that nasal polyposis in AIA subjects was associated with more extensive eosinophilic infiltration and mucosal hypertrophy in the paranasal sinuses compared with that in ASA tolerant asthma (ATA) subjects . The number of eosinophils in AIA patients is four times higher than that of ATA and is 15 times higher than that of individuals without asthma [16, 47]. The stimulation of the local bacterial biofilm formation resistant to antibiotics, where staphylococcal enterotoxins are the main component, is also important in the pathogenesis. A survey investigating the specific immunoglobulin E response to these enterotoxins in NPs from ASA-intolerant asthma showed that ECP levels in NP homogenates were higher in ASA-intolerant asthmatic subjects than in ATA subjects. Total IgE and specific IgE to both staphylococcal enterotoxin A and B, were detectable in some NPs, but median levels were markedly higher in ASA-intolerant subjects than in ATA subjects. It has been suggested that *Staphylococcus* superantigens may lead to eosinophilic inflammation in NP tissue, which is exacerbated in subjects with AIA [54].

Low production of prostaglandin (PG) E2 in AIA, low levels of PGs in NPs from AIA patients compared with those of ATA, lower release of PGE2 in peripheral blood cells from AIA patients compared with ATA, in addition to lower PGE2 levels in the cultured epithelial cells from the polyps of AIA patients compared to the ones obtained from ATA patients, a similar abnormality in PGE2 production by cultured bronchial fibroblasts of AIA patients has also been reported [26, 32, 44, 49]. Another study showed that AIA NPs appear to have a more severe abnormality of the COX-2 pathway than ATA, suggesting higher differential kinetics of COX-2 mRNA between nasal mucosa and NPs [45].

The main impairment in AI is related to the abnormal metabolism of arachidonic acid (AA). Some baseline abnormalities of AA metabolism in nonstimulated NPs from ASA-intolerant patients have also been reported, including decrease in PGE2 production and downregulation of COX-2 mRNA expression, and increased synthesis of cysteinyl leukotrienes [27, 42, 51]. COX-2 is markedly downregulated in polyps from AIA, which may account for the low production of PGE2 in NPs reported by various groups [42, 45]. The insufficient regulation of COX-2 might also explain the increased sensitivity of some asthma patients to the inhibitory effects of ASA on COX-1. This underlines a prominent role of COX mediators, which is in accordance with the findings in recurrent nasal polyposis of ASA-intolerant patients. Immunostaining of nasal polypoid tissue revealed a downregulation of COX isoenzyme-2 (COX-2) in these tissues as compared to normal nasal mucosa, unveiling a possible mechanism of the increased proinflammatory PGE2 inhibiting leukotriene release in the nasal mucosa of normal controls [37]. Although exogenous PGE2 given by inhalation prevents AIA, it has been suggested that downregulation of COX-2 may leave ASA-sensitive patients without the protective effect of endogenous PGE2, making them more susceptible to the inhibitory effect of ASA [40]. Nuclear factor (NF)-κB plays a key role in the transcriptional regulation of the expression of inducible genes including COX-2 [2, 41]. It has been shown that the low expression of COX-2 mRNA in NPs from ASA-sensitive patients is associated with a downregulation of NF-κB activity [2].

ASA-precipitated asthmatic attacks are not associated with changes in the systemic PGE2 production. In contrast, PGE2 systemic production becomes depressed by ASA in nonsensitive patients. This different response might indicate COX-1 dependent PGE2 control of inflammatory cells in AIA. Thus, PGE2 is released

during the reactions to ASA through an alternate COX-2 pathway. Clinical implications of this finding are in accordance with the current observations of good tolerance to the selective COX-2 inhibitors in sensitive patients [32].

Eotaxins coordinate the recruitment of inflammatory cells delivering chemocine (C–C motif) receptor-3 to sites of allergic inflammation. It was suggested that eotaxin-2 may be upregulated and may act differentially in patients with ATA compared to the ones with AIA [34]. Another survey suggested that a marked overrepresentation of LTC4 synthase in mucosal eosinophils is closely linked to ASA intolerance in the nasal airways, as in the bronchial airways [1].

Patients with AI suffer from a severe form of hyperplastic rhinosinusitis with recurrent polyposis. Decreased apoptosis of inflammatory cells in NPs from ASA-intolerant patients may be related to the persistence and severity of the disease [27]. The highest levels of eosinophilia, which seems to be the main feature in up to 90% of patients, were reported in patients suffering from both inhalant allergies and ASA intolerance [16].

14.3 Bronchial Hyperreactivity, Bronchial Asthma, and Aspirin-Induced Asthma

Nonspecific bronchial hyperresponsiveness (BHR) is the narrowing of the airways as a result of an exaggerated or different response to an irritating stimulus, due to the contraction of the bronchial muscles. BHR, which is the characteristic feature of asthma, is generally related to the severity of asthma and the effectiveness of the anti-inflammatory treatment, but it can also be seen in some other conditions including heart failure, sarcoidosis, and Kartagener syndrome. BHR and/or asthma are more frequent in patients with nasal polyposis than in the general population [8, 39].

Bilateral NPs are particularly common in patients with AIA. The complaints of the patient generally start with or during an upper airway disease in the third decade of life. Persistent rhinosinusitis (PR) or NP develop within months or years followed by asthma and AI, where on an average, the first asthmatic symptom appears within 2 years [7, 56]. This order is not valid in every patient, but the two "sine qua non" characteristics of AIA are asthma and AI. Asthma attack, sometimes being life-threatening, starts within minutes of ingestion of an analgesic in addition to acute rhinitis. Conjunctival irritation, and sometimes periorbital edema, flushing in head and neck may accompany these signs. Twenty-five percent of asthmatic patients requiring emergency mechanical ventilation had AIA [31].

Based on the patient's history alone, the incidence of aspirin sensitivity in adult asthmatics is 3–5%, but with provocation tests this rises up to 20% [55]. Even in adult asthmatics with no history of ASA intolerance, 9% show sensitivity to oral ASA challenge [55]. The extent of this condition is not well known in children. A survey in 729 analgesic intolerant patients diagnosed between 1991 and 2004 in authors' clinic showed that asthma was more frequent in adults whose AI started in childhood with atopy as an additional risk factor. In other words, AI and atopy in childhood were important risk factors for adult onset asthma [10]. The frequencies of asthma, persistent rhinitis, and NP and the associations of these conditions are shown in Fig. 14.1. The upper airway symptoms are the major problem also affecting the severity of asthma, which tends to be more severe and problematic in AIA patients.

AI has rarely been reported to disappear with time [46]. A clinical study suggested that the presence of BHR and/or ASA intolerance could be considered as a major risk factor for steroid insensitivity in patients

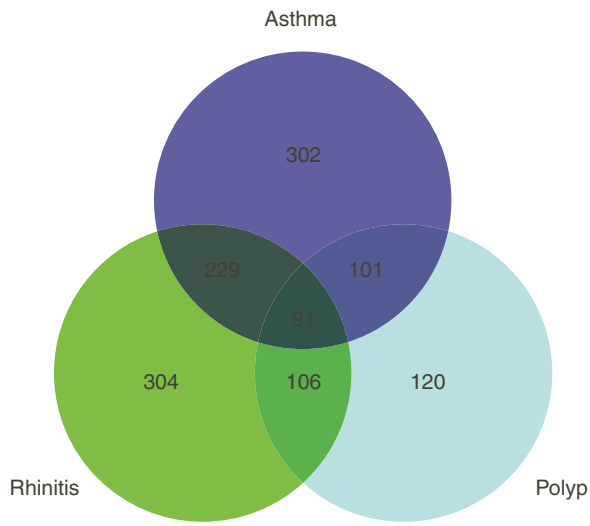

Fig. 14.1 The frequencies of asthma, persistent rhinitis, and nasal polyp in patients with AI ($n=729$) in our adult allergy clinic between 1991 and 2004 [11]

with nasal polyposis [8]. Nonreversible airflow obstruction development was reported in a 4-year follow-up study in topical steroid nonresponders with nasal polyposis requiring nasal surgery. Conversely, subjects with nasal polyposis who improved on topical steroids exhibited a remarkable stability of lung function over time [29]. Thus, lack of steroid responsiveness in patients with nasal polyposis may be accepted as a risk factor for chronic obstructive airway disease. It is generally accepted that nasal polypectomy does not have any effect on nonspecific BHR.

14.4 Clinical Features, Associated Conditions, and Quality of Life

Due to the high recurrence rate of NPs and the frequent need for endoscopic surgery, AIA is also described as an aggressive mucosal inflammatory disease by some authors [55]. It is generally assumed that chronic rhinosinusitis in ASA-sensitive asthmatic patients is more severe than that in ASA tolerant patients. A survey, investigating the factors affecting asthma severity performed in 300 asthmatics in Ankara, showed that prolonged asthma duration, AI, and NP were among the factors associated with severe asthma [5]. Severe asthmatic patients are known to have a higher rate of emergency room referral and hospitalization due to asthma [20]. Another survey of ours revealed that NP is an important risk factor leading to AIA in isolated AI patients (OR 2.75; 95% CI 1.09, 6.91) [22]. In fact, in daily medical practice, it is really rare to see other conditions in such a close relation and overlap like asthma, NP, PR, and AI. A patient diagnosed with one of the components of the syndrome a year ago, could come back a year later with the classical Samter's syndrome, or sometimes a successful polypectomy gets asthma almost into remission. There are some classifications showing the relations between these conditions. A classification used in our clinic is shown in Table 14.1 [17].

Another group of diseases that AI accompany are acute/chronic urticaria and angioedema. Since the frequency of AI is about 25% in patients with chronic urticaria, the frequency of coexistence of asthma and chronic urticaria is also expected to be higher in patients with AI [20]. Among the nine hundred fifty six patients diagnosed with chronic urticaria between 1991 and 2006 in our clinic 236 (24.8%) had AI. This group of patients had a higher rate of asthma, NP, antibiotic and metal allergy compared to the analgesic tolerant ones [14]. Rarely, ingestion of the improper analgesic in analgesic intolerant patients could trigger a series of reactions ending up with anaphylaxis.

Table 14.1 Classification for analgesic-induced asthma (AIA) used in our clinic [16]

Complete (classical) AIA
Asthma + analgesic intolerance (AI) ± persistent rhinosinusitis (PR) and/or nasal polyposis (NP)
Asthma + AI (nonbronchospastic reaction)/pseudo Samter's syndrome
Asthma + AI + food and/or antibiotic and/or mite allergy/intolerance/extended Samter's syndrome
Incomplete (partial) AIA (bronchospastic or nonbronchospastic reaction)
PR + AI
NP + AI
Asthma + first degree relative with AI and/or AIA
PR + first degree relative with AI and/or AIA
NP + first degree relative with AI and/or AIA
Asthma + NP + PR

Nasal polyposis is often associated with asthma and other respiratory diseases (such as cystic fibrosis, primary ciliary dyskinesia, chronic rhinosinusitis) and AI [38]. Nasal polyposis is not a life-threatening disorder, but may have a great impact on the quality of life (QL) because of nasal blockage, loss of smell, and rhinorrhea. A questionnaire-based survey measuring QL with short form-36 (SF-36) showed lower life quality scores in patients with NP compared to the general population [4]. The effect of the conditions accompanying NP on QL was investigated in a survey of 130 patients, which showed no significant differences on QL, nasal symptoms, polyp size, and CT scan scores between patients with ASA-tolerant and ASA-sensitive asthma, where nasal polyposis had considerable impact on QL. Moreover, asthma, but not ASA intolerance, had an additional negative impact on QL of patients with nasal polyposis [3]. NP recurrence rate has been reported to be almost three times higher in ASA intolerant than in ASA-tolerant patients and seven times higher than in atopic asthmatics [27].

14.5 Diagnosis of AI and BHR

Patients with symptoms of nasal and sinus obstruction should be assessed for polyposis. Bronchial hyperreactivity and/or asthma are conditions mainly diagnosed or suspected by anamnesis. AI diagnosis is considered when there are at least two similar reactions with NSAIDs, where medical history is accepted to be quite often unreliable. The golden standard for the diagnosis of AI is the oral provocation test with the suspected drug [36]. The evaluation of atopy is important in the diagnosis of the airway diseases like asthma and rhinitis. Testing for inhalant allergens includes epidermal prick, intradermal and RAST-testing followed by provocation testing (nasal, bronchial), if clinically indicated. The cheapest and the safest method used for the diagnosis of atopy in daily clinical practice is the skin prick test. Many studies showed no relation between atopy and NP.

The diagnosis of aspirin/AI is not always associated with the full clinical picture of Samter's syndrome, which consist of nasal polyposis, nonatopic asthma, analgesic-induced worsening of asthmatic symptoms, often along with naso-ocular symptoms [24]. However, in sensitive individuals, even very small single doses of ASA may cause rhinorrhea, bronchospasm, and shock symptoms. Asthmatic patients who reported a history of ASA- or NSAID-induced asthma attacks (i.e., believed they were "ASA sensitive") experienced positive oral ASA challenges up to 97% of the time in various surveys [53]. These observations point out the problem of overdiagnosing AIA when relying only on a history of asthma attack after ingestion of ASA or NSAIDs. In some patients, a coincidence occurred in that ASA or an NSAID was ingested within 3 h of the asthma attack, but the two events were unrelated to each other [53].

Not only ASA, but also most other NSAIDs interfere with the eicosanoid pathway. They are known to inhibit COX, which metabolize AA to PGs. This inhibition leads to an upregulation of the alternative pathway with lipooxygenases metabolizing AA to leukotrienes. The course, which began after IgE-mediated mechanism became inefficient in explaining the problem, has moved to the side of basophils after which the increase in cyteinyl leukotriene secretion, the role of PGE2; increased 15-hydroxyeicosatetraenoic acid (15-HETE), decreased lipoxin A4, and EP2 receptor levels are shown. These developments in the pathogenesis had a role in the use of COX-2 inhibitors as safe alternatives and antileukotrienes for the treatment of the disease.

Diagnostic tests also followed this development process in pathogenesis. An in vitro assay can be very valuable in the diagnosis of ASA intolerance. After demonstrating ASA triggering specific generation of 15-HETE from NP epithelial cells and peripheral blood leukocytes in ASA-sensitive but not ASA-tolerant patients with asthma/rhinosinusitis, Kowalski et al. in their next survey showed that aspirin-induced 15-HETE generation by peripheral blood leukocytes is a specific and sensitive ASA-sensitive patients identification test (ASPITest) [28]. However, the optimist opinion on this test has not yet been confirmed by other studies. CAST and basophil activation tests, which have high specificity, but low sensitivity, are not yet used routinely [30, 33, 43, 48].

ASA provocation test can be performed by oral, nasal, bronchial, and intravenous routes. Oral and bronchial challenges are the most commonly used ones. Since these procedures are time consuming, require special expertise and equipment, and thus are not suitable for use in general practice, they should be performed only in patients with a suspected history [55]. For a subject to undergo these tests, there must not have been an urticaria or angioedema attack in the last week, and asthma must have been stable (FEV1 at least 70% of the predicted value). Normal antiasthma treatment including steroids, betamimetics, and methylxantines should have been going on. Short-acting antihistamines must have been stopped for at least 24 h, long-acting antihistamines for 20 days, short-acting betamimetics 6–8 h and long-acting ones 24–48 h, long-acting theophylline 24–48 h, antileukotriens a week before the test. There must not have been any significant cardiac, hematologic, renal, and gastrointestinal disorders, beta-blocker usage, in addition to pregnancy or lactation [36, 55]. If the patient is steroid dependant the dose should be under 10 mg/day. If the patient does not have any complaints/symptoms and there is no decline in FEV1 over 15%, the test is accepted as negative. Tests should be performed in an experienced allergy clinic, where prompt cardiopulmonary ressucitation is available. Although rare, a reaction of severe asthma attack or anaphylaxis can be an indication for intensive care unit hospitalization. With our 16 years of experience in provocation testing, we had four such patients, where three had severe asthma attack and one had anaphylaxis, making up severe reaction rate of less than 0.1% for our clinic.

ASA challenge in vivo is accompanied by the release of leukotriene metabolites into urine; and cysteinyl leukotrienes, mast cell tryptase, and ECP into nasal washes [43]. The patients should be recommended for at least one or preferentially more than one safe alternative analgesic after the diagnosis is made [21, 36, 55]. These patients are generally suggested to use COX-2 inhibitor NSAIDs. Since we know that some of these patients are also reactive to these so-called safe NSAIDs, they should also be tested with these before telling that they can safely use them. We have suggested a time- and manpower saving, and a cost-effective method for testing this group of patients with the aim of finding safe alternatives [20]. ASA-intolerant patients who are usually cross-reactive to NSAIDs like metamizole, naproxen, and diclofenac tolerate paracetamol, codein, benzydamine, nimesulide, and meloxicam well [6, 20, 23, 53, 55].

14.6 Treatment

There is no ideal method for inhibiting polyp formation or recurrence. Combined treatment modalities of medical and surgical interventions, medical ones mainly including corticosteroids and to a lesser extent antileukotriens, should be used. These patients do not have a particular sensitivity to local or general anesthetic agents [9, 53, 55]. Although the outcome of asthma and/or BHR associated with nasal polyposis seems to be controversial, it is well known that asthma in patients who do not have any problem or a controlled disease in their upper airways is controlled easily.

There are no special data showing the effectivity of specific allergen immunotherapy in the atopic subgroup of these patients. Aspirin desensitization is a method used only in a few centers in the world as yet. Different opinions are suggested in the data about desensitization. Various aspirin doses (100–1,300 mg) and routes of administration (oral, intranasal) are reported in different centers from Europe and USA [12, 52, 56]. Some of these patients have side effects due to routine aspirin intake. This treatment modality should be performed in specialized centers. There is no experience of desensitization with other NSAIDs. Asthma can be controlled better in some of these desensitized patients, in addition to improvements in NP symptoms. It seems to be harder to apply the control strategy suggested in up to date asthma guidelines to patients with Samter's syndrome.

Take Home Pearls

- Nasal polyp (NP) is an important condition which impairs the quality of life.
- Analgesic intolerance seems to be definitely associated with NP.
- NP also frequently accompany chronic rhinosinusitis and asthma.
- Although the optimal treatment for NP is not yet clear, local and systemic steroids are the most effective ones at present.
- If there is no control with medical treatment, surgery should be applied. This group of patients generally improve with surgery, although recurrence is not rare.
- Aspirin desensitization can be used as a complementary treatment. Although scarce, there are hopeful data.
- It cannot be predicted in advance as to which patient will improve with which treatment modality.
- Analgesic intolerant patients can be recommended to use safe alternative analgesics after provocation tests.
- Patients with Samter's syndrome should be followed-up in cooperation with ENT specialists.

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Allergic Fungal Sinusitis

15

Matthew W. Ryan and Bradley F. Marple

Core Messages

- AFS is a form of noninvasive fungal sinusitis that causes nasal polyps
- Hypersensitivity to fungus is the basis for polyp formation in AFS
- *Aspergillus* and the dematiaceous fungi have been implicated in AFS
- AFS is overdiagnosed and often confused with other forms of polypoid CRS

15.1 Introduction/History

Allergic fungal sinusitis (AFS) is a well characterized, discrete clinicopathologic entity that is recognized as a cause of polypoid chronic rhinosinusitis (CRS). AFS was first recognized as a distinct pathologic entity when the thick, dark, inspissated mucus filling the paranasal sinuses of some patients was noticed to be similar both grossly and microscopically to that seen in the bronchial passages of patients with allergic bronchopulmonary aspergillosis (ABPA) [17, 30, 35]. The accurate diagnosis and appropriate treatment of AFS still generate controversy despite years of investigation.

One widely accepted criterion for the diagnosis of AFS has been the characteristic "allergic mucin" first responsible for the description of the disease. However, investigators soon noted that in some cases, the allergic mucin evacuated from the sinuses did not have identifiable fungal elements; these patients were labeled as having an "AFS-like syndrome" [1, 6]. Additionally, Ferguson [11] proposed the term "eosinophilic mucin rhinosinusitis" (EMRS) to describe cases in which fungus was not identified histologically. Some patients with clinical features of AFS may have demonstrable fungus within their allergic mucin, yet do not have allergy [32]. Some authors still report these AFS-like cases as AFS [16], and others have eliminated allergy as a requisite feature to make the diagnosis [41]. The report of Ponikau et al. [33] suggesting that most, if not all, CRS was a hypersensitivity response to fungi and that fungi could be universally cultured from nasal secretions also further clouded the distinction between AFS and AFS-like CRS. AFS has been overdiagnosed because of clinical similarity to other forms of CRS, and the problem of distinguishing AFS from other forms of CRS has fueled interest in the appropriate classification of polypoid rhinosinusitis.

A collateral benefit of these reports has been an increased interest in the pathogenesis of AFS and polypoid CRS in general. If patients with the clinical picture of AFS do not have allergy and/or do not have evidence of fungus in their eosinophilic mucin, how should these patients be classified? Is fungus really the stimulus for inflammation? Is allergy important in the pathogenesis of AFS? The clinicopathologic distinction of AFS from other forms of EMRS requires further investigation. Allergy is probably not the only

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cause of AFS, and other immunologic mechanisms, anatomic, and physical factors are required for explaining the clinical observations in AFS [26]. Investigations into the role that fungi play in CRS and eosinophilic mucin chronic rhinosinusitis (EMCRS) are discussed in greater detail in other chapters of this text. Questions regarding the proper diagnosis, classification, and pathogenesis of AFS are yet to be resolved and have important implications for treatment. The current controversies are not merely academic because refinement of our treatment approach will depend upon the development of better methods to differentiate AFS from other forms of chronic polypoid rhinosinusitis.

15.2 Epidemiology and Microbiology

AFS may be the most common form of fungal sinusitis. AFS accounts for about 7–12% of CRS cases taken to surgery in the United States [9, 15]. Perhaps because climate determines the exposure to fungi, the highest incidence in the USA is in the south and along the Mississippi basin [12]. The disease has a worldwide distribution, though there may be differences in the microbiology of the disease across continents. AFS develops primarily in young adults and adolescents [26]. Older patients with the clinical features of AFS may be more likely to have some other EMCRS syndrome. Affected patients are immunocompetent and have a history of atopy [9, 39]. Allergic rhinitis and asthma are common associated conditions. By definition, AFS patients have allergy that should be evident by skin or in vitro testing, but only about two-thirds of patients will give a history of allergic rhinitis [22].

Aspergillus was initially believed to be the causative organism in AFS, but further experience with cases in the USA showed that the dematiaceous fungi were most commonly found in AFS mucus [9, 24]. The terminology for this condition subsequently changed from "allergic *Aspergillus* sinusitis" to "AFS." In the series of AFS and nonallergic eosinophilic fungal sinusitis from other parts of the world, *Aspergillus* is still found to be a common isolate [16, 36, 41]. The specific fungal organism has not been shown to be an important or predictive clinical characteristic, but the identification of fungus in allergic mucin either via histopathology or culture is still considered to be important to make the diagnosis of AFS.

- AFS develops slowly and disease is usually severe at diagnosis
- Severe nasal obstruction from nasal polyps is common
- Proptosis or telecanthus are frequently present
- Patients often have dramatically elevated total serum IgE

15.3 Clinical Presentation

Symptoms of AFS are insidious in onset. Patients with AFS usually present with rhinosinusitis symptoms lasting for months or years and they may not seek medical attention until complete nasal obstruction, headaches, visual disturbances, or facial dysmorphia are noticed. Symptoms are frequently unilateral. Patients may report dark, thick nasal mucus. Proptosis or telecanthus are not infrequently seen at presentation, especially in younger patients [16, 21, 23, 26]. Disease is often well advanced before a diagnosis is made.

The physical exam findings in AFS often reflect the advanced nature of disease at presentation. There may be proptosis or hypertelorism. Intranasal examination will reveal polyps that are either unilateral or bilateral. It is not uncommon for the bulk of polyp disease to be asymmetric. On nasal endoscopy inspissated yellowish mucus may be visualized among the polyps.

Testing is important to establish evidence of atopy, and demonstration of type 1 hypersensitivity is required for diagnosis. This may be accomplished with skin testing or in vitro testing for antigen-specific IgE. In addition to fungal antigens, patients should be tested against a region-specific panel of seasonal and perennial allergens. Possible laboratory abnormalities in AFS patients include peripheral eosinophilia and elevated total IgE levels. Skin testing or RAST testing will usually demonstrate IgE-mediated hypersensitivity to multiple fungal and nonfungal antigens [26].

Diagnostic Criteria for AFS

- Polypoid rhinosinusitis
- Fungal allergy
- Allergic mucin
- Fungus detected by stain or culture
- Characteristic imaging findings

15.4 Diagnostic Criteria

The diagnosis of AFS requires a combination of clinical, radiographic, microbiologic, and histopathologic information. Therefore, the diagnosis of AFS cannot be made reliably until after surgical intervention. There is no universally recognized set of diagnostic criteria for AFS, though there is a general agreement about what constitutes AFS. An important criterion is the presence of allergic mucin. Grossly, allergic mucin is thick, tenacious, and darkly colored; it may appear similar to a fungus ball but microscopically the two are quite different. Microscopically, allergic mucin consists of onion-skin laminations of necrotic and degranulating eosinophils in a background of mucin with occasional Charcot–Leyden crystals (Fig. 15.1). Fungal hyphae are present but scarce, and special fungal stains may be needed for identification (Fig. 15.2). Fungal hyphae do not invade tissue: the presence of fungal tissue invasion is incompatible with a diagnosis of AFS. Adjacent mucosa and polyps demonstrate a prominent eosinophilic inflammatory infiltrate. Many patients with polypoid CRS and allergic mucin lack other important clinical characteristics of AFS: demonstrable fungi and fungal allergy. These patients should not be classified as having AFS.

A variety of diagnostic criteria for AFS have been proposed by various authors and these criteria have been further refined by a recent consensus conference on definitions of rhinosinusitis [29]. The classic and still widely accepted diagnostic criteria for AFS were described by Bent and Kuhn, who proposed the following: type 1 hypersensitivity; nasal polyposis; characteristic CT scan findings; eosinophilic mucus without fungal invasion into sinus tissue; and a positive fungal stain of sinus contents removed at surgery [3]. In the absence of better defined immunologic parameters to distinguish AFS from other forms of EMCRS, the Bent and Kuhn criteria are still important. The debate about the value of these diagnostic criteria has contributed greatly to the level of interest in the disease and helped fuel further investigation.

The controversy will continue as the boundaries between AFS and AFS-like chronic polypoid rhinosinusitis are explored. In one recent study, a considerable overlap in the findings between AFS and EMCRS groups was observed, but AFS subjects were more likely to have bony erosion, heterogeneous opacity, and sinus expansion on CT scan [36]. These findings are similar to those of Dhiwakar et al. who point out that the combination of nasal polyps, CT scan

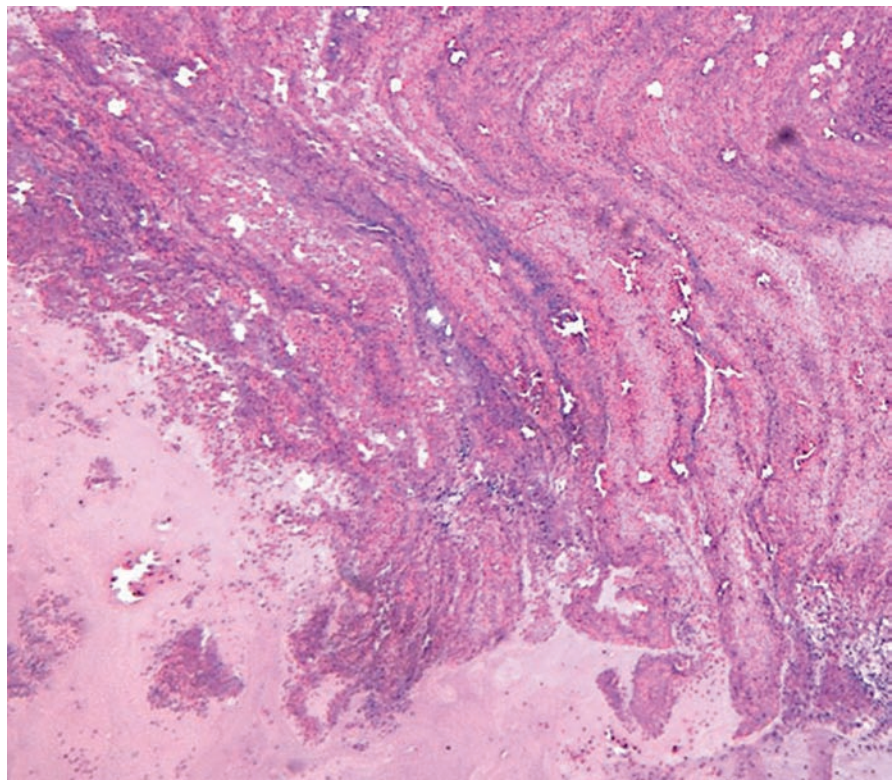

Fig. 15.1 Photomicrograph of an H&E-stained section of allergic mucin from a patient with AFS. There are layers of eosinophils in a background of mucin. No fungal hyphae can be seen (original magnification 40×)

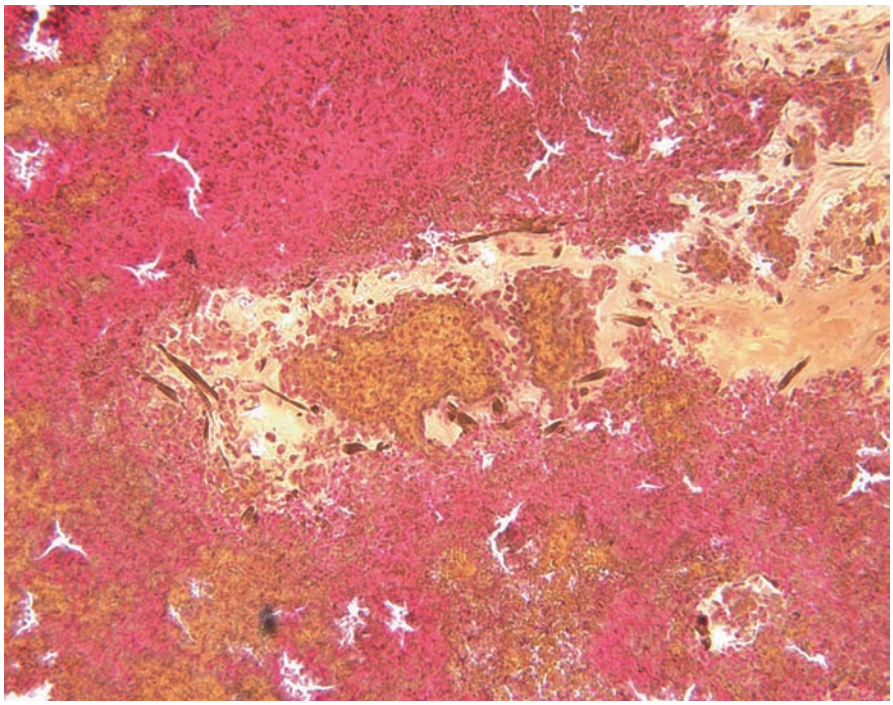

Fig. 15.2 Fontana-Mason stain of allergic mucin. The Fontana-Mason stains the melanin pigment of dematiaceous fungi. In this image, clusters of eosinophils as well as a few scattered, dark brown fungal hyphae are seen

hyperattenuation, and elevated titers of anti-*Aspergillus* IgE have a high predictive value for AFS, though considered in isolation they are not specific [8]. Clearly, considerable overlap exists between AFS, EMCRS, and CRS from other causes, and the Bent and Kuhn criteria are still helpful to distinguish between these.

Imaging Findings in AFS

- Hyperattenuation of sinus contents on CT imaging
- Bone erosion, sinus expansion, and mucocele formation
- MRI: low signal intensity of sinus contents on T1- and T2-weighted images

15.5 Radiologic Features

AFS has characteristic features on CT or MR imaging. The characteristic imaging findings of AFS cases are still considered extremely important for diagnosis. CT is the initial study of choice for evaluating these patients. CT imaging shows multiple opacified sinuses with central hyperattenuation, sinus mucocele formation, and erosion of the lamina papyracea or skull base with a pushing border (Figs. 15.3–15.5). AFS causes more bone erosion than other forms of CRS. Ghegan et al. showed that 56% of AFS cases presented with radiographic evidence of skull base erosion or intraorbital extension, while similar findings were noticed only in 5% of other cases of inflammatory sinusitis (mostly from mucoceles) [14]. Campbell et al. [5] reported that 50% of children with AFS had proptosis with orbital erosion, consistent with previous reports [21]. Bony erosion in the setting of polypoid sinusitis clearly is an important feature which should raise suspicions of AFS.

Magnetic resonance imaging is not usually clinically necessary, but may be indicated with CNS or orbital complications. Nevertheless, AFS has characteristic MR findings. On MR imaging, the sinuses have a central low signal on T1- and T2-imaging, corresponding to areas of allergic mucin, with peripheral high signal intensity corresponding to inflamed mucosa (Figs. 15.6 and 15.7) [2, 25, 45]. Sometimes the sinus contents have an isointense T1-signal. The low signal intensity of areas filled with allergic mucin

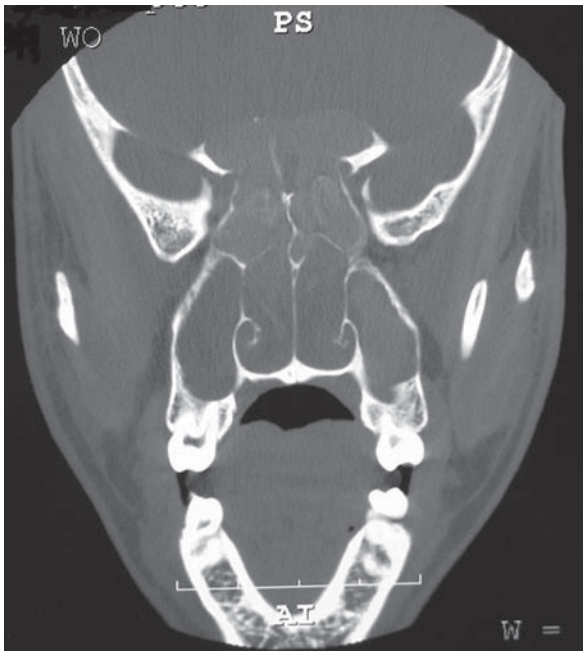

Fig. 15.3 Coronal noncontrasted CT image with intermediate windowing from a patient with AFS. Faint hyperattenuation of sinus contents are seen within the left maxillary sinus and bilateral posterior ethmoid cells. The planum sphenoidale has been eroded. Also note that the nasal cavity is occluded with polyps

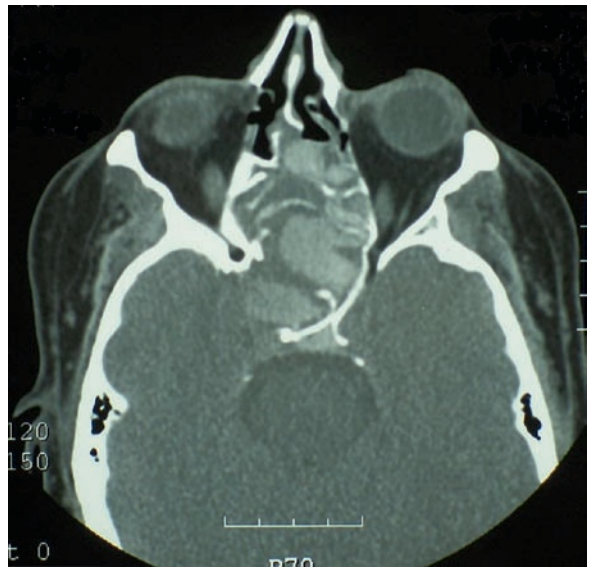

Fig. 15.5 Axial noncontrasted CT image with soft tissue windowing. Hyperdense sinus contents can be easily seen with this windowing. There has been distortion of the ethmoidal labyrinth and erosion of the posterolateral wall of the right sphenoid sinus. This patient had AFS

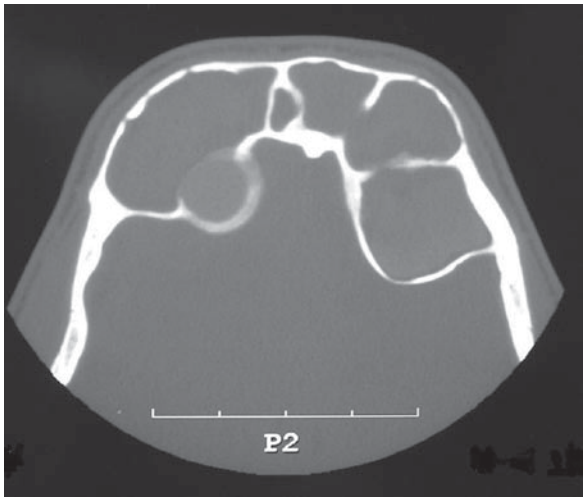

Fig. 15.4 Axial noncontrasted CT image of the frontal region in bone windows. There has been expansion of bilateral frontal sinuses with extension of supraorbital ethmoid cells intracranially. Note that the hyperdense sinus contents are not seen in this image. This patient had AFS

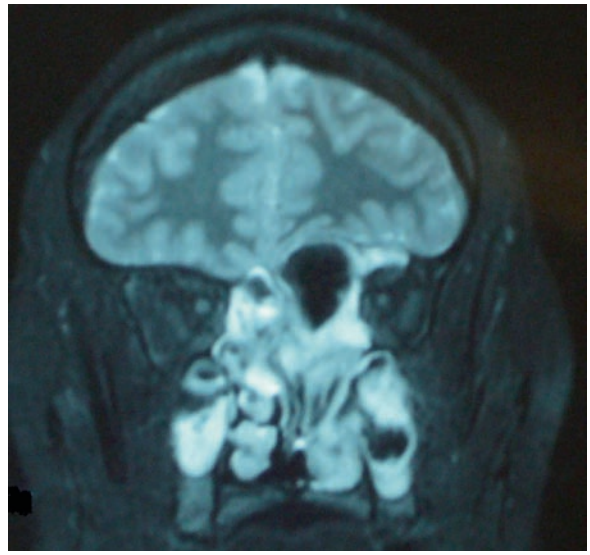

Fig. 15.6 T2-weighted coronal MR image with STIR fat suppression in a patient with AFS. Note the signal void in the left maxillary sinus and the expanded left posterior ethmoid cell with intracranial expansion. The signal void in this ethmoid cell is caused by allergic mucin with high protein and low water content

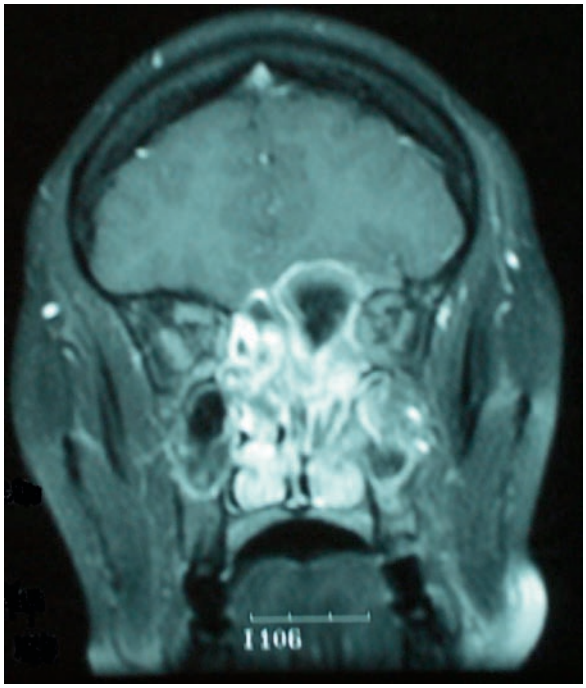

Fig. 15.7 Contrast-enhanced T1 coronal MR image from the same patient as Fig. 15.6 shows signal void in an expanded left posterior ethmoid cell, and peripheral mucosal enhancement

has been attributed to high protein and low water content within the mucin. While the CT and MR imaging findings in AFS are considered important in diagnosis, definitive diagnosis requires histologic verification and other clinical information.

15.6 Pathophysiology

A hypersensitivity to fungus is believed to underlie the pathogenesis of AFS, but the nature of this hypersensitivity is still debated. The dominant theory to explain the pathogenesis of AFS was adopted from the model of ABPA pathogenesis [26]: a combination of Gell and Coombs type 1 and type 3 hypersensitivity to fungal allergens causes sinonasal inflammation [39]. This paradigm was reinforced by the clinical association of AFS with allergy and the detection of elevated serum levels of total and fungal antigen-specific IgE and IgG in AFS patients [22, 43]. Most patients with AFS also have detectable fungal-specific IgE in their allergic mucin [7]. Elevated levels of fungal-specific IgG3 are a consistent finding in patients with AFS and AFS-like disease. A recent study of patients with EMCRS including AFS cases found that elevated fungal-specific IgG3 was a distinguishing serologic feature of both EMCRS and AFS patients, and IgE levels could be used to distinguish EMCRS from AFS [31]. Type 1 hypersensitivity to fungal antigens thus helps distinguish AFS from other forms of EMCRS.

These findings suggest that both "allergic" and "nonallergic" fungal hypersensitivity are important components of the underlying pathophysiology of AFS. However, the pathophysiologic mechanisms in AFS are likely more complicated. It appears that AFS develops in susceptible patients with a convergence of local anatomic as well as environmental factors [26]. Fungi enter the nose and sinuses and trigger an inflammatory response. This inflammation induces polyp formation and the accumulation of allergic mucin. Trapped fungi continue to stimulate the adaptive immune system in a vicious cycle. Over time, massive polyposis develops and fungal mucoceles distort the sinonasal anatomy.

Treatment of AFS

- Endoscopic sinus surgery
- Saline irrigations
- Topical nasal steroid
- Systemic corticosteroids
- Leukotriene modifiers
- Immunotherapy
- Antifungals

15.7 Treatment

The medical and surgical treatment of AFS advanced after widespread recognition that AFS is not a form of invasive fungal sinusitis. Aggressive surgery and toxic antifungal medications have been replaced by endoscopic surgery and medical therapy directed at suppressing inflammation and reducing the burden of fungal antigen in the nose. AFS is now considered, by definition, to be a noninvasive, immunologically mediated hypersensitivity to fungi, and treatment approaches have been altered accordingly.

Surgery is required initially in almost all cases of AFS. An aggressive surgical approach utilizing external approaches and stripping of sinus mucosa was often used in the past before the true nature of AFS was understood [18, 44]. But surgery today relies on endoscopic tissue preserving approaches that are sufficient to remove obstructing polypoid mucosa, evacuate sinus contents, and facilitate sinus drainage [26]. External surgeries are not necessary except in rare circumstances. The sinonasal expansion from massive polyposis and fungal mucoceles actually facilitates surgery by improving surgical access. However, this disease may distort the normal intranasal landmarks and erode the important bony barriers to the orbit or brain, potentially increasing the risk of surgery. Image guidance is helpful for orientation and to facilitate more complete surgery. Incomplete surgery, with retention of cells filled with allergic mucin appears to be a risk factor for early recurrence [27]. Surgical treatment for recurrences is indicated when intense medical management fails to clear an exacerbation. Intense medical therapy can reduce polyp volume, but massive polyposis and outflow tract obstruction may not respond to medical management if there is a significant polyp burden or allergic mucin within the sinuses. The goals of surgical treatment for recurrence are the same as for primary surgery.

Medical treatment for AFS is absolutely essential to prevent or delay recurrence of disease. A variety of medical therapies are now employed to suppress inflammation, prevent reaccumulation of allergic mucin, and maintain sinus drainage. Systemic anti-inflammatory agents are usually required in the treatment of AFS. Systemic steroids have the best substantiation in the literature [19, 38]. A brief course of preoperative systemic corticosteroids will shrink polyps and decrease bleeding during surgery [26]. Systemic corticosteroids given in the immediate post op period will prevent early recurrence of polypoid inflammation [42]. Prolonged treatment with systemic steroids may abrogate the vicious cycle of mucosal inflammation in AFS, but the ideal dosing and treatment course are yet to be defined. Long-term treatment with systemic corticosteroids entails considerable risk; therefore, short bursts are usually employed to keep sinonasal inflammation controlled. Leukotriene receptor antagonists are sometimes employed, and while strong evidence for efficacy is lacking, these antileukotriene agents are attractive because of their safety and possible steroid-sparing effect [37]. Other anti-inflammatory agents such as macrolide antibiotics may have a role, though again data are lacking [40]. Unfortunately there is no regimen of systemic anti-inflammatory medication that has proven superior to another for improving patient outcome or reducing the need for revision surgery.

In addition to systemic treatment, topical treatments are important medical adjuncts. Topical nasal corticosteroids, saline irrigations, and antifungal agents [4, 34], are all utilized, though saline irrigations and topical steroid sprays are the mainstays of treatment. Nasal steroids have a minimal side effect profile, and are effective at decreasing sinonasal inflammation or even shrinking nasal polyps. Some authors have recommended that nasal steroid sprays be used up to three times the usual dosage to boost their efficacy [19]. However, unfortunately, local treatments are often not sufficient to dampen the brisk inflammatory reaction of AFS and prevent recurrence.

Antifungal treatments are sometimes employed for AFS in an attempt to decrease the fungal antigenic burden within the sinonasal cavities [10, 19], but convincing data of their effectiveness in AFS are still lacking. Antifungal therapy has not been widely adopted because of a lack of evidence that it adds benefit beyond that achieved with corticosteroids or that it decreases reliance on systemic steroids. The fungi in AFS are not invasive and are present in scant numbers. Antifungal drugs have many serious toxicities that limit their usefulness. Though newer antifungal agents have an appropriate spectrum and lower incidence of significant toxicities, prolonged treatment is extremely expensive and may not be justified in the absence of data that demonstrate benefit. The anecdotally observed efficacy of agents like itraconazole [34] may not be due to a reduced fungal burden in the nose, but rather due to the anti-inflammatory properties of the molecule or its inhibition of prednisone metabolism. Should antifungal therapy be employed, topical delivery seems preferable because of the lower risk of systemic side effects and the benefit of delivering higher doses directly to the site of disease. Even agents like amphotericin B which have excellent activity against the usual fungi may be administered without the significant toxicities associated with systemic administration. However, antifungal therapies need further investigation to establish their efficacy before their use is widely adopted.

Immunotherapy (IT) is another treatment modality that has been proposed to decrease the reliance on systemic steroids in the treatment of AFS. The rationale for IT presupposes that AFS is an IgE-mediated process. Folker et al. reported their experience with IT in AFS

patients and made a comparison to nonimmunotherapy-treated historical controls. After an average 33 months of follow-up, they showed that the IT-treated patients had better endoscopic mucosal appearance, lower CRS survey scores, required fewer courses of oral steroids (2 vs. 0), and showed less reliance on nasal steroids (73 vs. 27%) [13]. While this was not a randomized double blind study, these results suggest an important role for IT in the management of AFS. In summary, the ideal medical regimen for AFS is unknown and clinical decisions must be made based on the patient's age, concomitant medical conditions, and response to treatment.

15.8 Natural Course

After AFS was distinguished as a clinicopathologic entity, clinical experience soon revealed that the recurrence of the disease was extremely common. Kupferberg et al. reported universal recurrence in patients treated surgically without vigorous postoperative medical treatment [20]. The reported recurrence rates for AFS range from 10 to 100% [26]. One longitudinal study showed that over a period averaging almost 7 years of follow-up, patients required an average of two surgical procedures and three courses of systemic steroids per year. After many years, even asymptomatic patients had persistent polypoid mucosal edema and elevated total serum IgE [28]. So, while the disease may become quiescent over a period of years, a significant number of patients will have persistent sinonasal inflammation. Recurrent disease may silently progress until massive intranasal polyposis again creates significant nasal obstruction. If discovered at this point, revision surgery may be required. Endoscopy is the best way to follow the activity of disease, but some have found IgE levels to be helpful in monitoring patients for recurrence. Because of the chronic and recurring nature of this condition, patients should be closely followed for extended periods.

Take Home Pearls

- AFS is a disease of teenagers and young adults. Mucocele formation with sinus expansion is a specific sign that distinguishes AFS from other forms of polypoid CRS.
- Topical and systemic steroids are the most effective medications for AFS. Most patients with AFS will require multiple surgeries

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Vasculitis Including Churg–Strauss Syndrome

16

Isam Alobid and Joaquim Mullol

Core Messages

- Systemic vasculitides, including Wegener's granulomatosis and Churg-Strauss Syndrome, may be associated with nasal manifestations such as allergic and non-allergic rhinitis, chronic rhinosinusitis with and without nasal polyps.
- Management of systemic vasculitides require a multidisciplinary approach and is based on clinical, histopathological, and immunological features for the diagnosis, and on oral steroids and immunosuppressive agents for the treatment.

16.1 Introduction

The systemic vasculitides is a general term used to refer to a group of diseases that are characterized by inflammation of blood vessels. The inflammatory process may involve vessels of any magnitude although different entities tend to preferentially target vessels of a particular size and this feature has been considered in Chapel Hill nomenclature [15] (Table 16.1). It may affect either arteries and/or veins. The inflammatory process leads in some instances to the generation of extravascular inflammatory masses and, frequently, to the occlusion of involved vessels with the ensuing ischemia and necrosis of supplied tissues. The inflammation may be focal, meaning that it affects a single location within a vessel; or it may be widespread, with areas of inflammation scattered throughout a particular organ or tissue, or even affecting more than one organ system in the body.

Among the systemic vasculitides, Wegener's granulomatosis (WG), and Churg–Strauss syndrome (CSS) typically involve the nasal cavity and paranasal sinuses. Less frequently, other necrotizing vasculitides such as microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), and mixed cryoglobulinemia may generate lesions in the ENT area.

16.2 Vasculitic Diseases

16.2.1 Wegener's Granulomatosis

WG is an uncommon disease with an annual incidence of 6–58 per million, according to epidemiologic studies conducted in Europe [30]. It classically involves inflammation of the arteries that supply blood to the tissues of the kidneys, lungs, and upper respiratory tract. Other organ systems that can be affected by the disease include the nervous system, ears, eyes, heart, and skin. WG can arise within a wide range of ages from childhood to old age. Men and women are equally affected.

WG is characterized by granulomatous involvement of the upper and lower respiratory airways. Microscopic examination typically discloses necrosis, mixed inflammatory infiltrates that frequently undergo granulomatous differentiation with multinucleated giant-cells, and inflammation of blood vessels.

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Table 16.1 The Chapel Hill nomenclature of the systemic vasculitides [15]

Large vessel vasculitis	
Giant-cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. It often involves the temporal artery. Usually occurs in patients older than 50 year and is associated with polymyalgia rheumatica
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50 years
Medium-sized vessel vasculitis	
Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
Kawasaki disease	Arteritis involving large, medium sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children
Small vessel vasculitis	
Wegener's granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessel (i.e., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common
Churg–Strauss syndrome	Eosinophil rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small- to medium-sized vessels, and associated with asthma and eosinophilia
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Necrotizing vasculitis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common
Henoch–Shönlein purpura	Vasculitis, with IgA dominant immune deposits, affecting small vessels (i.e., capillaries, venules, or arterioles). Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis
Mixed cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels and associated with cryoglobulins in serum. Skin and glomeruli are often involved
Cutaneous leukocytoclastic vasculitis	Isolated cutaneous leukocytoclastic vasculitis without systemic vasculitis or glomerulonephritis

Vasculitis may involve capillary vessels, small and medium-sized arteries and veins, and may affect a variety of organs leading to a protean array of disease manifestations.

Rhinosinusal manifestations are the presenting symptoms of WG in about 73% of patients and develop at some point during the course of the disease in 90% or more [12, 22, 27]. Infiltration of the nasal mucosa by granulomatous, necrotizing inflammation causes nasal obstruction, crusting, and bloody nasal discharge. Nasal mucosa disruption may lead to anosmia. Cacosmia due to tissue necrosis aggravated by secondary infection may also be present. Ulcers may also develop and the progression of inflammatory lesions may lead to necrosis of the nasal septum and to saddle nose deformity. Paranasal sinuses are frequently involved and recurrent episodes of sinusitis with bloody/purulent nasal discharge frequently precede the appearance of other disease manifestations. Lesions may be destructive leading to the development of fistulae, and disrupted sinus architecture facilitates bacterial and fungal colonization and infection, which is also favored by immunosuppressive therapy. Distinction between active disease and secondary infection may be challenging during the course of the disease. Chronic nasal carriage of *Staphylococcus aureus* is associated with higher relapse rates in these patients [29]. Additional ENT manifestations include recurrent serous otitis and mastoiditis. Hearing loss may appear and can be

conductive, caused by recurrent serous, granulomatous or infectious otitis, or sensorineural, the latter presumably due to vasculitis.

Subglottic stenosis by granulomatous tissue or its resulting scars is a typical complication of WG. This complication is more frequent in children/adolescents and may critically impair the airflow requiring transient or permanent tracheostomy [18].

The lower respiratory tract is involved in 85% of patients. Pulmonary nodules, cavities, atelectasia secondary to bronchial stenosis are the most typical manifestations. Diffuse alveolar hemorrhage is a life-threatening complication.

Eye involvement is frequent (50%) and may include a variety of lesions including episcleritis, granulomatous conjunctivitis, scleritis, keratitis, uveitis, and nasolacrimal duct obstruction. Granulomatous masses in the orbits may cause proptosis and impairment in ocular motion leading to diplopia. Patients may lose vision due to ulcerative keratitis or scleritis, orbit pseudotumor, or vasculitis leading to optic nerve or retinal ischemia.

Systemic vasculitis may involve any organ. The kidney is involved in 75% of cases and pauci-immune necrotizing glomerulonephritis is the underlying lesion. However, identical lesions can be found in other vasculitides such as MPA and renal-limited vasculitis. Granulomatous lesions can be found in some biopsies and this finding supports the diagnosis of WG. Early manifestations may only consist of urinary sediment abnormalities (microhematuria with red cell casts) and mild proteinuria. However, impairment of renal function is common and rapidly progressive renal failure may occur. Skin, and peripheral nerve involvement are not infrequent and systemic symptoms such as fever, arthritis, or weight loss may be observed in 30–50% of patients.

The diagnosis and management of WG requires a multidisciplinary approach. WG can be diagnosed when typical lesions (necrosis, granuloma, and vasculitis) are demonstrated in the upper or lower respiratory airways. Mycobacterial or fungal infection must be ruled out with specific stainings, cultures, or molecular techniques. Although biopsies from ENT lesions are easier to obtain than open lung biopsies, the diagnostic yield is lower. In a survey from 126 biopsies taken from the ENT area, mostly nose and paranasal sinuses, Devaney et al. found typical lesions in only 16% of WG patients. In 23% granuloma and vasculitis were found. Twenty-three percent showed only necrosis and the remaining nonspecific inflammatory changes [6]. Antineutrophil cytoplasmic antibodies (ANCA) are typically detected in sera from patients with WG and are thought to contribute to the development of vessel inflammation and injury. ANCA can be detected by indirect immunofluorescence and, in WG, almost invariably display a cytoplasmic pattern on ethanol-fixed neutrophils and recognize proteinase 3 (PR3). Overexpression of PR3, however, might predispose the patient to the development of autoimmune ANCA-associated vasculitis [8].

Several disorders must be considered in the differential diagnosis of WG. Destructive ENT lesions can be found in other processes such as nasal lymphoma of T/NK phenotype, relapsing polychondritis, and granulomatous infections. Lung infections and angiocentric lymphoma may mimic WG pulmonary lesions.

WG is a chronic, relapsing, and potentially life-threatening disease. Treatment relies at present on corticosteroids and immunosuppressive agents which have proved to be life-saving and efficient in inducing disease remission but not in curing the disease. Patients cumulate disease and treatment-derived morbidity over the years [12]. Cyclophosphamide must be given to patients with severe generalized disease but must be switched to a safer immunosuppressive agent (azathioprine, mycophenolate, or methotrexate) when remission is obtained [14]. These agents can be tried as first option in patients without kidney involvement [5]. Biologic therapies are under investigation. In spite of the expectations raised by experimental data and open-label studies, blocking TNF-α with etanercept has failed to add additional efficacy to the standard therapy in a large multicenter, randomized, placebo-controlled, double-blind study performed in patients with WG [31]. Preliminary results have suggested the potential efficacy of B-cell depletion and clinical trials are ongoing to assess this point.

Some forms of damage (such as subglottic stenosis or renal insufficiency) occur as the direct result of the disease; other forms (such as osteoporosis or gonadal failure) are the result of the drugs used to treat it. Future studies of this disease must focus on both the early identification and prevention of damage [26].

16.2.2 Churg–Strauss Syndrome

CSS is a rare condition that may complicate the outcome of patients with asthma. In 1951, Churg and Strauss first described the syndrome in 13 patients who had asthma, eosinophilia, granulomatous inflammation, necrotizing systemic vasculitis, and necrotizing glomerulonephritis [3]. Annual incidence of CSS in the general population is six cases per million and 64 per million among patients with asthma. CSS most frequently appears in patients between 30 and 50 years but may affect people within a wide spectrum of ages [9, 23, 27].

CSS frequently progress through three stages which may appear gradually over the years, may develop in a subacute or, in some cases, abrupt presentation. The first stage is characterized by asthma and increased blood eosinophil counts. In this stage ENT abnormalities are common and include allergic rhinitis, nasal polyps, and recurrent sinusitis. Eustachian tube dysfunction and secondary middle ear infection may also occur. Anosmia is very frequent. This stage may last from months to years before CSS fully develops. At this point the diagnosis of CSS syndrome must be considered and patients must be carefully evaluated and followed but a definite diagnosis of CSS cannot be established if no additional features are present since many patients never progress to subsequent stages. The following stage is characterized by tissue eosinophilia. Infiltration by eosinophils may involve the nasal and sinusal mucosa, lungs, skin, the gastrointestinal tract, and the heart. At this stage CSS may be difficult to distinguish from other hypereosinophilic conditions such as primary hypereosinophilic syndrome, fleeting lung infiltrates due to parasitic diseases, eosinophilic gastroenteritis, and chronic eosinophilic pneumonia. The existence of asthma and ENT symptoms is an important clue for the diagnosis. Fully developed disease includes manifestations related to systemic necrotizing vasculitis that may involve a variety of territories leading to a wide array of clinical manifestations. Involvement of peripheral nerves manifesting as mononeuritis multiplex is frequent. Skin, gastrointestinal, heart, and kidney involvement are also common.

A CSS-like syndrome develops as a rare complication in people with asthma who are steroid-dependent and who are treated with leukotriene receptor antagonists. The CSS-like complication is reported in people whose withdrawal of oral steroids is also facilitated by inhaled steroids. This complication is probably related to steroid withdrawal, which unmasks underlying CSS, rather than to the drugs themselves. However, in rare cases, this syndrome has developed when a leukotriene receptor antagonist has been substituted for inhaled steroids without a history of oral steroid withdrawal [2, 4].

From the histopathologic point of view, vasculitis in CSS may involve small- and medium-sized vessels and may be indistinguishable from other systemic necrotizing vasculitis. The presence of accompanying extravascular eosinophilic granulomas is highly suggestive of CSS. The diagnosis of CSS requires both clinical and histopathologic features. Diagnostic criteria are not fully established [16]. According to the American College of Rheumatism classification criteria, a patient with vasculitis can be classified as having CSS if it has any four of the following: asthma, eosinophilia >10%, peripheral neuropathy, pulmonary infiltrates, paranasal sinus abnormality, or extravascular eosinophil infiltration on biopsy findings [20]. ANCA with a perinuclear pattern (pANCA) can be detected in about 40–70% of patients and usually have specificity for myeloperoxidase.

Patients with CSS require treatment with corticosteroids. Several factors indicating poor prognosis have been identified and include, cardiac, gastrointestinal tract, CNS involvement, and proteinuria >1 g/24 h [11]. If at least two of these are present immunossupressive agents are warranted. Pulses of IV cyclophosphamide are usually used for these patients. Relapses are common when corticosteroids are tapered and frequently involve the ENT area. Rhinitis, nasal stuffiness due to congestion or polyps, sinusitis, and Eustachian tube dysfunction with secondary otitis are common forms of smoldering activity in these patients. About one third of the patients require sustained oral steroids to control asthma and rhinosinusal manifestations. Severe clinical manifestations related to vascular involvement are fortunately less common during relapses. CSS patients may eventually benefit from investigational products tested in the field of vasculitis or asthma. The rarity of this disease makes the performance of clinical trials difficult.

16.2.3 Microscopic Polyangiitis

MPA is a systemic necrotizing vasculitis involving small vessels. The age of onset is approximately 50 years. MPA incidence is approximately two cases per 100,000 persons in UK and approximately one case in

100,000 persons in Sweden [21]. Blood vessel inflammation may target a variety of organs but kidneys are the most characteristically involved. Renal lesions consist of necrotizing crescentic glomerulonephritis. Vasculitis in the interstitial vessels can also be found. Alveolar capillaritis is a typical pulmonary lesion and may lead to diffuse alveolar hemorrhage, which is a severe complication. Vessels supplying additional territories such as skin, perineural vessels, or the gastrointestinal tract can also be involved [27]. Glomerulonephritis and alveolar capillaritis are indistinguishable from those found in WG. Case reports have described an association of MPA with medications such as propylthiouracil and with diseases such as primary biliary cirrhosis [1]. The most distinctive feature differentiating both entities is the granulomatous involvement of the respiratory tract, characteristic of WG, and absent in MPA. MPA may involve the ENT area. Rhinitis and nasal crusting can be seen in MPA but are usually much less prominent than in WG. Histopathologic examination disclose chronic inflammation or vasculitis but not granulomatous lesions. ANCA can be detected in about 70% of patients with MPA. ANCA positivity assessed by indirect inmunofluorescence on ethanol-fixed neutrophils disclose a perinuclear distribution (pANCA) in MPA and usually recognize myeloperoxidase.

Patients with MPA must be treated with corticosteroids and immunosuppressive agents. When kidney or lung involvement is present, patients must receive cyclophosphamide, either in a daily oral or monthly IV pulse regime, depending on the severity. For less severe cases or for maintenance of remission, less aggressive immunosuppressive agents such as methotrexate or azathioprine can be used [9, 12, 13].

16.2.4 Polyarteritis Nodosa

Classical PAN is a systemic necrotizing vasculitis involving medium-sized arteries. Incidence in the general population is 0.7 per 100,000 people, and prevalence is 6.3 per 100,000 people. Although any organ can be affected, PAN most commonly involves the skin, joints, peripheral nerves, gastrointestinal tract, and kidney. A slightly higher incidence is found in males. Male-to-female ratio is 1.6:1–2:1. PAN has been described in all age groups. PAN predominantly affects individuals aged 40–60 years and rarely found in children [19].

ENT involvement is rare in this disease. Some cases reported in the literature with nasal ulcers or septum necrosis may correspond to other necrotizing vasculitis since they were published prior to the recognition of MPA as a separate entity or prior to the availability of ANCA testing [24]. PAN causes transmural necrotizing inflammation of small-sized or medium-sized muscular arteries. The lesions are segmental and may involve partial circumference only. The associated inflammation process may cause weakening of the arterial wall, aneurysmal dilatation, and localized rupture. The area supplied by the involved vessels may slow impaired perfusion, leading to ulceration, infarct, or ischemic atrophy. Steroids and immunosuppressive medications form the backbone of therapy. Prednisone can be administered as a single agent. As the patient's clinical status improves and the ESR returns to normal (usually within 1 month), tapering of the prednisone dosage can begin. In the absence of relapses, steroids can be stopped after 9–12 months. Intravenous methylprednisolone may be indicating for severe systemic disease and cyclophosphamide is indicated for patients with poor prognostic factors [10, 17].

16.2.5 Cryoglobulinemic Vasculitis

Cryoglobulinemic vasculitis (CGV) is defined by the presence of circulating immunoglobulins able to reversibly precipitate at cold temperatures. CGV may be classified in three types. In type I, cryoglobulins are monoclonal and are usually generated by late B-cell differentiation stage malignancies such as multiple myeloma or Waldeström macroglobulinemia. Type II or mixed cryoglobulinemias have a monoclonal component forming complexes with polyclonal immunoglobulins. The monoclonal component is usually an IgM with anti IgG activity leading to the formation of immune complexes with rheumatoid factor activity. Type III cryoglobulins are complexes formed by polyclonal immunoglobulins. Type II and type III cryoglobulins can be found in association with chronic infections, lymphoproliferative, or autoimmune diseases. The most common cause of type II cryoglobulinemia is hepatitis C virus (HCV) infection. Circulating type II cryoglobulins can be found in about 30% of patients infected by HCV but a minority of these patients develop CGV [7, 25].

CGV can produce tissue injury through two main mechanisms: vascular occlusion by cryoprecipitates or inflammatory vessel damage (vasculitis) triggered by immune complexes. Vascular occlusion due to cryoprecipitates usually occurs in type I monoclonal CGV in which the concentration of circulating cryoglobulins is high. Small vessels appear occluded by hyaline thrombi and the resulting necrotic lesions appear in distal body regions where temperature is lower, such as fingertips, ears, or nose. Vascular inflammation (vasculitis) mainly develops in the context of mixed cryoglobulins, which typically form immune complexes and is a much more frequent mechanism of vessel injury. Vasculitis frequently involves small vessels (capillaries and postcapillary venules) in the skin, leading to palpable purpura that can be seen at some point in 90% of patients. When arterioles or small arteries are involved in the deep dermis, necrotic skin ulcers may appear. Kidney involvement (membranoproliferative glomerulonephritis) and peripheral neuropathy presenting as mononeuritis multiplex or symmetrical polyneuropathy are common.

A variety of nonspecific nasal manifestations may be present: nasal obstruction, epistaxis, postnasal discharge, whistling, and crusting. Cases of nasal septal perforation secondary to CGV have been reported [28]. Since HCV-associated CGV is the most frequent, some of the nasal manifestations found in patients with CGV such as crusting may be related to Sjögren's syndrome, a recognized extrahepatic complication of HCV infection.

Treatment of patients with CGV is complex and is frequently unsatisfactory. The main efforts must be addressed to treat the underlying condition. HCV infection is by far the most common cause of CGV. Combination therapy with interferon alpha and ribavirin leads to a decrease in viral burden and improvement of clinical symptoms in a substantial proportion of patients but relapses are frequent and side effects are remarkable. Current efforts are addressed to more efficiently reduce the viral load and delete B-cell clonalities. The management of patients with prominent manifestations derived from vascular inflammation/occlusion is difficult and, regardless of the underlying disease, requires administration of corticosteroids and, in the most severe cases, immunosuppressive agents or plasmapheresis to remove circulating cryoglobulins. There are no clinical trials definitely supporting particular treatment regimens.

Take Home Pearls

- A variety of systemic vasculitides are associated with nasal manifestations, including allergic and non-allergic rhinitis, and chronic rhinosinusitis with and without nasal polyps.
- Among vasculitides, Wegener's granulomatosis and Churg-Strauss Syndrome typically involve nasal cavities and paranasal sinuses.
- Wegener's granulomatosis is a chronic, relapsing, and potentially life-threatening disease.
- Chrug-Strauss Syndrome is a rare condition that may complicate the outcome of patients with asthma, allergic rhinitis, chronic rhinosinusitis and nasal polyposis. A CSS-like complication is reported in patients treated with leukotriene receptor antagonists in whom oral steroid treatment is withdrawn.
- Diagnosis of systemic vasculitides usually require clinical, histopathological, and immunological features.
- The treatment of most systemic vasculitides, including Wegener's granulomatosis and Churg-Strauss Syndrome, is mainly based on oral corticosteroids and immunosuppressive agents.
- Since the diagnosis and treatment of vasculitidies require a multidisciplinary approach, primary care physicians as well as ENT specialists, pneumologists, pediatricians, and allergologists should always keep in mind their differential diagnosis when managing nasal and sinonasal diseases.

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Nasal Polyps in Cystic Fibrosis

17

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Core Messages

- Nasal polyps are common in cystic fibrosis (CF).
- Nasal polyps in children should prompt appropriate investigations for the potential diagnosis of CF.
- Possible etiologies for nasal polyp formation in CF include direct consequence of ΔF508 affecting chromosome 7, colonization with microorganisms including *Pseudomonas aeroginosa* and fungi, and IgE-mediated inflammation.
- Neutrophils are more common in polyps from CF patients compared with non-CF nasal polyposis.
- Conservative management with nasal irrigations and nasal steroids constitute first-line treatment.
- Surgical management of persistent and symptomatic polyps may also improve lung function, and consequently, quality of life.
- Simple polypectomy has a high rate of early recurrence, and thus, surgery should include at a minimum uncinectomy, middle meatal antrostomy, and anterior ethmoidectomy.
- Topical delivery of novel medications may reduce the need for surgery.

17.1 Introduction

Cystic fibrosis (CF) is an autosomal recessive inherited disorder affecting the exocrine glands and is characterized by thick, viscous secretions in multiple organ systems, including the sinuses, upper and lower airways, gastrointestinal system, skin, and reproductive system. It has a high incidence in the Caucasian population, affecting 1 per 2,500 live births in the United States [14]. Chronic rhinosinusitis (CRS) and nasal polyps are not uncommon in CF patients. In addition to the morbidity due to the polypoid CRS, it is suggested that the extent of sinus disease may influence the severity of pulmonary disease [16]. The purpose of this chapter is to review the clinical spectrum of sinonasal disease in CF and management issues, especially in those undergoing pulmonary transplantation.

17.2 Epidemiology of Sinonasal Disease in Cystic Fibrosis

The frequency of nasal polyposis in CF ranges from 31 to 56% [6, 12, 22, 26, 39]. Polyps are most commonly reported in children aged 5–14 years; however, they can also develop in older patients [2, 22]. Males and females are equally affected [6, 12, 26, 39]. Polyps usually occur bilaterally [44], but have been reported unilaterally in up to 38% [6] (Fig. 17.1).

17.3 Etiology

17.3.1 Genetics

CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

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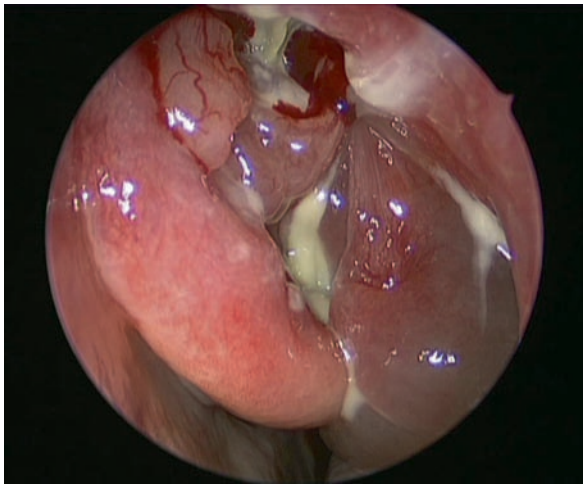

Fig. 17.1 Intraoperative view of left nasal cavity in child with CF showing polyps and mucopurulence in middle meatus

situated in region 31 on the long arm of chromosome 7 (7q31). This gene codes for a protein that functions as a cAMP-regulated chloride channel. Abnormal function of this channel results in abnormal sodium and chloride transport across the apical membrane of epithelial cells [45]. More than 1,000 mutations have been identified in the CFTR gene; however, the most common mutation, present in 70% of patients, is a deletion, designated ΔF508 mutation, which results in the loss of the amino acid phenylalanine at the 508th position. The most frequent genotype in CF is ΔF508/ΔF508 (i.e., ΔF508 homozygosity), followed by ΔF508 heterozygosity [28].

The genotype may influence the incidence of nasal polyposis in CF. Kingdom reported that CF patients with nasal polyposis undergoing surgery had a higher incidence of ΔF508/ΔF508 or ΔF508/G551D genotypes than those with CF and no nasal polyps [29]. Some found that ΔF508 homozygosity correlates with the presence of nasal polyps [26, 39]; however, others have not found otherwise [2, 6, 12, 22]. Interestingly, Kostuch reported a significantly higher incidence of ΔF508 heterozygosity in non-CF patients with nasal polyps (11.4%), compared to control subjects without polyps (1.4%) [31]. Thus, while the specific CFTR mutation may be connected with the development of nasal polyposis, it is likely that other factors also play an important role [6].

17.3.2 Pseudomonas Colonization

A significantly higher incidence of colonization with *Pseudomonas aeroginosa* is reported in CF patients with nasal polyps compared to CF patients without polyps [6, 22, 29]. *Pseudomonas* species produce several toxins, including hemolyzin and pyocyanin, a phenazine derivative. Pyocyanin has been shown to slow ciliary beat frequency and cause ciliostasis and epithelial disruption in vitro and, thus, may play a role in the pathophysiological events leading to the formation of nasal polyps [46].

17.3.3 Allergy

The role of allergy in the pathophysiology of nasal polyps in CF is unclear. The overall prevalence of atopy in CF does not appear to be different between polyp and nonpolyp patients [19, 22]. However, studies have shown that patients with positive skin prick tests are more likely to be colonized by *Pseudomonas species*, and this may be in fact responsible for the formation of polyps. Interestingly, a higher incidence of allergy to *Aspergillus fumigatus* in CF nasal polyps has been reported and allergic bronchopulmonary aspergillosis is known to affect 2–15% of patients with CF [42]. Thus, it is interesting to speculate whether fungi and allergy to fungi may have a role in causing nasal polyposis in these patients. Wise reported one third of fungal cultures to be positive among a series of 30 patients with CF, with two patients in their series being newly diagnosed with allergic fungal sinusitis [47]. Thus, allergic fungal sinusitis may be associated with nasal polyps in a subset of patients with CF; however, further studies are required.

17.4 Pathology

There are several important differences in histological characteristics of polyps from CF and non-CF patients. Polyps in non-CF patients are characterized by eosinophil infiltration, while those in CF are characterized by predominantly neutrophil infiltration [24, 38]. Eosinophils are seen in CF polyps; however, the numbers of these are significantly fewer than seen in non-CF polyps [24, 38]. The basement membrane of polyps is thinner and more delicate, the mucous glands mainly contain acid mucin, and submucosal hyalinization is absent. In contrast, non-CF polyps typically

have a thick basement membrane and contain mucous glands with neutral mucin [17].

CF polyps typically contain cytokines associated with a T helper 1 (T_H1) inflammatory response [43]. Neutrophil populations, levels of IL-8, and myeloperoxidase (MPO) are significantly higher, whereas levels of IL-5, eotaxin, ECP, and IgE are significantly lower in CF polyps compared with non-CF polyps. Proteins such as human β-defensins 2 (HBD 2) and toll-like receptor 2 (TLR-2) [8] and surfactant proteins A and D [43] are also increased. These may be a consequence of predisposition to recurrent infections due to dysfunctional CFTR in the nasal epithelium that causes impaired chloride transport, which changes the physiochemical properties of nasal mucus, resulting in thick and viscous mucus. Increased levels of interleukin-9 and upregulation of the calcium-activated chloride channel, hCLCA1, may contribute to mucus overproduction by upregulating the expression of soluble gel-forming mucins [21]. The viscosity of the mucus blanket is further increased by DNA macromolecules from degenerating neutrophils [7]. The increased viscosity of nasal mucus contributes to decreased effectiveness of the mucociliary transport, and consequently, increased the risk of infection and inflammation. The increased viscoelastic properties of mucus may also contribute to mechanical obstruction of sinus ostia and air spaces causing impaired gas exchange and mucosal edema that further decreases ciliary function and enhances bacterial colonization. Bacterial products such as pyocyanin and hemolysin from *P. aeruginosa* may further impair mucociliary function. Thus, a vicious cycle of impaired mucociliary function, sinus ostial obstruction, and bacterial infection is created. Furthermore, it is also postulated that chronic infection with *P. aeruginosa* and *Staphylococcus aureus* may cause upregulation of innate defensive proteins TLR-2 and HBD 2, leading to a dysregulated neutrophilic inflammation [8]. Neutrophil elastase is known to cause mucosal damage and may thus prolong mucosal inflammation and contribute to edema and polyp formation [38].

In postlung-transplant patients with nasal polyposis, consideration should be given to the possibility of posttransplant lymphoproliferative disorder (PTLD). PTLD is an uncontrolled lymphoproliferation in the setting of pharmacological immunosuppression, usually caused by unrestrained stimulation of B-lymphocytes by Epstein–Barr virus (EBV). Although PTLD affecting the head and neck usually occurs in the setting of disseminated disease, isolated sinonasal PTLD is not uncommon, and in many cases, is only diagnosed after "incidental" nasal polypectomy [23].

17.5 Clinical Presentation

Nasal obstruction is the most common presenting symptom of nasal polyposis in CF; however, not all patients with polyps complain of nasal obstruction. It is likely that nasal obstruction in these patients is so long-standing that most patients have adapted to it. Rhinorrhea is also common, particularly among younger children, while older children may also complain of headache.

Whenever possible, children with CF should undergo nasal endoscopy to definitively ascertain whether or not polyps are present. This may be difficult in younger children owing to the lack of cooperation. Nasal endoscopy will commonly reveal polyps arising in the middle meatus, with the middle turbinate thinned and pushed medially against the nasal septum. Nasal polyps are rare in children who do not have CF. Thus, children with nasal polyps should initially undergo a sweat test. A sweat chloride level of greater than 60 mEq/L is considered diagnostic of CF, and this should be followed up with genetic testing and counseling.

17.6 Investigations

17.6.1 Radiology

Sinus radiographs are of limited application and computed tomography (CT) of the sinuses is now the investigation of choice. Common sinus CT scan findings include frontal sinus hypoplasia, maxillary sinus expansion with medialization, or even loss of the medial maxillary wall and mucocele or pseudomucocele of the maxillary sinuses (Fig. 17.2). Frontal sinus hypoplasia is thought to result from diminished postnatal growth as a result of chronic inflammatory disease

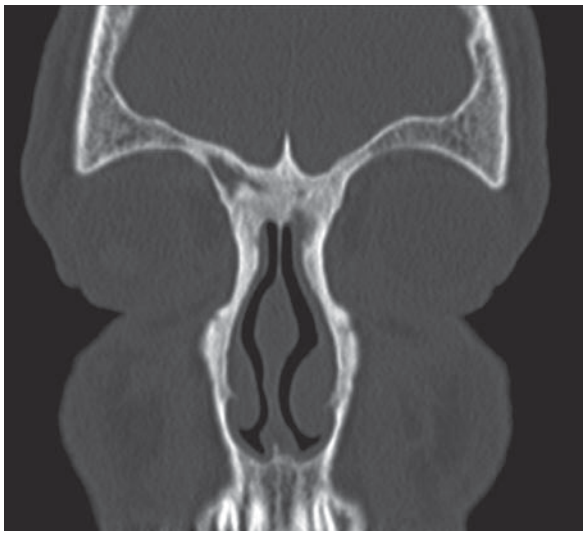

Fig. 17.2 Computed tomography scan of patient with CF showing hypoplastic frontal sinuses

and decreased sinus ventilation. A similar phenomenon may also be observed in the sphenoid sinuses. Of note, a significantly higher incidence of sinus hypoplasia has been reported in patients who are homozygous for the ΔF508 mutation [48]. The maxillary sinus findings are thought to result from the entrapment of thick inspissated mucus and polyp formation in the middle meatus. Like polyps, mucoceles are extremely rare in children and should suggest a diagnosis of CF. Magnetic resonance imaging (MRI) can differentiate between infectious material and thickened mucosa and thus complement CT scan findings [15].

17.6.2 Microbiology

Ideally, endoscopically guided bacteriological cultures should be obtained to guide antibiotic therapy, especially given the high levels of antibiotic resistance in CF; however, this may not be always possible in children. The most common bacteria found in CF sinusitis are *P. aeruginosa* and *S. aureus*. Of note, CF patients with polyps have been reported to show a significantly higher incidence of sinonasal *Pseudomonas* sp. infection compared to those without polyps [6, 22, 29]. Consequently, biofilm formation may be increased in CF compared to non-CF CRS patients [20].

17.7 Management

17.7.1 Medical

Medical treatment is the initial treatment step in the management of CF with CRS with and without polyps. Saline irrigation helps with clearing thick inspissated secretions, crusts, and proinflammatory mediators. Intranasal corticosteroids may also be effective in reducing CF polyp size [18]. Of note, children with CF who are commenced on systemic corticosteroids for pulmonary disease may also report improvement of their nasal symptoms. Systemic antibiotics are indicated where purulent secretions are present in the symptomatic patient and were possible, should be culture-directed, and where possible, should be culture-directed. The major target of antibiotic therapy is typically *P. aeruginosa*. Topical antibiotics have also been used and are being investigated. Nebulized tobramycin is used to treat endobronchial *Pseudomonas* where delivery of a high concentration enhances bactericidal activity while minimizing the risk of ototoxicity and nephrotoxicity. Moss and King found that the requirement for sinus surgery was reduced in CF patients who underwent serial sinus antimicrobial lavage in the postoperative period [35]. However, there are little data on the use of topical antibiotics beyond the perioperative period and on the long-term beneficial effects. Tobramycin may be administered as a 20 mg/mL solution and adverse effects at this concentration are not reported [13]. While topical tobramycin lavage is shown to reduce local bacterial counts in experimental animals, there is little evidence for eliminating biofilms [1, 4]. Recently, topical baby shampoo lavage has shown to be effective in removing bacterial biofilms in postsurgical patients and may have a role in select patients[5] (see below).

17.7.2 Surgery

Generally, surgery is indicated where medical measures fail to achieve adequate control of sinonasal disease. Following are the main issues of surgery in CF patients: (1) safety of the surgery; (2) impact of the surgery on nasal symptoms and quality of life; and (3) impact of surgery on pulmonary function. Major concerns relating to safety involve the risk of bleeding,

particularly where coagulation is abnormal due to vitamin K malabsorption and in the posttransplant patients, due to immune-suppressive therapy. Thus, consideration should be given to optimizing preoperative coagulation status in order to minimize bleeding and risk of complications [10]. Measures to reduce bleeding include preoperative oral corticosteroids and antibiotics. Surgery when performed by experienced surgeons, in close cooperation with experienced anesthesiologists and pulmonologists, there is good evidence that it may be performed safely [27, 40].

The second issue relates to whether or not surgery improves symptoms and quality of life in CF patients. Although there are little data regarding validated quality of life measures, many authors have reported significant improvement in sinonasal symptoms after surgery. Nasal obstruction is the most commonly improved symptom. Significant improvements in rhinorrhea and total rhinosinusitis symptom scores are also reported. Although headache is least likely to improve following surgery, its presence postoperatively may indicate recurrence of frontoethmoidal mucoceles [27, 44]. The third issue relates to the effect of surgery on pulmonary function and is controversial. There are conflicting reports on postoperative lung function, with temporary improvement shown by some [25, 41, 44] and no significant change by others [34, 37]. A significant decrease in the number of hospitalizations and mean number of intravenous antibiotic courses is also shown [41, 44].

17.7.2.1 Extent of Surgery

Surgical treatment includes simple nasal polypectomy and completely opening up the involved sinuses including maxillary, ethmoid, frontal, and sphenoid sinuses. The major drawback of simple polypectomy is shorter time to polyp recurrence [3, 44]. Although previous studies showed better long-term results in patients who underwent a "combined approach," including a Caldwell–Luc operation [3, 9], recent endoscopic studies have not shown a significant long-term beneficial outcome regardless of the extent of surgery [2]. We recommend that surgery in CF patients should include at least an uncinectomy, middle meatal antrostomy, and anterior ethmoidectomy. In most cases, the uncinate process will already be thinned and medially displaced, and in many cases, a pseudomucocele may be present within the maxillary sinus. Uncinectomy and removal of polyps will allow this pseudomucocele to drain and a large middle meatal antrostomy can be achieved endoscopically without the need for a Caldwell–Luc operation [41]. Anterior ethmoidectomy is also often required, whereas posterior ethmoidectomy and sphenoidotomy need only be performed when there is radiologic or endoscopic evidence of disease in these sinuses. As the frontal sinuses are generally underdeveloped, routine exploration of the frontal recess is unnecessary, but should be performed when disease is present in that location. We do not routinely resect the caudal middle turbinate; however, this may be performed as advocated by others [44].

Nasal polyp recurrence after surgery is common and reported in 13–89% of patients [2, 3, 49], depending on the length of follow-up and definition of recurrence. The extent of disease as indicated by Lund–Mackay scores from the preoperative CT scan has been reported to be a predictor of the risk of requiring further surgery in CF [2]. Importantly, even though polyps may recur in up to 32% of patients, the extent of polyps may be significantly better in the preoperative state [27, 44]. The median time interval to repeat surgery is approximately 4 years [49], thus studies with follow-up periods of less than this may not accurately report recurrence rates.

17.7.3 Novel Treatments

17.7.3.1 Dornase Alfa

Large amounts of DNA from degenerating neutrophils in CF are important contributors to the high viscosity of nasal secretions. Dornase alfa (recombinant human deoxyribonuclease) cleaves extracellular DNA and is shown to reduce sputum viscosity and improve lung function in CF (36). Intranasal use of dornase alfa postoperatively is shown in a randomized double blind trial to improve symptoms and endoscopic scores in CF patients compared to placebo treatment [7].

17.7.3.2 Ibuprofen

Upregulation of cyclooxygenase (COX) enzymes 1 (COX-1) and 2 (COX-2) has been reported in the nasal

polyps of patients with CF [36]. High-dose ibuprofen therapy can slow the decline in lung function in children with CF [30]. Recently, high-dose ibuprofen therapy has also been found to reduce the size of polyps in CF children [33]. Further data are awaited from controlled studies.

17.7.3.3 Antibiofilm Therapies

Pseudomonas biofilm formation in CF patients may be a significant contributor to sinonasal inflammation. Novel medications such as quorum sensing blockers and other antibiofilm therapies may contribute to our future management. Detergents, such as baby shampoo, have been reported to possess antibiofilm forming properties when used in irrigations at 1% [5].

17.7.4 Management of Nasal Polyps Prior to Lung Transplantation

Management of sinonasal disease is an important consideration in CF patients before and after lung transplant. *P. aeruginosa* infections are a serious consideration in postlung transplant patients, and the nose and paranasal sinuses are considered to be the reservoir for these infections [17]. Thus, several authors have described protocols that involve endoscopic sinus surgery, followed by various regimes of intrasinus tobramycin prior to transplant [11, 32]. It is unclear if such regimes improve outcomes or not.

17.8 Conclusion

Nasal polyps are common in children and adults with CF. Initial treatment in most patients consists of management with nasal irrigations and topical steroids; however, the treatment of large or persistent polyps may eventually require surgery to improve nasal airway and quality of life. When performed by an experienced endoscopic surgeon in conjunction with anesthesiologists and pulmonologists familiar with CF patients, surgery should be a safe undertaking. Further advances in our understanding of the pathophysiology of polyps in CF may allow the development of newer medical treatments, which may further improve patient outcomes.

Take Home Pearls

- Conservative management with nasal irrigations and topical steroids constitutes the first-line management of nasal polyposis in CF.
- When surgery is performed, at a minimum this should entail nasal polypectomy, uncinectomy, middle meatal antrostomy, and anterior ethmoidectomy. There is no known benefit to performing more extensive surgery in the absence of radiological evidence of inflammation in the posterior ethmoids, sphenoid, or frontal sinuses; however, if these areas are diseased, they should also be addressed at the time of surgery.
- Adequate postoperative medical therapy is essential to prevent early recurrence of nasal polyps or rhinosinusitis. In the future, improvements in our understanding of the pathophysiology of polyps in CF may allow for the development of new treatments, which may improve patient outcomes.

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Nasal Polyposis in Children: A Differential Diagnosis and Algorithm

18

Nick S. Jones

Core Messages

- The aetiology of many paediatric nasal polyps is not known; however, it is vital to make a diagnosis in order to help patients wherever possible.
- The term "a nasal polyp" is not a diagnosis but a sign of inflammation of the lining of the nose that can be due to a range of significant diseases.
- The main differential diagnoses are an antrochoanal polyp, cystic fibrosis, primary ciliary dyskinesia, immunodeficiency, chronic infection, allergic aspergillosis, inverted papilloma, haemangioma, angiofibroma, encephalocoele, a nasal glioma or malignancy.
- Antrochoanal polyps result from mucosal retention cysts in the maxillary sinus that have prolapsed either through the infundibulum or accessory ostia. The best way of reducing the chance of them recurring is to remove the mucosa around their base so that scar tissue forms and they do not recur.
- The management of paediatric polyposis is often disappointing because apart from those with an antrochoanal polyp, the recurrence rate is high.

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18.1 Introduction

Nasal obstruction and discharge are common in children [28], but nasal polyposis is uncommon. Most paediatric nasal polyps appear to be the result of inflammation. Approximately a third have a unilateral antrochoanal polyp [18, 57], another third have polyps secondary to the infective process that is associated with the mucus retention that occurs in cystic fibrosis (CF) [4, 57], and the remainder are associated with a range of inflammatory conditions, although many remain idiopathic. The aetiology of paediatric polyposis was idiopathic in 55% of one series [65], while in another series 70% had CF [66], so the referral pattern may influence the relative incidence of conditions reported in patient groups.

18.2 Antrochoanal Polyp

An antrochoanal polyp originates from inflammation within the maxillary antrum [38]. Macroscopically, it is composed of a cystic part that fills the maxillary sinus and a solid part that has prolapsed into the nasal airway. The interstitium is oedematous, but the eosinophilia that is seen in most other inflammatory polyps is absent. Many appear to originate from a mucus retention cyst that expands until it prolapses through the maxillary ostium or an accessory ostium to extend into the nasopharynx. The fluid content is similar to mucosal retention cysts [5]. There is a higher rate of antrochoanal polyps in children with chronic rhinosinusitis [72] and mucous gland obstruction may be a part of the pathogenesis of antrochoanal polyps. Evidence of atopy or a predisposition to type I hypersensitivity

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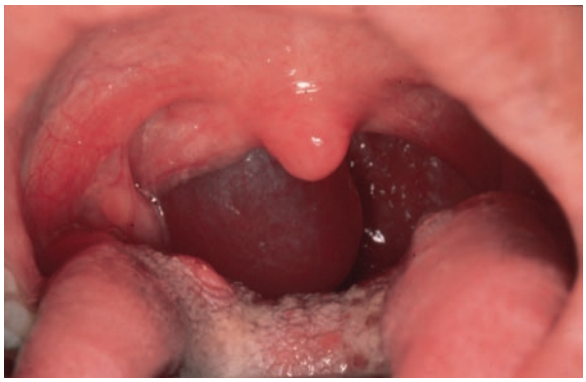

Fig. 18.1 An antrochoanal polyp that has prolapsed into the oropharynx

(skin prick test positive or a raised IgE) appears to be prevalent in a small minority of patients with unilateral polyps. However, this does not seem to play a role in the pathogenesis of most paediatric patients with unilateral nasal polyps [57]. Only two bilateral cases have been reported in the literature [3, 41].

A large, single nasal polyp can be seen, which may be visible at the back of the oropharynx (Fig. 18.1). CT shows a uniform hypoattenuating mass, occasionally with some remaining air in the roof of the sinus (Fig. 18.2).

The best way to minimize the likelihood of recurrence is to remove the whole base of an antrochoanal polyp. Simple avulsion is associated with a high recurrence rate. Historically, avulsion or a Caldwell–Luc approach was used to remove an antrochoanal polyp [57], but the frequency of post-operative facial pain has made this unpopular. With the use of the endoscope it is possible to not only open the maxillary sinus, but to visualize the base of the polyp using a 45, 70 or 120° endoscope [54]. A range of curved instruments, including the Heuwieser antrum grasping forceps, allow the whole base of the polyp to be removed, thereby reducing the chance of recurrence. If the polyp is based on the anterior wall, a large maxillary sinusotomy, a range of curved grasping forceps and perseverance are required. Some authors have used powered instruments [24], while others have recommended the combined use of the endoscope and the transcanine approach [34], although it is important to avoid damaging the roots of growing teeth in children. Sometimes an antrochoanal polyp is so large that the bulk of it has to be delivered transorally.

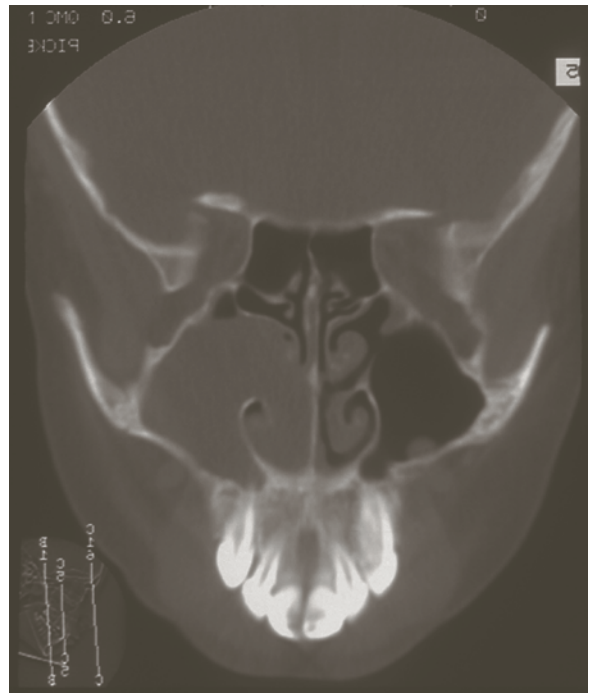

Fig. 18.2 A coronal CT scan showing a right antrochoanal polyp. Note the air above the convex surface of the polyp within the maxillary antrum showing that this is the top of a mucous retention cyst that has prolapsed into the nasal airway

The sphenochoanal polyp is rarer [35] and its stalk comes out of the sphenoid ostium.

18.3 Cystic Fibrosis

Nasal polyps as a sole presenting variant of CF are rare [67]. Patients are more likely to present with pneumonia, pancreatic insufficiency, meconium ileus, rectal prolapse, biliary cirrhosis or portal hypertension. Nevertheless, it is important to exclude CF in a child with nasal polyps. In adults, a search for the evidence of CF mutations in people with severe polyposis has also been unfruitful [26]. The prevalence of nasal polyps in CF varies between 6 and 48% [22, 44] and they typically develop after the age of 5 and before 20 [19].

Toss et al. [64] compared 11 CF polyps to 102 non-CF polyps and found no morphological differences between the two groups. This suggests similarities in the underlying mechanism of pathogenesis in CF and non-CF nasal polyps.

Eosinophils are rare but mast cells are found in abundance [21]. Therefore, histology cannot make the diagnosis. The key to making the diagnosis is the pilocarpine iontophoresis sweat test supported by genetic testing.

Screening of neonates can be done looking for the ΔF508 gene, although there are many others (see below). Alternatively, neonates can be tested for a raised level of immunoreactive serum trypsinogen.

CF is the most common monogenic recessive disease affecting people of Northern European extraction, occurring in approximately 1 in 2,500 live births [71]. The gene occurs in 1 in 20 to 1 in 25 of the population [25]. A wide range of clinical phenotypes are associated with mutations in the CF transmembrane conductance regulator (CFTR) gene.

Patients with CF have abnormal chloride transport across the apical cell membrane of epithelial cells. This results from a defective small conductance chloride channel regulated by cyclic AMP. The disease is caused by mutations in a gene located on chromosome 7 (7q31), which codes for the chloride channel protein.

The majority of patients with CF present in childhood with characteristic features including meconium ileus, recurrent chest infections, pancreatic insufficiency, failure to thrive and high sweat electrolyte concentrations. There is, however, great variability in the presentation.

The most common cystic fibrotic genotype is homozygosity for ΔF508, and these patients have the classic form of the disease, but nearly 1,000 mutations have been found [52, 53]. The "mild" mutations reported, such as R117H, R347P and R334W, are usually missense mutations compatible with the production of an altered CFTR protein with some function. Some uncommon mutations include R553X, G551D, G542X, G85E, 621+1, R1283M and W1282X. While the main problem is the lack of migration of the CFTR membrane protein, an increase in the number of open sodium channels has been described as having more ATPase-dependent sodium/potassium pumps. This leads to an increase in sodium absorption from extracellular fluid with an increase in mucus viscosity.

The main distinguishing feature of the sinusitis that occurs in CF is the range of organisms that are found and these include *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The main symptoms are nasal obstruction, mucopurulent secretions and headache.

Medical treatment has a limited role in sinusitis secondary to CF. One study showed clinical improvement in a third of patients [8]. A prospective, randomized, double-blind trial showed that topical betamethasone nasal drops produced a significant reduction in polyp size in adults [20], but the steroid profile of these drops means that they are unsuitable for children because of their effect on the hypothalamic–pituitary–adrenal axis. The benefit that oral steroids can produce stop as soon as they are discontinued [15]. Macrolide antibiotics have anti-inflammatory effects on nasal polyps and they benefit in the management of chronic rhinosinusitis and may help in CF [27, 73]. However, the evidence that it makes a significant clinical difference is still lacking (Fig. 18.3). For the lower respiratory tract, aggressive antibiotic therapy is instigated in order to limit the damage done by repeated infections [23]. The frequency of colonization of the lower respiratory tract with *Pseudomonas* is higher in cystic fibrotics with nasal polyps than those without, but it has not been found to alter patients' morbidity [22].

The rate of recurrence after surgery is much higher where a simple endoscopic polypectomy has been done when compared to ethmoidectomy [8, 10, 11, 58, 60]. However, even after a radical ethmodectomy in CF, more than 40% of patients have symptomatic recurrent disease after a mean of 3 years [13, 29, 43, 58, 66, 74]. As *Pseudomonas* is often present, Davidson et al. [14] recommended regular vigorous nasal irrigation to wash away the tenaceous secretions followed

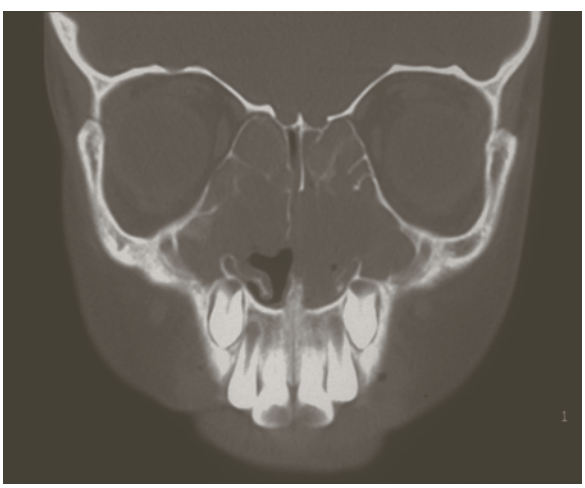

Fig. 18.3 Typical features of a CT scan in cystic fibrosis with complete opacification of the sinuses and a loss of the bony landmarks around the middle meatus and ethmoid air cells

once daily by topical tobramycin. There are some encouraging reports of the use of local irrigation with tobramycin or aminoglycosides, but a prospective study is needed to validate these observations [30, 50]. Recombinant deoxyribonuclease I or dornase alfa has been given to the lower respiratory tract in CF in order to break down the extracellular DNA, which is known to increase mucus viscosity and may also have a role in reducing the need for revision surgery [51]. One small study has suggested that long, high doses of ibuprofen may help some children's nasal polyps to resolve [36]. It is vital that patients with CF have a rigorous preoperative regime of physiotherapy and antibiotics in order to reduce the risk of a serious chest infection and atelectasis.

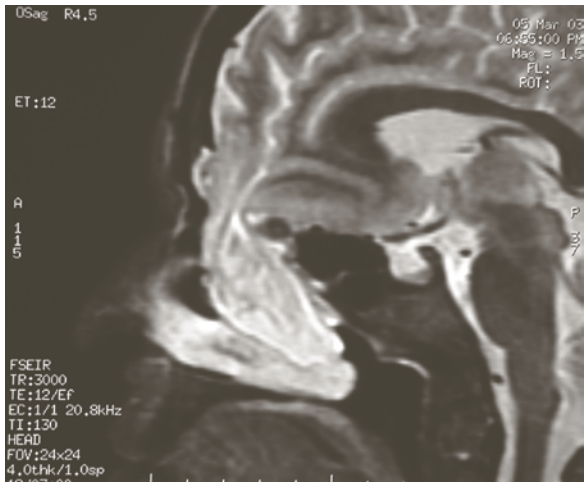

Fig. 18.5 A coronal MRI scan of a right-sided meningocele seen on physical exam in Fig. 18.4 (Courtesy of Metin Önerci)

18.4 Encephaloceles or Meningoencephalocele

Encephaloceles may be congenital in origin and represent a primary anomaly of the neural tube and its skeletal cover [42, 56]. Outpatient nasendoscopy and both a high-resolution coronal CT scan and magnetic resonance imaging scan delineate the extent of the skull base defect and its content (Figs. 18.4 and 18.5). The surgical technique is similar to that described previously for the treatment of CSF rhinorrhea [39]. The neck of the encephalocoele is identified and any overlying mucosa is removed. Difficulties can arise as the sac has usually become distended to the extent that the mucosa is very thin and not distinguishable from the dura. If the sac has ballooned out to the extent that it limits access and the visibility to define its neck and the extent of the herniation, the sac can be incised in order to deflate it. It is then possible to resect the sac up to the site of the defect. The encephalocoele is then excised and the edges of the bony defect are freshened. Either a piece of turbinate mucosa with attached turbinate bone is used as a composite underlay graft to seal the defect, or a conchal cartilage underlay graft is employed with a turbinate mucosal graft. In the sphenoid a fascia lata graft supported by a fat graft is used.

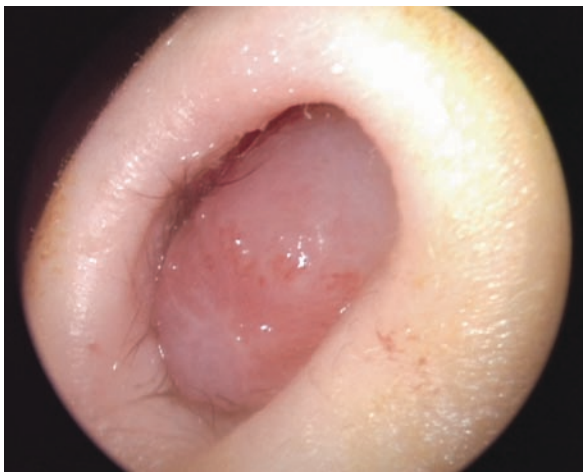

Fig. 18.4 A right meningocele visible at nasal vestibule (Courtesy of Metin Önerci)

18.5 Idiopathic Nasal Polyposis

In adults there is a well-recognized association between late onset asthma and nasal polyps. In children few series report a relationship except one study in which 50% of paediatric patients with nasal polyps had coexisting asthma and 10% had aspirin intolerance [46]. There appears to be a genetic component as in this series half the patients had a family history of nasal polyposis and/or asthma. In another study from France of 26 cases of idiopathic nasal polyposis, 50% had a family history of nasal polyposis or asthma [69]. There is no published evidence base for the management of these polyps, but if there are purulent secretions, a trial of macrolide antibiotics can be given, and whether there is evidence of infection or not, topical nasal steroids can be tried.

18.6 Primary Ciliary Dyskinesia (PCD)

Unlike CF, it is not uncommon for PCD to initially present with nasal symptoms. A persistent unrelenting nasal discharge without any symptom free intervals is typical. If grommets are inserted, a persistent discharge through the lumen of the grommet is a typical feature of this condition. The clinician should suspect a disorder of mucociliary clearance in a patient who has both rhinosinusitis and bronchiectasis, an individual with purulent rhinosinusitis who repeatedly fails to respond to medical treatment, or if the nasal airway is filled with tenaceous secretions. A significant proportion of patients with PCD have nasal polyps secondary to their sinus infection. It is well recognized that adenoid hypertrophy and allergic rhinitis are common in children and that recurrent upper respiratory tract infections are a fact of life causing symptoms associated with rhinosinusitis of rhinorrhea, nasal obstruction, mouth breathing, hyponasal speech and snoring. Most children grow out of adenoid hypertrophy and recurrent colds by the age of 8–10 and this means that the main treatment strategy should, therefore, be conservative and not surgical. An explanation to anxious parents, simple non-invasive measures such as teaching nose-blowing, the use of saline sprays or a trial of allergen avoidance and age-appropriate topical nasal anti-inflammatory sprays should be tried before surgery is even contemplated. However, if there are no periods when the child is symptom-free, PCD should be excluded. A useful screening test in the older child is the saccharine clearance test [37].

18.7 Saccharin Test

This involves the placement of a 1 mm diameter or quarter fragment of a saccharine tablet just behind the anterior end of the inferior turbinate or nasal septum, behind the area of slow anterior clearance [2], and the patient is then asked to sit quietly with his or her head forward, not to sniff, sneeze, eat or drink. The time taken from the placement of the tablet to the first perception of the sweet taste is the saccharin clearance time. The saccharin dissolves in the mucus layer and presumably the periciliary fluid layer and is transported to the nasopharynx and the base of the tongue. The average saccharin clearance time in a population free from nasal disease would be between 7 and 15 min. From these data, it is likely that patients who have a saccharin clearance time greater than 20 min have disturbed nasal mucociliary transport; but in PCD, the clearance time is greater than 60 min. In these patients, it is necessary to confirm their ability to taste saccharin.

When using the saccharin clearance test, it must be taken in conjunction with patients' symptoms and a proper examination of the nasal mucosa.

18.8 Ciliary Beat Frequency

Ciliary beat frequency can be measured by studying nasal brushings obtained with a 2-mm nylon brush. Ciliary beat can be measured using a photosensitive cell that converts the reflections of light from beating cilia into an electric current, which is displayed on an oscilloscope via an amplifier. The normal beat frequency of cilia is around 10–15 beats per second. Several other methods of studying mucociliary transport have been described such as gamma scintigraphy and tracking intranasal radioisotopic particles**.**

In Kartagener's syndrome where the patient has dextrocardia, sinusitis and bronchiectasis, there is an absence of the dynein arms on the nine peripheral microtubules. These individuals have only 40% of their ciliated cells working and also lack coordination or metachronicity [45, 68]. In PCD, impaired mucociliary clearance has been shown to be due to structural defects of the ciliary axoneme [1, 17, 62, 63]. In Young's syndrome (obstructive azoospermia with recurrent sinobronchial disease) there is a disorganization of cilial orientation, which is more pronounced at the cilial tip, but the other features of cilia are normal. Nasal acilia (Rothmund–Thomson) syndrome is an isolated absence of cilia in the nasal mucosa [16].

18.9 Electron Microscopy

Electron micrographs of transversely sectioned cilia can examine the incidence of compound cilia, central and peripheral microtubule defects, the numbers of inner and outer dynein arms per cilium and ciliary orientation. The ciliary beat axis is perpendicular to a line

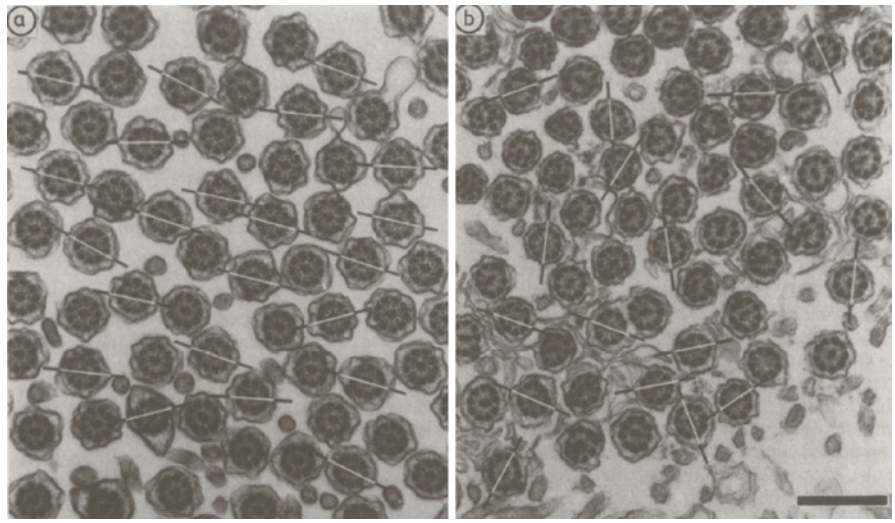

Fig. 18.6 An electron micrograph of transversely sectioned cilia showing normal orientation on the left and abnormal on the right

drawn through the centres of the two central microtubules. In a group of cilia sectioned axially and displayed on an electronmicrograph, the angle subtended by each cilia can be measured and the mean ciliary angle can be calculated. From this, the ciliary deviation can be calculated that is the standard deviation of the ciliary angle for the cilia sectioned can be determined. In normal patients the ciliary angle is 14° (Fig. 18.6) and at the tip the ciliary deviation is 4°. In cilia that show disorganization, this may be more marked at the cilial tip than at the base, as has been demonstrated in Young's syndrome.

The biopsy of nasal cilia is straightforward, but the equipment required to measure ciliary beat frequency and measure ciliary angles is complex and expensive and will only be available in a few centres. A complicating factor in making the diagnosis is that *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Pseudomonas* produce specific toxins that disrupt epithelial cells with loss of a confluent cilial field. Neutrophils that gather at the sites of purulent infection produce an elastase that is directly toxic to respiratory epithelium. Viruses responsible for the common cold also disrupt the ciliated cell's microtubules. Therefore to make the diagnosis, it is important to obtain a sample of healthy ciliated mucosa or any infection may produce a false positive result. When the paranasal sinuses remain infected in a child, this may only be possible by obtaining a biopsy of tracheal mucosa.

18.10 Immunodeficiency

In children with purulent secretions, with or without polyps, who do not respond to conservative management or who repeatedly fail to improve even temporarily with medical management, it is worth considering whether there is an immunological defect. The majority of children with an immunodeficiency who have severe purulent sinusitis with nasal polyps have inadequate humoral defences rather than cell-mediated problems [47]. As many immunodeficiency diseases are hereditary, it is worth asking about first degree relatives, or whether the patient has had recurrent pneumonias, urinary tract infections, cellulitis, candidiasis, chronic diarrhoea or failure to thrive. In one study, 56% of patients refractory to treatment were found to have reduced IgG subclass levels or a poor response to pneumococcal antigen [59]. Over 2 years of age, the antibody's response to pneumococcal polysaccharide provides more information about immunity. The commonest immunodeficiency due to a lack of antibodies is common variable immunodeficiency (CVID) where there is a reduction in IgG subclasses, although the number of B lymphocytes is usually normal. The incidence of CVID has two peaks, one in the first 5 years of life and again in the second decade. Antibody deficiencies are the commonest primary immunodeficiency and are also most likely to present with recurrent ENT infections. In X-linked agammaglobulinaemia, disorders of IgG subclass deficiency and CVID, treatment

with immunoglobulins may be effective where antibiotics on their own are not [9]. Prolonged courses of antibiotics with anaerobic cover are needed such as amoxycillin with clavulanic acid, cefuroxime axetil or cefixime. Measurements of CD4 lymphocytes and neutrophil function tests occasionally uncover other abnormalities that may present with recurrent unresponsive sinusitis. Primary defects of cell-mediated immunity, neutrophil function, or complement activity are relatively rare, and while ENT infections may occur in these diseases, they are more likely to present with features outside the upper respiratory tract.

The commoner immunodeficiencies are easy to exclude with a simple panel of blood tests. Where these are normal, but the clinical suspicion of immunodeficiency remains, further tests may be performed, but at this stage liaison with an immunologist is recommended.

Risk factors for human immunodeficiency virus (HIV) infection and a drug history including the use of steroids and second-line anti-rheumatic drugs should be sought. A detailed family history should be elicited, as many of the primary immunodeficiency disorders are hereditary (e.g. X-linked agammaglobulinaemia) or familial (e.g. common variable immune deficiency).

It is essential that the differential white cell count is examined closely looking for the following features that can predispose to infection. Neutropaenia is not uncommon and, if persistent, may contribute to infection. The lymphocyte count is normal in many immunodeficiencies, but can be reduced in HIV and certain rare primary syndromes such as severe combined immune deficiency. It is important that the "normal values" used as reference ranges are age-specific for the patient; remember that the normal lymphocyte count in an infant should be almost double that of an adult. Reduced immunoglobulin levels (IgG, IgA, or IgM) characterise the majority of primary antibody deficiencies. Selective IgA deficiency is surprisingly common, occurring in approximately 1 in 500 caucasians [7, 55]. Patients with CVID will usually have low levels of IgG and IgA and often have recurrent pyogenic upper respiratory tract infections related to *Pneumococcus*, *Streptococcus* and *Haemophilus* [12, 70].

If specific antibody levels are low to *Haemophilus influenzae* type b (Hib), *Pneumococcus* and tetanus toxoid, the patient should be vaccinated and blood taken for specific IgG in 3–4 weeks. An adequate response to all three vaccines excludes a significant humoral immunodeficiency. An abnormal response needs to be discussed with an immunologist.

Second-line immune function tests include nitrobluetetrazolium reduction test, complement deficiencies, tests of cell-mediated immunity, lymphoproliferative disorders and therapy with certain drugs (e.g. steroids).

First-line investigations:

- Microbial samples for cultures
- Full blood count, with differential white cell count
- Immunoglobulins
  - IgG, IgA, IgM
    Vaccine-specific IgG
  - Tetanus, Hib, *Pneumococcus*
    U&E, LFT, fasting plasma glucose
    HIV test

18.11 Allergic Aspergillosis

Allergic fungal sinusitis is a non-invasive disorder, seen in immunocompetent individuals. The criteria for diagnosis of this condition have been revised several times. However, most authors agree on the following: the presence in patients with chronic rhinosinusitis (confirmed by CT scan) of characteristic allergic mucin containing clusters of eosinophils and Charcot Leyden crystals, the presence of fungal organisms within that mucin detectable on staining or culture, the presence of type 1 (IgE mediated) hypersensitivity to fungi and nasal polyposis (unilateral or bilateral) [32]. *Aspergillus* species are believed to be the predominant cause of allergic fungal sinusitis. More recent series suggest that various dermatiaceous (brown-pigmented) environmental moulds, including *Alternaria*, *Bipolaris*, *Cladosporium*, *Curvularia* and *Drechslera* species, can also be responsible. This condition occurs in immunocompetent people with chronic relapsing rhinosinusitis, unresponsive to antibiotics, antihistamines or corticosteroids. Although patients do not have underlying immunodeficiencies, 50–70% are atopic. Cases of allergic fungal sinusitis have been described from different parts of the world, but the condition appears to be most prevalent in the warm humid areas such as the Indian subcontinent, Australasia and the southern United States. There are no unique pathognomonic symptoms and patients often present with

unilateral nasal polyposis and thick yellow–green nasal or sinus mucus. The nasal polyposis can be unilateral or bilateral and may form an expansive mass that causes bone necrosis of the thin walls of the sinuses. Should the lamina papyracea of the ethmoid bone be affected, it can expand the lamina papyracea and cause proptosis. Polypoid material can also push the nasal septum into the contralateral airway. CT scans often reveal a characteristic serpiginous sinus opacification of more than one sinus, mucosal thickening and erosion of bone, but this does not represent tissue invasion. The treatment of allergic fungal sinusitis includes surgical debridement to remove polyps and the allergic mucin. Adjunctive medical management is also required because not all the fungal elements can be removed. In studies, post-operative systemic corticosteroids reduced recurrence of disease, but there is a high recurrence rate [31, 33]. Allergic aspergillosis has been likened to allergic bronchopulmonary aspergillosis; in other words, it is a systemic reaction to an allergen in the respiratory tract. Oral itraconazole has been studied in a randomized controlled trial in the pulmonary form of allergic fungal sinusitis, allergic bronchopulmonary aspergillosis and has been shown to be effective [61]. In allergic fungal sinusitis there have been anecdotal reports of the use of post-operative itraconozole [6, 48, 49] and it was found that this regime may reduce the need for revision surgery.

There is no published evidence that topical antifungal treatment is of benefit. Immunotherapy has been advocated.

18.12 Tumours

Unilateral nasal polyps require a CT scan that will help in making a judgement about their extent and whether they have invaded local structures. Histology is required to determine whether the lesion is a haemangioma, nasal glioma, inverted papilloma, with or without a squamous cell carcinoma [40] or a rhabdomyosarcoma. An adolescent male with a unilateral magenta-coloured polyp should be suspected of having an angiofibroma (Fig. 18.7) and no biopsy should be taken because of the torrential bleeding it may cause. A MRI scan will demonstrate features that are pathopneumonic and diagnostic.

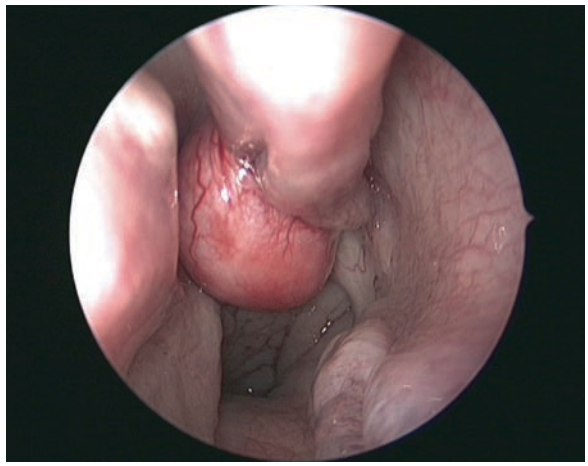

Fig. 18.7 An endoscopic view of a right-sided angiofibroma

In conclusion, nasal polyps in children are uncommon and best managed by clinicians with an interest in paediatric rhinological diseases.

Take Home Pearls

- Investigate all children with nasal polyps in order to try and make a diagnosis. Whilst many are idiopathic, in those where they are not it important to establish the cause.
- In removing an antrochoanal polyp it is important to remove their base otherwise they are likely to recur.
- Surgery is often resorted to in cystic fibrosis and primary ciliary dyskinesia but the results are dissapointing so do not raise the families expectations that surgery will be very helpful.

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Olfaction and Nasal Polyposis

19

Daniel B. Simmen and Nick S. Jones

Core Messages

- Smell plays an important role in the quality of life.
- Olfactory dysfunction is most commonly caused by nasal polyposis (NP).
- Smell is a sense that is all too often forgotten and may escape the notice of both surgeons and patients.
- Optimizing the medical treatment of mucosal disease is important in providing symptomatic relief either on its own or in conjunction with surgery.
- Routine preoperative smell testing is advisable in assessing patients prior to surgery.
- Subjective test methods are frequently used to assess olfaction because they can be done quickly and easily in a compliant patient – e.g., screening tests of olfaction.
- The exact size of the olfactory neuroepithelium in humans is still not well established.
- Olfactory function correlates with disease severity.
- Far less or no surgery is needed if medical treatment has been successful.
- In severe olfactory loss with CRS and NP, the objective measures of olfaction generally improve significantly after endoscopic sinus surgery, particularly if the olfactory cleft is widened.
- Impairment of smell may be the first sign of a recurrence of nasal disease and helps to motivate the patient to accept long-term medical treatment.

19.1 Introduction

Chronic rhinosinusitis (CRS) with nasal polyposis (NP) is the most common cause for olfactory impairment among patients presenting to an otolaryngologist [8]. Olfaction disorders are often not taken seriously because they are viewed as affecting the "lower senses" – those involved with the emotional life – instead of the "higher senses" that serve the intellect [41]. "Sense of smell? …. I never gave it a thought" – you do not normally give it a thought, but when you lose it, it is like being struck blind or deaf. Smell is a sense whose value seems to be appreciated only after it is lost. The sense of smell plays an important role in our interaction with the environment, and therefore, it can have a direct influence on human behaviour and can lead to a significant decrease in the quality of life [9, 15].

Although olfactory dysfunction is not universally associated with polyposis, patients with polyposis or a history of polypoid disease are more likely to suffer olfactory disability than those without [9, 42]. Rhinosinusitis with NP has the potential to impair olfaction in several ways. First, the inflammation of the nasal mucosa leads to a constriction of the airways,

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diminishing ortho- and retronasal airflow. This reduces the access of the odorant flow to the neuroepitheleum (conduction). Additionally, the composition of the mucus layers is altered and this can affect both access and binding of olfactory molecules to the receptor sites. Proteins secreted by diseased mucosa may alter or damage the function of the neuroepitheleum in a direct way. Ongoing inflammation may lead to histological changes that may prevent the regeneration of neuroepitheleum [8, 25]. Therefore, any medical and surgical treatment strategy for a rhinitis-induced olfactory disorder should focus on these issues in order to improve the quality of life for our patients.

19.1.1 Bullet Messages

- Nasal airflow has a strong impact on olfaction.
- Chronic nasal inflammation affects olfactory sensory neuron function.

19.2 Impaired Olfaction: An Important Primary Symptom in CRS with Nasal Polyposis

Unfortunately, surgeons often underestimate the extent of the importance of sense of smell to patients. It is a sense that is all too often forgotten and may escape the notice of both surgeons and patients [6]. The reason may be that the loss of this sense often creeps up on the patient slowly or because the patient does not recognize that this loss is responsible for his or her reduced enjoyment of food. In any case, the rewards for patients in preserving or restoring their sense of smell are enormous. The patient may mention any of a large array of symptoms in nasal disease, but it is important to focus on the patient's main complaints.

There are four primary symptoms that should always be addressed:

- Nasal obstruction
- Sense of smell
- Secretions or rhinorrhea
- Pain or pressure

It is important to rank these symptoms in their order of priority to the patient (the authors prefer to underline the patient's main complaint). This not only helps establish a diagnosis, but also focuses the surgeon's mind on how best to meet the patient's needs.

19.3 Clinical Olfactory Testing

In evaluating a patient who may have a possible olfactory disorder, clinicians have several tools at their disposal, including history, physical exam, olfactory testing and gustatory testing. With this, most of the information for the aetiology of the possible hyposmia can be obtained. Blood tests and diagnostic radiology do have a contributory role in the diagnosis of a smell disorder. Since the sense of olfaction can differentiate between thousands of different odorants, it is impossible to assess the whole sensory system with a few simple tests. Depending on the information that is needed, specific tests can be used to measure certain facets of the olfactory system. In rhinology, the *quantitative* assessment of smell is important because hyposmia or anosmia due to conductive olfactory loss is a frequent symptom of rhinological diseases such as severe allergic rhinitis or CRS [12, 24, 34]. *Qualitative* disorders, the so-called dysosmias (for example cacosmia or parosmia), are much more difficult to measure. Nevertheless, specific tests for the assessment of qualitative disorders have also been developed.

In addition, CRS can impair orthonasal as well as retronasal olfactory acuity. A significant proportion of patients have normal retronasal olfactory perception, but a significantly impaired orthonasal perception [27].

Discussion of olfactory test results will also remind the surgeon to counsel patients about hyposmia as a potential complication of nasal surgery [6] and to mention that patients should not expect their smell to return.

19.4 Taste and Smell

Taste and smell are independent, but it is often difficult to separate them in the patient's mind and on the basis of history alone. Patients with smell and/or taste deficits initially often complain of gustatory problems. For example, after a head injury a patient might report that a favourite tomato sauce no longer "tastes" right. However, rather than experiencing a problem with taste

per se, this patient is more likely experiencing an alteration in flavour perception. Because pure taste disorders are very rare, a simple taste test can be performed beforehand to rule out this specific diagnosis [19, 20].

19.5 Subjective Test Methods

Subjective test methods are frequently used to assess olfaction because they can be done quickly and easily in a compliant patient. Several simple chemosensory tests can be done in the primary physician's office, but in a specialized otolaryngology setup, a validated screening test with a printed form for documentation should be used. In the last decade, a few validated screening tests for olfaction have been developed worldwide and can be used by the physician or self-administered by the patient. To obtain an overview of the many different tests available, three different categories can be defined (Table 19.1).

Screening tests of olfaction are designed to detect whether or not a patient has an impaired sense of smell (identification test). These tests should be fast, reliable and cheap. A common example of such a test utilizes bottles containing odorants such as coffee, chocolate or perfume. Each nostril should be tested separately to ascertain whether the problem is unilateral or bilateral (lateralized screening). In recent years, more sophisticated tests have been developed that are both reliable and convenient to use. The "University of Pennsylvania smell identification test" (UPSIT) or "Smell Identification Test™" (Sensonics, Inc., Haddon Heights, NJ) is a well-known example. It is a scratch and sniff test with microencapsulated odorants, which is frequently used in the United States [10]. Other examples are the 12-item "Brief Smell Identification Test™" (Sensonics, Inc.,) [11], the Japanese odour stick identification test (OSIT), [17], the Scandinavian odour identification test (SOIT), [29] and the "smell diskettes" olfaction test (Novimed, Dietikon, Switzerland – www.smelldiskettes.com). This test presents eight odorants in reusable diskettes to the patient (Fig. 19.1a, b) along with a forced multiple-choice answer sheet that has pictorial representations [5, 36]. Another example is the "Sniffin' Sticks" test using a pen-like device for odour identification [26], and finally, a brief three-item smell identification test [23] that is validated and highly sensitive in identifying olfactory loss in patients with chemosensory complaints.

These test batteries are a common first-line investigation of olfactory disorder or can be used to document olfactory function before any form of nasal surgery. Each of those listed is validated (some with cultural biases) and well documented in the literature. However, with screening tests, one can only distinguish between normal and abnormal smell function. For further evaluation of smell dysfunction, a quantitative investigation is needed (Table 19.2).

Quantitative olfaction tests measure the threshold levels of certain odorants in order to quantify an impaired

Table 19.1 Subjective test methods to assess the sense of smell

Test method	Definition
Screening tests of olfaction	Fast evaluation of whether or not there is a smell disorder
Quantitative olfaction tests	Tests to quantify an existing smell disorder (threshold measurement)
Qualitative olfaction tests	Evaluation of qualitative smell disorders

Fig. 19.1 Screening test of olfaction with "Smell Diskettes" (**a**) and a forced multiple-choice answer sheet for the patient (**b**)

Fig. 19.1 (continued)

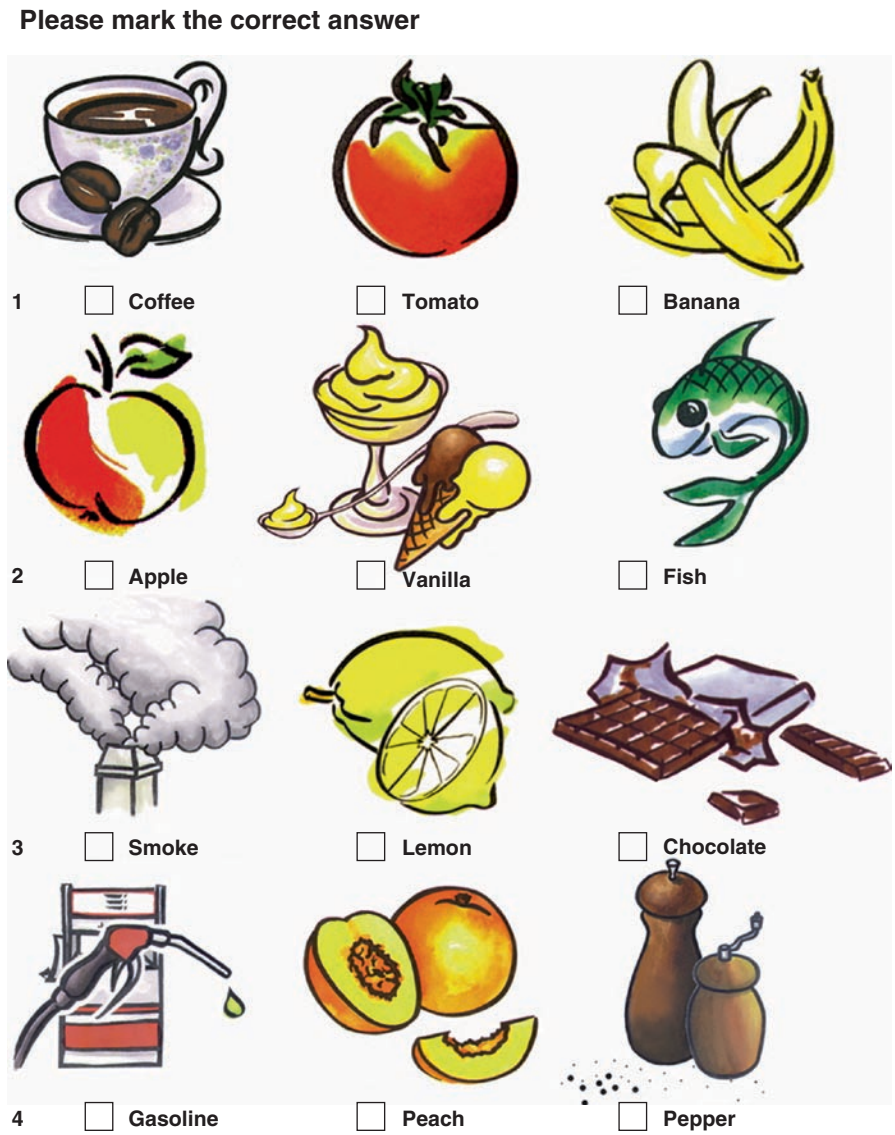

Table 19.2 Types of smell impairment

Quantitative olfactory dysfunction	
Normosmia	Normal sense of smell
Hyposmia	Diminished sense of smell
Hyperosmia	Enhanced odour sensitivity
Anosmia	Total loss of smell
Specific anosmia	Inability to perceive a certain odour
Qualitative olfactory dysfunction	
Parosmia	Aberrant odour perception Without odour stimulus: phantosmia With an odour stimulus: distortion

sense of smell. They are usually more time-consuming to perform, but are valuable in measuring the degree of hyposmia present. However, they are unable to determine the cause and provide prognostic information or therapeutic guidance. There are many threshold tests available today, with most of them using *n*-butanol as the odorant. Examples of such extended test kits are the connecticut test (CCCRC threshold test) [7]. The object is to find the weakest concentration of *n*-butanol that the patient can detect, starting with the weakest dilution. The "Sniffin' Sticks® threshold test" (Burghart Medizintechnik, Wedel, Germany) [22], the European Test of Olfactory Capabilities (ETOC), a cross-culturally

validated test [39] and the "Smell Threshold Test™" (Sensonics, Inc.) measure the threshold of phenyl-ethyl-alcohol [32]. These tests measure the olfactory performance separating anosmics from normosmics and also allow for an assessment of the degree of hyposmia. For every test, a different scoring system is used to determine the grade of hyposmia (mild, moderate and severe hyposmia or anosmia). Another accurate way of measuring smell thresholds is with an olfactometer. These machines are designed to present precise concentrations of odorants. An example of an olfactometer that is used to measure the threshold level of vanilla is shown in Fig. 19.2. Just as an audiogram is used to measure the hearing level, this computer-linked device is designed to measure the olfactory threshold for both sides separately. Currently, threshold olfactometers are mainly used in research projects and are not yet available for office use.

Although the aforementioned tests can provide useful information, they all have their limitations, especially when investigating children, people with cognitive impairment or people from different cultural backgrounds. The complexity of some tests, the price for extended smell-kits for threshold measurement and the time factor deter many physicians from routinely performing olfactory testing. Accordingly, comprehensive olfactory evaluation is still concentrated in specialized centres. To assess the primary symptom of olfaction in CRS, a screening test is adequate, but quantitative olfaction tests are needed to monitor the benefit of medical and/or surgical treatment.

Qualitative tests of olfaction are used to assess a wide range of qualitative smell disorders. These so-called "dysosmias" are difficult to measure because patients with dysosmias find it difficult to describe their altered sense of smell. Nevertheless, specific tests have been designed to assess some of these qualitative disorders. The ability to recognize certain odorants can be measured by identification tests. Discrimination tests assess the ability to distinguish between different odours. An example of such a test is the above mentioned "Sniffin' Sticks® extended test battery", which combines quantitative and qualitative measurement [22].

Fig. 19.2 Measurement of the threshold level of vanilla with an olfactometer

19.6 Trigeminal Nerve Assessment

In addition to olfactory epithelium, the nasal mucosa also contains trigeminal nerve endings. They are important in detecting tactile pressure, pain and temperature sensation. Trigeminal nerve function can be assessed by using special odorants with a trigeminal component such as amonia, mustard, menthol, capsaicin, vinegar and onion [19].

19.7 Objective Test Methods

The objective measurement of the sense of smell is difficult and relies on detecting changes in the central nervous system provoked by olfactory stimulants. It is the only way to assess olfaction in non-compliant patients or malingerers. A well-established method is olfactory evoked potentials [3, 21].

New techniques include functional imaging (functional magnetic resonance imaging, functional positron emission tomography), which allows the direct visualization of central changes caused by olfactory stimulants. These methods are currently used for scientific research, but also have the potential to become tools for routine clinical practice [16, 30, 38, 40].

19.7.1 Bullet Messages

- Smell testing is advisable in assessing patients prior to surgery.
- Although taste and smell are independent senses, their interdependence makes it difficult to separate them on the basis of history.
- A validated screening test with documented results is ideal.
- Quantitative olfaction tests measure the threshold levels of certain odorants in order to quantify an impaired sense of smell.

19.8 Nasal Airflow Patterns and Olfaction

Recent studies that have compared CT and MRI images of nasal anatomy and measures of olfaction in individual subjects have found a correlation between specific anatomical areas and performance on olfactory assessments. Anatomical changes in the olfactory region and the nasal valve area strongly affect airflow patterns and odorant transport through the olfactory region with effects on olfactory function [43].

The olfactory region of the nose is ventilated toward the end of inspiration, when air speed declines significantly, causing turbulence in the olfactory cleft between middle turbinate and septum (Fig. 19.3). During expiration the distribution of flow is much more even and the olfactory region is aerated early in and throughout the breathing cycle. The olfactory membrane is, therefore, not directly exposed to the high velocity airstream during inspiration, but rather to a much weaker "secondary flow" prolonging contact time of olfactory active particles with the sensing organ [37]. Modern technology using a nasal CT scan from an individual patient converting it into a 3D nasal model can be used to predict airflow and odorant transport and could become an important guide for the treatment in CRS with NP to optimise airflow and improve olfactory function [43].

19.8.1 Bullet Messages

- Orthonasal and retronasal airflow can reach the olfactory region.
- Ventilation of the olfactory cleft is important in maintaining olfactory function.

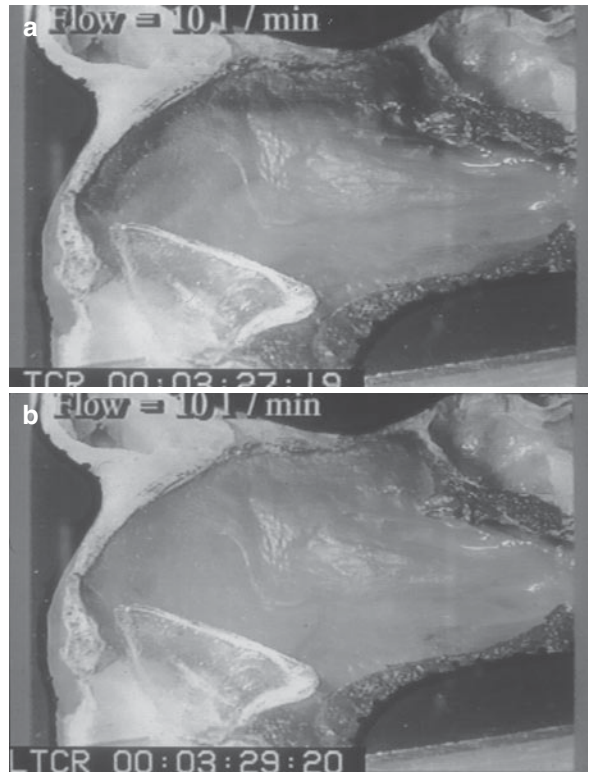

Fig. 19.3 After a steady state during inspiration (**a**) the olfactory region of the nose is only ventilated toward the end, when air speed declines significantly, causing turbulence in the olfactory cleft between middle turbinate and septum (**b**)

19.9 Location of the Olfactory Epithelium

Surprisingly, the exact size of the olfactory neuroepithelium in humans is still not well established. The distribution of olfactory mucosa and functional neuroepitheleum has been recently investigated by Leopold et al. with an electro-olfactogram and anatomically located biopsies. They concluded that the distribution of the olfactory mucosa is much more anterior on the lateral nasal wall and septum than was previously assumed [28].

The most likely area to find functional olfactory epitheleum is not only on the dorsoposterior region of the nasal septum and the superior turbinate, but also, surprisingly, more ventral and anterior on both septum and turbinates [14]. We still do not know the exact distribution of the functioning olfactory epithelium, so the surgeon should preserve potential olfactory mucosa at all cost (Fig. 19.4).

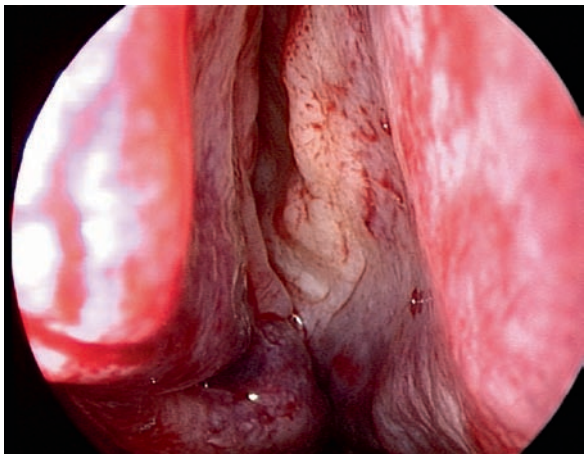

Fig. 19.4 We still do not know the exact distribution of functional olfactory epithelium, so the surgeon should preserve potential olfactory mucosa during surgery at all costs. Endoscopic view into the olfactory cleft in a patient with CRS and nasal polyposis

Volatile chemicals can be inhaled into the nasal cavity orthonasally through the nostrils or can enter retronasally from the mouth during swallowing [27, 35]. The airflow pattern defines the pathway into olfactory region where the molecules diffuse through the aqueous mucus layer to connect with the olfactory receptors. Then the signal is transported from the receptor neurons into the olfactory bulb and from there to the central nervous system.

19.9.1 Bullet Messages

- The exact site of the olfactory neuroepithelium in humans is still not well established.
- The distribution is much more anteriorly placed on the lateral nasal wall and septum than was previously assumed.
- There are differences between orthonasal and retronasal olfactory delivery of olfactory molecules and the functional reason for this is uncertain.

19.10 The Medical Management of Disordered Smell in CRS with Nasal Polyposis

Hyposmia and anosmia are common symptoms in patients with CRS and nasal polyps. The more extensive the disease, the more likely the patients' sense of smell will be reduced. Before embarking on surgery, a trial of medical treatment should take place. Even gross nasal polyps filling the nasal can sometimes be successfully managed by medical treatment alone. In any event, it is useful to try and obtain an estimate of the "olfactory reserve" that the patients have, so that they can be given an estimate as to how much, if any, improvement in their sense of smell they might obtain from surgery – followed by the maintenance of medical treatment.

Historically, medical treatment has often been started with local measures and then escalated. However, in someone with hyposmia and NP, it is often helpful to give maximum medical treatment with oral steroids to minimize any nasal symptoms and then try and maintain this situation with topical treatment. Systemic steroids should be avoided in those with a history of risk factors such as gastric ulceration, poorly controlled hypertension, diabetes, osteoporosis and psychosis among others. Patients should be warned of side effects, the most common being a change in mood, possibly with a disrupted sleep pattern, and stomach discomfort. Short courses are best to minimize any effect on the hypothalamic–pituitary–adrenal axis, and they are best taken in the morning when normal cortisol levels are highest. For patients with hyposmia or anosmia related to nasal polyps, oral steroids usually have a dramatic and gratifying result.

It needs to be stated that the term "nasal polyps" is not a diagnosis but a sign of diseased mucosa whose pathology can vary. The aetiology of CRS with or without nasal polyps is contentious [15] and does not usually appear to be the result of an unresolved acute sinusitis, so much so that the preface to a text on the subject started by saying "One of the most intriguing aspects of CRS is the growing appreciation that for most patients this is not an infectious disease" [13]. The treatment of idiopathic CRS with NP is largely empirical. Treatment is centred on systemic and topical steroids, with 12 studies showing significant benefit compared to three that showed none [15]. Systemic steroids appear to work well and while no placebo-controlled studies exist, some studies demonstrate a relationship between dose and response. There are no studies that have quantified the benefit of medical treatment on olfaction in nasal polyps. In one study, patients were treated with systemic steroids and topical steroids and were then randomized, so FESS was done on one side and the other remained untouched, and they were then given topical nasal steroids for a

further 12 months [4]. Their sense of smell was tested on each side separately. Surgery did not produce any added improvement although it helped nasal patency more, and a quarter required surgery on the un-operated side [4]. In a randomized study of patients with CRS and polyps who remained symptomatic after 6 weeks of intensive medical treatment and then went on to receive either surgery or medical treatment, both groups had an improvement in their symptoms at 6 and 12 months with the only difference being that the surgical group had a larger nasal volume [33]. In another randomized study, patients were either given oral steroids or endoscopic sinus surgery and both groups were given follow-up topical nasal steroids. At 6 and 12 months, both groups had an improvement in quality of life measures (SF-36), but the surgical group did better for nasal obstruction, sense of smell and polyp size at 6 months, but only for polyp size at 12 months [1]. The conclusion of EPOS[3] was that "In the majority of patients, appropriate medical treatment is as effective as surgical treatment. Sinus surgery should be reserved for patients who do not satisfactorily respond to medical treatment" [15].

19.11 Sinus Surgery and Olfaction in CRS with Nasal Polyposis

A patient whose sense of smell returns after oral steroids, only to rapidly deteriorate thereafter in spite of maintenance treatment with topical nasal steroids, may benefit from surgery. A patient with anosmia who had previous surgery is unlikely to regain any sense of smell if systemic steroids have not helped. This indicates that there is unlikely to be a useful reserve of functioning olfactory mucosa. However, a patient with anosmia who did not have previous surgery and did not respond to oral steroids may still regain his or her sense of smell after a fronto-ethmoidectomy and a gentle lateralizing of the middle turbinate. It is vital that the middle and superior turbinate are treated with meticulous care in these patients when surgery is done to open the olfactory cleft. We advise against suturing the middle turbinate to the septum as this closes the olfactory cleft. Lateralizing the middle turbinate after a fronto-ethmoidectomy may restrict direct endoscopic examination of the frontal recess after surgery, but it rarely causes stenosis if the mucosa in this area is preserved.

19.12 Tailor the Surgery to the Extent of the Problem

There is a price to be paid for extensive tissue removal. That price may be the loss of olfactory mucosa, frontonasal stenosis, altered sensation, dryness and an increased risk of violating the boundaries of the paranasal sinuses. Surgery is primarily aimed at improving ventilation of the sinuses and restoring paranasal clearance. Removal of tissue alone does not cure mucosal disease. After a trial of maximum medical treatment, including systemic and topical steroids, it is possible to assess the "olfactory reserve". This will indicate the olfactory potential as long as the olfactory mucosa is preserved and the olfactory cleft opened.

Overzealous trimming of mucosa and turbinates results in a non-physiological distribution of airflow and much less airflow passes into the olfactory cleft. Endoscopic sinus surgery can affect the nasal airflow pattern because the arched main stream of airflow passes the middle meatus with small eddy currents around the olfactory cleft. Surgery involving the middle meatus may significantly improve nasal airflow, especially in narrow and congested noses. Furthermore, a gentle lateralization of the middle turbinate after sinus surgery helps to open up the olfactory cleft and allows much better air–mucosa contact in this area, which may help olfaction (Fig. 19.5a, b) [8, 25, 37, 43].

19.12.1 *Bullet Messages*

- There is a price to be paid for extensive tissue removal, and this may be the removal of olfactory mucosa.
- Removal of tissue alone does not cure mucosal disease.
- Sinus surgery has the potential to produce an improvement in air–mucosa contact in the olfactory cleft, and therefore, help olfaction.
- Gentle lateralization of the middle turbinate after a fronto-ethmoidectomy helps the mechanical delivery of air to the olfactory area.

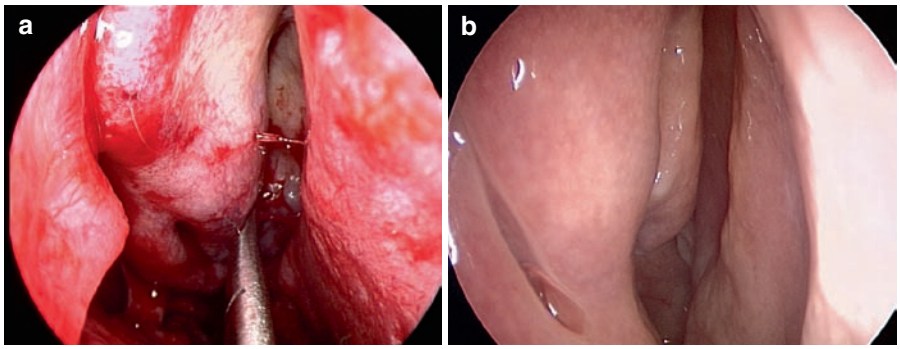

Fig. 19.5 Gentle lateralization of the middle turbinate after sinus surgery helps to open up the olfactory cleft (**a**), allowing a much better air–mucosa contact in this area, and therefore, can improve olfaction. Endoscopic view into the olfactory cleft after 6 months under medical treatment with topical steroids (**b**)

19.13 Impact of Endoscopic Sinus Surgery on Olfactory Function in CRS with Nasal Polyposis

There is strong suggestion from numerous articles in the literature that the degree of olfactory loss is correlated with disease severity. Severe loss is usually associated with the presence of NP [2]. In addition, patients with marked eosinophilia and aspirin intolerance experience a greater loss of their olfactory function [31]. Although many patients with Samter's triad often receive nasal surgery in part to improve the sense of smell, relatively little research has been done to investigate the postoperative outcome. Our clinical impression is that these patients' sense of smell is difficult to preserve for any length of time in spite of maximum surgery and medical treatment. Better understanding is needed here [15].

Although historically little objective sensory testing has been done to investigate the impact of CRS with NP and the outcome of endoscopic sinus surgery on olfactory function [9], studies that include a quantitative assessment of smell have recently been published [31]. The best improvements were obtained in patients with marked polyposis, eosinophilia and aspirin intolerance, although these patients started with worse pretreatment scores. Neither age, presence of allergy or asthma, nor the number of previous surgical interventions had a significant impact on the outcome of surgery in terms of olfactory function. Overall, in CRS with and without nasal polyps, only 1 out of 5 patients experienced a measurable improvement of olfactory function at 6–12 months after surgery. There is no current information about the long-term results and the impact of medical treatment in maintaining olfaction.

19.13.1 Bullet Messages

- Patients with polyposis and eosinophilia experience the greatest improvement in olfactory scores, perhaps because they start from a lower baseline.

19.14 Conclusions and Perspectives

On the basis of current reports, 1–2% of the American population below the age of 65 experience an impaired sense of smell and more than 200,000 people visit a physician each year seeking help with a smell disorder or related problems [18]. This illustrates the importance of being able to adequately assess patients' sense of smell.

Smell disorders are a common finding in patients with nasal disease. In one study, 10.3% of patients prior to nasal surgery had an altered sense of smell [6]. Routine preoperative smell tests are, therefore, an essential step to avoid a postoperative claim that surgery has been responsible for a pre-existing olfactory disorder.

Smell tests also help to provide data for comparison in studies auditing the outcome after treating nasal disease. Smell tests also help to focus both the patients' and the surgeons' attention to this aspect of their disease so that it has not been forgotten until it is too late. A patient's sense of smell is often a useful "barometer" in assessing the extent of his or her mucosal disease: if it declines, it may help motivate the patient to accept long-term medical treatment.

Take Home Pearls

- Olfaction is important and often underrated in a person's quality of life.
- Remove olfactory mucosa, including polyps in the olfactory cleft, and you may severely damage a patient's capacity to smell.
- A trial of oral steroids, unless they are contraindicated, will often disclose the "olfactory reserve".
- Opening up the olfactory cleft after a radical frontoethmoidectomy in someone with severe idiopathic polyposis, followed by topical medical treatment, will often have gratifying results as far as the patient's ability to smell is concerned.
- If you test your patient's sense of smell, it will help you to focus on it as a symptom that deserves to be addressed.

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New Areas for Investigation: Nitric Oxide

20

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Core Messages

- Nitric oxide (NO) has been implicated in the regulation of several physiological and pathological events.
- In the respiratory mucosa, NO synthases can be found mainly in ciliated epithelium.
- In addition to controlling ciliary beat frequency and providing antimicrobial activity, NO is implicated in the pathophysiology of nasal polyposis, including recruitment of inflammatory cells, inhibiting apotosis of eosinophils, disturbance of the cytoarchitecture leading to modifications of the extracellular matrix, and extravascular leakage with consequent edema.
- A better understanding of NO's role in pathological events is needed to direct appropriate diagnostic and therapeutic approaches aimed at the treatment of inflammatory disorders such as nasal polyposis.

20.1 Introduction

Several decades ago, nitric oxide (NO) was considered merely a noxious gas in the atmosphere. In 1980, Furchgott and Zawadzki [14] described endothelial-dependant smooth muscle relaxation, but it was not until 1987 that two independent groups identified the NO molecule as the mediator for smooth muscle relaxation [22, 48]. In 1989, Furchgott, Ignarro, and Murad were awarded the Nobel Prize for uncovering the role of NO as a signaling molecule in several homeostatic events. Since then, a growing body of research has shifted focus from NO's regulatory role in physiological functions to its contribution in pathological processes.

20.2 Nitric Oxide Synthesis and Metabolism

NO is endogenously produced from the amino acid L-arginine and oxygen (O_2), and catalyzed by a nitric oxide synthase (NOS), which uses electrons donated by NADPH. This reaction, known as the L-arginine-NO pathway, ultimately leads to the formation of NO and L-citrulline: one molecule of L-arginine forms one molecule of NO [1, 45] (Fig. 20.1). Once synthesized, NO acts as an intracellular or extracellular messenger. NO can act locally as an autacoid, paracrine messenger, or as a neurotransmitter, and also be transported in a stable, protected complex to affect distant sites. As a consequence of the multiple oxidation states available for nitrogen (from oxidation state +1 to +5), and because NO has an unstable chemical structure with an unpaired electron in its composition, NO is extremely reactive and does not persist for a long time in biological

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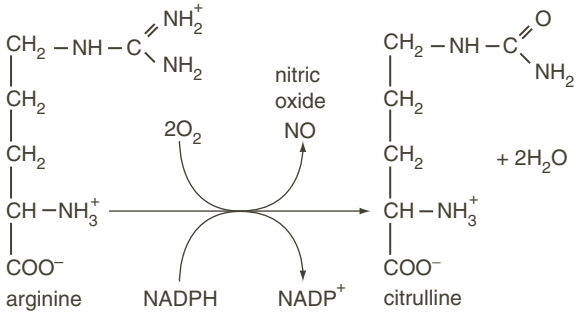

Fig. 20.1 NO is liberated from the metabolism of arginine to citruline by nitric oxide synthase

systems. Rather, NO is oxidized, reduced, or complexed with other molecules present in a determined microenvironment.

The modifications in the NO molecule may have biological consequences. First, NO reactivity can be modified so that NO can be transported from the site of production to the effector site. Second, local reactions with NO may inhibit or enhance its toxicity. The mode and rate of NO degeneration also vary within the gaseous and the aqueous phases. Whether NO exists in the gaseous or aqueous phase depends on the concentration of NO, its diffusibility, and the surrounding concentration of other bioreactants, such as metals and thiols. Due to NO's short half-life (0.1–5 s) and the lack of storage source of free NO, the concentration of NO in many tissues is dependent on a precisely regulated enzymatic system.

Three isoforms of NOS have been identified and classified as constitutive or inducible (Table 20.1). NOS-1 (nNOS) and NOS-3 (eNOS) are constitutively found in neurons and endothelial cells, respectively.

Table 20.1 Isoforms of nitric oxide synthase (NOS) in humans

	NOS-1	NOS-2	NOS-3
Cell source	Neurons	Hepatocytes, macrophages, airway epithelium cells	Endothelial cells
Inhibitors	L-NAME, L-NNMA	L-NAME, L-NNMA, L-NIL, aminoguanidine	L-NAME, L-NNMA
Ca^{2+} calmodullin dependence	Yes	No	Yes

NOS-2 (iNOS), primarily found in rodent macrophages, is classified as an inducible NOS because it is expressed in activated cells (e.g., macrophages, dendritic cells, NK cells, and hepatocytes) during infection or in response to inflammatory mediators such as toxins or proinflammatory cytokines. NO produced by NOS-2 is believed to act as an antimicrobial, increasing cytotoxicity and aiding in the inflammatory response. Though NOS-2 is classified as inducible, it is also constitutively present and active in normal human paranasal sinuses, making the traditional classification of the NOS isoforms not completely accurate [39].

Despite the flaws in the conventional NOS isoform classification system, NOS-1 and NOS-3 do have characteristics that are distinct from NOS-2. The molecular mechanisms that govern constitutive NOS activities are different from the mechanisms that govern inducible NOS activities. NOS-1 and NOS-3 are calcium- and calmodulin-dependant, and require intracellular calcium for activation. In response to certain neurotransmitter signals or vasoactive substances, the elevation of intracellular calcium and binding to calmodulin lead to the activation of preformed proteins that trigger the production of NO [8]. The activation of NOS-1 and NOS-3 is transient, working in a pulse-like signal to yield small amounts of NO.

On the other hand, NOS-2 is tightly bound to calmodulin. NOS-2's unusual binding to calmodulin and the role of intracellular calcium for this enzyme require further investigation. Once NOS-2 is present in a cell or tissue, large amounts of NO are produced. NO production mediated by NOS-2 does not seem to be controlled on an enzymatic level, but rather is dependent on the expression of the enzyme, and by the length of time the enzyme is present in a given cell or tissue. NOS-2 is produced primarily by de novo synthesis, and depends on the stability of the NOS-2 mRNA and proteins [33]. NOS-2 expression is stimulated by transcriptional factors, including nuclear factor-β (NF-β), and proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). Furthermore, glucocorticoids have shown to decrease NOS-2 expression in many organs in humans and rats [26, 29, 39]. In addition to the classical enzymatic pathways, NO can be produced through an alternative pathway involving the reduction of nitrite to nitrous acid, which ultimately leads to the formation of NO.

20.3 Biological Activities

NO is a free radical gas that modifies cell-signaling mechanisms directly or through its metabolites, thereby allowing it to be involved in a variety of vital biological functions, including antimicrobial activity, blood flow regulation, platelet function, neurotransmission, immunity, and inflammation control [7, 31, 45]. Most of the physiological and pathological effects are thought to be mediated by the NO derivatives rather than the NO molecule itself [18].

NO's direct actions can be mediated either by oxidation reactions (redox) or by altering the activity of DNA or proteins through covalent ligations. NO has a high affinity for binding to metals and a lower affinity for thiol-residue binding [56]. One example of an interaction with a metal-associated protein (metalloprotein) is the reaction with the heme group of guanylyl cyclase. NO binds to and stimulates guanylyl cyclase, which then converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). cGMP is responsible for the control of several protein kinases that are involved in neuronal transmission, inhibition of platelet aggregation, and smooth muscle relaxation. On the other hand, NO can inhibit some metalloproteins such as cytochrome P-450, cytochrome oxidase, and catalase. It is thought that NO can modulate oxidative and inflammatory processes by directly interacting with high-energy free radicals, inhibiting the peroxidation of proteins and lipids [18].

The indirect effects of NO are mediated through redox reactions with oxygen (O_2) and superoxide anions (O_2^-), producing reactive nitrogen oxides [16]. Dinitrogen trioxide (N_2O_3) and peroxynitrite ($ONOO^-$) are the most common examples of reactive nitrogen oxides. Both can induce nitrosative and oxidative reactions to trigger proinflammatory responses and cytotoxicity in the airway. These reactive nitrogen oxides can oxidize thiols and nitrate amino acids such as tyrosine and guanosine that cleave DNA or inactivate enzymes and other proteins involved in vital cellular functions such as the mitochondrial respiratory chain [18].

Although NO and its counterpart reactive nitrogen species may participate in pathophysiological events in a variety of inflammatory diseases, their precise role in inflammation remains unclear. Reactions of nitrogen oxides may be toxic or protective to the cell depending on the underlying condition and the nature of the insult. Under certain physiological conditions, NO can modulate vascular tone and platelet aggregation, down-regulate adhesion molecules to diminish leukocyte adhesion, and act as an antioxidant to protect cells against oxidant injuries. But, under some circumstances, nitrogen oxides are overproduced or have impaired clearance due to decreased redox status of the cells (e.g., decreased pool of thiol and metal), which leads to oxidative and nitrosative stresses with harmful effects. The homeostasis of NO depends on a fine cellular adjustment that involves gene activation, control of transcriptional factors, and enzyme regulation.

NO is involved in immune defense mechanisms. In vitro and in vivo studies show that NO contributes to innate immunity through bacteriostatic/bactericidal and antiviral effects, inhibiting protein and DNA synthesis and cell replication [21, 41]. NO also affects immune cells by regulating macrophage apoptosis, stimulating macrophage cytoplasmic motility, modulating leukocyte adhesion, and regulating inflammatory cell production of cytokines. Some of these antimicrobial effects can be explained by the activation of host defense mediators, like the increase in production of IFN-γ [10], inhibition of clonal expansion of Th1 but not Th2 cells [59], and promotion of T cell proliferation through activating DNA synthesis [13]. NO's function in both innate and adaptive immunity has opened new horizons in understanding the physiological and pathological role of NO in many inflammatory disorders.

20.4 Considerations of Nitric Oxide Measurement

The quantification of NO and its activity has been considered an important diagnostic tool and a surrogate marker for airway inflammation. Since exhaled NO was first described in 1991 [19], several authors have used different methods to quantify NO in the airways. Factors including ambient NO concentration, breath-hold time, nasal volume and nasal aerodynamics, as well as transnasal airflow interfere with the NO concentration measurement [2, 11]. Also, the normal levels of nasal NO measurements vary greatly among individuals. To standardize the quantification technique and minimize conflicting results seen in the

literature, the American Thoracic Society and the European Respiratory Society have published guidelines on NO measurement [2, 25].

The chemiluminescence technique is currently the preferred method of nasal NO measurement. NO chemiluminescence analyzers work by mixing NO with ozone, producing an activated NOx molecule, which in turn produces a light quantum. The light energy is then recorded, analyzed, and converted to proportional concentrations of NO present in the gas mixture. The minimum detectable concentration of NO is 1 part per billion (ppb).

Measurement of nasal NO requires generation of airflow through the nasal cavities. This can be achieved by inspiring or insufflating air via one nostril while the velum is closed or inspiring from one or both nostrils during breath holding. The complete closure of the pharynx by the velum is crucial to block air from the oral and lower airway, thereby restricting the air measurement to the nasal and paranasal cavities. The closure is obtained by asking the patient to exhale against a resistance or to hold his breath with the velum elevated. After a certain time, a constant transnasal flow produces a washout phase, followed by the establishment of a steady NO plateau. At this point, a sampling probe records the NO concentration. Nasal NO measurement can be taken during quiet exhalation, aspiration, breath holding, or even while humming (phonating the consonant "m"), with similar NO steady state plateaus [2, 25].

The NO output can be calculated by the product of transnasal flow rate and the measured NO concentration. Some studies have demonstrated that NO is relatively constant over a range of transnasal flow rates between 1 and 5 L/min and that nasal NO output is between 205 and 455 nL/min in healthy primates. At low transnasal flow rates (<1 L/min), NO may be absorbed by nasal tissues, reducing the calculated NO [12]. A target airflow rate of 3 L/min (50 mL/s) should be used when measuring nasal NO output, as this flow provides a steady plateau level of NO concentration in most patients within 20 s. This flow rate is also close to the physiologic range of transnasal flow in a resting adult human and provides a turbulent flow pattern that facilitates ventilation of the nasal cavity. If a steady plateau is not achieved at this flow rate, other flow rates (3–6 L/min) may be used to obtain a steady plateau NO concentration, as NO output is relatively stable in individual subjects over this flow range. It is recommended that each individual NO measurement be recorded with the precise airflow utilized [2]. As the transnasal flow does not evenly ventilate the cavities in the nose and paranasal sinuses, it is important to emphasize that the nasal NO output measured does not necessarily represent the NO produced by the nasal and sinus mucosa, but the release of NO that can be recorded by the equipment.

NO can also be indirectly quantified by measuring its metabolites, such as the products of redox reactions in the presence of oxygen (O_2), like nitrite (NO_2^-) and nitrate (NO_3^-), and the products yielded from reactions with superoxide anions (O_2^-), such as peroxynitrite ($ONOO^-$) and peroxynitrous acid (ONOOH). The disadvantage of measuring NO metabolites is that they do not reflect the concentration of NO in the tissue or the biological activities promoted by NO.

20.5 Nitric Oxide in Airway Physiology

Several studies have demonstrated that exhaled NO is mainly produced in the upper airways. Measurements in tracheostomized individuals show that most of the exhaled NO originates from the nasal region [36], and strong evidence suggests that NO is produced mainly in the paranasal sinuses rather than the mucosa of the nasal cavity [28, 38, 40, 57]. For instance, mammals like baboons that do not have paranasal sinuses have low levels of NO in their exhaled and nasal air [32]. In addition, maxillary sinuses seem to work as a reservoir for NO, and NO concentration measured in the exhaled air depends on the patency of the natural maxillary ostium [3].

NOS-3 is constitutively expressed in normal human turbinate mucosa and can be found in surface epithelium, vascular endothelium, and submucosal serous glands. NOS-3 expression is unchanged in the presence of inflammation. On the other hand, expression of the inducible NOS (NOS-2) is significantly upregulated in the setting of inflammation, such as allergic rhinitis and nasal polyposis [35]. NOS-2 expression is found mainly in inflammatory cells, in addition to surface epithelium, vessels, and glands [15, 62].

In ciliated respiratory cells, NO stimulates mucociliary transport and acts as a second messenger for several ciliostimulatory neurotransmitters [66]. Ciliary beat frequency (CBF) analysis performed on healthy

sinus mucosa biopsies has shown an increased baseline CBF proportional to increasing concentrations of L-arginine when incubated for longer than 30 min. Also, when these explants were incubated with the NOS inhibitor L-NAME (N^G-nitro-L-arginine methyl ester), the CBF increase caused by incubation with L-arginine was blocked. The counterpart inactive isomerer D-NAME did not change the effects caused by L-arginine, indicating that the CBF increase was mediated by NO. Another study using the NO synthase inhibitor N^G-monomethyl L-arginine (L-NNMA) in bovine bronchial ciliated cells showed a reduction in the CBF increase when prestimulated with isoproterenol, bradykinin, or substance P [23]. An in vivo and in vitro study using the administration of the substrate L-arginine or the NO donor sodium nitroprusside (SNP) increased mucociliary activity independent of cholinergic, β-adrenergic, or cyclooxygenase mediators [52]. Similarly, nebulized administration of SNP in healthy human volunteers showed an increase in nasal CBF and nasal blood flow. The vasodilation caused by the NO is not directly related to the stimulation of the CBF [53]. Evaluation of patients with either chronic rhinosinusitis (CRS) or recurrent lower airway infection has demonstrated that a low concentration of NO is associated with lower rates of CBF and longer saccharin transport time [34]. Overall, these data show that NO is involved in modulating ciliary beating activity.

Besides NO's effects on the upper airways, NO can also cause vasodilation and bronchodilation, modulating ventilation–perfusion and gas exchange in the lower airways [16]. In an intricate interaction between upper and lower airways, NO is produced and released from the nasal and sinus cavities, and transported to the lower airways during physiological breathing, possibly acting as a common-airway signaling molecule.

20.6 Nitric Oxide in Chronic Airway Inflammatory Diseases

20.6.1 Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) was one of the first entities to shed light on the possible involvement of NO in inflammatory airway disease. Lundberg et al. [37, 40] found low levels of NO in the exhaled air of children with PCD compared to controls [37]. The low levels of nasal NO in PCD may have several causes, including impaired NO synthesis. Although some authors suggest that NO measurement as a screening test for PCD has high sensitivity and specificity close to 100%, other disease states, such as cystic fibrosis (CF) and diffuse bronchiolitis, are characterized by low levels of NO. But the presence of a normal nasal NO concentration is highly sensitive for ruling out the diagnosis of PCD [65].

20.6.2 Cystic Fibrosis

In vitro and in vivo evidence using human and CF mice have shown decreased levels of NOS-2 expression in upper and lower airways. Also, in CF cells, cytokines that stimulate NOS-2 mRNA in normal cells did not induce an increase in NOS-2 [68]. Some hypotheses for these findings have been postulated, such as impaired mechanism of phosphorylation of calmodulin-binding protein, reduced diffusion through the thick mucus, increased metabolization of NO, epithelial cell destruction, and defects in ciliary function. The consequences for low NO in the airways are still unclear, but low NO levels could lead to an impaired innate defense mechanism, increasing host-susceptibility to infections [43].

20.6.3 Allergic Rhinitis

Several studies have demonstrated the presence of NOS-1 in glands, surface epithelial cells, and olfactory mucosa in both healthy and allergic rhinitis patients [30]. Other groups have demonstrated over expression of NOS-2 and NOS-3 in nasal epithelial cells of allergic patients [24, 58]. The increased NOS-2 expression of epithelial cells in patients with allergic rhinitis may be explained by an increase in NOS-2 activity due to persistent mucosal inflammation.

Several studies have attempted to assess nasal NO levels in allergic rhinitis, with conflicting results due to differences in technique. But overall, most of the studies reveal higher NO levels in allergic patients compared to control subjects [57]. Some authors have shown that exhaled NO correlates with the severity of

the disease [17, 44, 63]. Other studies have demonstrated that topical administration of L-NAME decreased NO in both healthy and allergic patients, with a greater decrease of NO in allergic rhinitis patients [42, 47].

Given these reports, several recent studies have investigated whether common drugs used to treat allergic rhinitis may interfere with the production and measurement of exhaled NO. Fexofenadine hydrochloride, a second generation H1-receptor antagonist, suppressed the NO production of nasal polyp fibroblasts induced by TNF-α in vitro and, when used longer than 1 week, it suppressed NO production detected in plasma after induction with intraperitonial LPS [5]. Some studies, however, have shown that antihistamines do not affect nasal NO in subjects with perennial or seasonal allergic rhinitis [6, 64]. Similarly, leukotriene antagonists did not influence NO in seasonal allergic rhinitis [64]. On the other hand, studies revealed that topical administration of nasal steroids decreased NO exhaled nasally but not orally, likely resulting from downregulation of NOS-2 transcription [6, 26, 64].

20.6.4 Chronic Rhinosinusitis with and Without Nasal Polyposis

Measurement of NOS activity demonstrates an upregulation in patients with the combination of nasal polyps, asthma, and aspirin sensitivity (Samter's triad) when compared to patients with nasal polyps only or to patients with nasal polyps and asthma [48]. This high NOS activity in patients with Samter's triad is mainly mediated by NOS-2 (iNOS), suggesting that NO helps to maintain inflammatory events in aspirin-sensitive patients with asthma and nasal polyps. Although the NOS activity and NOS upregulation have been shown to be increased in nasal polyps compared to normal nasal mucosa, the exhaled NO concentration in nasal polyposis is lower than healthy patients and is inversely correlated to the extent of disease [4, 50, 51]. This paradoxical finding reinforces that the paranasal sinuses are the major source of production of NO. It follows that the sinus ostium patency is critical in determining the concentration of exhaled NO, as evidenced by the rise in measured NO following medical or surgical reduction of nasal polyps [9]. NO levels are also elevated in patients where inflammation of the nasal mucosa is present with patent sinus ostia, such as in allergic rhinitis.

In a rabbit model of chronic sinusitis, as well as in human CRS, NO metabolites such as nitrate, nitrite, *S*-nitrosothiol, and peroxynitrite are increased [46, 55]. This discrepancy may be explained by either the blockage of the sinus ostium, preventing NO from reaching the nasal cavity or viscous mucus trapping NO [46]. NO would then be metabolized before reaching the nose. Additionally, messenger RNA for cytokines such as IL-4, IL-6, and transforming growth factor has been identified in patients with CRS and these cytokines can reduce NOS-2 expression both in vitro and in vivo [67]. In light of this evidence, NO measurement could function as a noninvasive marker for sinus ostium blockage and as a gauge to monitor therapeutical success in CRS with or without nasal polyposis.

NO can also directly enhance eosinophil survival by modulating apoptotic mechanisms in sites of inflammation. Studies have shown that NO prevents Fas ligand–Fas receptor interaction, an important mechanism that regulates eosinophil apoptosis [20]. Thus, in inflamed tissues such as in nasal polyps where NOS-2 is upregulated, the overproduction of NO can lead to longer survival of eosinophils, which in turn produce more cytokines (i.e., IL-5), recruit and activate more inflammatory cells, and lead to a positive feedback maintaining the cascade of chronic inflammation. For instance, NO can control inflammatory cell influx through the upregulation of macrophage inflammatory protein 2 and monocyte chemoattractant protein 1 production [61].

Tewfik et al. demonstrated that primary cultured fibroblasts derived from eosinophilic nasal polyps, when exposed to the NO donor *S*-nitroso-*N*-acetyl-D,L-penicillamine (SNAP), resulted in a 2.2-fold increase in the production of type III collagen, confirmed by immunocytochemestry and Western Blot analysis, which led to a shift in the ratio of type I to type III collagen. When fibroblasts were incubated with a NO scavenger (oxyhemoglobin), type III collagen was not hyperproduced [60].

NO is implicated in the pathophysiology of nasal polyposis, including recruitment of inflammatory cells, inhibiting apotosis of eosinophils, disturbance of the cytoarchitecture leading to modifications of the extracellular matrix, and extravascular leakage with consequent edema.

20.7 Future Perspectives

Although some evidence suggests that NO aids in upper airway homeostasis and immunity by modulating blood flow, augmenting mucociliary clearance and acting as an antiviral and antimicrobial, NO may also be toxic under certain conditions. The complicated biological pathways of NO in the upper airways, especially involving the pathogenesis of chronic inflammatory disorders such as CRS and nasal polyposis, demand further investigation. The elucidation of NO's precise role in these inflammatory diseases may allow for earlier and more accurate diagnosis, noninvasive follow-up monitoring, and new therapeutic approaches that will prevent the harmful direct and indirect effects mediated by NO.

Take Home Pearls

- NO regulates ciliary beat frequency and mucociliary clearance.
- The paranasal sinuses appear to be the primary source of NO in the respiratory system.
- The exact role of NO in respiratory homeostasis and pathophysiology is still unclear.

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Current Concepts on the Pathomechanisms of Chronic Rhinosinusitis and Nasal Polyps

21

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Core Messages

- Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the upper airway subdivided into CRS with or without nasal polyps.
- CRS with or without nasal polyps is characterized by the infiltration of inflammatory cells, predominantly eosinophils or neutrophils and mast cells and T cells and inflammatory mediators, adhesion molecules, and matrix metalloproteinases.
- CRS without nasal polyps is more neutrophilic in nature, whereas CRS with nasal polyps especially when associated with aspirin sensitivity, asthma, or allergy is more often eosinophilic in nature.
- Remodeling like squamous metaplasia, basement membrane thickening, collagen deposition, hyperplasia of mucus glands and goblet cells are features found in both the subgroups of CRS.

21.1 Introduction

Rhinosinusitis, defined as a heterogeneous group of disorders characterized by the inflammation of the nose and paranasal sinuses, is one of the most common upper airway disorders, and is associated with significant morbidity and a lower quality of life [23]. On the basis of the International Consensus on Rhinosinusitis, CRS is defined depending upon the duration of time over which the symptoms persist (>12 weeks), and is subdivided into two subgroups, CRS without nasal polyps and CRS with nasal polyps [20]. CRS with nasal polyposis (NP) is one of the most difficult challenges to treat, as its etiology and pathophysiology are still not well defined, and despite medical and/or surgical treatment recurrences are frequent. Moreover, patients with nasal polyps often have other comorbidities such as asthma, aspirin hypersensitivity, sino-bronchial syndrome, or cystic fibrosis. Clinically, a diagnosis of CRS requires at least two or more symptoms comprising nasal blockage, anterior or postnasal drip, facial pain or pressure, and reduction in or loss of smell. In addition to the symptoms, there must be endoscopic evidence to document the presence of inflammation, such as discolored mucus or edema of the middle meatus or ethmoid and evidence of rhinosinusitis on imaging by CT. In case of CRS with polyps, endoscopic evidence of the presence of polyps in the middle meatus, and evidence of bilateral disease on imaging by CT are needed.

21.2 Etiology

The trigger factors leading to the development of rhinosinusitis comprises both host factors and external factors. Contributing host factors include cystic fibrosis

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or immotile cilia syndrome, allergic/immune conditions, anatomic abnormalities, systemic disease, endocrine metabolic neuromechanisms, or tumors. External or environmental factors include infectious/viral agents, trauma, noxious chemicals, iatrogenic, medications, and surgery. Histopathologically, chronic rhinosinusitis is predominantly a proliferative process associated with fibrosis of the lamina propria, in which lymphocytes, plasma cells, and eosinophils predominate along with, perhaps, inflammation in the bone.

Although the precise etiology of the inflammation associated with CRS is not completely understood, often the presence of bacteria within the nose and paranasal sinuses are well documented [4, 40].Yet, there is much diversity on the type of pathogens identified primarily due to the precise point of time, manner, and mode of sample collection, treatment methods used, and techniques of bacterial cultures. In CRS without underlying infection, bacterial colonization is considered to exacerbate a noninfectious inflammatory response via bacterial allergic mechanisms. Bacteria-specific IgE has been reported in 57% of patients with CRS as compared to only 10% in subjects with allergic rhinitis [6], and bacteria such as *Staphylococcus aureus* possess the ability to elicit exotoxins, and superantigens can activate subpopulations of the T-lymphocytes (5–30%) [21]. Schubert hypothesized a potential unifying role for bacterial superantigen in the pathogenesis of CRS, and proposed that microbial persistence, superantigen production, and host T-lymphocyte response are crucial components of all common chronic eosinophilic-lymphocytic respiratory mucosal disorders [34] and staphylococcal superantigen-specific IgE antibodies to the superantigens SEA and SEB were detected in nasal polyp tissue [3]. Yet, the precise mechanisms are not well known and are currently under investigation. However, in another recent study, the investigators could not observe a higher prevalence of S. aureus in CRS patients with or without nasal polyps than in controls, and could not substantiate that S. aureus intensifies the T(H2) shift in CRSNP(+) patients [24].

21.3 Inflammatory Mechanisms in CRS and Nasal Polyps

CRS is characterized by goblet cell hyperplasia, limited extent of subepithelial edema, inflammatory cell infiltration, and fibrosis. The histological characteristics of the inflamed mucosa and the inflammatory cells in sinus exudate depend on the allergic status of the patient. In the sinus fluid of patients with CRS, neutrophils are predominant, but a low percentage of eosinophils, mast cells, and basophils may also be observed [1, 33, 36]. Markedly high levels of histamine, leukotrienes C4, D4, and E4, and prostaglandin D2 are detected suggesting mast-cell/basophil activation [11, 19, 37]. High levels of IL-1β, ICAM-1, and E-selectin have been detected in sinus tissues [11] and IL-8 in the nasal discharge of patients with CRS [39]. IL-8 is a chemoattract for neutrophils. Apart from IL-8, neutrophils also produce IL-1, IL-6, IFN-γ, and TNF-α in vitro [5, 9], further contributing to the chemotaxis and activation of other inflammatory cells.

In patients with allergic disease and/or asthma and chronic hyperplastic sinusitis (CHS), there is massive infiltration of eosinophils in the paranasal sinus, and the extracellular deposition of major basic protein (MBP) is associated with damage to sinus respiratory epithelium [15]. The relative abundance of eosinophils and fewer numbers of neutrophils in those patients with CRS with NP with coexisting asthma suggests that this type of inflammatory response may be independent of infection and may represent an allergic inflammation, although it is likely that infection impacts upon this disease process. Clinically, there appears to be a continuous spectrum of illness ranging from chronic infectious rhinosinusitis to relatively pure noninfectious inflammation. In addition to upregulated cytokines/chemokines, adhesion molecules like ICAM-1 and E-selectin are upregulated [14, 18, 38]. Clinical, radiographic, and histologic changes suggest that the bone may actually be involved and play an active part in the disease process and that the inflammation associated with CRS may spread through the Haversian system within the bone [16, 17]. In a study comparing the rate of bone turnover in patients with CRS vs. controls, the rate of bone turnover in CRS was found to be similar to that seen in osteomyelitis.

In CRS with nasal polyps, typical histological characteristics of the nasal polyps (NP) include edematous fluid with sparse fibrous cells, and few mucous glands with no innervation, squamous metaplasia of the surface epithelium, proliferation of stromal and epithelial elements, and a thickening of the basement membrane. Other characteristics of nasal polyps include the existence of different types of epithelium from respiratory pseudostratified to transitional epithelium and a lowered density of goblet cells. The cellular components comprise a variety of

cells, including eosinophils, mast cells, lymphocytes, neutrophils, and plasma cells. There are four histological types of nasal polyps of which the eosinophilic (mainly eosinophils) or chronic inflammatory type (mainly neutrophils and lymphocytes) are the most common [30]. In majority of eosinophilic edematous nasal polyps, eosinophils comprise more than 60% of the cell population, except in cystic fibrosis where neutrophils are increased.

In chronic hyperplastic sinusitis with nasal polyps (CHS/NP), there is an increase in the Th2 cytokines like IL-4, IL-5, and IL-13 [22, 28] and the intensity of eosinophils in the tissues of these patients is markedly increased in the presence of coexisting asthma or positive allergy skin tests. The increased presence of IL-4 and IL-13 can play a role in upregulating VCAM-1 and thus facilitates further infiltration of eosinophils; and activated mast cells release histamine and tryptase, which upregulate the production of RANTES and GM-CSF from epithelial cells, thus facilitating eosinophil infiltration and survival [12, 13, 22, 25, 28, 29]. In fact, increased levels of tryptase and histamine (exceeding levels of 4,000 ng/mL) have been found in nasal polyps and a good correlation between the levels of ECP and histamine and tryptase is also documented [8, 22, 29]. IL-4, IL-13, and TNF-α from mast cells and T cells can upregulate eotaxin production in epithelial cells [25]. Immunoglobulins like IgA, IgE, IgG, and IgM are also increased in polyp fluid and tissue [22] and the concentrations of total IgE, IL-5, eotaxin, ECP, $LTC_4/D_4/E_4$, and sCD23 were significantly higher in nasal polyp tissue as compared with nonpolyp tissue [32]. Total IgE correlates significantly with IL-5, ECP, $LTC_4/D_4/E_4$, and sCD23 and with the number of eosinophils in nasal polyps [41]. Thus an association between increased levels of total IgE, specific IgE, and eosinophilic inflammation in NPs can be considered, which may be of relevance in the pathophysiology of NP. However, some polyps do not have many eosinophils, while mononuclear cells are the dominant infiltrating cell types [22]. The mechanism of formation and development of such mononuclear cell dominant polyps is not yet well defined and needs further investigations.

21.4 Remodeling in CRS and NP

Remodeling is defined as a process leading to transient or permanent changes in tissue architecture, which involves break down of tissue structures such as basement membranes and interstitial stroma, as well as repair. In CRS, there is damage to the respiratory epithelium, squamous metaplasia, ciliary destruction, increase of microvillus cells, and mucous gland and goblet cell hyperplasia. However, epithelial shedding, which is characteristic of asthma is not observed in the maxillary sinus. The basement membrane thickening seen in CRS is the result of a dense fibrotic response characterized by the enhanced accumulation of fibronectin and types I, III, and V collagens [10, 35]. In CRS, there is thickening of the maxillary sinus mucosa and the mean grade of subepithelial collagen deposition is significantly higher in patients with CRS as compared with controls [7]. However, the clinical relevance of subepithelial collagen deposition in CRS is still unclear. In CRS, there is an increase in submucosal acinar cells and this may be important in the mucus hypersecretion in CRS. EGF-R expression is increased in submucosal gland cells of CRS patients [2] thus indicating that EGF and EGF-R may regulate the proliferation of submucosal gland cells.

There is evidence for remodeling in NP with increase in basement membrane thickening and tissue degradation. MMPs are known to play a role in cell migration, edema, and extracellular matrix degradation (ECM). Our recent studies have shown an increase in MMP-9 in nasal polyps with relatively low levels of TIMP 1 and 2 [31] Moreover, the levels of MMP-9 were in good correlation with the levels of ECP and tryptase [22]. Furthermore, mast cells themselves expressed MMP-9 and mast cell tryptase and chymase could upregulate the production of MMP-9 from nasal polyp epithelial cells suggesting an important role for mast cells in not only inducing eosinophil infiltration but also in the ECM degradation in NP. More importantly, MMP-9-positive inflammatory cells were localized around and inside the pseudocyst formations suggesting their direct role in the degradation of the ECM. MMP-9 may thus help the inflammatory cells to migrate inside the ECM. The migrated cells can then release their enzymes creating a pseudocyst formation around them. If dysregulated, these microcavities are then progressively filled by tissue fluid, such as plasma proteins and especially albumin. The inflammatory cells expressing MMP-9 are mainly mononuclear cells including mast cells, but some polymorphonuclear cells can also be observed. Matrix metalloproteinase-7 (or matrilysin) which can degrade fibronectin, laminin, gelatin, aggrecan, and elastin and can also stimulate

MMP-9 expression is also increased in NP [42]. Moreover, tryptase and chymase from mast cells can upregulate MMP-9 production from epithelial cells and fibroblasts (Pawankar, unpublished observations). By degrading several components of the basement membrane, MMP-9 could also increase vascular permeability, leading to airway edema and inflammatory cell transmigration. MMP-9 could also facilitate epithelial and endothelial cell migration observed during polyp development and growth. Thus MMP-9 in nasal polyps may play a crucial role in upper airway remodeling during NP.

Again, an increase in the levels of TGF-β in NP can contribute to the stromal fibrosis seen in nasal polyps. Also TGF-β can upregulate eosinophlic inflammation by enhancing the IL-4 and LPS-induced production of eotaxin and vascular endothelial growth factor (VEGF) in nasal polyp fibroblasts and TGF-β and the expression of VEGF [26, 27] important for angiogenesis and edema. Taken together, mast cells may contribute to NP growth and the remodeling process, and the latter may be a sequel of chronic inflammation.

Glandular proliferation, increased vascularization, an increase in α-SMA$^+$ myofibroblasts, and deposition of collagen types I, III, and V are documented in NP. An increase in profibrotic cytokines have been documented in NP, including GM-CSF, TGF-β, PDGF, FGF and VEGF, EGF, and KGF. These factors may contribute to NP growth and the remodeling process, and the latter may be sequelae of chronic inflammation. Recent studies have shown that TGF-β can upregulate the function of fibroblasts by enhancing the IL-4 and LPS (bacterial product)-induced production of eotaxin from these cells [27]. VEGF which is important for inducing angiogenesis and edema is also increased in nasal polyps and its expression is further upregulated by TGF-β. Myofibroblasts are a major source of collagenous and noncollagenous matrix molecules and α-SMA and TGF-β are upregulated in NP especially in the pedicle than in the central and tip suggesting that myofibroblasts may be involved in the growth of nasal polyps by inducing ECM accumulation.

21.5 Conclusion

A variety of inflammatory cells, including neutrophils, lymphocytes, eosinophils, and mast cells play a role in CRS, in addition to proinflammatory cytokines, IL-8, and IL-3. In CHS with nasal polyps, eosinophils are the main infiltrating cells, and locally produced IgE may contribute to the process of noninfectious inflammatory mechanisms via the mast-cell-IgE–IgE-receptor cascade. In CRS, an increase of mirovillous cells, squamous metaplasia, and goblet cells is observed in many patients with CRS. An upregulation of MMP-9 with low levels of TIMP may contribute to the accumulation of ECM in nasal polyps. Glandular proliferation, increased vascularization, increases in α-SMA$^+$ myofibroblasts, and deposition of collagen types I, III, and V in NP along with increased profibrotic cytokines may contribute to NP growth and the remodeling process, and the latter may be a sequelae of chronic inflammation. Both the mast cells and eosinophils are potential sources of profibrotic cytokines thus inducing fibrosis and probably contributing to remodeling. Further studies are essential to fully understand the inflammatory mechanisms and remodeling associated with CRS with and without nasal polyps.

Take Home Pearls

- Chronic rhinosinusitis with nasal polyps associated with asthma is eosinophilic in contradistinction to CRS without NP which is more usually neutrophilic and more often associated with IL-8.
- Remodeling histologically occurs in CRS with or without NP and agents such as matrix metalloproteinase 9, TGF-b, profibrotic cytokines and adhesion molecules are under active investigation as to exact role in nasal polyps.

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Relapses After Surgery and Their Prevention

22

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Core Messages

- Nasal polyps represent a common endpoint in several disease processes (perennial nonallergic rhinitis, asthma, intolerance of acetylsalicylic acid/nonsteroid anti-inflammatory drugs, allergic fungal rhinosinusitis, cystic fibrosis, and ciliary dyskinesia).
- Nasal polyposis is an eosinophilic inflammatory disease, which requires constant clinical treatment.
- Relapses of nasal polyps after surgical treatment are very common.
- Clinical prevention: the choice of the surgical treatment and the surgical experience may influence the rate of relapses.
- Prevention of eosinophilic inflammation: local corticosteroids are effective in preventing nasal polyp relapses.
- Prevention of changes in arachidonic acid metabolism in aspirin-sensitive subjects: (1) avoid aspirin; (2) take a leukotriene receptor antagonist; (3) undergo aspirin desensitization.
- Prevention of edema formation: topical nasal furosemide treatment is at least as effective as topical steroid.
- Antifungal prevention: a long-term topical treatment with lysine acetylsalicylate and amphotericin B was found effective in patients with nasal polyposis and mycotic infection.

Abbreviations

ASA	Acetylsalicylic acid
BFGF	Basic fibroblast growth factor
CCR	Chemokine receptor
COX-2	Cyclo-oxygenase-2
ECP	Eosinophil cationic protein
EG2+	Activated eosinophils
ERK	Extracellular signal regulated kinase
GM-CSF	Granulocyte macrophage colony stimulating factor
IL-5	Interleukin-5
IL-12	Interleukin 12
IL-13	Interleukin 13
IL-5R	Interleukin-5 receptor
LTC4	Leukotriene C4
Mab	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
MBP	Major basic protein

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MMP	Metalloproteinase
NF-k B	Necrosis factor-k B
NKCC	Na+/K+/2Cl cotransporter
NSAIDs	Nonsteroid anti-inflammatory drugs
PBMCs	Peripheral blood mononuclear cells
RANTES	Regulated on activation, normal T expressed and secreted (cytokine, member of IL-8 superfamily).
SE A, SE B	*Staphylococcus aureus* enterotoxin A, B
SOL IL-5R	Soluble IL-5 receptor
TCR-MHC	T cell receptor-major histocompatibility complex
TGF	Tumor growth factor
Th	T helper lymphocyte
TM IL-5R	Membrane anchored IL-5 receptor
TNF	Tumor necrosis factor
VCAM	Vascular cell adhesion molecule
VLA	Very late antigen (expressed by most leukocytes)

22.1 Introduction

Nasal polyposis is an inflammatory disease occurring in about 2% (1–4%) of the general population [45, 52]. Polyps are usually associated with perennial nonallergic rhinitis, asthma, acetylsalicylic acid (ASA)/nonsteroid anti-inflammatory drugs (NSAIDs) intolerance, allergic fungal rhinosinusitis, cystic fibrosis, and primary ciliary diskinesia.

Following a long period of rhinitis with persistent nasal blockage, "edematous bags" arise from the mucosa of the lateral nasal wall in the region of the ostiomeatal complex. Despite their appearance, nasal polyps are not to be considered simple edema, but are more likely an inflammatory growth of the mucosa of the lateral wall of the nose, which represents a common endpoint in several disease processes [15].

Relapses of nasal polyps after surgical treatment are very common, and their prevention is the focus of interest of clinicians and researchers.

The recurrence rate of NP following endoscopic sinus surgery has been widely reported, with varied results:

- 75% (243 patients) [40]
- 13% (181 patients) [24]
- 40.9% (72 patients) [55]
- 39.9% (386 patients – conventional surgery) [56]
- 37.1% (97 patients – microsurgery) [56]
- 25.5 % (94 patients – microsurgery with resection of parasympathetic innervation [56]
- 30.7% (64 patients) [14]
- 17.5% (97 patients – Furosemide) [51]
- 30.0% (40 patients – no treatment) [51]
- 24.2% (33 patients – Mometasone) [51]
- 60% (118 patients) [68]
- 50% (30 patients) [21]
- 24% (225 patients) [2]
- 22.7% (39 patients – radical ethmoidectomy) [34]
- 58.3% (37 patients – functional ethmoidectomy) [34]
- 18% (194 patients) [42]

Successful prevention of postsurgical NP recurrence is theoretically reliant on an understanding of the pathophysiology of NP and is aimed at blocking the early phase of their development. The sustained inflammatory state associated with CRS and NP requires persistent administration of therapy aimed at combating inflammation [25]. Infectious, noninfectious, inflammatory, anatomic, and genetic abnormalities should be taken into consideration [36]. Nasal polyps are characterized by edema and inflammatory cells, among which activated eosinophils (EG2+) are prevalent in most of the cases (about 80%) [6, 18]. Interleukin (IL)-5 plays a major role in the recruitment, activation, and inhibition of apoptosis of eosinophils [5, 6]. High-affinity IL-5 receptors (IL-5R) are expressed on eosinophils and basophils. Two isoforms of IL-5R alpha have been studied in nasal polyposis: SOL IL-5R alpha is the secreted receptor and is upregulated in polyp tissue, while TM IL-5R alpha is the membrane anchored-receptor, which is downregulated in nasal polyps [10].

TGF-β1 is a cytokine that acts as chemoattractant for fibroblasts, thereby stimulating extracellular matrix formation. It inhibits the synthesis of IL-5 and the effect of haemopoietins on eosinophils [1]. Lower concentrations of TGF-β1 were found in NP tissue than in mucosa from patients with CRS without NP [66]. It is likely that elevated IL-5 and decreased TGF-β1 enhance eosinophil survival, thereby favoring degradation of tissue matrix during the formation of NP. The eosinophilic inflammation is mediated by T cells, which show a mixed T helper (Th1/Th2) profile [58]. Macrophages and mast cells may also contribute to the release of citokines.

Although IL5 and eotaxin are known to play key roles as chemoattractants and activators of eoisinophils

[6], the initial trigger of the eosinophilic inflammation is not known. Bacterial colonization has been proposed as a potential factor contributing to disease severity. Bachert et al. [7, 8] demonstrated increased levels of *Staphylococcus aureus* enterotoxin-specific IgE in polyp tissue and suggested that the eradication of *S. aureus* colonization in the nose may favor the management of nasal polyposis at least in a subgroup of patients. Two metalloproteinases (MMP-7 and MMP-9), able to degrade extracellular matrix proteins, were found to be increased in polyp tissue [66].

22.2 Clinical Prevention

The clinical picture of nasal polyps is characterized by nasal blockage, rhinorrhea, and occasionally hyposmia. Recurrence of symptoms and polyp growth may be monitored by symptom scores, rhinomanometry and nasal endoscopy.

In a long-term follow-up study of nasal polyp patients after simple polypectomy, Larsen and Tos [40] found large polyps in 3% of the patients, moderately sized polyps in 30%, and small polyps in 42%. No polyps were visible at the endoscopic examination in 25% of the patients.

Nonsteroidal anti-inflammatory drugs (NSAIDs) intolerance, asthma, revision surgery, and polyp extension can be considered prognostic factors of recurrence, but only NSAID intolerance and asthma are independent predictive factors. In other words, patients with NSAID intolerance and asthma are at higher risk for relapses after endonasal surgery for CRS without NP [2, 3, 31, 40, 68].

The choice of the surgical treatment and the surgical experience may influence the rate of relapses [42]. Radical ethmoidectomy appears to provide better long-term results in comparison with functional ethmoidectomy. In fact, in a retrospective 5-year study, a recurrence rate of 22% in the radical ethmoidectomy group, and of 58.3% in the functional ethmoidectomy group ($p < 0.01$) was found [34]. The effect of the resection of parasympathetic innervation has been evaluated with interesting results: the rate of recurrence was 39.9% after conventional surgery, 37.1% after microsurgery, and 25.5 % after microsurgery combined with resection of parasympathetic innervation [56].

22.3 Prevention of Eosinophilic Inflammation

Corticosteroids are able to control several steps of the inflammatory cascade. Local corticosteroids are effective in preventing nasal polyp relapses [4, 19, 20, 27, 28, 32, 44, 55, 57] by:

- Inhibiting the liberation of vasoactive mediators, thereby decreasing vasodilation and fluid extravasation (edema).
- Reducing the recruitment of inflammatory cells, which are responsible for the amplification of the inflammatory reaction, especially affecting eosinophil infiltration, activation, and survival.
- Decreasing of the fibroblast proliferation and synthesis of extracellular matrix protein.
- Reducing many cytokines and chemokines, among which IL-5, IL13, eotaxin, granulocyte macrophage colony stimulating factor (GM-CSF), and momocyte chemoattractant protein-4.
- Reducing the release of preformed and newly generated mediators such as histamine, prostanoids, and leukotrienes.
- Modulating the overexpression of MMP-9.

Corticosteroid insensitivity of inflammatory cells may be due to different mechanisms [59] such as:

- Downregulation of the alpha-receptor
- Inhibition by the beta-isoform of the receptor
- Repression by trascription factor NF-k B

Researchers are trying to introduce new therapeutic approaches for the management of eosinophilic inflammation with a better tolerability than corticosteroids. Neutralization of IL-5 could be useful to control eosinophilic disorders [60]. Anti-IL-5 mAb treatment in vitro induced eosinophil apoptosis [61]. On the other hand, SOL IL-5R alpha was upregulated, while TM IL-5 receptor was downregulated in polyp tissue [10]. On the whole, IL-3, IL-5, and GM-CSF exert a dynamic regulation of eosinophil receptors, leading to reduced expression of TM IL-5R alpha: as a consequence tissue eosinophils become relatively insensitive to anti-IL-5 mAb treatment. At the moment, this approach is not able to achieve clinical efficacy in the prevention of nasal polyposis relapses, but small molecules inhibiting IL-5 synthesis or action might be effective in the future.

Several antibodies directed against cytokines have been used in human and animal experiments, but have only hypothetical use in the treatment of relapses [15]:

- Anti-TNF-alpha and anti-IL1-beta downregulate inflammatory cytokines.
- Anti-VLA-4 and anti-VCAM-1 decrease attachment of eosinophils to vascular endothelium.
- Anti-RANTES and anti-eotaxin decrease attraction of eosinophils to lamina propria.
- Anti-IL-3 inhibits eosinopoesis.
- Anti-GM-CSF inhibits eosinophil survival.
- Anti-IL-12 inhibits Th1 cytokines.

Another possible approach involves chemokine receptor 3 (CCR-3) antagonists. Trials in nasal polyposis are not available at the moment, but an in vitro study demonstrated that eosinophil transmigration was inhibited by pretreatment with anti-CCR3 antibodies [35]. On the clinical point of view, the anti-eotaxin mAb bertilimubab (CAT-213) was administered as local pretreatment before nasal challenge to grass pollen-sensitive patients: nasal obstruction, eosinophil and mast cell influx were reduced compared with placebo pretreatment [64].

22.4 Prevention of Changes in Arachidonic Acid Metabolism

In aspirin-sensitive subjects, changes in arachidonic acid metabolism are involved in nasal polyps pathogenesis. Among the possible alterations, leukotriene C4 (LTC4) synthase was demonstrated to be upregulated in nasal polyps from aspirin-sensitive individuals [62]. In this subgroup of patients prevention of relapsing could be achieved following at least one of three options [10]:

- Avoid aspirin and other nonsteroid anti-inflammatory drugs (NSAIDs); paracetamol, nimesulide, and selective cyclo-oxygenase (COX)-2 inhibitors are allowed [63].
- Take leukotriene receptor antagonists or synthesis inhibitors.
- In a nonrandomized clinical trial [26] 40 aspirin-sensitive patients with nasal polyps received Montelukast (a LTD4 receptor antagonist) at the dosage of 10 mg/day for 6 months. The control group was treated with topical corticosteroid and antihistamines. In both cases, absence of local recurrence, good nasal patency, and lack of nasal symptoms were pointed out.
- In 18 patients with ASA-intolerance triad the treatment with Montelukast after surgery reduced the recurrence of nasal polyps, the serum ECP-level, the rate of EG2-positive cells, and the nasal mucosa level of IL-5 [30].
- In a prospective double blind comparative study Mostafa et al. [43] evaluated the effects of Montelukast in comparison with beclomethasone on the postoperative course of patients with nasal polyps. Group I (20 patients) received 10 mg Montelukast orally daily and group II (20 patients) received 400 μg Beclomethasone local spray daily. After 1-year follow up, no difference in the recurrence rate between the groups was pointed out. Montelukast had more marked effect on itching, postnasal discharge, and headache, while beclomethasone was more effective on smell disturbance and obstruction. Further studies are needed to determine which patients should receive each treatment.
- As leukotriene C4 (LTC4) concentrations at the time of surgery were higher in patients with recurrences of nasal polyps than in patients without recurrences, LTC4 might have a prognostic value [37].
- Undergo aspirin desensitization, administering incremental oral doses, to reach the maintenance dose.
- The clinical course and the parameters of eicosanoid release were followed up in 30 patients, who were undergoing adaptive desensitization for aspirine intolerance, between 1 and 3 years [29]: the desensitization with only 100 mg a day of oral aspirin, after an initial application of higher doses, was successful in 25 of the 30 patients. According to this study, the recurrence rate of nasal polyps after surgical therapy can be reduced by aspirin desensitization, but only long-term treatment can maintain the good results, as discontinuing of aspirin therapy leads to worsening of the clinical picture.

Because of the gastrointestinal adverse effect, treatment with daily aspirin could be indicated for steroid insensitive patients [10].

22.5 Prevention of Edema Formation

Studying the bioelectric properties of cultured nasal polyp and turbinate epithelial cells obtained from children affected with cystic fibrosis [17], an altered ion transport, was pointed out [16].

At the basolateral surface of nasal epithelial cells, the entry of sodium is combined with the passage of chlorine [48]. On the same surface an ATPase-dependant pump is responsible for the outtake of sodium and intake of potassium. Furthermore, a selective channel is the way for the penetration of sodium right into the epithelial cells from their luminal surface following an electrochemical gradient. A similar channel allows the chlorine come out the epithelial cells. Finally, ions and water may go through the tight junctions in both directions [16].

In cystic fibrosis the chlorine channel is altered, allowing the chlorine and, consequently, the sodium, concentration to increase, resulting in water accumulation in the submucosa. Furosemide is a loop diuretic, which demonstrated to act as inhibitor of the Na+/K+/2Cl cotransporter (NKCC) at the basolateral surface of the respiratory epithelial cells and to reduce edema in preoperative management of nasal polyposis [38]. Furthermore, it has been shown to reduce arachidonic acid-stimulated production of prostaglandins [41]. The control of sodium/chlorine balance involves also the calcium transport. The depletion of calcium results in the stabilization of inflammatory cells, reducing the release of inflammatory mediators [33, 46, 54, 69]. In more details Furosemide inhibits production and release of cytokines Il-6, Il-8, and tumor necrosis factor-alpha from peripheral mononuclear cells [54].

NKCC controls the extracellular signal regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signal transduction pathway in fibroblast and lymphocyte culture: so NKCC inhibition by furosemide in nasal polyps may play a role in blocking the proliferation of cells that are a main source of GM-CSF, which is responsible for the prolonging of eosinophil survival [47].

In a prospective controlled study [49] we have compared furosemide vs. no treatment in the follow-up of patients, who underwent surgery for nasal polyposis. The active group was subjected to daily inhalation of furosemide at the dosage of 10 mg diluted in 1 mL saline solution. The solution was administered as nasal spray or as nasal lavage with nasal douche indifferently according to the compliance of patients. When administered as nasal spray, two puff per nostril (each puff corresponding to 500 μg of furosemide) were administered every day on alternate months during the first and second year after surgery. From the third to the fifth year after surgery, 1 month of therapy was followed by 2 months of washout. The schedule was changed, increasing or decreasing the number of administrations, according to the results of follow-up and the patient's compliance. The treatment was followed for two courses of 3 months/year. At the end of a 4 years follow-up, we found no relapses in the active group. In another trial, we [50] studied the efficacy of inhaled form of furosemide to prevent postsurgical relapses of rhinosinusal polyposis vs. no treatment and have pointed out more recurrence in the control group 6 years after surgery. The efficacy of topical nasal furosemide treatment is recognized in the protection of nasal polyp recurrence: furosemide is at least as effective as topical steroid and is better than no treatment [13]. Inhaled furosemide in preoperative management of nasal polyposis is as effective as conventional oral steroids treatment on subjective improvement of nasal symptoms and polyp size reduction; it's more effective on edema showing no influence on eosinophil count reduction [38].

22.6 Prevention of Tissue Growth/Remodeling

The potential relation between basic fibroblast growth factor (bFGF) expression and polyp recurrence was studied comparing recurrent with nonrecurrent polyps [21]. The bFGF expression was seen as staining of polyp surface, gland epithelium, mononuclear cells, fibroblast-like cells, and vascular epithelium. As the level of immunohistochemical expression of bFGF in recurrent and nonrecurrent polyps was equivalent, this parameter cannot predict a subsequent recurrence.

Matrix metalloproteinases are involved in the tissue remodeling processes of nasal polyps growth [66]. As Doxycycline demonstrated to inhibit MMP-9, a placebo-controlled randomized study in nasal polyposis is currently in progress.

22.7 Antimicrobial Prevention

Coagulase-positive *S. aureus* are the most frequent bacteria found on the nasal mucosa of patients with nasal polyps [10] and a possible role of *S. aureus* enterotoxins in the etiology/pathomechanism of nasal polyps had been suggested [7, 8].

Gram-positive *S. aureus* releases enterotoxins, which show superantigen activity, that is to say activation of

T cells, induction of the synthesis of IgE in B cells, and stimulation of proinflammatory cells, such as eosinophils [11]. T cells are activated via the T cell receptor (TCR)-MHC class II-complex: once activated T cells produce interleukins, including IL-4, IL-5, IL-13, and eotaxin [70]. The consequent type 2 T helper cell-polarized eosinophilic inflammation and the multiclonal IgE production are responsible [9] for the severe inflammation via activation of mast cells [12].

Interestingly, IgE antibodies to staphylococcal enterotoxins correlate with disease severity in terms of total IgE formation, inflammatory markers, and clinical expression of the disease [11]. The finding of IgE antibodies to *S. aureus* enterotoxins SEA and SEB in nasal polyp tissue indicates that these superantigens could be involved in the pathogenesis of nasal polyposis [70]. Furthermore, the ECP concentration, reflecting the eosinophilic inflammation is increased in the presence of IgE antibodies to enterotoxins vs. samples without IgE, suggesting superantigens have a strong inflammatory effect [70].

S. aureus has been demonstrated to invade non-phagocytic eukaryotic cells, persisting for weeks [39]. In fact, *S. aureus* is able to internalize into the epithelial cells of the nasal mucosa, releasing superantigens into the tissue from its protected niche. This phenomenon may be due to an alteration either in innate or adaptive immunity. The internalization and the survival within host cells may explain the resistance of polyp disease to antibiotic therapy, as well as the propensity for NP recurrence.

The administration of antibiotics to patients who have previously undergone surgery for nasal polyposis could help prevent relapses. Macrolide antibiotics have been shown to decrease the virulence of colonizing bacteria and also to exhibit anti-inflammatory activities [22].

Other approaches to be developed in the future are [70]:

- Antibiotic treatment with intracellular activity
- Long-term antibiotic treatment with intracellular activity in combination with corticosteroid
- Vaccination therapy

22.8 Antifungal Prevention

In a subgroup of patients with nasal polyposis, fungal infection may be considered an etiopathogenetic factor. More specifically, Ponikau et al. demonstrated that in vitro peripheral blood mononuclear cells (PBMCs) from patients with CRS with/without nasal polyps produce, after stimulation with fungal antigens, large amounts of IL-5 and IL-13 compared with healthy control subjects. According to this observation, in some patients the harmless resident fungi in the nasal mucus can activate the immune system inducing the release of cytokines with eosinophil chemoattractant properties [67]. The eosinophils are directed to leave the vessels and enter the tissue, leaving the tissue and surrounding the fungi in the nasal mucus. There, eosinophils release major basic protein (MBP) that not only destroys fungi, but also, by "collateral damage," damages respiratory epithelial cells. These damages are responsible for CRS and polyp formation. In a randomized placebo-controlled double blind trial using amphotericin B lavage vs. placebo twice daily, Ponikau et al. [53] showed a reduced inflammatory mucosal thickening on both CT scan and endoscopy and decreased levels of some inflammatory markers (EDN but not IL-5) for eosinophilic inflammation in nasal lavage. A long-term topical treatment with lysine acetylsalicylate and amphotericin B was found effective in the prevention of recurrence after surgical treatment in patients with nasal polyposis and mycotic infection in comparison with a control group [23].

Take Home Pearls

The rate of recurrences was reduced after

- Radical ethmoidectomy in comparison with functional ethmoidectomy
- Microsurgery combined with resection of parasympathetic innervation
- Long-term treatment with nasal spray corticosteroids
- Long-term treatment with oral Montelukast
- Treatment with daily aspirin for sensitive patients
- Long-term treatment with inhaled furosemide
- Long-term topical treatment with lysine acetylsalicylate and amphotericin B

Possible future approaches

- Anti-TNF-alpha and anti-IL1-beta; anti-VLA-4 and anti-VCAM-1; anti-RANTES and anti-eotaxin; anti-IL-5; anti-IL-3; anti-GM-CSF; anti-IL-12; anti-CCR3

- Inhibition of MMP-9 by Doxycycline
- Treatment against *S. aureus* with intracellular active antibiotic alone or in combination with corticosteroid

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Cortison Therapy in Nasal Polyposis

23

Ranko Mladina and Berrylin J. Ferguson

Core Messages

- Perioperative systemic corticosteroids are frequently utilized in patients with nasal polyps.
- Preoperative steroids reduce blood loss and facilitate sinus surgery.
- Postoperative steroids are commonly used to decrease early return of nasal polyps and protect against exacerbation of asthma.
- There is no evidence that long-term outcomes from sinus surgery are impacted with perioperative steroids.
- Most, but not all, nasal polyps respond to corticosteroids.
- Steroid therapy results in a temporary medical polypectomy in some responsive patients, but disease usually recurs with cessation of steroid therapy.
- Benefits of steroid therapy must be weighed against the risks.
- Patients with nasal polyps should demonstrate failure to resolve their symptoms with topical steroids and sometimes a short course of oral steroids before surgery is considered.

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23.1 Introduction

Steroids, both topically and systemically, are widely advocated for the treatment of nasal polyposis [7, 12, 15]. Yet not all nasal polyps are equally responsive. What is most encouraging is how frequently nasal polyps do respond to systemic steroids, regardless of association or suspected etiology. Topical nasal steroids are the main stay in the medical treatment of nasal polyps. The evidence for efficacy and differences in indications and side effects are discussed in Sect. 23.2.

The causes of nasal polyps are complex and diverse. While histologically and grossly nasal polyps can be differentiated into nasal polyps with intense eosinophilic component associated with allergic mucin or the glistening polyps relatively devoid of inflammation and finally the antral choanal polyp, within each of these gross classifications, there are variable responses to topical or systemic steroids. The polyp categorization, which is an exception to steroid responsiveness, is the antral choanal polyp, which is not responsive to steroids and interestingly also lacks the proinflammatory cytokines present in most other forms of polyps. Professor Mladina has categorized nasal polyps by appearance and responsiveness to steroid therapy in Table 23.1. This categorization has not been validated, but serves as a potential basis for the study of nasal polyps by gross appearance and responsiveness to steroid therapy.

This chapter reviews the evidence for topical and systemic corticosteroids in patients with nasal polyps and suggested dosage regimens. Unfortunately, systemic steroids inflict a wide range of adverse effects, and the risks associated with systemic steroid use must always be part of the discussion held with the patient before oral corticosteroids are instituted and outlined.

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Table 23.1 Nasal polyps categorized by appearance and responsiveness to steroid therapy

Polyp type	Mucous quality	Polyp appearance and associations	Estimated incidence in Croatia (%)	Steroid responsiveness
Eosinophilic mucin nasal polyps	Viscous, eosinophilic, and difficult to aspirate	Allergic fungal; or asthma association	15	High
Infectious	Purulent	Bacterial	15	Moderate
Unilateral polyps without secretions including antral choanal polyp	Absent	Solitary polyps without mucous	5	Low to absent
Bilateral polyps without secretions	Absent	Translucent nasal polyps	65	High

23.2 Intranasal Steroids (INS)

As early as 1994, Muluk et al. reported that patients with CRS treated with budesonide nasal spray for 1 month demonstrated a significant reduction in the proportion of activated eosinophils and CD3, CD4, and CD8 lymphocytes present histologically in turbinate mucosa compared to untreated patients [8]. With regard to nasal polyps, it is widely held, though not yet studied systematically, that INS are of most benefit in the treatment of small and medium-sized nasal polyps and of little use for nasal polyps that are completely obstructing the nasal cavity. In this latter situation, surgery or a short course of systemic steroids (a medical polypectomy) is generally prescribed in order to reduce these larger polyps and allow effective application of an INS.

In the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 (EPOS), 12 of 16 randomized placebo controlled trials demonstrated nasal polyp responsiveness to a variety of topical steroids, including betamethasone sodium phosphate nose drops and beclomethasone dipropionate, fluticasone propionate, budesonide nasal sprays, and mometasone furoate. In one trial efficacy was not demonstrated at a dosage of mometasone 200 μg once daily, but efficacy was present at 200 μg twice daily [3]. In general, most trials of topical nasal sprays and drops use a dose twice that used for allergic rhinitis therapy. Currently, in the United States the only commercially available INS with an FDA indication for the treatment of nasal polyps is mometasone furoate. Many clinicians use INS interchangeably for the treatment of nasal polyps. Commercially available INS in the United States are listed in Table 23.2.

Table 23.2 Commercially available INS in the United States

Name Generic	Brand	Indicated nasal polyps
Beclomethasone	Beconase	No
Budesonide	Rhinocort Aqua	No
Ciclesonide	Omnaris	No
Flunisolide	Nasalide/Nasarel	No
Fluticasone propionate	Flonase	No
Fluticasone furoate	Veramyst	No
Mometasone furoate	Nasonex	Yes
Triamcinolone acetonide	Nasacort AQ	No

INS may reduce the need for endoscopic sinus surgery (ESS). In a 12-week double blind placebo controlled study of 54 patients with nasal polyps, CRS, or both who had been scheduled for ESS, the group randomized to fluticasone propionate nasal drops was significantly less likely to still require surgery. In fact, almost twice as many patients in the steroid treated group (13 of 27) had sufficient resolution of polyps and no longer required ESS compared to slightly less than 25% (6 of 27) of patients randomized to placebo. While fluticasone propionate nasal drops are not available in the United States, the off-label usage of the topical steroid drop, budesonide respules, is widespread [2].

No studies have directly compared efficacy of nasal steroid sprays to nasal steroid drops, although many practitioners consider steroid drops more efficacious

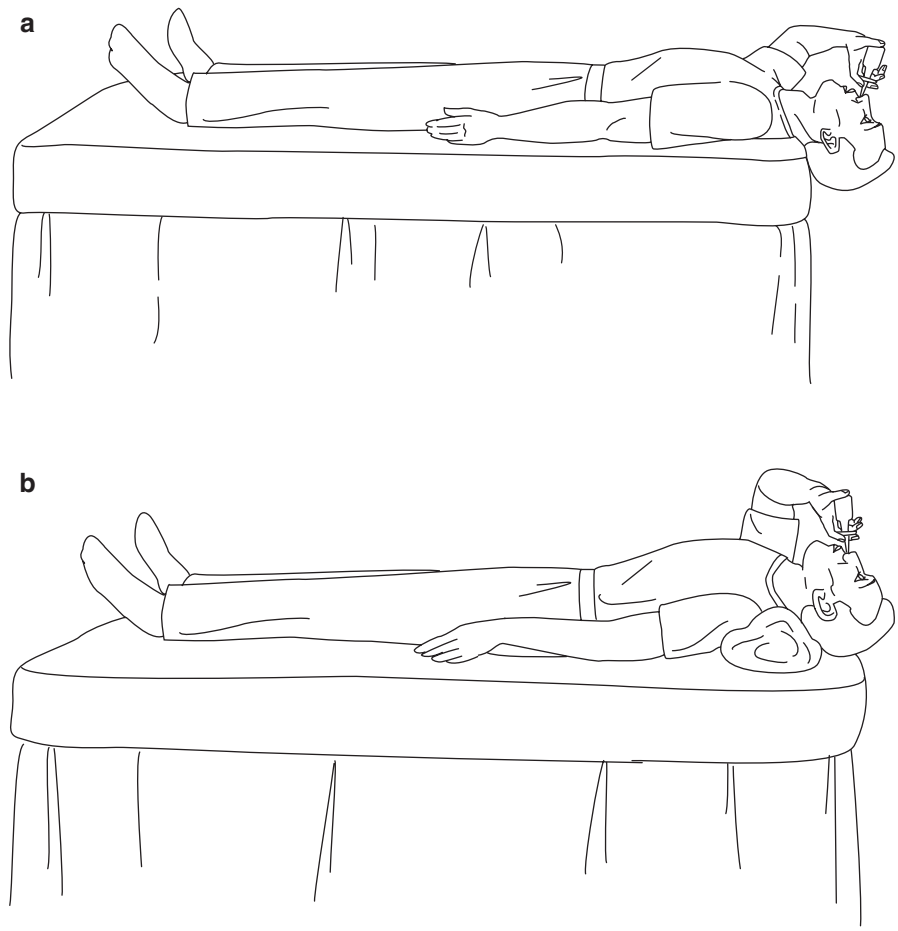

Fig. 23.1 (**a**, **b**) Nasal steroid drop delivery to frontal recess and olfactory cleft can be optimized by having the patient lie supine on a bed and hyper extend head over the edge or use a pillow or shoulder roll under the shoulders while applying nasal steroid drops

than sprays in patients with difficult disease. Frequently, the patient is encouraged to use a vigorous saline nasal wash of the nose followed by the application of the topical steroid either through nebulization or applying the steroid drop in a head hanging position to maximize the delivery and contact time of the steroid with the olfactory cleft. In Fig. 23.1a, b, the position of the patient with the head hyper extended in the supine position in order to place the olfactory cleft in the most dependent location is demonstrated.

23.2.1 Postoperative Use of Topical Corticosteroids

Although it is common practice for patients with nasal polyps to be placed on topical corticosteroids postoperatively to prevent recurrence of nasal polyps, there are few studies to support this practice. In a double blind clinical trial of 162 patients with nasal polyps or CRS who were randomized to fluticasone propionate aqueous nasal spray or placebo for 1 year following ESS, there was no significant difference between patients treated with a topical corticosteroid nasal spray vs. the placebo and this included analysis of subgroups of patients with nasal polyps and patients without prior sinus surgery [6]. In a nonblinded controlled longitudinal study of three groups of 54 patients undergoing endoscopic nasal polypectomy, treated postoperatively with saline lavage, fluticasone propionate following saline lavage, or beclomethasone dipropionate following lavage, the recurrence rate of nasal polyps in the group without steroids at 1 year was 44%; in contrast, the recurrence rate in the fluticasone propionate group and the beclomethasone dipropionate group at 1 year was 15 and 26%, respectively. Immediate postoperative use of fluticasone propionate has been reported to be

associated with increased epistaxis and infection. There was no increased rate of postoperative infections in any of the three groups in this study with infections developing in 2 patients in the placebo group and in one patient in the beclomethasone group [4].

23.2.2 Side Effects of Intranasal Steroids

The most common side effects of INS are septal excoriation and bleeding. This can be minimized with proper technique and instructing the patient to direct a nasal spray laterally toward the turbinates and not toward the midline and the septum. The cross hands technique instructs the patient to use the right hand to spray the left nose and the left hand to spray the right nose, which usually directs the nozzle of the spray laterally away from the septum (Fig. 23.2a, b).

In the more bioavailable topical nasal steroids, delay in growth in prepubescent children has led to an FDA warning on all INS; however, fluticasone propionate, fluticasone furoate, and mometasone furoate all have an indication for usage to at least age 4 and demonstrated no reduced rate of growth in prepubescent children in randomized placebo controlled trials [13].

Beclomethasone dipropionate nasal spray is associated with the onset of increased intraocular pressure. This was shown in a fairly convincing series of patients whose intraocular pressure normalized with the cessation of the beclomethasone dipropionate nasal spray. Whether such risks exist with the less systemically bioavailable INS is unknown and this response is uncommon. In a study of 360 subjects randomized to placebo, mometasone fuorate, fluticasone propionate, or beclomethasone dipropionate and monitored for intraocular pressure changes, variations in intraocular pressure were found in all INS groups; however, these

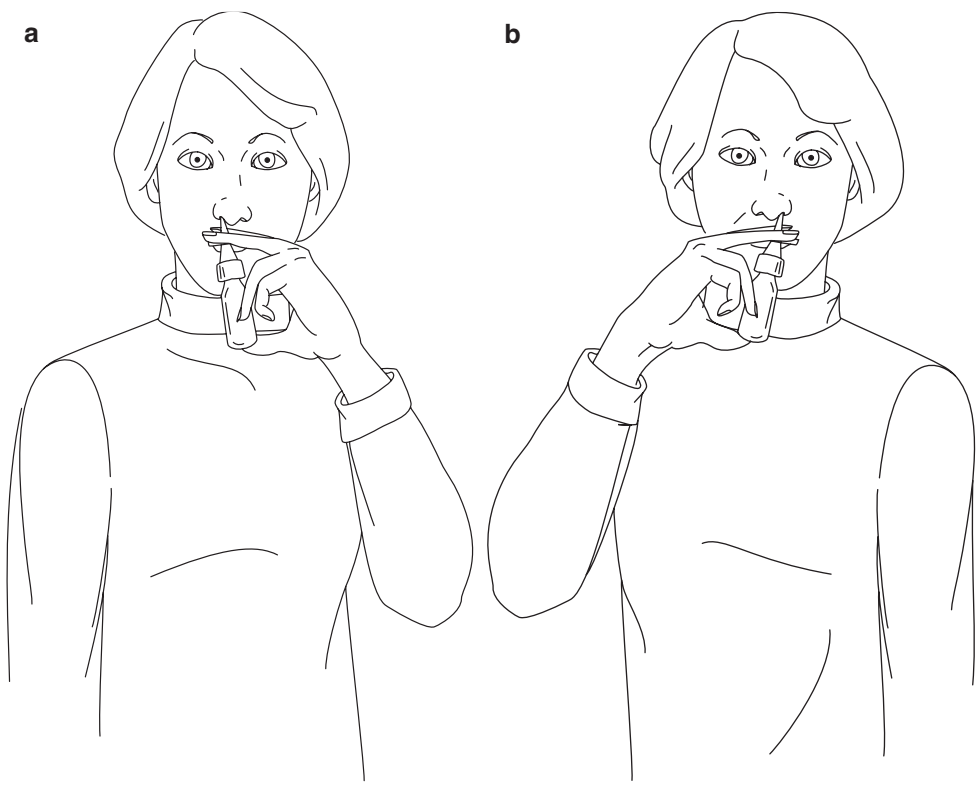

Fig. 23.2 (**a**, **b**) The "cross hands" technique of steroid nasal spray application, in which one uses the right hand to spray the left nose and the left hand to spray the right nose, naturally directs the nozzle of the spray toward the lateral wall of the nose and away from the nasal septum, thereby minimizing the incidence of septal excoriations and bleeding

variations were all considered to be within normal limits [5].

Although an older and at-risk population studied with INS might reveal an occasional patient who showed an increase in intraocular pressure, the better part of prudence is to recommend measurement of intraocular pressure (glaucoma screening) in patients over the age of 65, who are at increased risk for glaucoma, within a few months of the initiation of long-term INS for nasal polyp control.

23.2.3 Oral Corticosteroids and Maximal Medical Therapy

The effectiveness of oral corticosteroids in combination with topical corticosteroids was demonstrated in a study of patients with CRS with and without nasal polyps who were randomized to oral prednisone for 2 weeks vs. ESS. Both groups of patients received intranasal budesonide for 12 months. In both medical and surgical groups, significant improvement in the quality of life, nasal symptoms, and reduction in polyp size was seen at 6 and 12 months with no difference between the two treatment arms [1]. This study reinforces a widely held management principal that patients only be considered as candidates for ESS when they have failed maximal medical therapy that usually involves a short course of systemic steroids.

23.3 Perioperative Use of Oral Corticosteroids

In a double blind placebo controlled trial of 24 patients with chronic rhinosinusitis with nasal polyps (CRS with nasal polyps), Wright and Agrawal showed that perioperative systemic steroids reduced the technical difficulty of ESS and resulted in an improved endoscopic assessment up to 6 months postoperatively, although the strongest effect was seen 2 weeks postoperatively. There was, however, no difference in postoperative symptoms of patients on placebo or perioperative systemic steroids and both groups improved significantly postoperatively. The population of patients randomized was highly selected and had to be over 18 years of age with persistent symptoms and disease, despite 3 months of INS twice daily and saline irrigations and a 4–6-week course of endoscopically guided culture based antibiotic. Patients also had to have recurrent or persistent polyps within a 2-month period of a 2-week tapering trial of systemic steroids. Patients with suspected allergic fungal sinusitis (AFS) were excluded.

The oral steroid dose used in this study was 30 mg of prednisone taken each morning for 5 days preoperatively. Thirty mg of prednisone represents a moderate dose. This dose was continued for 9 days postoperatively without a taper. The current view of systemic steroid therapy is that less than 2 weeks of therapy does not require a steroid taper [15]. Two randomized controlled studies have shown efficacy in CRS with nasal polyps, one in a perioperative dosage and a second study in AFS with details listed in the following section (Table 23.3).

23.3.1 Allergic Fungal Sinusitis

Early recommendations for the postoperative prednisone dose in adults with AFS suggested 60 mg of prednisone tapered over several weeks. Rupa et al. recently published results of the first randomized controlled study of high-dose postoperative oral steroids in patients with AFS. She showed persistence of

Table 23.3 Randomized placebo controlled trials showing steroid efficacy in CRS

Condition	Dosage	Steroid effective	References
Perioperative CRS with and without nasal polyps, AFS excluded	Prednisone 30 mg daily × 5 days preop and for 9 days postoperatively	Yes	Wright and Agrawal [15]
AFS (all patients had nasal polyps)	Prednisone 50 mg once daily × 6 weeks, with a 6-week taper postoperatively	Yes	Rupa et al. [9]

disease endoscopically in 11 of 12 patients randomized to surgery, itraconazole 200 mg daily, and topical steroid × 12 weeks, but 8 of 12 patients randomized to surgery, itraconazole × 12 weeks, topical steroid and prednisone 60 mg daily × 6 weeks, with the prednisone tapered off over 6 weeks resolved completely. Not surprisingly, 5/12 randomized to postoperative high-dose prednisone became Cushingnoid. If after resolution of disease at 12 weeks the patient stopped using their INS, disease recurred, sometimes contralateral to the initial AFS, suggesting a host susceptibility to AFS and reinnoculation. Patients randomized to the high steroid taper were less likely to recur long term [9].

23.4 Risks and Side Effects of Oral Corticosteroids

Relative contraindications for the oral use of steroid drugs include gastric ulcer, some psychiatric diseases, glaucoma, invasive fungal infections, and tuberculosis.

23.4.1 Risks of Corticosteroids

Use of oral corticosteroids requires, at a minimum, counseling the patient regarding potential side effects. For short-term usage, the following should be relayed: insomnia, personality change, and avascular necrosis (AVN) of the hip (which is very rare). Long-term usage of corticosteroids includes truncal obesity, weight gain, glaucoma, cataracts, osteoporosis (requires greater than 3 months usage), peptic ulcer disease, and increased incidence of infection. The perioperative risks include increased risk of invasive fungal infection, impaired wound healing, as well as all the short-term risks listed.

The most common toxicities attributable to long-term use of glucocorticoids are skin thinning and purpura. Ocular toxicities from oral glucocorticoids include cataracts in a posterior subcapsular location, which can usually be distinguished from senile cataracts and glaucoma. Patients most likely to develop increased intraocular pressure often have a family history of glaucoma. A rare adverse effect of systemic, local, or even topical use of glucocorticoids is central serous chorioretinopathy. This type of chorioretinopathy is associated with edema formation that can separate the retina from the choroid [10].

The development of Cushingoid features (truncal obesity, buffalo hump, moon face, and weight gain) can occur within 60 days and usually occurs at doses above the physiologic range (greater than 7.5 mg/day of prednisone or equivalent). Alternate day therapy, which causes less hypothalamic pituitary adrenal axis suppression, may result in a lower incidence of the Cushingoid appearance.

Erin Wright in his Triologic Thesis outlined not only the relative benefits of preoperative steroids, but also a comprehensive analysis of the risks. Quite interestingly, the most unpredictable and potentially most debilitating aspect of short- (less than 7 days) or long-term systemic steroid usage was AVN of bone and frequently the hip. This quite rare complication may potentially be further reduced by the usage of the statin class of cholesterol lowering medications, which can prevent adipogenesis in the bone marrow [15]. In a review of the literature of AVN and corticosteroids from 1975 through 2008, Weldon found only case reports, reviews of osteonecrosis, and animal and human studies (mostly open, nonrandomized, and observational) and that most patients affected had confounding comorbidities such as hyperlipidemia, alcoholism, smoking, connective tissue disorders, and/or previous trauma to the affected area [14].

Survival curves demonstrating the time to the development of the first serious adverse event (i.e., the probability of remaining free of an adverse event) in patients with rheumatoid arthritis treated with no or different doses of prednisone shows a clear dose dependence of side effects: odds ratio 4.5 for 5–10 mg/day, and 32.3 for 10–15 mg/day [11] (Fig. 23.3).

23.4.2 Risks of Intrapolyp Injection

To date, no complications from intrapolyp injection of corticosteroids have been reported.

The injection of turbinates is associated with retrograde arterial embolization and blindness. While this

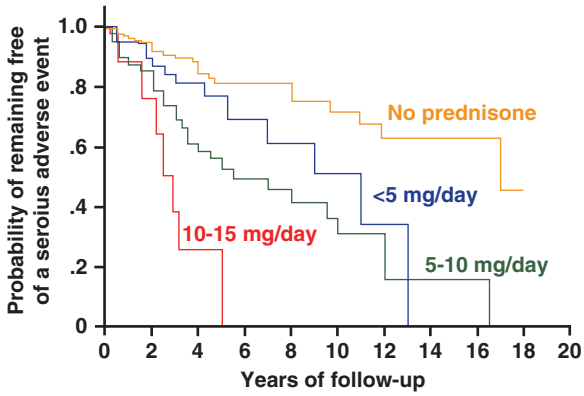

Fig. 23.3 Time course of steroid side effects

is possible, it is quite unlikely in nasal polyps that lack significant blood supply.

The accompanying video displays the technique for injection of the nasal polyp. Most polyps will not accommodate more than 0.05 mL of steroid. The preferred steroid is triamcinalone acetonide 40 mg/mL (KENALOG), which has a small molecular size. In my experience I cannot get more than 0.2 mL of steroid at most to stay in the polyps. CT scan may be vastly different after steroid therapy. CT scans are recommended after maximal medical therapy to show the extent of irreversible mucosal and bony disease (See Video).

Take Home Pearls

- The majority of NP are responsive to systemic steroids.
- Use of systemic steroids is limited by significant side effects, contraindications, and mortality of prolonged usage including glaucoma, cataracts, peptic ulcer disease, diabetes mellitus, fungal infections, tuberculosis, osteopenia, and osteonecrosis of the hip.
- Mladina characterizes NPs by gross characteristics and steroid responsiveness: almost solitary, steroid resistant polyps (5–7% out of all), NP with purulence and bacteria, steroid responsive (12–17%), NP associated with fungi, steroid responsive (14–15%), and NP with "glassy" appearance (about 60% out of all), steroid responsive.
- Topical nasal steroid sprays may successfully relieve symptoms and reduce need for sinus surgery in some patients and should be part of the initial medical management of NP patients.
- Preoperative systemic steroids at a dose of 30 mg of prednisone daily for a week reduce intraoperative bleeding, but have no longer-term impact on the success of surgery.
- Systemic and topical steroids are frequently used concomitantly; however, in massive nasal polyposis topical steroids are of no benefit.
- Based on randomized controlled trials, a variety of topical nasal steroids showed efficacy in treating NP; however, the dosage is generally twice that utilized for allergic rhinitis. Only mometasone has FDA approval for NP in the US.
- Intrapolyp injection of steroid preparations appears safer than intraturbinate injection, but efficacy in NP remains unstudied.
- A 12-week course of high-dose prednisone and itraconzaole is far superior to itraconazole alone in preventing long-term postoperative AFS recurrence, but is associated with a high incidence of Cushing's syndrome during therapy.
- Postoperative topical steroids are important in preventing NP recurrence in AFS and some but not all NP patients.

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Antifungal Treatment (Topical/Systemic)

24

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Core Messages

- The exact origin of chronic rhinosinusitis (CRS) is still unknown. The disease is most likely to be caused and maintained by multiple factors.
- A recent theory suggested fungi to be significantly implicated in the generation of CRS and nasal polyposis (NP).
- Preliminary reports suggested that topical antifungal treatment improved NP and CRS, whereas randomized, blinded, and placebo-controlled trials did not find antifungal lavages or sprays to be better than saline.
- Similarly, systemic antifungal treatment did not show any effect on CRS.
- Despite disappointing clinical trials, there is evidence that amphotericin B efficacy (a) depends upon the dosage and duration used and (b) probably acts via a selective cytotoxic effect on NP cells, rather than its antifungal properties.
- Whatever the future of amphotericin B in rhinology, one must not forget that this drug has side effects and that extensive use might induce resistances.

24.1 Introduction

The etiology of chronic rhinosinusitis (CRS) with or without nasal polyposis (NP) is unclear. In contrast to acute rhinosinusitis, which is usually bacterial or viral and easily treated, symptomatically or with antibiotics, CRS remains more difficult to manage. CRS, as defined in the European position paper on rhinosinusitis and nasal polyps (EPOS) 2007, consists of inflammation of the nose and the paranasal sinuses characterized by key symptoms such as facial pain/pressure, nasal blockage/obstruction/congestion, nasal discharge (anterior/posterior nasal drip), and reduction or loss of smell for more than 12 weeks [6, 7]. Many causes such as anatomical variants, microbial infection and/or colonization, fungal stimulation, atopic response, acetylsalicylic acid intolerance, and a combination of all have been proposed. 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 [5]. However, what has been hypothesized is not fungal infection, but rather fungal presence in sinonasal secretions, colonization following an allergic or an altered local (nonallergic) T helper 2-type immunologic reaction in predisposed individuals, resulting in the

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generation of chronic eosinophilic rhinosinusitis and NP [16]. If the inflammation observed in CRS with and without NP is an immune reaction to fungi, reducing the presence of this inflammatory trigger might improve the course of the disease [16]. Ideally, treatment should eliminate the fungus without causing harm to the host. In 1996, Bent and Kuhn studied 22 fungal cultures grown from 15 allergic, fungal sinusitis patients in vitro, for their susceptibility to five common antifungal drugs (ketoconazole, amphotericin B, itraconazole, nystatin, and fluconazole) [2]. Ketoconazole and amphotericin B were shown to be most effective, independent of the fungal organism tested [2]. Amphotericin B is active against most fungi frequently identified within the nose and paranasal sinuses [26]. 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 administration that use the injectable formulation including the administration of amphotericin B into the pleural cavity, bladder, synovial joints, and peritoneal space have been reported [5].

Various studies investigating the effectiveness of topical and systemic antifungals in CRS with and without NP have been published within the last decade (Table 24.1).

24.2 Topical Antimycotics: An Open Debate

In 2002, Ponikau et al. [17] published a prospective open-label trial using amphothericin B in 51 randomly selected patients with CRS with NP. 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. This study found symptomatic improvement in 75% and endoscopic improvement in 74%, mainly after long-term 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 ongoing. Although the authors concluded that amphotericin B is both safe and effective, the results fell under much criticism due to factors such as only 13 of the 51 patients being selected for a post-treatment sinus CT scan and the lack of a placebo-controlled comparison. Similar to the aforementioned study, an unblinded, uncontrolled study with 115 patients having medically resistant NP was performed by Ricchetti et al. [20] 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 NP were cured, but the treatment was not effective in patients with stage III of NP, suggesting that polyp stage is a relevant factor for treatment success. Patients who had previously undergone endoscopic sinus surgery (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. Similarly, Jen et al. [12] tested fluconazole nasal spray in addition to systemic steroids and itraconazole unblinded and uncontrolled on 16 patients having CRS with and without NP. They found stabilization or improvement in the subjective patients' perception and on nasal endoscopy in 75% of the patients, respectively. 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, randomized, double-blind, placebo-controlled trials have been conducted. In Germany, Weschta et al. [25] studied the application of 200 μL per nostril of amphotericin B (3 mg/mL) saline spray four times daily over an 8-week period in patients with NP. 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, quality of life scores, endoscopy scores, and presence of fungal elements in

Table 24.1 Topical and oral antifungal treatment in CRS and NP

Author	Indication	Number	Drug name	Solvent	Dose	Duration	Method	Study design	Symptoms	Objective	Level of evidence	Outcome
Ponikau et al. [17]	NP	51	Amphotericin B	Sterile water	100 µg/mL 20 mL twice daily each nostril	3–17 Months	Nasal lavage	Nonplacebo-controlled single-center study	Significant improvement (75%)	Significant improvement on endoscopy (74%) and CT (92%)	III	Positive
Ricchetti et al. [20]	NP	115	Ampho-moronal (Bristol-Myers Squibb) + topical corticosteroids	Sterile water	100 µg/mL 20 mL twice daily each nostril vs. 200 µL twice daily each nostril	4 Weeks	Nasal lavage vs. Nasal spray	Nonplacebo-controlled single-center study	–	Improvement (not significant) on endoscopy (40%), significant improvement on endoscopy in Stage I and II (48%)	III	Positive
Weschta et al. [25, 24]	NP	60	Amphotericin B (Bristol-Myers Squibb)	5% glucose solution (sodium phos-phate buffered)	3 mg/mL 200 µL four times daily each nostril	8 Weeks	Nasal spray	Randomized placebo-controlled double-blind single-center study	Significant worsening	No difference on CT, ECP, or tryptase levels	Ib	Negative
Shin and Ye [22]	NP	41	Amphotericin B	Sterile water	100, 50 µg/mL 10 mL twice daily each nostril	4 Weeks	Nasal lavage	Randomized placebo-controlled double-blind single-center study	–	Reduction in IL-5 concentration (not significant), no changes in the other cytokines	Ib	Negative
Jen et al. [12]	CRS + NP	16	Fluconazole (SinuCare, Inc.)	Saline water	200 µg/mL 2,500 µL twice daily each nostril	3 Months	Nasal spray	Nonplacebo-controlled single-center study	Stabilization or improvement (75%)	Stabilization or improvement on endoscopy (75%)	III	Positive (symptoms and endoscopy)
Ponikau et al. [18]	CRS + NP	24	Amphotericin B	Sterile water	250 µg/mL 20 mL twice daily each nostril	6 Months	Nasal lavage	Randomized placebo-controlled double-blind single-center study	No difference	Less mucosal thickening on CT, less EDN, but not IL-5, Alternaria protein, and eosinophils in lavage	Ib	Negative (symptoms) & positive (CT)

(*continued*)

Table 24.1 (continued)

Author	Indication	Number	Drug name	Solvent	Dose	Duration	Method	Study design	Symptoms	Objective	Level of evidence	Outcome
Helbling et al. [10]	NP	21	Amphotericin B	Sterile water	10 mg/mL 100 µL three times daily each nostril, total daily dose: 3 mg	3 Months	Nasal spray	Nonplacebo-controlled single-center study	Improvement (not significant) (33%)	Improvement on endoscopy (not significant) (14%)	III	Negative
Ebbens et al. [4]	CRS + NP	116	Amphotericin B (Bristol-Myers Squibb)	2.5% glucose solution	100 µg/mL 25 mL twice daily each nostril	13 Weeks	Nasal lavage	Randomized placebo-controlled double-blind multicenter study	No difference	No difference on polyp scores, PNIF, RSOM-31, and SF-36	Ib	Negative
Kennedy et al. [15]	CRS	53	Terbinafine (Novartis Pharma AG)	Not applicable	625 mg/day	6 Weeks (+ 9 weeks follow-up)	Oral	Randomized placebo-controlled double-blind single-center study	No difference	No difference on CT, MRI, endoscopy, and RSDI patient and physician	Ib	Negative
Rains and Mineck [19]	NP	83	After ESS: Itraconazole (Janssen Pharma.) + low-dose oral corticosteroids + topical corticosteroids	Not applicable	400 mg/day	6 Months	Oral	Retrospective chart review	–	Same recurrence rate as the total study population, less reoperation necessary (no statistics)	III	Positive
Corradini et al. [3]	NP	89	After ESS or medical polypectomy (triamcinolone i.m., total dose: 120 mg): topical lysine acetylsalicylate + amphotericin B	5% glucose solution	3.3 mg/mL; 0.5 mg/day	20 Months	Nasal lavage	Nonplacebo-controlled single-center study	–	Significant lower recurrence rate on endoscopy	III	Positive

ECP eosinophil cationic protein; *EDN* eosinophil-derived neurotoxin; *ESS* endoscopic sinus surgery; *IL* interleukin; *PNIF* peak nasal inspiratory flow; *RSDI* Rhinosinusitis Disability Index; *RSOM-31* rhinosinusitis outcome measure-31; *SF-36* Medical Outcomes Study Short Form-36

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. One hypothesis that was further investigated was that CRS patients may show different immunologic responses to fungi, which means that fungi in sinonasal secretions may activate the patient's immune system and induce the production of inflammatory cytokines, such as interleukin (IL)-3, IL-5, interferon (INF)-γ, and GM-CSF (granulocyte macrophage colony stimulating factor). Shin and Ye [22] published a randomized, placebo-controlled, double-blind trial studying this hypothesis by testing the effect of nasal antifungal treatment on the inflammatory cytokine levels in NP. NP were collected before and 4 weeks after irrigation treatment with topical amphotericin B or placebo. The cytokine – IL-5, IL-8, INF-γ, RANTES (regulated upon activation of normal T-cell expressed and secreted) – protein content of polyp homogenates was determined by means of ELISA (enzyme-linked immunosorbent assay). They found that NP 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 evaluations are needed to establish the efficacy and anti-inflammatory effects of antifungal treatments in CRS/NP patients.

Similar to the aforementioned study, Weschta et al. [24] published data on the effect of nasal antifungal treatment on the levels of eosinophil cationic protein (ECP) and tryptase in the CRS with NP patients already enrolled in the 2004 trial [25]. The purpose was to take another objective look at whether or not amphotericin B could reduce inflammation in the nasal mucosa of CRS with NP patients. 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 CRS with NP patients. Consequently, they found no benefit for the use of amphotericin B nasal 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. [18] conducted a randomized, 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. In this study, no significant effect on symptoms was demonstrated, 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) were 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, multicenter trial was done in 2006. Ebbens et al. [4] randomly selected 116 patients 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, multicenter study. Subjective symptom scores were assessed with the visual analog scale (VAS), the amount of nasal obstruction by peak nasal inspiratory flow (PNIF), nasal endoscopy scores, polyp scores, and quality of life 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 NP in patients with a normal immune status. These results were repeated

in a prospective, nonplacebo-controlled single-center 3-month trial by Helbling et al. [10], who looked at the effect of amphotericin B on NP. They also did not find significant improvement in symptoms, or decreased NP stages at the nasal endoscopy. Although initial reports were promising, the results of these more recent studies, taken together, suggest that topical amphotericin B is not significantly efficacious in treating CRS with NP.

24.3 Systemic Oral Antimycotics

In 2005, Kennedy et al. [15] published a randomized, double-blind, placebo-controlled, multicenter trial studying the use of high-dose oral terbinafine on CRS and NP. Fifty-three adults with CRS received either 625 mg/day ($n=25$) terbenafine 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 either subjective or objective benefits after terbinafine treatment, and concluded that the treatment failed to improve the radiographic appearance and the symptoms 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 the 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 posttreatment sinus biopsies of selected patients, demonstrating that terbinafine levels were well within minimum inhibitory concentration ranges for fungal isolates thought to play a role in CRS. 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. [16], 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 sinunasal 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 NP, that terbinafine is inadequately secreted into the sinonasal mucus or less, that the duration of therapy was inadequate.

24.4 Antimycotics After Endoscopic Sinus Surgery

In a study looking at the effects of oral antifungal treatment after functional ESS, Rains and Mineck [19] reviewed a 12-year chart-cohort. They extracted data on 139 patients with allergic fungal sinusitis treated with high-dose itraconazole, short-burst oral corticosteroids, and topical steroids after functional ESS. Although 50.3% experienced recurrence, only 20.5% required reoperation, which was a low rate when compared with the literature results for that time period (48–56%). No severe adverse effects were seen from itraconazole over 36,000 doses prescribed. Consequently, they concluded that the combined regimen above, including oral antifungal treatment, was a safe and effective management strategy after surgery and may result in a reduction of revision surgery. However, the study was done retrospectively and the question if the observed results are caused by a steroid potentiating effect of oral itraconazole or the result of its antifungal action cannot be answered.

A recent open randomized trial published by Corradini et al. [3], comparing the protective effects of lysine aspirin (LAS) and LAS combined with amphotericin B on NP recurrence in 89 patients who underwent medical treatment 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. 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 NP in the groups treated with amphotericin B plus LAS was significantly lower ($p=0.018$) than that in the two groups treated only with LAS post-"polypectomy." They concluded that the presence of fungi could be a secondary cofactor in NP, acting by the way of enhancing the inflammatory response of the NP, and that long-term topical treatment with LAS and amphotericin B may be clinically effective in the treatment of NP.

24.5 Effects of Amphotericin B

It has been suggested that topical amphotericin B treatment can reduce fungal load, thereby reducing the inflammatory response in the nasal cavities and

paranasal sinuses, resulting in the improvement of CRS and NP. In response to the controversy in the literature regarding the use of amphotericin irrigation in CRS and NP patients, Shirazi et al. [23] published an in vitro study on the use of amphotericin B against ten 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 300 and 200 μg/mL solutions, however, had a fungicidal effect after 5 and 6 weeks, respectively. The results of this study support another clinical trial using higher doses of topical amphotericin B at shorter treatment intervals (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 NP, in particular, poses huge difficulty in drug delivery. Since most authors believe that CRS with NP has a greater association with fungus than CRS without NP, Shirazi et al. 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 different study designs and solvents used in the in vivo trials (Table 24.1) make comparisons on the therapeutic effect of antifungal solutions unreliable.

Recent studies suggest that amphotericin B may have clinically beneficial effects in addition to its antifungal properties. In common with other polyene antibiotics and antimycotics, amphotericin B acts on cellular membrane permeability [9]. 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 NP epithelial cells with amphotericin B (50M, 4 h daily for 5 days), Jornot et al. [13] observed an increase in cell permeability and, as a consequence, a disruption of the integrity of epithelial monolayer derived from NP (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 differential effect on both cell types [13]. For turbinate epithelial cells, Jornot et al. [14] later observed that amphotericin B treatment results in a decrease in transepithelial potentials, short-circuit currents, and Na+ absorption. This inhibition of Na+ transport was at first associated with decreased apical sodium channel (EnaC) activity 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 subsequent to the 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 NP epithelium remains unclear.

In addition to a possible cytotoxic effect on epithelial cells of CRS and NP, 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), was not shown to result in a significant reduction in IL-5, IL-8, IFN-γ, and RANTES levels [22]. In addition, an 8-week treatment regimen with a topical amphotericin B spray (3 mg/mL, 200 μL per nostril, four times daily) was also not shown to result in a significant reduction in ECP and tryptase levels in nasal lavage fluid from patients with CRS with NP. 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 [24].

These are possible mechanisms for the clinical effect of amphotericin B that are independent of its antifungal role, reducing the size of NP by decreasing edema, leading to subjective improvement.

24.6 Side Effects of Antimycotics

Although the advantages are clear, topically applied drugs may have cytotoxic effects. To rule out this possibility, Hofer et al. [11] studied the effect of topical

amphotericin B on ciliary beat frequency (CBF). When diluted in saline, no effect of amphotericin B (0.1 mg/mL) on CBF was observed. When diluted in distilled water, CBF was irreversibly lowered to about 50%, suggesting that physiologic solvents should be used. Confirming the findings by Hofer et al. [11], Gosepath et al. [8] observed minimal ciliotoxicity upon treatment with low concentration of amphotericin B (2.5, 5%). After increasing the concentration to a 10% solution, CBF dropped. The effect of long-term and repeated dosing on CBF 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 randomized placebo-controlled trial was similar in the active and placebo groups [4]. However, major adverse events were more common in the active treatment group (9% in active vs. 0% in placebo group, respectively), although only 1 event was judged to be drug-related (asthma attack). In a similar trial, Ponikau et al. [18] 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. However, similar to Ebbens et al. [4], 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, nonplacebo-controlled trials of topical antimycotics, adverse events were shown between 0 and 20%, mostly describing a burning sensation and nasal blockage during drug application [17].

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 certain 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 randomized placebo-controlled trial of Kennedy et al. [15], oral treatment with terbenafine for 6 weeks did not induce more adverse events than placebo, none was drug-related, and no difference in liver function was observed between the active and placebo group after 6 weeks. In the retrospective work of Rains et al. [19], no severe adverse effects were described in a total of 139 treated patients. The noticed adverse effects were minor like subjective malaise and nausea (8 patients), lower-extremity edema (11 patients), and significant liver enzyme elevation (6 patients). In case the 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 work every 1–2 months is indicated, along with patients' understanding of the risks, benefits, and alternatives.

Another concern regarding the use of amphotericin B as topical treatment for CRS and NP 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 increased drug resistance in common fungal pathogens which still demonstrate low resistance, like Candida and Mucor [1, 21, 27]. This is a real possibility due to different drug distribution pattern in the sinus cavities (some spaces have subtherapeutic drug concentration), and, in time, we may lose a valuable antifungal systemic drug, which still demonstrates low resistance.

24.7 Conclusions

The use of antifungal irrigation and oral antifungal treatment in patients with CRS and NP is not justified by the majority of recent data. 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 three uncontrolled trials, four subsequent placebo-controlled studies either failed to show clinical benefit or showed, at best, only modest benefit of topical antifungal treatment in patients with CRS and NP (Table 24.1). Although the therapeutic effects of amphotericin B are said to result from its antifungal effect, they may also result from a selective cytotoxic effect and possible anti-inflammatory properties. There also exists no clear evidence for justifying the routine use of any adjuvant topical or oral antifungal therapy after ESS in patients with CRS and NP [19]. Further research needs to be performed to test whether variations in

topical antifungal dosage, formulation, application methods, and duration of treatment, oral antifungals, and postendoscopic sinus surgery therapy could improve clinical signs and symptoms and decrease the recurrence rate in patients with CRS and NP.

Take Home Pearls

- Based on clinical observations, antifungal treatment and especially amphotericin B have been postulated to improve symptoms and reduce NP stage.
- No evidence-based trial confirms this claim.
- In vitro and in vivo studies suggest that amphotericin B has cytotoxic properties mainly restricted to NP cells but not to normal respiratory epithelium.
- The debate whether amphotericin B is a useful and efficient drug for CRS and NP remains open.

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Antibiotic Treatment (Topical/Systemic)

25

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Core Messages

- The role of bacteria in the pathogenesis of chronic rhinosinusitis (CRS) with and without nasal polyps is still controversial.
- Contrary to acute rhinosinusitis, CRS often exhibits polymicrobial infections with Gram-positive, Gram-negative, and anaerobic bacteria present.
- Bacterial biofilms, intracellular residency, and exotoxins potentially contribute to the inflammatory processes of CRS.
- Macrolide antibiotics have anti-inflammatory, immunomodulatory, antimucus, and antibacterial actions.
- There is no clear evidence for topical intranasal antibiotic agents in the treatment of CRS. Several antiseptic solutions and saline nasal lavages are of increasing interest.
- There is no clear evidence for short-term systemic antibiotic agents in the treatment of CRS, but culture-directed short-course oral therapy should be considered on an individual basis.
- There is good evidence that long-term macrolide antibiotic treatment improves symptoms, decreases nasal polyp size, and reduces inflammatory markers in CRS. Further, associated bronchial asthma seems to improve in parallel by this treatment.
- It is important to be aware of the potential side effects of antibiotic agents.

25.1 Background

While the etiology of chronic rhinosinusitis (CRS) with and without nasal polyps (NP) remains uncertain, bacteria have traditionally been regarded as major contributors to the pathogenic processes behind this disease [6, 70]. 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. 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 [8]. 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*) [7, 9, 12–15, 17, 23, 31, 49]. The pathogenicity of some of the low-virulence organisms, such as *Staphylococcus epidermidis*, is questionable [28, 35]. In contrast, Gram-negative rods are more likely to play a

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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, between [5, 46] and *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* [9, 11]. 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 complications (such as mucocele, osteomyelitis, abscess formation) and intracranial complications [10].

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 *Staphyloccocus aureus* exotoxins (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 [1, 27]. A biofilm consists of clusters of bacteria held together by an extracellular glycocalyx, with interspersed water channels. Using scanning electron microscopy, bacterial biofilms have been found on the mucosa of 80% of a small population of CRS patients, compared to none in healthy controls [54]. Biofilm formation may be promoted by antibiotic use, particularly in the setting of poor antibiotic tissue penetration or antibiotic resistance, which leads to persistent, viable microbes. Once established, biofilms tend to protect the bacteria within them from the action of antibiotics, rendering them resistant to antimicrobial agents.

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 [50]. There is also concern that antibiotic use might promote the development of this intracellular reservoir, particularly for *Staphylococcus aureus* [20].

Staphylococcus aureus can also secrete *exotoxins (SAEs)*, substances which can act as superantigens, capable of stimulating an immense inflammatory response. In studies on NP, *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 NP [3, 77]. However, another recent study found no difference in the presence of SAEs in nasal tissue from patients with CRS with and without NP. In addition, SAEs are not present in all cases of CRS with or without NP (Heymans et al., submitted).

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

Given the lack of data, practically, the issue of antibiotic use must be decided individually for each patient, weighing the impact of possible side effects against potential benefits for that patient (Tables 25.1–25.3).

25.2 Potential Therapeutic Actions of Antibiotic Agents

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 reviewed, as much research has recently improved our understanding of this interesting class of antibiotic agent.

Possible mechanisms of action of macrolides in the therapy of CRS with and without NP are shown in Fig. 25.1.

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 [62]. This is a nuclear transcription factor that stimulates the expression of several proinflammatory cytokines

Table 25.1 Topical antibiotic treatment in CRS and NP

References	Indication	Number	Drug name	Solvent	Dose	Duration (weeks)	Method	Study design	Symptoms	Objective	Level of evidence	Outcome
Sykes et al. [65]	CRS	50	Dexamethason, tramazoline with/without neomycin	Saline water	Dexamethason 20 µg, tramazoline 120 µg, neomycin 100 µg four times daily each nostril	2	Nasal spray	Randomized placebo-controlled double-blind single-center study	Improvement: 70 vs. 60 vs. 20% (placebo)	Improvement: 70 vs. 60 vs. 20% (placebo)	Ib	Negative
Kobayashi et al. [37]	CRS	208	Aminoglycoside, fosfomycin, cefmenoxime	Saline water	Aminoglycoside 5, 10, 20 mg, fosfomycin 30, 50 mg, cefmenoxime 20, 40 mg, three times a week	8	Aerosol	Nonplacebo-controlled single-center study	Improvement (43–72%)	Improvement on X-ray (32–59%)	III	Positive
Desrosiers et al. [21]	Refractory CRS after ESS	20	Tobramycin	Saline water	80 mg three times daily	4	Aerosol	Randomized placebo-controlled double-blind single-center study	No difference	No difference	Ib	Negative
Scheinberg et al. [56]	Acute infection in CRS after ESS	41	Cefuroxime, ciprofloxacin, levofloxacin, tobramycin	Not mentioned	Cefuroxime 285 mg three times daily, ciprofloxacin 90 mg twice daily, levofloxacin 70 mg twice daily, tobramycin 95 mg twice daily	3–6	Aerosol	Retrospective chart review	Improvement (83%), significant improvement in total sinonasal signs and symptoms	–	III	Positive
Vaughan et al. [69]	Acute infection in CRS after ESS	42	Tobramycin, levofloxacin, ceftazidime, ciprofloxacin, ofloxacin, gentamicin	Not mentioned	Tobramycin 95 mg twice daily, levofloxacin 70 mg twice daily, ceftazidime 550 mg twice daily, ciprofloxacin 90 mg twice daily, ofloxacin 90 mg twice daily, gentamicin 95 mg twice daily	3	Aerosol	Retrospective chart review	–	Infection free at 3 months of follow-up in 67%, improvement in RSOM-31	III	Positive

RSOM rhinosinusitis outcome measure

Table 25.2 Systemic short-term antibiotic treatment in CRS and NP

References	Indication	Number	Drug name	Solvent	Dose	Duration (weeks)	Method	Study design	Symptoms	Objective	Level of evidence	Outcome
Legent et al. [39]	CRS (excepted NP)	251	Ciprofloxacin vs. amoxicillin/ clavulanate	–	Ciprofloxacin 500 mg twice daily, amoxicillin/clavulanic acid 500 mg three times daily	9 days	Oral	Nonplacebo-controlled, double-blind, single-center study	Improvement in both groups (59 vs. 51%)	Improvement in both groups on endoscopy (91 vs. 82%), bacteriological eradication (89 vs. 91%)	Ib	Negative
Fombeur et al. [25]	CRS + NP	56	Ciprofloxacin + prednisolone	–	Ciprofloxacin 500 mg twice daily, prednisolone 40 mg once daily	9 days	Oral	Nonplacebo-controlled single-center study	Improvement (74.5%)	Bacteriological eradication (90%)	III	Positive
McLeod et al. [41]	CRS + NP	25	Clarithromycin	–	500 mg twice daily	2 weeks	Oral	Nonplacebo-controlled single-center study	Improvement	Statistically significant reduction in CD68, EG2, elastase, IL-6, IL-8, TNF-α, and edema score	III	Positive
Subramanian et al. [61]	CRS + NP	40	Trovafloxacin, amoxicillin/ clavulanate, levofloxacin, and others + prednisone + adjunctive therapy (nasal saline irrigation, intranasal steroids)	–	Antibiotics not mentioned	4–8 weeks	Oral	Retrospective chart review	Improvement (73%)	Improvement on CT-scan (85%)	III	Positive
Namyslowski et al. [48]	CRS + acute infection of CRS	206	Amoxicillin/ clavulanate vs. cefuroxime axetil	–	Amoxicillin/ clavulanate 875/125 mg twice daily, cefuroxime axetil 500 mg twice daily	2 weeks	Oral	Nonplacebo-controlled multicenter study	Clinically cured: 95 vs. 88%	Bacterial eradication: 65 vs. 68%	Ib	Negative

CD68 marker of macrophages; *EG2* marker of eosinophilic activity; *IL* interleukin; *TNF-α* tumor necrosis factor-α

Table 25.3 Systemic long-term antibiotic treatment in CRS and NP

References	Indication	Number	Drug name	Solvent	Dose	Duration (weeks)	Method	Study design	Symptoms	Objective	Level of evidence	Outcome
Gandhi et al. [26]	CRS in children	26	Amoxicillin, amoxicillin/clavulanate, trimethoprim/sulfamethoxazol, cefaclor	–	Dose not mentioned, once daily	12 months	Oral	Nonplacebo-controlled single-center study	Decrease of acute exacerbation by 50% in 73%	–	III	Positive
Scadding et al. [55]	CRS	10	Amoxicillin, flucloxacillin, cefadroxil, co-trimoxazole	–	Dose not mentioned	3 months	Oral	Nonplacebo-controlled single-center study	Improvement (80%)	Significant increasing in ciliary beating	III	Positive
Ichimura et al. [34]	NP	20	Roxithromycin	–	150 mg once daily	2 months	Oral	Nonplacebo-controlled single-center study	–	Decrease of polyp size (52%)	III	Positive
Hashiba et Baba [32]	Refractory CRS	45	Clarithromycin	–	200 mg twice daily	2–3 months	Oral	Nonplacebo-controlled single-center study	Improvement (71%)	–	III	Positive
Kimura et al. [36]	CRS + NP	30	Roxithromycin	–	150 mg once daily	3 months	Oral	Nonplacebo-controlled single-center study	Improvement (80%)	Improvement on X-ray (53%)	III	Positive
Suzuki et al. [63]	CRS + NP	12	Roxithromycin	–	150 mg once daily	4–11 months	Oral	Nonplacebo-controlled single-center study	–	Significant decrease in neutrophil score, reduction of nasal IL-8 and improvement on CT-scan	III	Positive
Suzuki et al. [64]	CRS	16	Clarithromycin, roxithromycin	–	Clarithromycin 200 mg once daily, roxithromycin 150 mg once daily	2–3 months	Oral	Nonplacebo-controlled single-center study	–	Higher response rate in patients with normal Ig E and lower eosinophil counts in the peripheral blood	III	Positive

(*continued*)

Table 25.3 (continued)

References	Indication	Number	Drug name	Solvent	Dose	Duration (weeks)	Method	Study design	Symptoms	Objective	Level of evidence	Outcome
Yamada et al. [74]	NP	20	Clarithromycin	–	200 mg twice daily	3 months	Oral	Nonplacebo-controlled single-center study	–	Correlation between reduction of IL-8 and decrease of NP size	III	Positive
Cervin et al. [19]	Refractory CRS after ESS	17	Erythromycin, clarithromycin	–	Erythromycin 250 mg twice daily, clarithromycin 250 mg once daily	12 months	Oral	Nonplacebo-controlled single-center study	Improvement (77%), significant improvement in VAS (nasal congestion, sticky secretion, runny nose, headache)	Significant improvement in saccharine transit time and on endoscopy	III	Positive
Ragab et al. [51]	CRS + NP	90	Erythromycin vs. ESS	–	500 mg twice daily for 2 weeks, 250 mg twice daily for 10 weeks	3 months	Oral	Randomized prospective nonplacebo-controlled single-center study	Significant improvement (VAS) without difference between the two groups	Significant improvement in SNOT-22, SF36, nitric oxide, acoustic rhinometry, saccharine clearance time and nasal endoscopy, no difference between the two groups except for total nasal volume	Ib	Positive
Wallwork et al. [72]	CRS without NP	64	Roxithromycin vs. placebo	–	150 mg once daily	3 months	Oral	Randomized placebo-controlled double-blind single-center study	Significant improvement in global patient rating compared to placebo	Significant improvement in SNOT-20, nasal endoscopy, saccharine transit time, IL-8 levels in the macrolide group	Ib	Positive
Moriyama et al. [45]	After ESS: CRS + NP	149	After ESS: Erythromycin vs. no treatment	–	600 mg three times daily, 400 mg twice daily, 200 mg once daily	3–6 months	Oral	Retrospective open study	Significant overall improvement (88 vs. 68%)	Normal findings on endoscopy (82 vs. 70%), good improvement on X-ray (72 vs. 56%)	III	Positive

IL interleukin; *Ig* immunoglobulin; *VAS* Visual Analog Score; *SNOT* sinonasal outcome test; *SF36* Short Form 36 Health Survey; *ESS* endoscopic sinus surgery

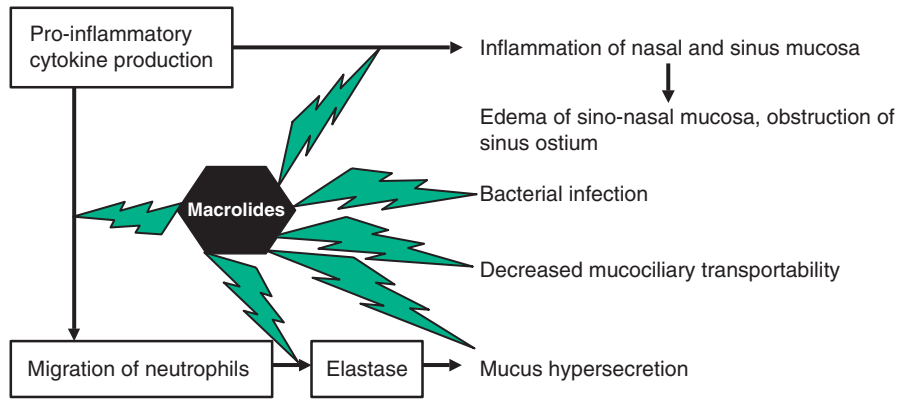

Fig. 25.1 Macrolides reduce inflammation of the sinonasal mucosa by inhibiting the production of proinflammatory cytokines, neutrophil elastase, and migration of neutrophils. Macrolides also have antibacterial properties, direct inhibitory effect on mucus hypersecretion and increase mucociliary transportability (modified from [42])

[44]. Specifically, macrolides reduce the expression of interleukin (IL)-2, IL-6, tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1, and, importantly, IL-8. IL-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 granulocyte/macrophage colony-stimulating factor [71]. Clinically, in CRS 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 edema of the nasal mucosa [41]. 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 [64].

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 bacteriocidal. 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, hemolysin, lectins, phospholipase C, and eotaxin A produced by *Pseudomonas aeruginosa* [33]. The effect is a reduction of damage to the surrounding tissue [59]. In a similar fashion, low-dose roxithromycin (RXM) reduced the virulence of pneumococci in a mouse model of pneumonia. Specifically, expression of matrix metalloproteinase-7 and activation of keratinocyte-derived chemokine production was inhibited in the lungs, while mononuclear cell responses were increased, resulting in enhanced bacterial clearance [75].

Importantly, macrolides are effective against some intracellular pathogens, such as *Corynebacterium diphteriae*, *Bordetella pertussis*, *Legionella pneumophila*, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae* [60]. Another class of antimicrobials, tetracyclines, also has this effect and, interestingly, evidence of their immunomodulating activity is emerging.

Macrolides have also been shown to alter the structure and function of the biofilm produced by *Pseudomonas aeruginosa* [67, 73]. Azithromycin inhibits interbacterial communication, also referred to as quorum-sensing [47]. This is an important bacterial virulence factor in the production and maintenance of biofilm.

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 [30]. Clarithromycin and erythromycin inhibited mucus secretion from human mucoepidermoid carcinoma cells and human nasal epithelial cells [57]. In animal studies, clarithromycin and erythromycin block the infiltration of neutrophils into airway goblet cell clusters, reducing goblet cell hyperplasia and, consequently, mucus secretion [66, 68]. Macrolides may also inhibit the expression of the mucin geneMUC5AC, which is found primarily in goblet cells [66, 68].

Clinically, clarithromycin 500 mg twice daily for 2 weeks given to patients with purulent rhinitis, restored nasal secretions to normal, decreased secretion volume by tenfold, and increased mucociliary transportability by 30%, compared to healthy controls [52].

There are efforts under way to develop a new group of macrolides which lack an antibacterial effect, the so-called "immunolides" or "designer macrolides" [18, 22]. If they were to prove effective, it would reduce the potential problem of bacterial resistance developing upon long-term macrolides treatment.

25.3 Topical Intranasal Antibiotic Agents (Table 25.1)

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 and, indeed, there is a lack of data to support their use. 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.

Two retrospective studies have examined the efficacy of nebulized antibiotic agents on CRS patients who were refractory to medical and surgical treatment. One study described 3–6 weeks of topical treatment given to 41 patients: 82.9% experienced a significant improvement of their total sinonasal symptom score [56]. A similar study reviewed results at 3 months and found that 67% of patients were free of infection and reported improvements in posterior nasal discharge, facial pain/pressure, and emotional sequelae. Nebulized antibiotic treatment was associated with a longer infection-free period (average, 17 weeks) compared with standard therapy (average, 6 weeks) [69].

In 208 patients with CRS, an ultrasound-type inhaler was used to deliver a topical aminoglycoside (fosfomycin) and cefmenoxine three times a week during 2 months. There was a clinical efficacy rate of 43–72% and a radiologic efficacy rate of 32–59%, increasing with the dose of the drugs [37].

Studies of better design seem to contradict these data. In a randomized, double-blinded, placebo-controlled trial of 50 patients with CRS, three treatment groups were 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 [65].

Another randomized, double-blinded 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 pretreatment scores [21].

On the available evidence, there is currently no place for topical antibiotics in the treatment of (CRS) with and without NP. The pharmacokinetic and pharmacodynamic parameters of topically applied antibiotics need further investigation, so dosing and scheduling of regimens can be better defined.

25.4 Systemic Antibiotic Agents

If antimicrobial agents are prescribed for the treatment of CRS with and without NP, 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 antianaerobic efficacy (e.g., levofloxacin, moxifloxacin, and gatifloxacin). A fluoroquinolone with adequate antianaerobic 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 cephalosporins (e.g., cefoxitin, cefotetan, cefmetazole), combinations of a 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 [16, 17].

25.4.1 Does Short-Term Antibiotic Treatment Confer a Benefit? (Table 25.2)

In a prospective study on 56 patients with acute exacerbations of CRS with and without NP, patients were given 500 mg ciprofloxacin twice daily for 9 days and 40 mg prednisolone once daily for 6 days [25]. There was no placebo group. Of the patients with positive pretreatment 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 [41]. A significant reduction was seen in eosinophilic activity (EG2), macrophages (CD68), IL-6, IL-8, TNF-α, elastase, and mucosal edema 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 retrospective study of 40 patients with CRS with and without NP, treatment had been given with different antibiotics for 4–8 weeks, a 10-day course of systemic corticosteroids, nasal saline irrigations, and intranasal steroids [61]. Clinical and radiological outcome measures improved (73 and 85% respectively). The improvements in both measures correlated in a statistically significant manner, but it is difficult to determine the specific benefit of the antibiotic agents.

25.4.2 How Do Different Antibiotics Compare? (Table 25.2)

In a prospective, double-blinded study, 251 adult patients with CRS were treated with ciprofloxacin or AMX/CA for 9 days [39]. 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, among patients who had a positive initial culture, ciprofloxacin recipients had a significantly higher cure rate than those treated with AMX/CA 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 [48]. Overall cure rates were similar: 95% for AMX/CA and 88% for cefuroxime. Rates for eradication of the originally identified pathogen 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 oral antibiotic therapy is associated with a 51–95% improvement in CRS symptoms, although the studies have no placebo-control arms, so it is difficult to interpret this as a definite therapeutic benefit. Also, there is no separation of CRS without and with NP. There is no overall difference between the therapeutic effects of ciprofloxacin vs. AMX/CA and cefuroxime axetil vs. AMX/CA.

25.4.3 Does Long-Term Macrolide Treatment Confer a Benefit? (Table 25.3)

Long-term courses of macrolide antibiotics have been extensively studied in the treatment for CRS with and without NP. One study examined the effect of RXM (150 mg a day) for at least 8 weeks on 20 patients with

CRS with NP. There was a NP decrease in 52% of patients and those with smaller polyps were more likely to improve. Associated allergic conditions and the extent of eosinophilic infiltration had no relation to the treatment result [34]. RXM (150 mg daily) given for 3 months to 30 patients with CRS with and without NP during 4 to 11 months, significantly improved all the symptoms ($p<0.001$), except for the sensation of foul odor [36]. RXM 150 mg daily was given to 12 patients with CRS with and without NP during 4 to 11 months [63]. 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.

There was no control group in any of these studies.

The effect of clarithromycin on refractory cases of CRS has also been examined in a study of 45 adult patients, treated with 400 mg/day for 8–12 weeks [32]. There was a clinical improvement in 71% and clinical efficacy depended upon the duration of treatment. Again, there was no control group.

In a study of 16 patients with CRS given 200 mg clarithromycin or 150 mg RXM daily for 2–3 months [64], 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. Another study showed that IL-8 levels in nasal lavage from patients with NP were reduced during macrolide treatment and this reduction was significantly correlated with a reduction in the size of the NP [74]. Neither study had control groups.

Longer-term treatment has also been studied. Initially, 17 patients with persistent CRS after sinus surgery, systemic steroids, and long-term (nonmacrolide) antibiotics were enrolled in a study and treated with erythromycin 250 mg twice daily or clarithromycin 250 mg daily [19]. 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 analog 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 NP were randomized to a group receiving oral corticosteroid followed by 3 months of topical corticosteroid plus erythromycin, or a group receiving endoscopic sinus surgery followed by topical corticosteroids for 3 months [51]. Follow-up at 1 year showed significant improvement in VAS scores of symptoms, sinonasal outcome test (SNOT-22), Short Form 36 Health Survey (SF36), nasal nitric oxide concentration, acoustic rhinometry, saccharine clearance time, and nasal endoscopy score in both the groups. 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 NP. 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-blinded, randomized, placebo-controlled clinical trial, 64 patients with CRS without NP received either 150 mg RXM daily for 3 months or placebo [72]. 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. [26] followed 26 children with CRS who were treated prophylactically for more than 1 year in a prospective, nonplacebo-controlled open single-center study. The 12-month period before the use of 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 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. [55], in a nonplacebo-controlled single-center study, observed nasal symptoms and measured the ciliary beat frequency in 10 patients with CRS before and after 3 months of antibiotic treatment. They showed that these patients 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.

Thus, long-term, low-dose macrolide antibiotics seem to be effective in treating CRS with and without NP. The few available prospective studies show improvement in symptoms varying from 71 to 80% of patients.

25.5 Antibiotic Agents After Endoscopic Sinus Surgery (Table 25.3)

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 trial involving intranasal antibiotics in the postoperative treatment to prevent recurrences of CRS with and without NP is available.

In a retrospective study of 149 postoperative patients with CRS with and without NP, 57 had been treated with systemic erythromycin, starting at 1,800 mg daily and reducing every second month [45]. The remaining patients served as controls. The overall clinical improvement was significantly higher in the treated group (88 vs. 68%, $p<0.01$).

25.6 Side Effects of Antibiotic Agents

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 the cessation of the medication. Irreversible toxicities include aminoglycoside-induced ototoxicity, Stevens–Johnson syndrome, and toxicity secondary to nitrofurantoine.

Topical antibiotic treatment have demonstrated side effects in 10–21% of patients, including sore throat, cough, dry skin around the nose and lip, tinnitus, and joint pain/myalgia. All of these side effects resolved after stopping the drug. No serious side effects were described [56, 69]. Ciliotoxicity occurs with ofloxacin and the effect of long-term and repeated dosing on ciliary beat frequency is unknown [29]. In the randomized placebo-controlled double-blind single-center study by Desrosiers et al. [21], 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 [25, 39, 48]. Most frequent were gastrointestinal adverse effects (diarrhea, loose stools, abdominal pain, nausea/vomiting). Other adverse events were facial edema, asthma, vagal discomfort, genital herpes, skin pruritus, and urticaria medicamentosa. Severe or life-threatening adverse events were reported to be up to 2.5%, with only one considered related to the study drug (urticaria, cefuroxime) [48]. All of these adverse events resolved after stopping the administered antibiotic.

Adverse events reported after the use of long-term low-dose oral macrolide antibiotics in CRS treatment were rare (0–3%) [32, 34, 51, 72]. Two patients suffered from nausea/vomiting and another two patients had epistaxis. All of these adverse events resolved after ceasing the antibiotic. If treatment with high doses continues for several years, there is the potential of ototoxicity. Audiograms at regular intervals are recommended. Possible interactions exist between macrolides and dicumarol, antiepileptic drugs, terphenadine, methotrexate, and antidepressant drugs [18].

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 [2, 4, 38, 40, 43, 53, 58, 76]. A shift from the old narrow-spectrum antibiotics to the new broad-spectrum antibiotics has being seen. Higher rates of antibiotic resistance are found in high consuming countries, probably related to this higher consumption.

25.7 Conclusions

The role of bacteria in the pathogenesis of CRS with and without NP is still controversial. While certain bacteria are commonly associated with CRS, their presence has not definitively been demonstrated as causative. Recent theories include the roles of bacterial biofilm formation, intracellular bacterial residency, and bacterial exotoxins as possible contributing factors to the inflammation of CRS.

While antibiotic agents are associated with common mild side effects, they also have serious rare side effects. Macrolide antibiotics have recently been shown to have anti-inflammatory, immunomodulatory, and antimucus properties, in addition to their antimicrobial action.

There is no clear evidence that topical antibiotic nasal washes confer any benefit in CRS treatment, as demonstrated by the results from two randomized, double-blinded, placebo-controlled studies. Culture-directed, short-term oral antibiotic therapy seems to be a reasonable treatment option for patients with CRS with and without NP. The few available prospective studies show a symptomatic improvement in 51–95% of patients. There is a lack of randomized, placebo-controlled studies on this matter.

Long-term macrolide therapy is an effective treatment in CRS with and without NP. In vivo and in vitro studies suggest that erythromycin, clarithromycin, and RXM are effective at modulating inflammation in CRS, leading to an improvement in symptoms from 71 to 80%. Macrolides also appear to decrease the size of NP.

Take Home Pearls

- The role of bacteria in the pathogenesis of chronic rhinosinusitis (CRS) with and without nasal polyps (NP) deserves further well-designed clinical studies.
- Current data do not support the use of topical antibiotic agents.
- Culture-directed short-term oral antibiotic therapy should be considered on an individual basis, but there is no clear data supporting this practice.
- There is good evidence to suggest the beneficial effects of long-term macrolide therapy in CRS with and without NP.
- Macrolides have multiple mechanisms of action (anti-inflammatory, immunomodulatory, antimucus, antimicrobial) which confer symptomatic improvement in CRS.

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Aspirin Intolerance

26

Wolf J. Mann and Jan Gosepath

Core Messages

- Disturbances of the arachidonic acid metabolism, resulting in a pathologic eicosanoid shift, represent a common pathway in the pathophysiologic spectrum of chronic rhinosinusitis.
- Patients suffering from nasal polyposis and aspirin intolerance (AI) have a high risk of markedly increased long-term recurrence rates after surgical therapy.
- AI is always associated with a significant eicosanoid shift that can be successfully addressed by oral aspirin desensitization.
- A low-dose desensitization regime reduces adverse effects of aspirin and is necessary to achieve favorable clinical results along with long-term compliance.
- Pathologic expression of cyclooxygenase isoenzymes and their interaction with growth factors like vascular endothelial growth factor may play a relevant role in nasal polyp growth in both aspirin-intolerant and -tolerant patients.

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26.1 Introduction

Despite growing evidence of common pathways in underlying immunologic deficiencies or sensitizations, medical therapy still has to address a spectrum of potentially causative etiologic factors of chronic rhinosinusitis (CRS). A complete etiological workup is the key to defining an individualized medical treatment protocol suitable to prevent or reduce the risk of repeated recurrence after primary surgery failure.

A difficult challenge in treating CRS is to offer a therapeutical concept that addresses individually relevant etiological factors, but is based on well-standardized criteria and validated pathways of medical therapy, especially in patients with recurrent disease after previous surgical treatment. So far, regardless of the surgical technique applied, a fair amount of patients, especially with polypoid changes, will at some point in time present with recurrent disease.

Until today, we have not succeeded in elaborating a universal causative medical treatment for recurrent – especially polypous – CRS, which would reverse the disease process and make a surgical revision obsolete. The goal in treating CRS therefore is to evaluate the individual constellation of pathophysiologic aspects of a patient. An emerging development with increasing relevance for the future is the application of in vitro assays validated to individually test patients for the relevance of single etiologic factors. This will help to better target medical treatment both pre- and postoperatively in an effort to reduce the risk of yet another recurrence after the necessary surgical revision.

- CRS has been understood as a systemic disorder, potentially influenced by various factors. A causative treatment would therefore have to be systemic as well and individualized to a patient's situation.

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In postoperative medical management, effective topical treatment should be combined with well-tolerable long-term systemic therapy as the causative mechanisms in CRS always represent a systemic disease. Disturbances of the arachidonic acid pathway and consecutive pathologic leukotriene release have been identified as a common pathway and frequent driving force behind mucosal inflammatory disease of the upper as well as the lower airway, most frequently, but not only in patients with aspirin intolerance (AI).

Aspirin desensitization can be performed successfully and, using a novel low-dose protocol, can be applied as a lifelong treatment. As this is effective on the enzyme level of the arachidonic acid pathway, it is more causative and, based on clinical trials, more effective than leukotriene antagonists.

26.2 Postoperative Care and Long-Term Medical Management to Prevent Recurrence

Taking all the above-mentioned aspects into consideration, certain applications of medical therapy should have a prominent role in the treatment of CRS and can be valuable in reducing the risk of recurrent nasal polyposis, especially in patients who previously underwent one or multiple surgical interventions. In an untreated course of CRS, patients may show improvement of subjective symptoms to an extent of approximately 25% in so-called "stable episodes" over a 4-week period, whereas objective clinical parameters vary insignificantly. In such episodes, mRNA of IL-1β, IL-6, IL-8, MCP-1, and TNF-α as well as pLT and PGE_2-levels are still detectable and appear to play a role in the persistence of inflammation in CRS [13].

Initial postoperative medical management will be focused on the support of immediate wound healing and the prevention of scarring, synechia formation, and wound infections. The preferred protocol to achieve these goals varies to a certain extent between surgeons and is mostly based on topical applications of irrigations and solutions including creams, decongestants, and steroids. Patients are usually seen in the office in weekly intervals for endoscopic follow-up and crust removal from the surgical cavity as necessary.

The goal of any long-term medical treatment in the postoperative phase will be to achieve a steady decrease of relevant inflammatory mediators, calming the state of the nasal and paranasal sinus mucosa, and thus to prevent the formation of recurrent disease. Some regimes play a prominent role in this scenario.

26.3 Characteristics of Aspirin Intolerance in Polypous CRS

One critical group in the range of patients suffering from CRS, especially in the subgroup with nasal polyposis, comprises individuals with AI. It has been understood early on that this particular entity goes along with a very high risk of recurrence of sinunasal polyposis independent of the number and kind of previous surgical interventions [6]. The diagnosis of AI is not always associated with the full clinical picture of the aspirin triad, which consists of (1) nasal polyposis, (2) intrinsic bronchial asthma, and (3) aspirin-induced worsening of asthmatic symptoms, often along with naso-ocular symptoms [22]. However, in sensitive individuals, even very small single doses of aspirin may cause rhinorhea, bronchiolar constriction, and pseudoanaphylactic shock symptoms related to a nonIgE-mediated pharmacological hypersensitivity reaction [27]. Not only aspirin, but most other NSAID interact with the eicosanoid pathway (Fig. 26.1). In 143 patients, characterized in a retrospective investigation, we diagnosed AI in 55 (38.5%) [12]. Patients diagnosed with AI revealed to be the subgroup with (1) the highest rate of revision surgeries performed over time and (2) the shortest interval between the respective operations. According to the definition of AI, it is obvious that the subgroup of CRS patients with nasal polyps is likely to have the highest incidence of AI.

However, in sensitive individuals, even very small single doses of aspirin may cause rhinorhea, bronchiolar constriction, and shock symptoms related to a non-IgE-mediated pharmacological hypersensitivity reaction [16, 19, 29]. The screening of patients for the presence of AI by an otolaryngologist in case of an uncertain medical history is mainly based on rhinoscopic findings such as nasal polyposis, especially if polyps quickly recur after surgery. Although there is little agreement as to the causative mechanisms of nasal polyposis, the risk of recurrence seems to be significantly increased in patients with AI [11, 14].

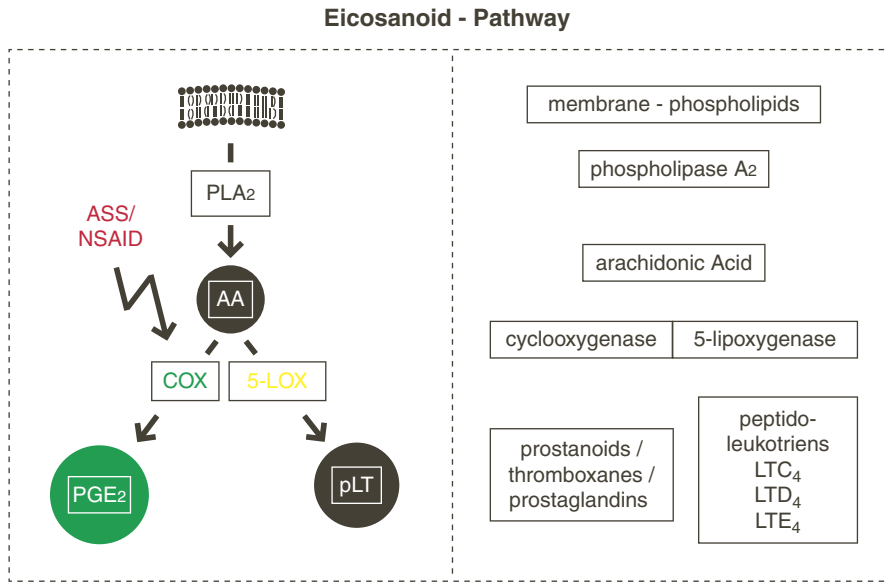

Fig. 26.1 Interaction of NSAIDs with the arachidonic acid pathway

It is known that not only aspirin, but most other NSAID interact with the eicosanoid pathway (Fig. 26.1). They are known to cause inhibition of the cyclooxygenases (COX, mainly isoenzyme COX I), which metabolize arachidonic acid to prostaglandins. This inhibition leads to an upregulation of the alternative pathway with lipoxigenases metabolizing arachidonic acid to leukotrienes. However, this cannot be the sole cause of AI, since this effect of NSAID occurs in healthy individuals as well. Several additional factors have been discussed like alterations in COX inhibition and the kinetics of enzymes like leukotriene synthase or an increased sensitivity of respiratory mucosal tissue to leukotrienes [1, 3, 24]. While the exact causative mechanisms have to be further elucidated, the individual chronologic sequence of symptoms is known to be considerably variable. First symptoms usually occur within the fourth decade of life with recurrent rhinitis, followed by nasal polyposis. Intrinsic bronchial asthma can develop some years later, and often it takes years again for the clinical sensitivity to NSAID to recur.

26.3.1 Role of an In Vitro Assay

Several studies have shown that aspirin-sensitive individuals can be desensitized by administration of small doses of aspirin over a longer period of time [2, 5, 15], which may result in a decreased risk of recurrence of nasal polyps. Therefore, it is essential to correctly identify those individuals with AI even if they show other coexisting factors such as allergies. An in vitro assay can therefore be very valuable in establishing the diagnosis of AI [6]. The alteration of arachidonic acid metabolism and eicosanoid release can as well be detected in patients with an incomplete manifestation where the clinical picture of the aspirin triad has not yet fully developed.

- The diagnosis of AI is frequently delayed due to an incomplete clinical picture lacking aspects of Samter's triad. In vitro testing can be helpful in uncertain cases.

So far, the diagnosis of AI was made mainly on the basis of medical history or the result of an oral, nasal, or bronchial challenge [2, 19, 25]. Mewes et al. reported in 1996 that they found significant differences in the in vitro cysteinyl leukotriene release from blood leukocytes after incubation with acetylsalicylic acid in individuals with AI compared to both normal individuals as well as to individuals with nasal polyposis but no AI [17]. In a study published in 1997, Sainte-Laudy also pointed out that the leukotriene release after stimulation with ASA in vitro could be the clue to a reliable diagnostic test [23]. At our institution, the following functional in vitro assay has been successfully used,

following a recently published protocol [27]: blood is drawn from the patient and a mixed leukocyte culture is prepared using dextran sedimentation. Thereafter, the eicosanoid release of pLT and PGE_2 is analyzed using competitive enzyme immunoassays [26]. The release of pLT and PGE_2 is assayed simultaneously and in duplicate for each sample. The antibody directed against pLT recognizes LTC_4, and the metabolites LTD_4 and LTE_4 with equal sensitivity. Detection limit is 3 pg/well for pLT and PGE_2. The changes in eicosanoid release determines a positive or negative test result: A positive test result is defined as elevated pLT release and lowered PGE_2 release, while a negative result is defined by normal pLT and PGE_2 release when compared to the release levels in a healthy control group. The eicosanoid levels of this healthy control group, consisting of 50 individuals that showed no clinical evidence of any symptoms consistent with AI, were assessed by the same above-mentioned assay in the same laboratory, when the protocol of the assay first had been established. We were able to show that analyzing eicosanoid release in mixed leukocyte cultures offers an alternative to oral, bronchial, or nasal challenge tests [27].

26.4 Aspirin Desensitization

After patients undergo revision sinus surgery, the best timing to initiate a scheduled aspirin desensitization would be following the initial wound healing around the third or fourth, but no later than the sixth postoperative week to commence the treatment before edematous or polypoid changes might recur. To start desensitization therapy, patients need to be hospitalized for 2 days for close monitoring for potential pseudoanaphylactic reactions. Oral aspirin is given in increasing dosages over these 2 days (day 1: increase up to 100 mg, day 2: increase up to 500 mg). Doses are slowly increased only after a repeated check of airway resistance and FEV1, excluding a decrease in FEV1 of 25% or greater after the respective preceding dose. Should that occur, the previous dose is repeated without further increase at the time of the next application until lung function has recovered. On the third day, aspirin is reduced to 100 mg to be kept as a long-term maintenance dose. In prospective trials, clinical reassessments as well as the functional in vitro assay were repeated at each follow-up visit of every patient in an attempt to identify changes in the release of eicosanoids over time and to correlate these with the clinical course [8].

- A low maintenance dose is the key to long-term compliance in aspirin desensitization.

Since there is a relative overproduction of pLT in aspirin-sensitive individuals, it is desirable to achieve an increase of the "PGE2/pLT index" over time. We observed a significant improvement of vitro findings, which was positively correlated to the individual clinical course and the recurrence rate of nasal polyps observed in this group of patients [7].

The data underline the role of an in vitro assay and indicate the effectiveness of a desensitization protocol that can be maintained as a long-term treatment without adverse side effects. The excellent compliance and low rate of adverse effects associated with 100 mg of aspirin a day has been sufficiently validated in large cohorts of cardiovascular and neurologic patients, using equivalent dosages for prevention protocols. Results suggest that the recurrence rate of nasal polyps after surgical therapy can be reduced; however, only long-term treatment can secure a beneficial outcome over time.

All patients diagnosed with AI have a considerable chance of clinical improvement or decreased risk of recurrence, if adaptive desensitization therapy is performed. In vitro analysis of eicosanoid release from mixed leukocyte cultures using a functional enzyme immuno assay offers a new tool not only to help establish the diagnosis of AI, but also to individually monitor the effect and verify the success of a desensitization therapy over time. In prospective studies, we were able to show the effectiveness of a new low-dose protocol using a maintenance dose of only 100 mg of oral aspirin a day [7]. This low dosage along with its minimal risk of adverse side effects offers the option of a long-term and if possible, lifelong treatment, which is ultimately mandatory as a lasting effect of desensitization after cessation of the oral intake of aspirin has never been shown and the refractory period of the pseudoallergic cascade is limited to approximately 48 h. Long-term follow-up over at least three years in a group of patients undergoing desensitization using a daily maintenance dose of as little as 100 mg of aspirin revealed to be effective both clinically as well as in vitro [8] (Fig. 26.2a, b). Eicosanoid levels shifted back to a normal release pattern during therapy with

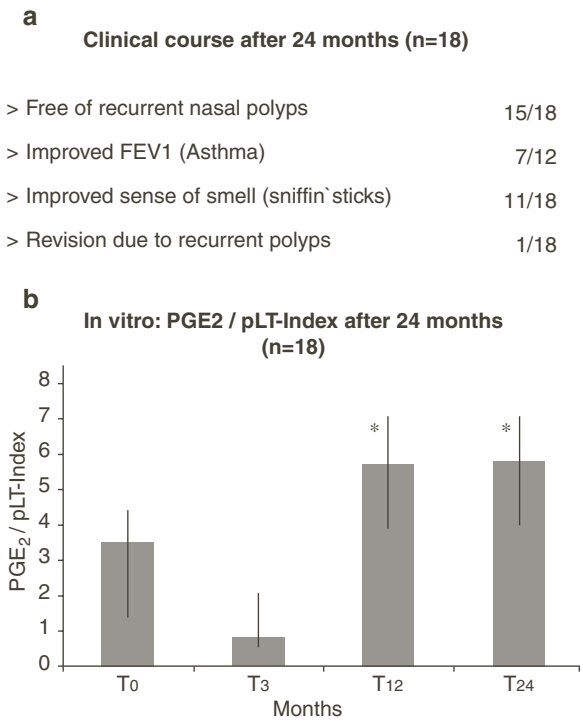

Fig. 26.2 (**a**) Clinical parameters after a 2-year course of low-dose aspirin desensitization with a daily maintenance dose of 100 mg ($n=24$). (**b**) The corresponding in vitro parameters of the same group of patients after 2 years of low-dose aspirin desensitization with a daily maintenance dose of 100 mg ($n=24$)

an increase of prostaglandin – in relation to leukotriene release. This underlines a prominent role of COX-dependant mediators, which is in keeping with findings in recurrent nasal polyposis of aspirin-tolerant patients.

26.5 Implications of Eicosanoid Imbalance on the Pathophysiology of Nasal Polyps

Recent studies suggest that variations in the eicosanoid metabolism, especially in the expression of the inducible COX-2, might play a key role in the immunologic etiology of all clinical variations of nasal polyps [10, 18, 20, 21]. In an immunohistochemical study on COX-2 expression in nasal polyps, we were able to show a downregulation of this enzyme as compared to its constitutively expressed isoform COX-1. This downregulation was not seen in nonpolypous inflamed or noninflamed nasal mucosa [10]. A significant role of COX as well as VPF/VEGF has been well established in the pathogenesis of intestinal polyps and in the angiogenesis of intestinal malignoma [4, 31]. Interestingly, it has been shown by different authors that COX-2, by elevating prostaglandin E_2-levels, induces an upregulation of VPF/VEGF, which in turn promotes tumor angiogenesis [28]. It has also been shown in colon cancer that while COX-2 is a modulator of angiogenic factors in cancer cells, COX-1 predominantly regulates factors like VPF/VEGF in endothelial cells [30].

Immunohistochemical staining of polypoid tissue from patients suffering from polypous CRS revealed a downregulation of COX-2 in these tissues as compared to normal nasal mucosa [28]. This unveils a possible mechanism of the increased proinflammatory leukotriene release in nasal polyps, since COX-mediated prostaglandin E2 inhibits leukotriene release in nasal mucosa of normal controls.

- An eicosanoid imbalance is frequently observed in patients with nasal polyposis even in the absence of AI.

Until today, the exact etiologic mechanisms leading to the formation of nasal polyps remain obscure. However, this entity of chronic inflammatory disease of nasal respiratory mucosa is associated with remarkable edema. Vascular permeability/vascular endothelial growth factor (VPF/VEGF) plays an important role in inducing angiogenesis and/or modulating capillary permeability. We investigated the expression and localization of VPF/VEGF in nasal polyps as compared to healthy controls in order to evaluate its significance in the pathophysiology of nasal polyps. The expression of VPF/VEGF in specimens of nasal polyps was markedly stronger than in specimens of healthy nasal mucosa of controls [9]. VPF/VEGF labeling in polypous tissue was located in vascular endothelial cells as well as in basilar membranes and epithelial cells. The observed expression pattern in nasal polyps as opposed to controls of healthy nasal mucosa suggests that VPF/VEGF might play a significant role in the etiology of nasal polyposis. Polyp growth and the associated stromal edema might be closely related to permeability–regulatory actions of VPF/VEGF in microvessels and/or basal membranes. However, the angiogenic effect of

VPF/VEGF appears to be of secondary significance as compared to the modulating effect on permeability, since the histopathological findings in nasal polyps include heavy tissue edema as well as a reduced – rather than increased – vascularization (12,27). These findings need to be discussed with respect to the differential expression of COX isoenzymes-1 and -2 (COX-1 and COX-2) in nasal polyps, where COX-1 is up- and COX-2 is downregulated, following immunohistochemical analysis. Studies involving intestinal hyperplastic polyps suggest that especially COX-1 can upregulate VPF/VEGF [28]. It may be hypothesized that the relative overweight of COX-1 in nasal polyp epithelia in the presence of large amounts VPF/VEGF in vascular endothelia and basal membranes of these tissues may lead to the formation and perpetuation of the remarkable edema associated with nasal polyposis.

This mechanism might play a key role in polyp growth and edema formation in nasal polyposis.

26.6 Conclusion

Adaptive desensitization therapy can be successfully performed in patients with AI; however, only long-term treatment can secure a beneficial outcome over time as previously documented clinically and in vitro. Using a novel low-dose protocol, this treatment can be maintained as a long-term treatment without adverse side effects.

Pathologic eicosanoid release patterns similar to those of patients suffering from AI have also been shown in recurrent nasal polyposis and are currently evaluated as therapeutical targets in these patients.

As our understanding of pathophysiological mechanisms will further evolve, we will most likely derive more medical treatment modalities for inflammatory diseases such as CRS. A therapeutical concept of the future will individually tailor a therapeutical strategy to a respective risk profile of a patient. Research will be dominated by identifying missing links between in vitro and in vivo parameters and between chronic inflammation of the upper and lower airway as their systemic parameters are most likely identical to a large extent. Aspirin desensitization represents a treatment modality aiming at a common pathway in chronic inflammatory respiratory disease.

Take Home Pearls

- Recurrent nasal polyposis is frequently associated with a pathologic eicosanoid imbalance, especially in patients with coexisting bronchial asthma, which can be measured even if the clinical picture of Sampter's Triad is not (yet) evident at an early stage of airway inflammation.
- Aspirin desensitization therapy can be performed to normalize the pathologic eiconsanoid shift, however only low dose maintenance doses are suitable for the necessary long-term treatment regime. There is evidence that nasal polyposis recurrence rates can be decreased after successful desensitization.

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Where Are We in the Medical Treatment of Nasal Polyps

27

Valerie J. Lund

Core Messages

- Nasal polyposis (NP) is associated with a number of medical conditions and may be considered to be the end-point of a number of different pathological processes.
- For many patients, NP should be regarded primarily as a medically managed condition in which surgery often plays a role. It could be argued that the surgery facilitates the instillation of nasal medication.
- A range of medical treatments are available though the mainstay remains corticosteroids in various forms. However, there are a number of other approaches both new and old which may be considered. Randomised placebo-controlled trials are available for a relatively small number of preparations and more need to be conducted.

27.1 Introduction

The menu of medications available for the treatment of NP has considerably lengthened in recent years although the mainstays of management remain the same (Fig. 27.1). One of the first consensuses on nasal polyps concluded that the primary treatment of NP was medical. Indeed it could be argued that NP are at best managed by a combination of medical and surgical therapies and that the role of surgery is to optimise the administration of the medication. As outlined in previous chapters, there are a number of possible aetiologies and conditions with which NP are associated and, therefore, it might be anticipated that some medical treatments would work better than others. In the literature it can sometimes be quite difficult to determine the inclusion criteria, and a heterogenous group with and without asthma or aspirin sensitivity may be included. Nonetheless, there are a number of studies concentrating on medical treatment and this chapter will summarise these, drawing heavily on the analysis published in the latest EPOS document [11]. This used the established criteria of evidence-based medicine in preparing the guidelines [49].While it may be difficult to perform a genuinely randomised placebo-controlled trial to assess a surgical procedure, the same is not true of medical treatments. So there are a number of preparations which remain to be assessed in this way and for this reason are not included in the chapter. We should continue to strive to provide the highest level of evidence that we can, not only in the assessment of new treatments but also in the evaluation of old ones (Tables 27.1 and 27.2).

27.1.1 Treatment of Nasal Polyposis with Corticosteroids

It has been well known for some years that both oral and parenteral corticosteroids have a dramatic effect on NP, the so-called "medical polypectomy". However, concerns about the systemic side effects of these drugs limited their long-term utility. The introduction of topically administered glucocorticoids in the 1970s improved both the treatment of upper (rhinitis, nasal polyps) and lower (asthma) airway inflammatory

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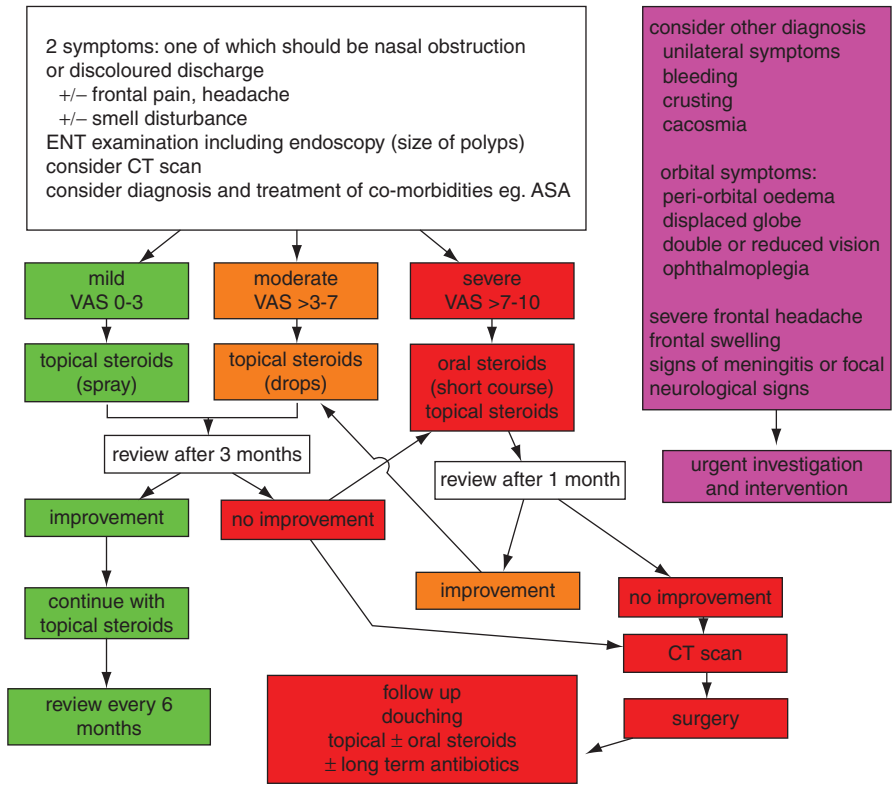

Fig. 27.1 Treatment scheme for ENT specialists for adults with nasal polyps. After Fig. 13.5 from [11]. Reproduced with permission from *Rhinology*

Table 27.1 Categories of evidence [11]

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

Table 27.2 Strength of recommendation

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

disease, and their protean effects on inflammation are covered in Chap. 24. Most notable is their direct and indirect effect on eosinophils [34–36, 46, 58, 59] and activation of intracellular glucocorticoid receptors [28]. However, glucocorticoid resistance is a future area of interest in drug development.

Every commercially available topical corticosteroid from becolmethasone dipropionate onwards has been shown to be efficacious in treating nasal polyps, either primarily or secondary to surgery. These are summarised in Table 27.3. It is difficult to say that one is better than another as few studies have been comparative [20, 31].

A few dose-ranging trials have been performed which suggest that in the case of fluticasone propionate and mometasone, NP are best treated with higher doses

Table 27.3 Treatment of nasal polyposis with intranasal corticosteroids

Study	Drug	Number	Treatment time (weeks)	Effect on nasal symptoms (*stat sig)	Objective measures (*stat sig)	Effect on polyps	Level of evidence
Mygind et al. [38]	BDP	35	3	Total symptom score*		N.S.	Ib
Deuschl and Drettner [7]	BDP	20	2×4	Blockage*	Rhinomanometry*	N.S.	Ib
Holopainen et al. [21]	Bud	19	16	Total symptom score*	Nasal peak flow* Eosinophilia*	Yes	Ib
Vendelo Johansen et al. [55]	Bud	91	12	Blockage* Sneezing* Secretion* Sense of smell N.S.	Nasal peak inspiratory flow*	Yes	Ib
Lildholt et al. [29]	Bud	116	4	Blockage* Sneezing* Secretion* Sense of smell N.S.	Nasal peak expiratory flow*	Yes	Ib
Holmberg et al. [20]	FP/BDP	55	26	Over all assessment*	Nasal peak inspiratory flow*	Yes in BDP	Ib
Tos et al. [53]	Bud	138	6	Total symptom score* Sense of smell*		Yes	Ib
Lund et al. [31]	FP/BDP	29	12	Blockage* rhinitis N.S.	Nasal peak inspiratory flow* Acoustic rhinometry*	Yes FP	Ib
Keith et al. [24]	FPND	104	12	Blockage* Rhinitis* Sense of smell N.S.	Nasal peak inspiratory flow* Olfactory test N.S.	N.S.	Ib
Penttilä et al. [41]	FP	142	12	Blockage* Rhinitis* Sense of smell N.S.	Nasal peak inspiratory flow* Olfactory test*	Yes	Ib

(*continued*)

Table 27.3 (continued)

Study	Drug	Number	Treatment time (weeks)	Effect on nasal symptoms (*stat sig)	Objective measures (*stat sig)	Effect on polyps	Level of evidence
Hadfield et al. [14]	Betametasone	46 CF children	6	N.S.		Yes	Ib
Aukema et al. [1]	Fluticasone propionate nasal drops	54	12	Nasal obstruction *rhinorrhea *postnasal drip *and loss of smell*	Nasal peak inspiratory flow* CT scan	Yes	Ib
Small et al. [50]	Mometasone	354	16	Obstruction* Loss of smell* Rhinorrhea*	Nasal peak inspiratory flow*	Yes	Ib
Stjärne et al. [51]	Mometasone	310	16	Obstruction*Loss of smell N.S. Rhinorrhea*	Nasal peak inspiratory flow*	200 µg o.d. no 200 µg b.i.d. yes	Ib
Stjärne et al. [52]	Mometasone	298	16	Obstruction*Loss of smell* Rhinorrhea* QOL	Nasal peak inspiratory flow*	Yes	Ib

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than those used for allergic rhinitis [41, 50–52]. The majority of RCTs have considered corticosteroid sprays, though, as in the Pentilla study, some have considered fluticasone in drop form. Betamethasone drops have been used for many years as a first-line medical treatment and much debate and some investigation has concerned the optimal method of instillation, with opinion divided between the "head down and forwards" vs. head hanging back over the end of the bed. Ultimately, patient preference and thus compliance will probably dictate the methodology. There is little evidence of any systemic absorption of the newer generation of corticosteroid sprays, but betamethasone drops are undoubtedly absorbed which in turn may contribute to their efficacy, but also limits their long-term usefulness especially in children. Both sprays and drops improve the symptoms of nasal blockage, secretion, and sneezing, but their effect on the sense of smell is less. For this symptom nasal drops are probably more effective.

Generally, there are few side effects from intranasal administration of corticosteroids, the most common of which is minor nose bleeding. Very rarely, septal perforations have been attributed to their use though this may relate more to local trauma than the medication per se [48]. However, this should be put in context as minor nose bleeds are common in the population, occurring in 16.5% of 2,197 women aged 50–64 years over a 1-year study [32]. It has not been possible to show structural damage such as atrophy in nasal biopsy studies after long-term administration of intranasal corticosteroids [19].

As previously mentioned, the systemic bioavailability of modern intranasal corticosteroids is generally low (<1%), but had been up to 40–50% in the past which would risk systemic adverse effects. These might include effects on growth, eyes, bone, and on the hypothalamic–pituitary–adrenal axis (HPA) [3]. However, prospective studies have not identified significant effects on the HPA axis with continued treatment using intranasal corticosteroids that have low systemic bioavailability.

27.1.1.1 Systemic Corticosteroids

Although systemic steroids have been used in patients with NP for a long time, there was surprisingly little level I evidence until quite recently. This was in part due to the fact that doing RCTs on medication which are not sponsored by the pharmaceutical industry is remarkably difficult and expensive. Several open studies had demonstrated prolonged benefit, comparable in some cases to conventional polypectomy, but no dose-defining or comparative studies have been done on the various preparations [5, 30, 54].

One of the positive effects of reviews such as EPOS [11] is to identify these gaps in the literature, and recently, two well-designed RCTS have shown the effect of systemic steroids in NP [2, 18]. Depot injection of corticosteroids or local injection into polyps or the inferior turbinate have not been well studied and are also associated with potentially serious side effects.

Unfortunately, systemic steroids also have other side effects when given for any length of time and some individuals, especially middle aged women should be regarded as particularly at risk of effects on bone metabolism [4]. Even for short courses, relative contraindications should be discussed e.g. insulin dependant diabetes, glaucoma, hypertension, cataract formation or gastric ulceration.

Topical steroids can also be of benefit post-operatively. Flunisolide [8], BDP [23], budesonide [15] and fluticasone [47] have all been shown to be of benefit in both the short and the long term (Table 27.4).

27.1.2 Treatment of Nasal Polyps with Antibiotics

Short-term antibiotics have little role in the treatment of nasal polyps except for secondary bacterial infections. However, antibiotics such as the macrolides or doxycycline may be used, primarily for their anti-inflammatory properties which resemble many of those seen with corticosteroids. Initially used in diffuse panbronchiolitis in Japan [16], macrolides were extended to CRS and have been used with considerable success in nasal polyposis (NP), comparing well with surgery in a recent randomised trial [44] and placebo [56]. However, therapy has to be given for extended periods of 3 months or longer and improvement takes some time to occur. Nonetheless, it is well worth considering especially in asthmatics as significant improvement in the lower respiratory tract can also be anticipated [45].

Table 27.4 Treatment evidence and recommendations for post-operative treatment in adults with nasal polypsa[a]

Therapy	Level	Grade of recommendation	Relevance
Oral antibiotics short term <2 weeks	no data	D	Immediately post-operative, if pus was seen during operation
Oral antibiotics long term >12 weeks	Ib	A	Yes
Topical steroids after FESS	Ib (two studies one + one −)	B	Yes
Topical steroids after polypectomy	Ib	A	Yes
Oral steroids	No data	D	Yes
Nasal douche	No data	D	Yes

After Table 13.6 from [11]. Reproduced with permission from *Rhinology*

[a]Some of these studies also included patients with CRS without nasal polyps

Recent interest has also focused on the instillation of topical antibiotics by various techniques with or without other agents such as surfactant. These have generally been used in refractory post-operative cases, and have concentrated on CRS without polyps [6]. These approaches might avoid some of the potential side effects of antibiotics such as gastrointestinal disturbance, but concerns remain regarding the induction of resistance [13].

27.1.3 Other Medical Management for Nasal Polyposis

A wide range of other medications have been used in the treatment of NP though the evidence base is rather small (Table 27.5). Of these, nasal douching with isotonic/hypertonic saline or alkaline solutions have been shown to help in CRS, but there are no controlled trials of saline treatment alone in NP.

CT studies before and after *decongestant* application in patients with NP did not show any densitometric changes in the sinuses or polyps, only decongestion of the inferior turbinates [10]. Similarly, a recent RCT did not show any difference between placebo, epinephrine and naphazoline on polyp size at endoscopy and lateral imaging [22], and the potential side effects of rebound congestion and ultimately rhinitis medicamentosa [12] deter their regular use.

There have been no clinical trials on *mucolytics* in nasal polyps. Of the *anti-histamines*, cetirizine in a dose of 20 mg/day for 3 months has been shown to significantly reduce sneezing, rhinorrhoea and obstruction compared to placebo in the post-operative treatment of recurrent polyposis, but had no effect on polyp size [17].

Despite considerable interest in the role of fungi and *anti-mycotics*, level I evidence is lacking. In three large RCTs, comparing amphotericin B in solution with saline or dextrose, washing the nose helped, but there was no advantage with the addition of the antifungal [9, 56, 57]. A smaller study comparing sterile water with and without amphotericin B [42] showed a reduction in mucosal thickening on CT in the antimycotic group of 10 patients vs. placebo, but no improvement in symptoms between the two. Similarly, anecdotal reports supporting the use of oral antifungals in NP have not thus far been supported by RCTs [25]. The role of fungi and the potential mode of action of these drugs are still unclear and the results of a large FDA-sponsored trial of topical amphotericin in the USA are awaited with interest.

No controlled trials on nasal polyp treatment with *phytopreparations* were found and no data could be found on treatment with *bacterial lysates* in NP, both of which have been used in CRS without NP with some success.

Capsaicin, the active substance from red hot chilli peppers, is a neurotoxin which depletes substance P with some other neurokinins and neuropeptides, leading to long lasting damage of unmyelinated axons and thinly myelinated axons when repeatedly applied to the respiratory mucosa. The hypothesis that neurogenic

Table 27.5 Treatment evidence and recommendations for adults with nasal polyps[a]

Therapy	Level	Grade of recommendation	Relevance
Oral antibiotics short term <2 weeks	No data	D	No
Oral antibiotic long term >12 weeks	Ib	A	Yes
Topical antibiotics	No data	D	No
Topical steroids	Ib	A	Yes
Oral steroids	Ib	A	Yes
Nasal douche	Ib no data in single use	A	Yes for symptomatic relief
Decongestant topical/oral	No data in single use	D	No
Mucolytics	No data	D	No
Anti-mycotics – systemic	Ib (–)[b]	D	No
Anti-mycotics – topical	Ib (–)[b]	A	No
Oral antihistamine in allergic patients	Ib (1)	A	Yes, in allergy only
Capsaicin	II	B	No
Proton pump inhibitors	No data	D	No
Lysine aspirin desensitisation	Ib	A	Yes
Fruosemide	Ib	A	Yes
Anti-leukotrienes	III	C	No

After Table 13.5 from [11]. Reproduced with permission from *Rhinology*

[a]Some of these studies also included patients with CRS without nasal polyps

[b](Ib) study with a negative outcome

inflammation may play a role in the pathogenesis of nasal polyps has led to trials of capsaicin in NP of which one RCT showed reduced polyp recurrence after endoscopic surgery when applied topically on five occasions [60]. However, the main disadvantage of the treatment is a severe burning sensation in the nose and lips, and lacrimation unless the nose is completely anaesthetised.

The use of *diuretics* such as furosemide has also been considered in NP, based on positive findings when inhaled by asthmatics [37]. Reduced recurrence after surgery with 1–9 years follow-up was demonstrated after topical post-operative application of furosemide in 97 patients vs. mometasone furoate in 33 patients, in a prospective non-randomised controlled trial (IIa) [40]. An RCT comparing the effect of short-term pre-operative treatment with oral methylprednisolone vs. inhaled furosemide solution in 40 NP patients showed that both were effective, but no difference was found between the two treatment modalities after 7-day treatment, in terms of polyp size reduction on endoscopy, nasal symptom scores (except for olfaction, which was better in steroid group) and intraoperative bleeding [27]. RCTs, especially long-term treatment, are however lacking.

Leukotrienes are up-regulated in asthma and NP, especially in aspirin-sensitive disease and several open studies have suggested that *anti-leukotrienes* such as montelukast might be of benefit in NP [26, 43]. However, level 1 evidence thus far is lacking with negative findings in one prospective double-blind comparative study on 40 patients [33].

As many patients with NP also have aspirin-sensitive asthma, systemic *aspirin desensitisation* or topical lysine–aspirin treatment has been used and may reduce the recurrence of polyps after surgery [39] though evidence from RCTs is conflicting. See Chap. 27.

Promising initial results are being reported with anti-IL-5 given systemically but larger studies are needed. See Chap. 22.

27.2 Conclusion

A wide range of pharmaceutical approaches have been tried in NP, of which corticosteroids remain the most effective due to their pluripotential effect on inflammation. However, there are clearly other mechanisms or portions of the inflammatory pathway that could be targeted and are the subject of continued research.

Take Home Pearls

- Unilateral polyps should be imaged and biopsy considered.
- Unless the nose is completely blocked by the polyps, it is usually worth a trial of intensive medical therapy.
- It is important that patients understand the natural history of nasal polyps and that long-term maintenance therapy will be required irrespective of whether surgery is undertaken or not.
- Nasal polyposis is a respiratory disease which is often associated with asthma and aspirin/nonsteroidal anti-inflammatory sensitivity. Optimum medical treatment of the nose can help the chest.

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Anesthetic Management in Nasal Polypectomy

28

Nalan Çelebi and Varol Çeliker

Core Messages

- Proper preoperative evaluation of the patients who are aspirin-sensitive and need nasal polyps operation, and choosing appropriate anesthesia method are critical to minimizing pre- and post-operative complications.
- In these patients, standard anesthesia protocol may be used; atropine and diazepam should be administered for premedication; fentanyl and propofol should be used for induction, and muscle relaxation can be established using vecuronium anesthesia that should be maintained with sevoflurane and fentanyl.
- At an earlier preoperative stage, pain can be controlled with fentanyl, known to be a potent and safe analgesic.

The prevalence of analgesic intolerance (AI) in the community is reported to be about 1%, and AI is higher in special cases such as bronchial asthma. AI affects 10% of adult asthmatic patients and one fourth of those suffering from nasal polyps and chronic urticaria. Asthma, nasal polyp, and AI triads are defined as aspirin-induced asthma (AIA) or Samter Syndrome described by Samter and colloquies in 1967 [2, 4–6, 14, 15].

Genetic predisposition is shown to play a critical role in AI and AIA. Moreover, severe and advanced symptoms are accompanied by severe inflammation of airways. Patients with inflammation of upper respiratory system are inclined to develop nasal polyps and pan-sinusitis. Recent studies on AIA indicate that excess production of cysteinyl leukotrienes alters arachidonic acid metabolism [4–6, 13].

Severe sensitivity to aspirin, first described in 1911 by Gilbert, was shown to cause acute asthmatic attacks. Aspirin sensitivity and nasal polyps are present in 8–20% of adult asthmatic patients and the clinic findings for Samter Syndrome are exclusive. The symptoms are not observed in most of the patients during the third and fourth decades of their lives and they are rarely seen in children. The symptoms typically start around 20–40 years of life with nasal congestion, running nose, vasomotor rhinitis, decrease or loss of smell. In general, AI emerges 5–10 years after the appearance of first symptoms [1, 2, 5, 15, 18].

Furthermore, in AIA patients, nasal polyps are bilateral. Aspirin sensitivity and bronchial asthma are reported in 35 and 40–70% of the patients with nasal polyps, respectively.

In addition to AIA patients, nasal polyps can be present in nonallergic asthma, sinusitis, cystic fibrosis, Kartagener, Churg–Strauss, and Young's syndromes [10].

Inflammation in the lower respiratory tract shows itself as bronchial asthma. Asthmatic symptoms appear a couple of months after the start of sinusitis and these symptoms are generally exacerbated. The feature of this type of asthma is the appearance of its symptoms after the intake of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Typically, it is characterized with running nose, broncospasm, skin flare, nausea, vomiting, diarrhea, and abdominal pain within 15–180 min after the administration of the medicine. In general, epinephrine and bronchodilatators are used for the treatment of the disease.

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Furthermore, nasal polyps, sinusitis, and rhinitis are reported to be present in 72.2, 81.2, and 100% of aspirin-sensitive patients, respectively. Moreover, after encountering with allergens, these patients develop urticaria, angioedema, and eosinophilia in blood and mucous membranes.

In the etiology of the AIA triad, inflammation in the upper respiratory tract triggers reflexive bronchial activity. Aspirin and NSAIDs lead to an increase in the synthesis of leukotrienes (LTs) and a decrease in production of prostanoids by affecting the cyclooxygenase (COX) pathway. Further, in the presence of nasal polyps, inflammatory mediators such as histamine and LTs are released from the nasal mucosa, thereby causing mucosal edema and bronchospasm [2, 11, 14].

Development of severe sensitivity and violent bronchospasm against NSAIDs creates serious difficulty in the management of postoperative pain handling for anesthesia physicians. Unfortunately, NSAIDs like diclophenac, ibuprofen, indometasin, ketoprophen, kethorolac, piroksikam, and metamizol are very effective COX inhibitors, and anaesthesiologists are still using them [14].

Surprisingly, aspirin-sensitive asthmatic patients can safely use some of the NSAIDs such as sodium salicylate, choline magnesium trisalicylate, and salicylamide. The reason for this might be the feature of these medicines not to inhibit the COX pathway. Aspirin-sensitive patients may also need anesthesia for nasal polypectomy or other medical conditions. Therefore, AIA or AI patients should receive proper pre- and postoperative anesthesia preparation and be evaluated for allergic reactions. The evaluation of these patients must be carried out by the allergy unit and they must be given anesthesia according to the protocol developed for asthma patients [4].

28.1 Anesthetic Management

Asthma is the chronic inflammation of the respiratory system characterized with diffused irritation and obstructed airways, often in response to one or more triggers. Asthma creates resistance against airflow and air stays in the airways, causing the increased effort for respiration. Likewise, respiratory gas exchange is impaired due to ventilation–perfusion imbalance. Significantly increased expiratory airflow resistance and air detainment result into increased residual volume and total lung capacity. Wheezing, indication of turbulent airflow is frequently seen in asthma as well.

Inclusive medical history is critical for the precise preoperative evaluation of the patient. Wheezing, coughing, and shortness of breath in patients should be relieved and the termination of the asthma flares ought to be verified by listening to the lungs. Pulmonary function tests, particularly expiratory airflow rate and chest films are used to precisely assess the clinic findings of the disease.

Treatment of asthmatic patients should go on during pre- and postoperative stages. Elective operation should not be done in the presence of infection or untreated bronchospasm. Preoperative preparation consists of physiotherapy, administration of bronchodilatator, antibiotics, and corticosteroids [17].

Asthma patients suffering from bronchospasm and requiring urgent operation should receive intensive care. In addition to their normal respiration, administration of O_2 and β_2 agonist or glucocorticoids to patients ease their lung functions noticeably in a couple of hours through their bronchodilatator, anti-inflammatory, and membrane stabilization effects. The use of bronchodilatator should continue throughout the surgery. Patients under long-term glucocorticoid treatment should receive additional steroid doses to prevent adrenal suppression [17].

Preoperative sedation is required for asthmatic patients and benzodiazepines can be chosen for this purpose. Even though petidin increases the secretion of histamine more than morphine does, it is used as bronchodilatator. At normal doses, opiates have not been shown to produce bronchocontriction. Although inhibiting secretions, atropine is used to achieve a smooth anesthesia induction. Atropine is a blocker of the vagal bronchoconstrictive effect and therefore wide bronchi are dilated.

In AIA patients, administration of bronchodilatator, e.g., salbutamol and beclomethasone are recommended 5 min prior to anesthesia induction [3].

The most critical stage for an asthmatic patient under general anesthesia is the moment of tracheal intubation. Pain, stress, or a stimulus under light anesthesia can elicit bronchospasm. Similarly, during tracheal intubation mechanic stimulus, particularly carina stimulation can cause bronchospasm. Consequently, it should be done after establishing complete muscle relaxation under deep anesthesia [7, 16, 19].

Achieving a smooth anesthesia induction and avoiding the use of thiopental, meperidine, atracurium, mivacurium, succinylcholine, and such drugs known to increase histamine release are key to maintain an

effective and desirable anesthesia. Propofol and etomidate are suitable drugs for anesthesia induction. Moreover, Ketamine is the only anesthetic drug that produces bronchodilatation and can be used in hemodynamically unstable patients [16, 19].

Vecuronium bromide is preferred as a muscle relaxant. Volatile anesthetics due to their bronchodilatator effect can be safely used in the maintenance of the anesthesia. It should be kept in mind that the use of aminophilin and β-adrenergic agonists in the presence of halothane during the anesthesia sensitizes myocardium for fibrillation. Gas mixture used during the ventilation of the patient should be warmed up and moisturized and CO_2 level in expiration air should be monitored if possible. Intraoperative bronchospasm is characterized with wheezing, increased peak inflation pressure, and decreased tidal volume. In such cases, the anesthesia should be deepened quickly. If wheezing still continues, opening of the endotracheal tube and the presence of pulmonary edema or emboli should be checked. Bronchospasm is treated with β-adrenergic agonists and steroids.

At the end of the surgery, anticholinesterase agents that are used to eliminate the effect of nondepolarizing muscle relaxants should be administered with the proper amount of anticholinergic agent to prevent the risk of anticholinesterase-mediated bronchoconstriction. Besides, the endotracheal tube should be removed under deep anesthesia to avoid bronchospasm.

Furthermore, one should also remember that high spinal or epidural anesthesia is shown to block sympathic innervation to lower respiratory tract and thereby can increase bronchospasm. Vagal afferent endings in bronchia are sensitive to histamine and various stimuli. Reflexive vagal stimulus can cause bronchoconstriction by increasing cyclic guanosine monophosphate [12].

Another problem that anesthesiologists might encounter with AIA patient is the development of markedly increased sensitivity against NSAIDs used to handle postoperative pain. Analgesics, for instance morphine and meperidine, can lead to strong bronchospasms through triggering histamine release and result in various side effects depending on the individual. Opioids are extensively used for analgesia in the treatment of postoperative pain and are safely recommended in allergy clinics.

As many of the Samter triad patients undergo endoscopic surgery because of nasal polyposis, an anesthetic approach for endoscopic sinus surgery should also be considered. Endoscopic sinus surgery is performed in narrow spaces and bleeding in the surgical field may cause a poor view of the area that may lead to complications. In order to reduce these complications, it is very important to provide a surgical field that is free of bleeding. This can be achieved with the use of local anesthesia, with topically applied vasoconstrictors or general anesthesia with controlled hypotension. A technique of controlled hypotension during general anesthesia may be performed when the aim is to lower the mean arterial pressure between 50 and 65 mmHg, in order to reduce bleeding significantly in normotensive patients. Techniques for controlled hypotension include controlling venous return and a number of pharmacological interventions including volatile anesthetics (halothane, isoflurane, sevoflurane, desflurane); direct-acting vasodilator drugs (sodium nitroprusside, nitroglycerine, hydralazine); trimethaphan; α-adrenergic receptor blocking drugs (phentolamine, urapidil); β-adrenergic receptor blocking drugs (propranolol, esmolol); combined α- and β-adrenergic receptor blocking drugs (labetalol); calcium channel blockers (nicardipine) and prostoglandin E1. Additionally, an IV anesthetic agent, propofol, which is used for induction and maintenance of anesthesia, can also be preferred for its hypotensive effect. Controlled hypotension during general anesthesia can reduce blood loss in nasalpolypectomy by 80–141 mL. However, controlled hypotension is not without potential complications, which include permanent cerebral damage, delayed awakening, cerebral thrombosis, brain ischemias, and death [3, 16, 19].

We would like to present our experience of anesthesia on 47 patients who were admitted to our department for thoracic diseases and adult allergy unit between 1991 and 2003, and were diagnosed with asthma and underwent general anesthesia for the treatment of various medical conditions. The patients' mean age was 43.7 ± 14.01 and 30 of them (63.8%) were female. The mean age and ratio of the females that we had for the present study were in line with the literature. These 47 patients received 53 operations under general anesthesia and 35 (66%) of the operations were performed for removing nasal polyps. None of the patients had complications owing to anesthesia method and pain management. Only one female aged 44 years developed allergy during postoperative pain management. Even though it was recorded in the patient's file that metamizol is contraindicated for the patient, the health giver relied on patient's information and used metamizol for pain management. Consequently, this patient developed acute urticaria and arrhythmias and stayed in the

intensive care unit overnight. This suggests that relying on patient information can mislead the health giver and lead to serious problems, particularly in patients whose cognitive functions are impaired for several days due to anesthesia. It is critical to manage patient health according to information provided by allergy doctors in his/her file and not to completely rely on patient information regarding his/her medical condition [6–9].

Take Home Pearls

- Asthma and aspirin sensitization can complicate anaesthetic management.
- Fentanyl can be used safely for pain control.
- Surgical management of nasal polyps requires a teamwork of the surgeon, the anaesthesiologist and the imminologist.

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Surgical Treatment of Nasal Polyposis

29

Kevin C. Welch and David W. Kennedy

Core Messages

- Nasal polyposis represents the end point of multiple inflammatory pathways.
- Radiological findings for polyposis demonstrate benign-appearing expansile lesions with soft tissue attenuation, occasional evidence of bony rarefaction, and rare evidence of bony erosion.
- When appropriately directed medical management, including topical and oral corticosteroids, culture-directed antibiotics, and specific treatments (e.g., immunotherapy), either fails or is contraindicated, surgery is warranted in the symptomatic patient with nasal polyps.
- Meticulous dissection with mucosa-sparing techniques during functional endoscopic sinus surgery can successfully eliminate polypoid disease; however, in the absence of postoperative care and medical management, recurrence is highly likely within a variable period of time.
- Further investigation into the optimal perioperative medical management is needed in order to ensure optimal surgical results.

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29.1 Introduction

As previously described, nasal polyps represent a common end point for a wide variety of inflammatory conditions that affect the nasal mucosa. When the underlying medical disorder cannot be controlled and the patient continues to be symptomatic, surgery is indicated. This chapter describes briefly the pathogenesis, physical examination, radiological findings, surgical treatment, and postoperative management of nasal polyposis.

29.2 Pathogenesis

29.2.1 Nasal Polyps

Nasal polyps have been the subject of active research for many years. One of the first descriptions of nasal polyps was by Zuckerkandl [37], who observed polyps originating from the lateral nasal wall within the ethmoid partitions. In later years, Stammberger [33] described the origin of polyps in approximately 200 surgeries, and reported that approximately 80% of polyps originated from the middle meatus (see Fig. 29.1). Indeed, inspection of computed tomography (CT) scans frequently shows expansion of ethmoid cells in polyposis with the intercellular partitions extending down toward the middle meatus. Less commonly, polyps originate medial to the middle turbinate or olfactory cleft.

The etiology of polyps is multifactorial as they represent the end point of multiple extrinsic stimuli and intrinsic responses. In the face of allergic rhinitis, polyps can be seen in approximately 26% of patients when compared to only 4% of normal patients [9]. Similarly,

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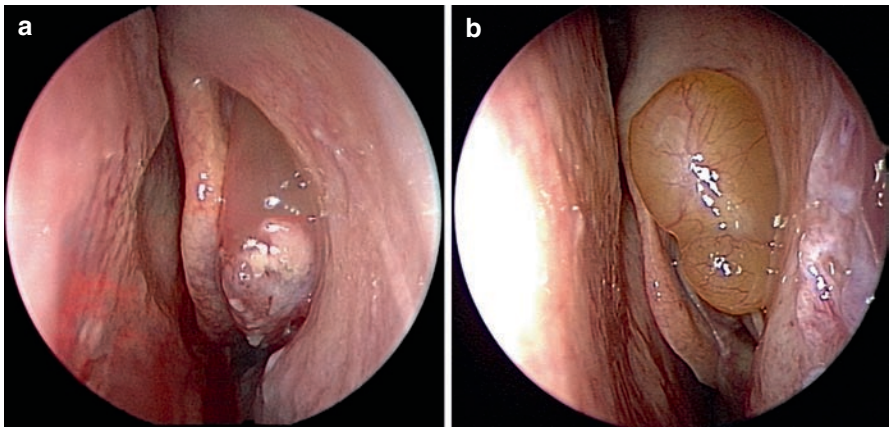

Fig. 29.1 Endoscopic still pictures of patients with moderate nasal polyposis. Smooth glistening expansile lesions can be seen originating from the middle meatus. As previously described, polyps are generally lined with pseudostratified columnar epithelium. A portion of the polyp seen in (**a**) has undergone metaplasia to squamous cell epithelium. Note the vascularity in the second polyp (**b**)

atopic disease is seen in 10–65% of patients with polyps [2, 5, 20, 21]. Other disease entities such as cystic fibrosis, primary ciliary dyskinesia, and aspirin-sensitive asthma, all present with chronic sinusitis and nasal polyposis in some fashion.

Histologically, polyps are heterogeneous structures arising from the mucosa along the lateral nasal wall; thus, the surface epithelium of most polyps is pseudostratified columnar epithelium [1, 5, 34, 35]. However, the epithelium undergoes metaplasia when exposed to the right stimulus, such as when polyps are exposed to significant airflow. Squamous and transitional epithelium have been seen in polyps within the anterior ethmoid cavity where they are exposed to significantly more airflow [11, 12, 19], and less frequently in the posterior ethmoid cavity. The stroma of nasal polyps is characterized by extensive edema that results from transudation of fluid from stromal blood vessels. Fibroblasts and epithelial cells are encountered most frequently; however, inflammatory cells are abundant [13]. The eosinophil is the most common, representing approximately 50–60% of the leukocyte population [22–24, 30]; however, mast cells, lymphocytes, and neutrophils can be found as well. Increased expression of inflammatory cytokines and chemokines is also identified in polyp tissue and contributes to ongoing inflammation, edema, alteration of epithelial growth, and new gland formation. Cytokines such as interleukin (IL)-1β IL-3, IL-5, tumor necrosis factor (TNF)-α, granulocyte/macrophage colony-stimulating factor, and transforming growth factor (TGF)-β all promote eosinophil chemotaxis, fibroblast proliferation, and upregulation of intracellular adhesion molecules. Overproduction of IL-5 and RANTES attracts eosinophils to the perivascular space where degranulation of eosinophilic cationic protein (ECP), major basic protein (MBP), and eosinophilic peroxidase (EPO) occurs and promotes local damage, ongoing inflammation, and persistence of disease [23, 24].

Key elements in the histology and pathogenesis of nasal polyps include:

- Polyps are primarily lined with pseudostratified columnar epithelium and are marked by extensive edema and an abundance of inflammatory cells.
- The eosinophil is the most common inflammatory cell within polyps; however, mast cells, lymphocytes, and neutrophils are also common.
- Multiple proinflammatory mediators such as IL-1, IL-3, IL-5, TNF, ECP, MBP, and EPO have been characterized in nasal polyps.

29.2.2 Antrochoanal Polyps

Although similar in composition to middle meatal polyps, antrochoanal polyps deserve some special attention due to their proposed mechanism of origin. Antrochoanal polyps typically arise from obstructed or ruptured mucous glands, are solitary and unilateral in nature, and originate from the maxillary sinus. They typically extend into the nose through an accessory ostium and fill the nasal cavity and nasopharynx (see

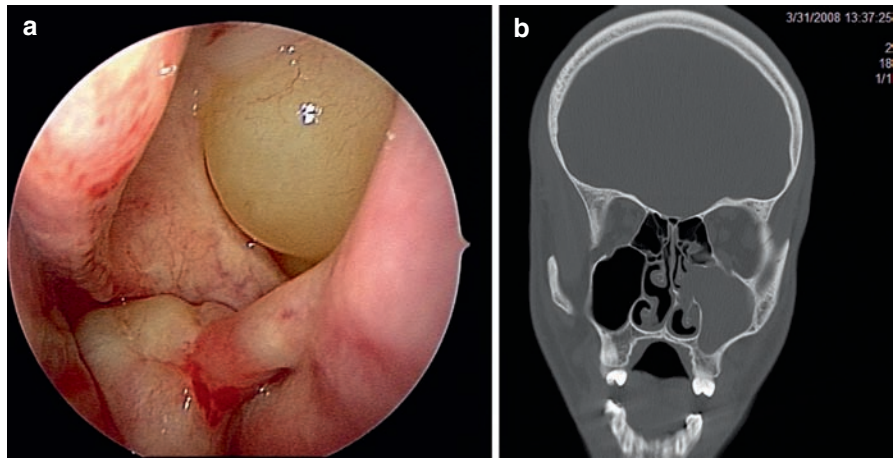

Fig. 29.2 Endoscopic picture of an 18-year-old man with two antrochoanal polyps originating from the same maxillary sinus (**a**). CT of the paranasal sinuses shown in the coronal plane shows the typical soft tissue attenuation of the antrochoanal polyps, with complete opacification of the maxillary sinus, and extension of this opacification into the nasal cavity (**b**)

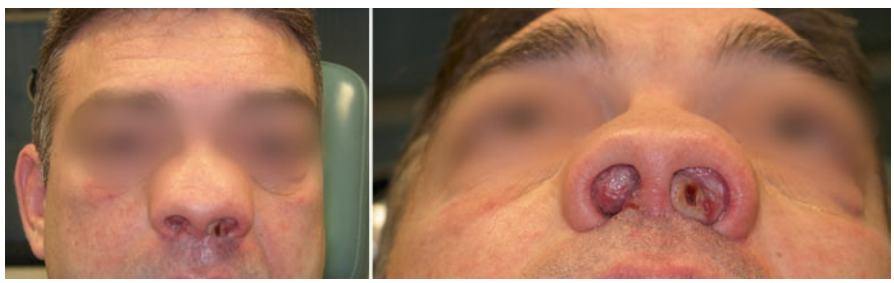

Fig. 29.3 These frontal and basal photographs are of a man presenting with a chief complaint of nasal obstruction, anosmia, and hypogeusia. Nasal polyps can be seen emanating from his nares bilaterally, and significant distortion of his nasal architecture can be observed. A brief course of medical management was deployed before surgery was performed (photograph courtesy of Dr. Alexander Chiu)

Fig. 29.2). The portion within the sinus is typically cystic whereas the part extending into the nose is polypoid. Antrochoanal polyps and traditional nasal polyps share similar histological profiles and CT & MRI characteristics; however, recent evidence suggests a role for upregulation of TGF-β and fibroblastic growth factor in the pathogenesis of antrochoanal polyps that seems to differentiate them from typical nasal polyps [15].

29.3 Examination

Patients presenting with nasal polyposis frequently complain of nasal obstruction and loss of sense of smell. When polyps are significant enough to obstruct the outflow tracts of the sinuses, inflammation and inspissated secretions may cause pressure referred to those particular sinuses. Patients presenting with antrochoanal polyps may complain of unilateral nasal obstruction (occasionally bilateral nasal obstruction if the polyp is large enough to fill the nasopharynx) and, in rare cases, an oropharyngeal mass. These patients may suffer from symptoms of obstructive sleep apnea and speak with a muffled voice.

Examination begins with an external inspection. In extreme cases, polyps may cause deformation of the nasal anatomy (see Fig. 29.3) or even telecanthus (also seen in Woake's Syndrome). Anterior rhinoscopy with a headlight often can be sufficient for identifying large polyps; however, a detailed examination of the nasal cavity can be achieved only with an endoscope. The rigid endoscope provides a superior view of the sinonasal anatomy when compared to other

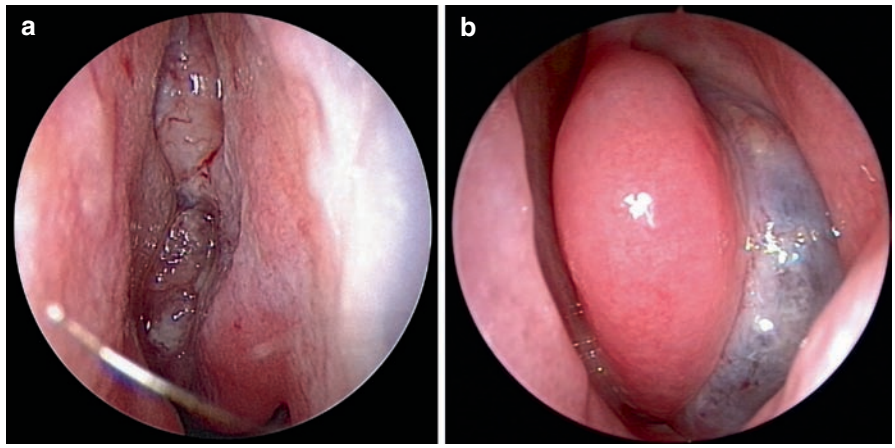

Fig. 29.4 Not all that appears to be a polyp is a polyp. These patients were referred for nasal obstruction and chronic rhinosinusitis with polyposis refractory to medical management. Biopsy in patient (**a**) revealed sinonasal undifferentiated carcinoma, and CT & MRI confirmed an encephalocele in patient (**b**). In these cases, detailed inspection with the endoscope made differentiating these lesions from polyps easier

modalities, including the flexible endoscope. The rigid endoscope has provided clinicians with the ability to perform office-based examinations that permit the identification of sinonasal disease, as well as performing endoscopically guided cultures and better understanding the pathophysiology that occurs in rhinosinusitis.

The first inspection should involve the inferior meatus, floor of the nasal cavity, and nasopharynx. Whenever possible, an angled endoscope should be used to visualize the sphenoethmoidal recess and any obstructing polyps. The second pass allows inspection of the middle turbinate and the middle meatus and the relationship of any polyps with these anatomic structures, as well as examination of the sphenoethmoidal recess. In many patients, an endoscope can then be passed into the middle meatus, to allow more detailed inspection of the ethmoid anatomy and pathology. The endoscope has the advantage over other diagnostic modalities in that polyps often can be distinguished clinically from lesions resembling polyps (see Fig. 29.4).

29.4 Imaging Studies

Imaging of the paranasal sinuses can be helpful with the diagnosis and surgical planning of chronic rhinosinusitis with polyposis. CT is now the preferred imaging modality for investigating this disease and to assist with surgical planning and navigation. Magnetic resonance imaging rarely plays a role in the routine imaging of sinonasal inflammatory disease, rather its utility lies in the investigation of malignancy, skull base injury, and the investigation of mucoceles.

29.4.1 Computed Tomography

CT should be performed at a minimum in the coronal plane with 3 mm slice thickness. This permits the surgeon to visualize the sinuses as well as the ostiomeatal complex (OMC) as they are encountered endoscopically. For the most thorough analysis, CT imaging can be performed in the axial plane with 1 mm slice thickness so that images may be reconstructed in the coronal and sagittal planes (see Fig. 29.5).

Polyps have typical findings on CT imaging and are characterized by smooth, expansile lesions within the middle meatus or nasal cavity that have soft tissue attenuation (see Fig. 29.6). Amalgamation of polyps may create spaces in which inspissated secretions can be found, and this is reflected by changes in the level of attenuation (differential density) or the findings of calcifications that can be seen on bone windows and more prominently on soft tissue windows (see Fig. 29.7). Bony rarefaction is common in extensive nasal polyposis; however, bone erosion is much less likely to occur and should prompt the clinician to consider neoplastic lesions or further work-up with endoscopy or MRI [31]. Unilateral nasal polyposis should alert the physician to the possibility of either a neoplasm or of allergic fungal sinusitis. Antrochoanal polyps, although differing in etiology, appear similar to typical nasal polyps on CT imaging (see Fig. 29.2).

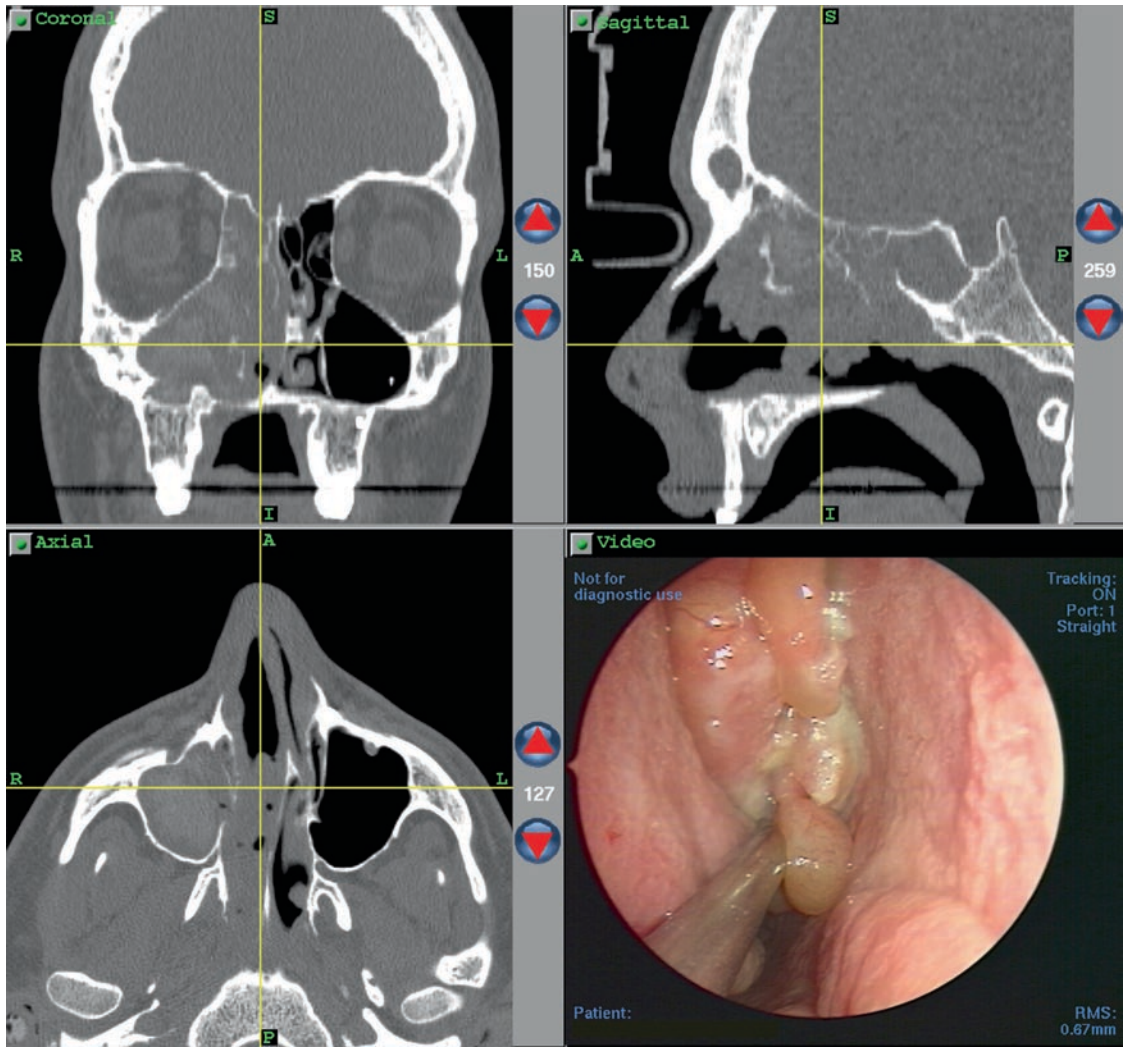

Fig. 29.5 CT images acquired in the axial plane with 1 mm or less slice thickness can be reformatted in coronal and sagittal planes to create triplanar images useful for stereotactic image-guided surgery. Here an intraoperative photograph of a patient with allergic fungal sinusitis and polyposis is correlated in three dimensions using a navigation probe

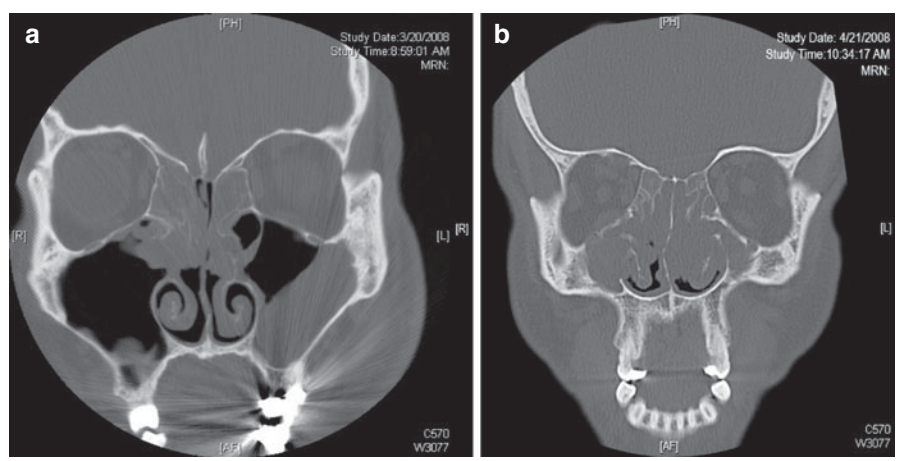

Fig. 29.6 Coronal CT images of two patients with moderate (**a**) and severe (**b**) nasal polyposis. Note the soft tissue attenuation of the polyps in patient (**a**) with bony rarefaction of the middle turbinate and ethmoid partitions. Recurrent polyposis in patient (**b**) is accompanied by significant inflammation and bony osteitis. In both cases, coronal imaging using CT was useful for thorough investigation of the extent of disease and preoperative planning

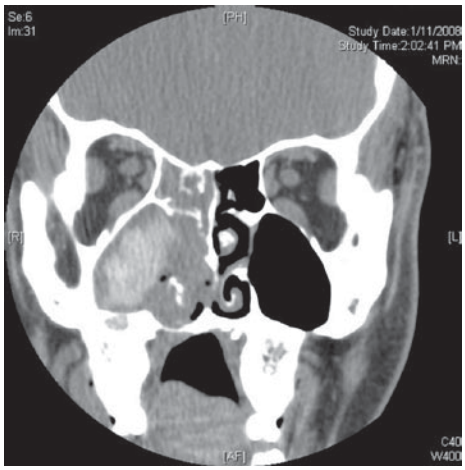

Fig. 29.7 This coronal CT in soft tissue windows is characteristic of a patient with allergic fungal sinusitis and polyposis. Note the unilateral disease, the soft tissue attenuation characteristic of nasal polyposis as well as accumulation of allergic mucin within the maxillary sinus and among the polyps that presents as a differential density due to its increased density relative to soft tissue

Key findings of nasal polyposis with CT imaging include:

- Soft tissue lesions expanding the middle meatus or occasionally medial to the middle turbinate demonstrating soft tissue attenuation
- Bony remodeling or rarefaction of the middle turbinate and/or lamina papyracea in advanced cases
- Differential density or calcifications within a sinus suggesting inspissated secretions or allergic fungal disease

29.4.2 Magnetic Resonance Imaging

As previously described in this text, polyps undergo histological changes (e.g., edematous stage, fibrotic stage, etc.), and these stages can be identified on MRI with variable signal intensity depending on MR pulse sequence. The variability in signal intensity is due to the proteinaceous and water content within polyps. Polyps display medium or isointense signals on T1-weighted MR images that may enhance peripherally with the administration of gadolinium, and owing to their water content, are bright on T2-weighted images. The mixture of water, protein, and glandular tissue within polyps can result in a very heterogeneous appearance on MRI that is atypical of neoplasms and helps identify their occurrence. Antrochoanal polyps, while different in etiology, appear similar on MRI as do typical nasal polyps [25, 31].

Key features of polyps on MRI are:

- Medium intensity (isointense) signal on T1-weighted MRI
- Bright intensity (hyperintense) signal on T2-weighted MRI
- Heterogeneity owing to differential stage of polyp development

29.5 Surgical Therapy

29.5.1 General Principles

The medical management of nasal polyps requires an understanding of the underlying cause of nasal polyposis and should be catered to the individual patient and is discussed elsewhere in this text. When the symptomatic patient fails to derive benefit from medical therapy or complications are impending, surgical therapy is warranted. It is critical that the clinician inform the patient that surgery is not likely to cure the patient and that ongoing medical therapy will be required in most cases to control the underlying inflammation that was the cause of polyps in the first place.

General principles surgery for nasal polyposis:

- Selection of the patient who has exhausted medical management and remains symptomatic; the patient must understand the absolute necessity of often prolonged postoperative care.
- Selection of appropriate anesthetic method and preparation of the surgical field to maximize visualization and minimize bleeding.
- Accurate identification of surgical landmarks such as the lamina papyracea, anterior ethmoid artery, and skull base on preoperative CT imaging.
- Use of stereotactic image-guided surgery when necessary to confirm the skull base, cribriform plate, and lamina papyracea.
- Atraumatic removal of polyps and diseased bone while preserving as much mucosa as possible.

- Meticulous removal of osteitic bone and bony partitions.
- Ongoing postoperative medical management to prevent disease recurrence.

29.5.2 Functional Endoscopic Sinus Surgery

Since its introduction [6, 7], functional endoscopic sinus surgery (FESS) has proven to have lower morbidity and improved results over prior surgical techniques. It has proven to be a safe and effective surgical treatment of chronic rhinosinusitis and nasal polyposis in patients who have failed medical management. With the goals of mucosa preservation, removal of osteitic bone and restoration of sinus health through improved ventilation of the natural drainage pathways, FESS has become the standard of care for the surgical treatment of nasal polyposis over earlier external or intranasal approaches.

Visualization of the paranasal sinuses during endoscopic sinus surgery has been greatly aided by the rigid endoscope. Once used purely for diagnostic purposes, the endoscope provides the dual role of illuminating and magnifying the nasal cavity while allowing close inspection and the simultaneous manipulation of the nasal tissue. The operating surgeon may perform his or her dissection by directly viewing through the telescope or by coupling a camera to the telescope. A beam splitter may be incorporated to allow direct visualization through the scope while displaying video for teaching purposes.

The use of pistol-gripped and through-cutting instrumentation, implementation of straight and angled telescopes using high resolution digital and analog camera systems, and refinements in anesthesia technique have reduced operating times and has made safer, more meticulous dissection attainable. However, one of the most revolutionary advances and useful tools used in surgery for nasal polyposis is the microdebrider.

Originally developed by Stryker Corporation and described by Setliff and colleagues [28, 29], the microdebrider has become a mainstay tool of the endoscopic sinus surgeon and is capable of atraumatically cutting and removing (by suction-irrigation) soft tissue, loose bone, and polyps (see Fig. 29.8). The primary advantages the microdebrider has over traditional

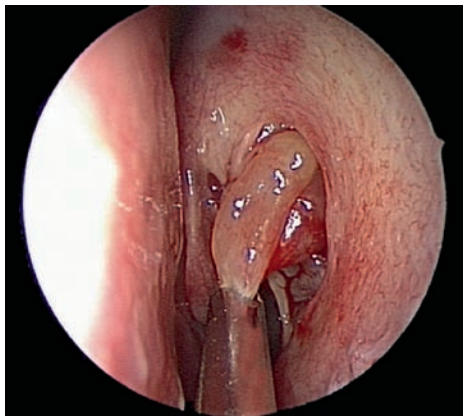

Fig. 29.8 An endoscopic picture of the microdebrider at work: suction provided by a central port in the microdebrider helps draw soft tissue (e.g., polyps) into shaft where an oscillating blade briskly cuts through the soft tissue

cutting instruments include disposable rotating microdebrider tips that are always sharp and have been shown to reduce mucosal trauma (i.e., mucosal stripping) [10] when compared to traditional hand-held cutting instruments. The microdebrider also contains a suction and irrigation system to assist with disposal of cut tissue from the surgical field. Debate exists whether the tissue removed via the suction port should be collected for routine histopathological diagnosis [3, 8, 26]; however, in rare instances, patients with preoperative diagnoses of nasal polyposis, especially recurrent polyposis, may demonstrate atypical findings on pathologic examination [3] that require further workup, long-term follow-up, and possibly surgical management.

Although polyps typically do not fill the frontal sinus proper, the frontal recess and infundibulum may be diffusely diseased by polyps. In these cases, 40 and 60° angled microdebrider tips can be useful in atraumatically clearing polypoid debris and hyperplastic mucosa obstructing the frontal ostia.

Many of the original disadvantages (easily clogged suction ports, ergonomics) of the microdebrider have been resolved over the past 10 years since its inception. However, a number of critical shortcomings still exist. Disposable microdebrider tips, while always sharp, can be expensive. Use of straight and multiple angled tips during endoscopic sinus surgery can add cost to the procedure, and the clinical utility of one curved microdebrider tip over the other is debatable. Motor vibration and tip rotation decreases tactile

sensation, making it difficult to palpate bony partitions and soft tissue while in use. The continuous suction and rotation of the blade presents danger to critical anatomic structures such as orbital contents, the anterior ethmoid artery, and the skull base. Coupled with the lack of tactile sensation, a great deal of injury to a patient can occur rapidly with a microdebrider, and microdebriders are capable of stripping mucosa when used without sufficient care.

Recommended instrumentation for endoscopic removal of polyps:

- 0, 30, and 45° rigid endoscopes with appropriately selected endoscope sheathes for scope irrigation
- Microdebrider with straight and curved tips for removal of polyps within middle meatus, maxillary sinus, ethmoid cavity, and frontal recess
- Straight, angled, and curved through-cutting instruments for the atraumatic removal of diseased bone and polyps

29.5.3 Image-Guided Surgery

Preoperative CT imaging in the axial plane can be used by a number of image-guidance systems to assist with surgical navigation during endoscopic sinus surgery. These navigation systems localize bony anatomy using probes that are registered via infrared light or electromagnetic energy. Such tools to date have not been proven to reduce the risk of complications, enhance surgical skills, or replace surgical decision-making; however, these tools can help orient the surgeon when bony anatomy is distorted, especially during revision cases.

29.5.4 Surgical Steps

Success in surgery is often dependent upon patient selection and preoperative medical management. Preoperatively, patients with evidence of active infections should be administered culture-directed antibiotics to help eradicate infection and to decrease mucosal inflammation. Preparation of the surgical field in the presence of nasal polyps should include the administration of preoperative oral corticosteroids if there are no medical contraindications. Administration of prednisone (or equivalent corticosteroid) at the dose of 20–40 mg/day 4–10 days prior to surgery helps reduce polyp size, stabilizes the mucosa by decreasing local inflammation, and decreases the incidence of bleeding. In the patient with relative contraindications to corticosteroids (e.g., diabetes, glaucoma), it is prudent to consult with the appropriate specialist to establish the specific limitations that need be placed on perioperative administration of corticosteroids.

The selection of general anesthetic method is an important consideration for the surgery of nasal polyposis. In studies comparing inhalational anesthesia to total intravenous anesthesia with remifentanil and propofol, improved visual field with decreased blood loss has been demonstrated. This appears to be mediated by overall reductions in mean arterial pressure, cardiac output, and heart rate [4, 36]. Therefore, the use of total intravenous anesthesia with remifentanil and propofol is advised during polyp surgery.

Immediate steps to reduce intraoperative blood loss during polyp surgery begin with adequate nasal decongestion with topical 0.1% oxymetazoline prior to the surgical procedure. In combination with topically applied cocaine powder, improved visualization can be achieved. Injections with 1% lidocaine with 1:100,000 superior to the axilla of the middle turbinate as well as through the greater palatine foramina are performed to assist with vasoconstriction. A 25-gauge needle bent at 2.5 cm for the tip is used to inject 1.5 mL of 1% lidocaine with 1:100,000 epinephrine through the greater palatine foramen, which is opposite the second molar. When performed, an intravascular injection can be avoided by performing multiple aspirations through the course of the injection. By taking the aforementioned steps, significant improvements in visualization can occur and with meticulous, atraumatic surgical technique, blood loss can be minimized.

Polyps obstructing the nasal cavity or emanating from the middle meatus are best addressed with the microdebrider. The oscillating blade of the microdebrider easily removes polyps until recognizable anatomy is seen. After obstructing polyps are removed, each sinus is best addressed systematically in order to thoroughly treat disease and prevent missteps.

The maxillary sinus is best addressed with 0 and 30° endoscopes. The uncinate process should be removed in its entirety to ensure that postoperative scarring near the natural ostium does not occur and to prevent recirculation. This can be done with a sickle

knife, a backbiting instrument, and the microdebrider. The natural ostium of the maxillary sinus should be probed and visualized with a 45° endoscope; it is crucial that the natural ostium is widened and that any surgically created ostium is brought into continuity with the natural as in order to prevent recirculation of mucus. This is best assured by using the backbiter to rotate residual or retained portions of the uncinate process away from the infundibulum. In the case of polyposis, postoperative irrigation (discussed later) is important; therefore, large antrostomies are recommended. The sinus should be inspected with at minimum the 45° endoscope; a 70° endoscope is advised for analyzing the floor and anterior-most portions of the maxillary sinus to inspect for polyps and any infraorbital ethmoid cells that may obstruct the ostium. Inspissated secretions need to be evacuated, cultured, and sent to pathology for analysis of possible fungal disease.

The ethmoid sinuses are addressed next. Attention to the landmarks in the ethmoid cavity is important, as the majority of skull base injuries and cerebrospinal fluid leaks occur during this portion of the dissection, especially when polyps and bleeding can impair the surgeon's view. Anterior ethmoid cells should be meticulously dissected using through-cutting instruments and polypoid debris removed with the microdebrider. The first important landmark to identify is the medial orbital wall and the dissection is continued along the medial orbital wall rather than medially, because the skull base is significantly thicker and less likely to be injured laterally as opposed to medially where it slopes down into the middle turbinate. Care should be taken to avoid undue trauma to the middle turbinate and to avoid stripping mucosa. It is imperative that foci of ostetic bone along the lamina papyracea and middle turbinate be removed to help reduce inflammation and prevent polyp recurrence in these areas. Once the basal lamella is identified, the posterior ethmoid cells should be dissected in a similar fashion. Dissection of the ethmoid cavity typically occurs in an anterior to posterior fashion, identifying landmarks along the lamina papyracea and skull base until the anterior face of the sphenoid is encountered. Although the majority of the dissection is performed with a 0° telescope, once the skull base has been identified, a 30° endoscope and a curved microdebrider blade are often helpful for removing polyps along the roof of the ethmoid cavity. The superior turbinate is next identified in order to enter the sphenoid sinus through the sphenoethmoidal recess and its natural ostium.

The sphenoid sinus is entered through its natural os, either through the sphenoethmoidal recess transnasally or transethmoid (following ethmoid dissection). Regardless, entry though the natural ostium is important so that the sinus is entered away from critical structures such as the carotid artery (dehiscent in up to 20% of cases) and the optic nerve (dehiscent in 5–10% of cases). This method also ensures that a sphenoethmoidal (Onodi) cell is not mistakenly treated as the sphenoid sinus. The sphenoid sinus should be opened widely from the skull base to lamina papyracea; care must be taken to avoid the septal branch of the sphenopalatine artery during this dissection. The sphenoid sinus typically does not become diseased with polyps, and due to the critical anatomy surrounding the sphenoid sinus, excavation of polyps within the sinus should be performed judiciously.

Once the sphenoid sinus is opened, dissection along the skull base occurs in a retrograde fashion in order to clear lamella along the skull base until the frontal recess is encountered. The region of the anterior ethmoid artery is identified and avoided. It typically lies at the uppermost limit of the anterior wall of the ethmoidal bulla, and may be in the skull base or several millimeters below it, close to the point where the skull base becomes horizontal at the posterior limit of the frontal recess. If an injury to the anterior ethmoid artery occurs, bipolar electrocautery is used to coagulate the vessel, and physical examination of the eye should be performed to assess for tension on the globe, signs of bleeding, and pupilary defects. If an orbital abnormality is identified, prompt consultation with an ophthalmologist is indicated.

Dissection of the frontal sinus presents the most challenge to endoscopic sinus surgeons. It is infrequent that the frontal sinus is diseased with polyps; however, the frontal recess can be extensively diseased with polyps, resulting in obstruction of the frontal sinus itself. Much of the dissection involves angled instruments and endoscopes, and the surgeon must be familiar with this array of instruments and be facile with angled endoscopes. Experience is critical in order to prevent injury to the skull base and to prevent iatrogenic stenosis of the frontal recess postoperatively. In this region, preoperative review of the CT scans is critical, as a variety of drainage pathways may lead to the frontal

sinus and a host of ethmoid air cells may invade the frontal sinus, complicating its anatomy and dissection, and polyps within the frontal recess can impair vision of these anomalies. Prior to initiating dissection in this area, the surgeon should have a clear concept of the anatomy and the likely site of the frontal sinus drainage pathway, based upon the preoperative CT scans. Through-cutting instruments are used to dissect the anterior ethmoid lamella until the skull base is skeletonized and the anterior ethmoid artery identified, just posterior to the frontal recess. The frontal sinus drainage pathway, if not visually obvious at this point, is confirmed by the gentle passage of a malleable probe. Partitions separating the frontal sinus from the supraorbital ethmoid cells are then taken down meticulously. The agger nasi cap is identified, resected, and frontal recess evaluated. With the recess opened, it is critical to avoid injury to the mucosa in this region, as stenosis is inevitable if mucosa is stripped and the bone exposed.

After a complete dissection of the paranasal sinuses has been performed, the field should be inspected for loose fragments of bone, missed ethmoid partitions, and points of bleeding. Wherever possible, any exposed bone is removed. A controlled synechiae between the middle turbinate and septum can be created or the middle turbinates sutured across the septum should the middle turbinate be floppy. Merocel spacers are placed for 24 h and removed on postoperative day one when debridement occurs.

29.6 Postoperative Management

As previously mentioned, surgery represents an adjunct to medical therapy in chronic rhinosinusitis with nasal polyposis and must be performed in the context of a thorough preoperative work-up to address the underlying cause of the inflammation. Postoperatively, failure is almost assured if the ongoing medical therapy to prevent recurrence is not administered. Patient expectations need to have been addressed so that long-term follow-up can be established.

Routine postoperative debridement of the sinonasal cavity is critical to assuring success. The ideal timing of such debridements has not been established; however, we recommend that they begin within the first week of surgery. Thereafter, regular debridement of blood, exposed bone fragments, inspissated secretions, and recurrent polypoid mucosa can be challenging in the office setting; however, utilization of appropriate instrumentation and use of topical anesthetics, gentle atraumatic technique and, when necessary, the local injection of anesthetic can make the experience very tolerable for patients. Routine CT imaging is not required following endoscopic sinus surgery; however, CT scans should be obtained when symptoms do not correlate with endoscopic findings or if recurrent polyposis obstructs visualization of a previously achieved patent sinus cavity.

The utility of antimicrobial agents in the postoperative management of nasal polyposis is difficult to study given the diverse flora associated with chronic rhinosinusitis and the role they play in the underlying disease. Growing resistance patterns have prompted some physicians to limit antibiotic usage and to reserve them for situations in which symptoms change or evidence (i.e., growth on cultures) of infections exists. Culture-directed antibiotics in the postoperative setting should be utilized to limit iatrogenic infection, treat osteitis, and eradicate sources of inflammation. Recent evidence for the role of macrolide antibiotics in patients with nasal polyposis has demonstrated decreases in cytokines associated with nasal polyposis as well as decreases in polyp-associated inflammation [16, 27, 32]. The utility of macrolide antibiotics in the postoperative setting needs further study and their role in postoperative care ultimately must be examined in the face of more potent anti-inflammatory effects achieved by corticosteroids and other culture-directed antibiotics.

Oral corticosteroids exert significant anti-inflammatory actions on the nasal mucosa and can be effective medical therapy for nasal polyposis associated with chronic rhinosinusitis. In diffuse nasal polyposis, the patient should be discharged with a tapering course of prednisone over a prolonged period, and overlapping administration of topical corticosteroids should begin before cessation of oral corticosteroids is considered. If the patient tolerates prolonged oral corticosteroids, it is important to taper the medication, as abrupt withdrawal of this therapy cannot only result in hypoadrenalism but also prompt recurrence of inflammation. If the patient cannot tolerate a prolonged course of oral corticosteroids, bursts in steroid therapy may be used intermittently to help reduce sinonasal inflammation and polypoid recurrence. All patients should be counseled regarding the potential risks of corticosteroids (e.g., hyperactivity, insomnia, dyspepsia,

iatrogenic hyperglycemia, weight gain, gastritis, and avascular necrosis of the hip), and therapy with proton pump inhibitors is recommended. Patients unwilling to undergo oral corticosteroid therapy may benefit from topical administration of budesonide 0.5 mg/2 mL mixed in 240 mL normal saline for irrigation. Irrigation with topical budesonide is not FDA approved; however, improvements in mucosal inflammation and reduction in recurrent nasal polyposis have been observed by these authors without the significant side effects experienced while on oral corticosteroids.

29.6.1 Steroid Injection

Triamcinolone acetonide is a synthetic corticosteroid typically marketed in an aqueous suspension in 10 or 40 mg/mL preparations for depot use that is not FDA-approved for the intralesional treatment of nasal polyposis. Considerations for steroid injection include patients who cannot tolerate oral or topical corticosteroids, isolated, symptomatic polypoid disease, or for postoperative recurrence. There are no controlled studies evaluating the efficacy of triamcinolone injections for nasal polyposis or for recurrent polyposis; however, many case series and anecdotal reports demonstrate success [14, 18]. Infrequent reports of visual loss [17, 18] following intraturbinal or intralesional injection of corticosteroid preparations can be found in the literature; however, when using appropriate techniques of topical decongestion, slow injection with small gauge needle and multiple injection sites can help minimize complications [14]. A slow intralesional injection of 1 mL of 10 mg/mL solution is performed using a 27-gauge needle. The physician should aspirate prior to injecting the steroid in order to ensure that medication is not injected within a vessel. If injecting bilateral lesions, it is prudent to stage injections several minutes apart so that visual checks may be performed. Prompt consultation with an ophthalmologist is necessary if any visual disturbance is encountered during an injection.

The key goal of postoperative therapy in nasal polyposis is to continue to treat any persistent asymptomatic mucosal disease, until such time as a stable cavity is obtained. Accordingly, the postoperative visits and endoscopic follow-up are continued until the mucosa returns to normal, or any persistent inflammation is demonstrated to be well controlled with the ongoing medical therapy. In severe polyposis, moderately intensive medical therapy and intermittent debridement may need to be continued for several years before a stable cavity is achieved. Exacerbations of mucosal disease, often associated with viral infections or allergy exposure, are treated with increased topical or systemic steroids. Ancillary medical therapy with antileukotrienes, antihistamines, or anti-IgE monoclonal antibodies all may be helpful in some cases. Additionally, although the role of fungus in nasal polyposis remains controversial, there are some patients who respond dramatically and positively to oral itraconazole at a dose of 200 mg b.i.d., when other methods of polyp control fail. Whether this response is secondary to a steroid potentiating effect or a direct antifungal effect remains unclear. Patients receiving itraconazole require liver function tests prior to therapy and during therapy and should be removed from other liver metabolized medications. Additionally, since itraconazole is not FDA approved for fungal sinusitis or nasal polyposis, informed consent should be obtained prior to therapy. Itraconazole is contraindicated in patients with a tendency toward heart failure.

29.7 Conclusions

Nasal polyposis presents a significant challenge to the otolaryngologist. No single therapy has been found to be effective for all patients presenting with this condition, as multiple pathways have led to this common nasal manifestation. When the underlying medical condition cannot be controlled and symptoms are unrelieved, surgery is indicated. Thorough preoperative workup and preoperative medication coupled with meticulous surgical technique and stereotactic image guidance can result in improved surgical outcomes. However, it is the prolonged and continued postoperative management that can increase the chances of successful long-term treatment for nasal polyposis. The goal of the surgery and the postoperative treatment is not just the resolution of symptoms in the short to medium term, but rather is the creation of stable mucosa within the cavity, early active medical therapy for any recurrences, and the avoidance of further surgery in the future.

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Nasalisation in the Surgical Treatment of Nasal Polyposis

30

Roger Jankowski

Core Messages

- The definition, pathophysiology and surgical approach of nasal polyposis (NP) are still under debate.
- In this chapter, NP is considered as a chronic inflammatory *disease* of the ethmoidal sinus mucosa characterised on nasal endoscopic examination by the presence, bilaterally, of non-infected white-oedematous polyps originating into the ethmoidal labyrinths and most of the time, arising from the middle and/or superior meatus and/or the sphenoethmoidal recess. This definition is aimed at stressing that NP is a specific disease that can easily be recognised among all other forms of rhinosinusitis and other nasal diseases.
- Our opinion is that sinus ventilation/drainage or obstruction in the ostio-meatal complex is a minor pathogenic factor in NP disease.
- Our hypothesis is that NP is a disease generated by remnants of vestigial olfactory mucosa scattered in the ethmoidal sinuses. Only people who have remnants develop NP. This vestigial olfactory mucosa has probably lost its histological features, but has kept some biological properties, among which is the ability to attract eosinophils. Olfaction is probably one of the oldest phylogenetic senses and eosinophils are probably one of the oldest cells of the innate immune system. Our hypothesis is that NP could be regarded as an inflammatory disease resulting from a dysfunction of the innate immune system associated to the olfactory organ. In this concept, the role of surgery for NP is to remove as much as possible of the vestigial ethmoidal mucosa.
- The role of the sinuses is still unclear and the need to retain more or less of the compartmentalisation of the ethmoidal labyrinths is also questionable. Our hypothesis is that, when dealing with the NP disease, complete removal of the bony lamellas partitioning the ethmoidal labyrinth is not more harmful than trying to restore ventilation/drainage in the different ethmoidal compartments.
- The combination of both hypotheses led us to propose the nasalisation procedure as a surgical approach for NP. The aim of the nasalisation procedure is to remove the ethmoidal mucosa as completely as possible without hazards, and to transform the ethmoidal labyrinth into a unique cavity opening into the nose (nasalisation).
- To achieve the nasalisation procedure, it is more important to know the anatomy of the ethmoidal walls than the compartmentalisation inside the ethmoidal labyrinth.
- The technical key point to safely perform a nasalisation procedure is to gently strip the mucosa to follow the bony structure of the medial orbital wall, ethmoidal roof and conchal lamina.
- Our results show that NP is a chronic disease which cannot be cured, but that the underlying chronic eosinophilic ethmoiditis disease seems

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to be better controlled after nasalisation than after ethmoidectomy.

› When the medical treatment with corticosteroids fails to stop the eosinophil attraction, the aim of surgery should be to remove as completely as possible the ethmoidal mucosa, which seems to be the main attractant for eosinophils.

30.1 Introduction

The definition, pathophysiology and surgical approach of nasal polyposis (NP) are still under debate. On the basis of 20 years of surgical experience, this chapter has been written for physicians seeing polyposis patients with overwhelming recurrences after limited surgical procedures or who cannot be rid of the multiple/continuous courses of systemic steroid treatments, or who want better functional results, especially in the sense of smell restoration.

30.2 Philosophy of the Nasalisation Surgical Procedure

The surgical treatment of NP is aimed at improving the *illness* of patients affected by chronic symptoms of rhinitis, sinusitis and for most of them, severe hyposmia or anosmia.

The pathophysiology of NP is still unclear and so are, also, the diagnosis criteria. In this chapter, NP is considered a chronic inflammatory *disease* of the ethmoidal sinus mucosa characterised on nasal endoscopic examination by the presence, bilaterally, of non-infected white oedematous polyps originating at the ethmoidal labyrinths and, most of the time, arising from the middle and/or superior meatus and/or the sphenoethmoidal recess. This definition is aimed at stressing that NP is a specific disease, which can easily be recognised from all other forms of rhinosinusitis and other nasal diseases.

The surgical concept of nasalisation has specifically been developed to treat the NP disease and improve NP illness. Our opinion is that sinus ventilation/drainage or obstruction in the ostio-meatal complex is a minor pathogenic factor in NP disease. NP is primarily a chronic inflammatory disease of the mucosa of the ethmoidal labyrinths.

The ethmoidal labyrinths look like vestigial structures of the primarily olfactory organ: human embryologic development still shows that the olfactory grooves have secondarily been exploited by the respiratory apparatus, a phenomenon, which probably occurred when life spread from water onto earth to adapt respiration to air breathing. The ethmoidal labyrinths, which are sinuses only described in humans, are the closest sinuses to the olfactory clefts, and may have been covered with olfactory mucosa (as are currently, for instance, the frontal and sphenoid sinuses in macrosmatic animals like the fox) in former times, before the bipedal human locomotion (which freed the hand and enhanced the role of vision) decreased the role of olfaction for survival and restricted the olfactory mucosal area to the roof of the olfactory clefts.

Our hypothesis is that NP is a disease generated by remnants of this vestigial olfactory mucosa scattered in the ethmoidal sinuses. Only people who have remnants develop NP. This vestigial olfactory mucosa has probably lost its histological features, but could still have kept some biological properties, among which the ability to attract eosinophils. Olfaction is probably one of the oldest phylogenetic senses and eosinophils are probably one of the oldest cells of the innate immune system. Our hypothesis is that NP could be regarded as an inflammatory disease resulting from a dysfunction of the innate immune system associated to the olfactory organ. In this concept, the role of surgery for NP is to remove as much as possible of the vestigial ethmoidal mucosa.

The role of the sinuses is still unclear and the need to retain more or less of the compartmentalisation of the ethmoidal labyrinths is also questionable. Our hypothesis is that, when dealing with the NP disease, complete removal of the bony lamellas partitioning the ethmoidal labyrinth is not more harmful than trying to restore ventilation/drainage in the different ethmoidal compartments.

The combination of both hypotheses led us to propose the nasalisation procedure as a surgical approach for NP. The aim of the nasalisation procedure is to remove the ethmoidal mucosa as completely as possible without hazards, and to transform the ethmoidal labyrinth into a unique cavity opening into the nose (nasalisation).

30.3 Nasalisation Technique

30.3.1 Anatomical Considerations

To achieve the nasalisation procedure, it is more important to know the anatomy of the ethmoidal walls than the compartmentalisation inside the ethmoidal labyrinth, as the dissection is performed centripetally along the medial orbital wall, the ethmoidal roof and the conchal lamina.

The *turbinate wall of the ethmoidal labyrinth* [1] is the medial wall, which separates the ethmoidal sinus from the *olfactory cleft*. The *conchal lamina* is a rectangular bony plate, which is attached below the cribriform plate, and from which the different ethmoidal turbinates originate (middle, superior and inconstant supreme turbinates). Since the cribriform plate lies more caudal than then the ethmoidal roof, the turbinate wall of the ethmoidal labyrinth is attached to the ethmoidal roof, thanks to the *lateral lamella* of the intracranial *olfactory groove* (Figs. 30.1 and 30.2).

The *olfactory cleft* is a narrow chamber between the turbinate wall of the ethmoidal labyrinth and the corresponding nasal septum, closed superiorly by the cribriform plate, posteriorly by the anterior wall of the sphenoid, anteriorly in its superior portion by the nasal bone attached to the frontal bone, and opened into the nasal fossa inferiorly and anteriorly in its inferior portion. The olfactory neuroepithelium is located at the

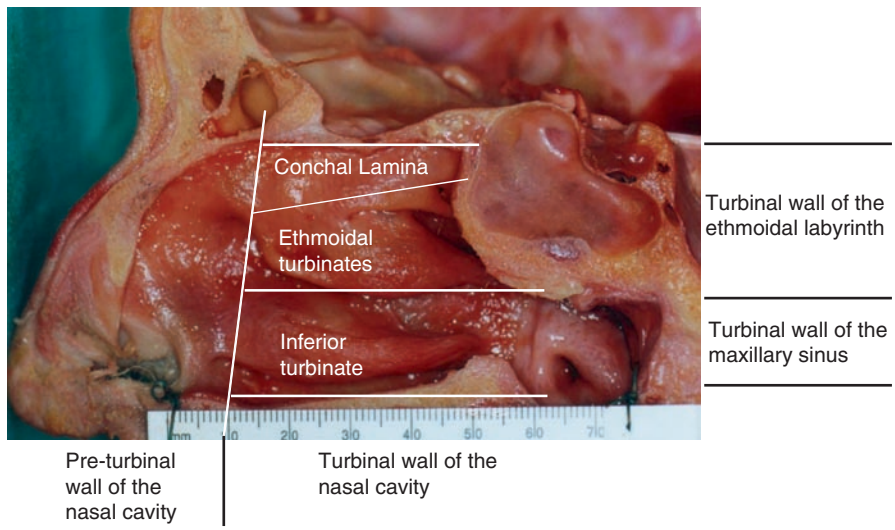

Fig. 30.1 Description of the lateral nasal wall [1]

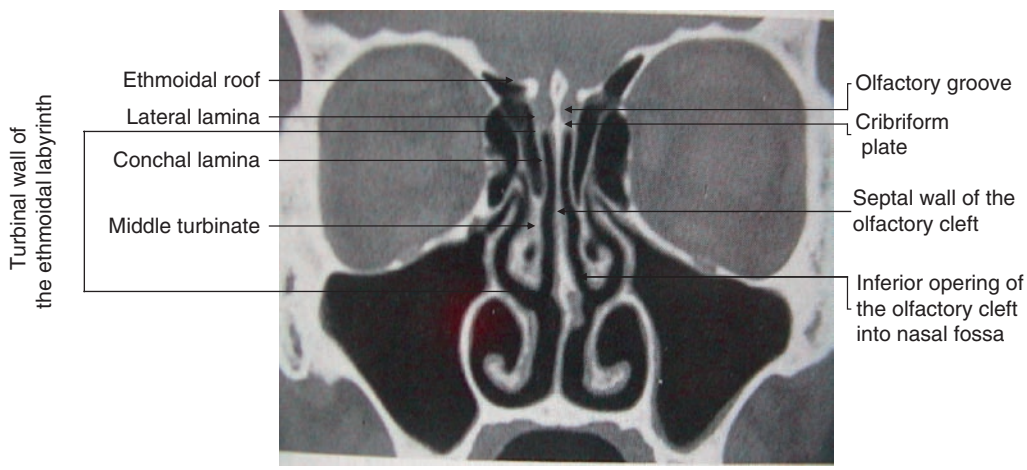

Fig. 30.2 Relationship between olfactory cleft and groove and the ethmoidal labyrinth [14].

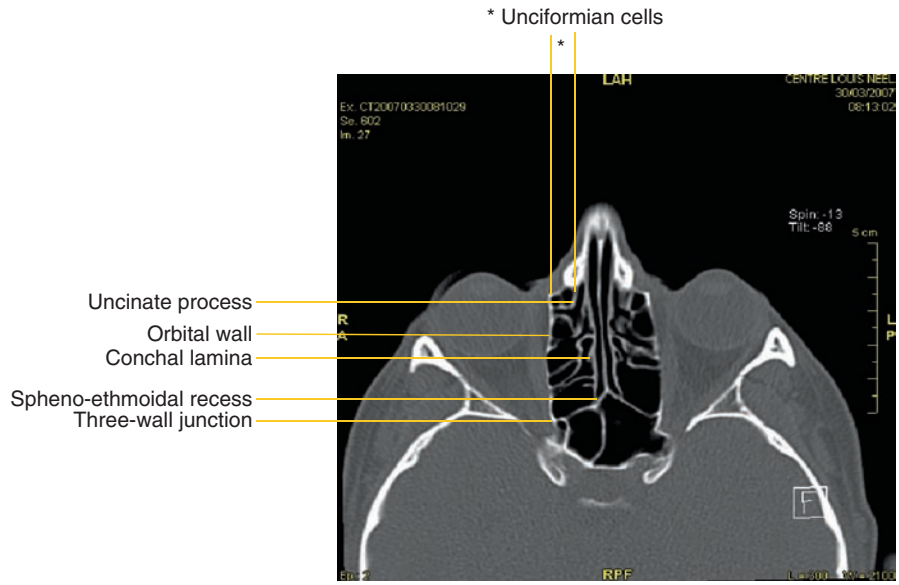

Fig. 30.3 The J shape of the anterior ethmoidal wall and compartment of unciformian cells

upper portion of the olfactory cleft, spreading from the cribriform plate onto the conchal lamina and corresponding nasal septum, whereas the inferior portion of the olfactory cleft (middle turbinate and corresponding nasal septum) is covered with respiratory mucosa. Functionally, the olfactory cleft can be divided in two portions: inferiorly, the *olfactory cleft vestibule* and superiorly, the *sensory olfactory cleft* (Fig. 30.2).

On the coronal plane, the *median orbital wall* has a C shape and its attachment to the ethmoidal roof can follow a sharp angle with the presence of the supra orbital cells (Fig. 30.2). On the axial plane, the median orbital wall has, anteriorly, a horizontal J shape (Fig. 30.3). In between both the attachments of the uncinate process and the orbital wall on the ascending process of the maxilla is a group of ethmoidal cells forming the *unciformian compartment*.

30.3.2 Set-Up

The nasalisation procedure is performed under general anaesthesia. The following four measures are helpful to control the bleeding per-operatively:

- A deep and stable general anaesthetic administered along with efficient analgesic agents [2].
- A 10–20° inclination of the operating table to bring the head up and the feet down.
- Local infiltration, with 8–12 mL of a solution made up of 20 mL 1% lignocaine and one ampoule of 0.25 mg adrenaline, of the neurovascular pedicles around the nose (supra and infra orbital nerves, dorsal nasal branch of ophthalmic artery, termination of facial artery along the nasogenial groove) and the anterior border of the septum and anterior aspect of the inferior turbinates.
- Packing of the nasal fossa with swabs soaked in lidocaine 5% with naphazoline 0.02%.

30.3.3 Surgical Dissection (Video)

After the removal of the nasal packing, a meticulous cleansing of the nasal fossa with the succion tube is combined with an endoscopic check-up looking for the origin and aspect of the polyps, the identification of the middle turbinate and the aspect of the olfactory cleft.

Polypectomy is performed to debulk the inferior and middle meati. Polyps prolapsing into the olfactory cleft are left intact, because at this stage of the procedure, it is frequently difficult to identify their true origin.

Using straight and/or 30° up biting Blakesley forceps, the heart of the ethmoidal labyrinth is holed to open an antero-posterior channel between the turbinate

wall of the ethmoidal labyrinth, the medial wall of the orbit and beneath the ethmoidal roof, staying at safe distance of these three walls.

The main steps of the nasalisation procedure, i.e. dissection of the medial orbital wall, ethmoidal turbinate wall and roof, are started now in an order and combinations that vary from one patient to another according to anatomic and pathologic variations. For the sake of the description, dissection of each wall is described separately.

The medial and inferior orbital walls form a continuous bony structure with a C-shape around the orbital content (Fig. 30.2). The easiest way to identify the inferior orbital wall is to enter the maxillary sinus. A large middle antrostomy dissected from the maxillary natural ostium anterior to the palatine bone, posterior and above the superior edge of the inferior turbinate, exposes clearly the inferior orbital wall. Mucosa can then be elevated in the underperiostium plane over a few millimetres to expose the bony inferior orbital wall into the maxillary sinus.

Dissection of the medial orbital wall actually starts anteriorly by elevating the mucosa on the ascending ramus of the maxilla bone. The underperiostium plane can easily be found here by strongly grasping without risking the full thickness of the mucosa, including the periostium on the solid bone of the maxilla ascending process. This flap elevated in posterior direction divides itself into two secondary flaps: one inferior, which detaches itself above the superior edge of the inferior turbinate, one superior, which turns around the maxilla ascending process towards its posterior face and opens the unciformian cell compartment towards the medial orbital wall.

Dissection of the unciformian compartment is carefully achieved by removing all bony partitioning lamellas and mucosa found behind the ascending process and above the maxillary natural ostium until the medial orbital wall is reached. At this stage, the junction between the inferior and medial orbital wall can clearly be identified at the level of the maxillary natural ostium through the large middle antrostomy.

Dissection of the junction is continued posteriorly, where Haller cells can be found and need to be opened and dissected. Remarkably, the dissection of the junction between the two orbital walls reaches the anterior sphenoid wall at the level where the posterior wall of the maxillary sinus reaches the anterior sphenoid wall.

Once this remarkable three-walled junction (Fig. 30.3) has been dissected, the dissection of the medial orbital wall can safely be continued superiorly. Elevation in the underperiostium plane and removal of the mucosa helps to follow this very thin bony plate without hazards. This dissection leads constantly to the discovery of the ethmoidal roof at one place or another.

Dissection of the turbinate wall of the ethmoidal labyrinth starts with the resection of the middle turbinate. C-curved cisors with the concavity turned down are placed 2 or 3 mm below the anterior attachment of the middle turbinate on the lateral nasal wall. A horizontal section separates the middle turbinate from the anterior portion of the conchal lamina and leads to the superior meatus. The middle turbinate falls down into the nasal fossa, but is still attached to the lateral nasal wall by its posterior end in the area of the sphenopalatine foramen. Section of posterior end and removal of the middle turbinate leave intact the conchal lamina and the superior (and supreme) turbinate(s) (Fig. 30.1), which protects the olfactory mucosa in the upper, sensory portion of the olfactory cleft.

Underperiostial elevation of the mucosa on the ethmoidal face of the conchal lamina can then easily be achieved by starting on the cut edge of the conchal lamina, where the three layers (ethmoidal mucosa – conchal lamina bone – olfactory cleft mucosa) are easy to identify. The conchal lamina is a thin uninterrupted bony plate [1] which prolongs the lateral lamina below the level of the cribriform plate (Fig. 30.2).

Elevation and removal of the mucosa allow better recognition and dissection of the ethmoidal cells attached on the conchal lamina bony plate and help to follow this bony plate without hazards from its anterior attachment on the maxillary ascending process to its posterior curvature towards the anterior sphenoid wall to form the sphenoethmoidal recess (Fig. 30.3). Upwards, dissection does not show any remarkable anatomic landmark or articulation between conchal lamina and lateral lamella. Actually, careful dissection with bony exposition of the conchal lamina plate on its ethmoidal face is helpful to avoid any damage to the cribriform plate, which is located on the other side of the conchal lamina and forms the roof of the olfactory cleft (Fig. 30.2). In most cases, polyps found in the olfactory cleft are prolapsing through the superior or supreme meati and originate in the ethmoidal cells attached on the posterior portion of the conchal lamina. Removal of the middle turbinate is necessary to access and clear these posterior ethmoidal cells with their polyps.

Dissection of the ethmoidal roof starts anteriorly. Anterior ethmoidectomy has already partially been achieved with the dissection, after middle turbinate resection, of the anterior conchal lamina and the dissection of the unciformian compartment with bony exposure of the medial orbital wall. The frontal natural ostium is usually easy to find at this stage by exploration of the anterior roof with a blunt, curved succion tube. The help of irrigation through a frontal drain is necessary in exceptional cases. Dissection of the ethmoidal cells and bullas around the frontal ostium can be challenging, but becomes easier after elevation and removal of the mucosa to expose the white hard bone of the anterior ethmoidal roof around the ostium. The anterior ethmoidal artery is encountered in 80% of the cases and is usually separated from the frontal ostium by one ethmoidal cell [6].

Dissection of the posterior ethmoidal roof is usually easy after former exposition of the bony anterior ethmoidal roof within the lateral bony limits of the conchal lamina and medial orbital wall. Dissection can now follow in the posterior direction these three landmarks, removing carefully a few residual ethmoidal cells, usually located at the junctions between the main ethmoidal walls. Dissection can, however, become difficult at the level where the ethmoidal roof reaches the sphenoid anterior wall, because of the presence of an Onodi cell or a particular sphenoethmoidal recess, or because like the Onodi cell on the lateral orbital wall, a posterior ethmoidal cell can expand medially or above the sphenoid sinus. A transethmoidal sphenoidotomy, starting inferiorly and progressing towards the ethmoidal roof in between the medial orbital wall and the conchal lamina, is usually helpful in these situations.

The procedure ends with revision of the surgical field, to suction the blood and remove the remaining bony lamellas or small mucosal flaps. No packing is necessary in our clinical set-up.

In summary, the technical key point to safely perform a nasalisation procedure is to gently strip the mucosa to follow the bony structure of the medial orbital wall, ethmoidal roof and conchal lamina.

30.3.4 Post-Operative Care

During surgery, antibiotic cover is provided by a single dose of cefuroxime (or, if allergic, erythromycin) on induction of anaesthesia. Packing is rarely necessary in case of bleeding. If a septoplasty has also been performed, silastic splints are inserted for 48 h.

Before 2004, the patient was given, before discharge from hospital, an intramuscular injection of slow release steroid (except contraindications) to control post-operative oedema and favour rapid healing of the mucosa in large (maxillary, frontal, sphenoidal) sinuses and in the nose. We have stopped this injection since then without apparently experiencing worse functional or anatomical results. Patients receive instructions to douche the nose three or more times each day. They are also prescribed a nasal steroid spray to use topically after douching only once or twice a day.

The first routine post-operative review is at 1 month when, if lavages have been carried out regularly, a few crusts will be noted and are removed to facilitate definitive cavity healing. In cases where lavage has been inefficient, certain patients require earlier review for more vigorous decrusting.

In approximately 10% of cases, patients present with significant headaches during the period between 3 and 15 days post surgery. Once meningitis has been excluded, treatment with antibiotics and analgesics is commenced and is generally effective within 48 h.

Nasal douching once or twice a day and local steroids once a day are recommended in the long term as part of the therapeutic plan for the treatment of NP.

30.4 Results

NP can be considered a chronic inflammatory disease. With this view in mind, nobody can cure NP. Therapeutical goals in chronic disease management are to improve symptoms and quality of life, to stabilise the disease-specific evolution and to avoid disease-specific complications by controlling the underlying pathophysiological mechanisms. Therapeutical goals in NP management are to restore normal nasal breathing and sense of smell and to control rhinorrhea, to stabilise and control recurrent attacks of sinusitis or asthma, and to prevent recurrence of nasal polyps by controlling the underlying chronic eosinophilic ethmoiditis on a long-term basis.

Simple polypectomy does restore nasal breathing in polyposis with severe obstruction and can be considered an effective treatment. There is no study in the literature comparing simple polypectomy to functional ethmoidectomy, which associates polypectomy to ventilation/

drainage restoration in the sinuses according to the extent of the disease. We have compared nasalisation to ethmoidectomy, but our results need to be confirmed by others.

1. Improvement in symptoms and quality of life

Data of our comparison study [11] show that 24 months after nasalisation, nasal obstruction, rhinorrhea and sense of smell are significantly improved than after ethmoidectomy. On a 10-point visual analogue scale, asking the patients 24 months after surgery "please evaluate your current nasal discomfort between 0=same nasal discomfort as before surgery and 10=I have a normal functioning nose", the answers were significantly better in the nasalisation than in the ethmoidectomy group. Figure 30.4 shows on one hand, that in the ethmoidectomy group only a few patients reported having a normal functioning nose whereas one third already reported feeling the same discomfort as before surgery. Figure 30.4 shows on the other hand, that in the nasalisation group half of the patients reported a normal functioning nose whereas no one felt the same discomfort as before surgery, no one scoring, actually, below five. On another visual analogue scale asking the patients to "please evaluate your current asthma status between +10=no asthma symptoms since surgery and −10=severe worsening of asthma since surgery, with 0=same asthma status as before surgery", the answers were also significantly in favour of nasalisation (Fig. 30.4).

2. Stabilisation of the disease-specific evolution

In a group of patients resistant to medical treatment, i.e. needing three or more short courses of systemic steroids per year despite permanent topical steroid therapy, we have observed that nasalisation was able to stabilise the disease again [9, 10]. Figure 30.5 shows that if we take the sense of smell as a marker of disease evolution on a repeatedly administered 10-point visual analogue scale, these patients had, at entry in the study, a very poor sense of smell, which was significantly improved after 7 days of systemic steroids, but this effect was of short duration as 2 months later, the sense of smell had disappeared again in most patients. The patients were then operated on according to the nasalisation procedure and received one intramuscular injection of slow release steroid the day after surgery.

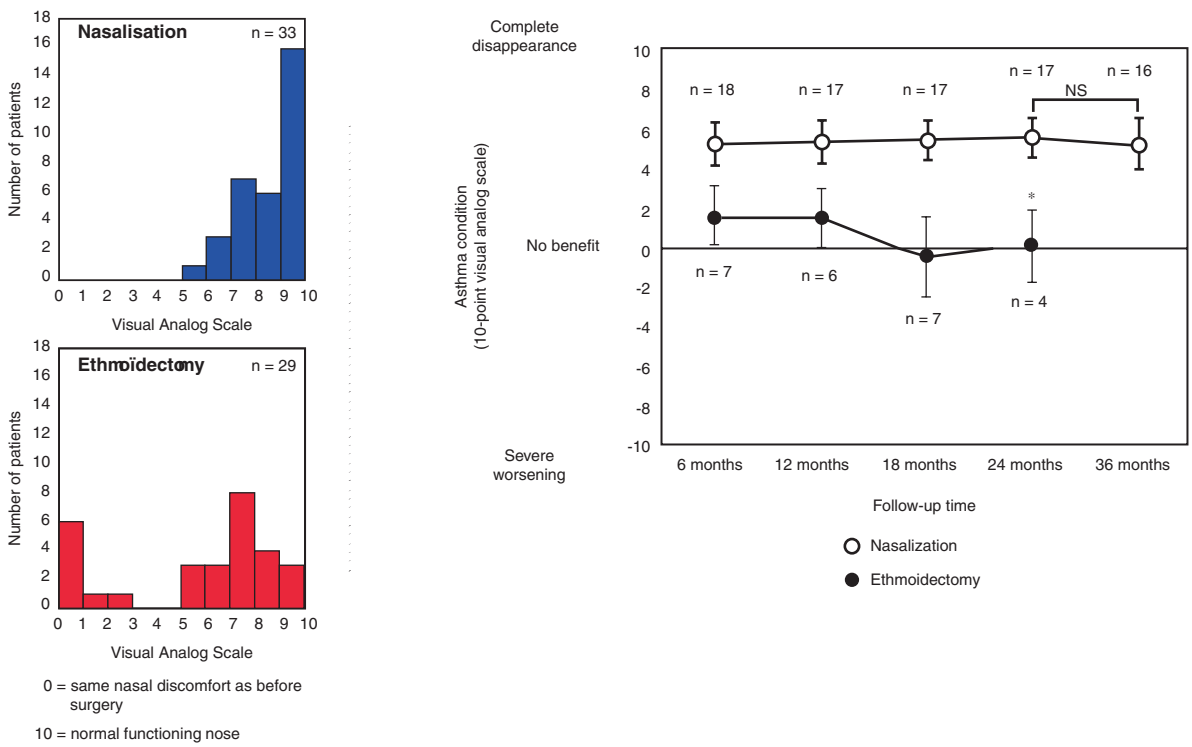

Fig. 30.4 Improvement in nasal discomfort and asthma 24 months after surgery [11]

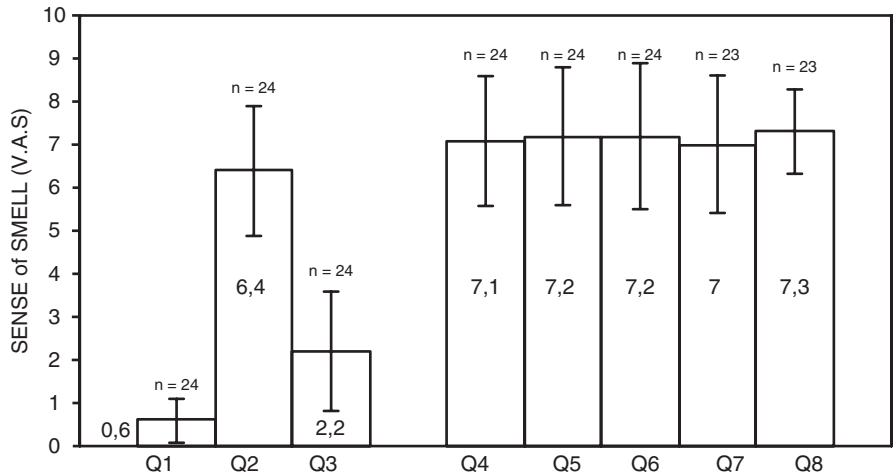

Fig. 30.5 Subjective evolution of the sense of smell after a 7-day treatment with systemic steroids and after nasalisation in anosmic patients (ANOVA $p<0.0001$) [9, 10]

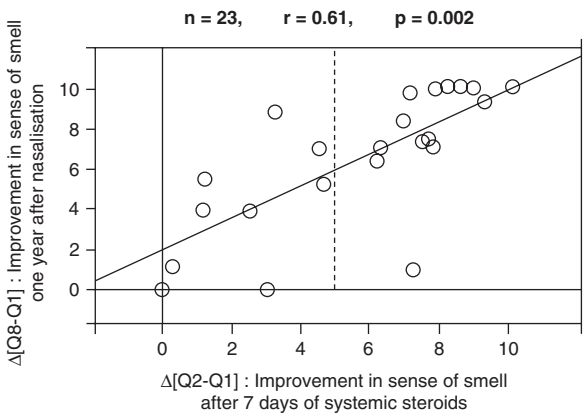

Fig. 30.6 Correlation between the subjective improvement in the sense of smell after 7 days of systemic steroids and the improvement 1 year after nasalisation [9, 10]

Figure 30.5 shows that 1 month later, the sense of smell had recovered to the level observed after 7 days of systemic steroids and that this level was maintained at least for 1 year after surgery, which was the end point of the study [9, 10]. None of these patients needed systemic steroid treatment during the year of follow-up after surgery. Interestingly, a significant correlation was found between the level in sense of smell restoration after the short course of systemic steroids and the level in sense of smell restoration after nasalisation (Fig. 30.6). The same schematic evolution was also observed for nasal obstruction and rhinorrhea [9, 10], indicating that nasalisation had stabilised the disease again and in most patients for far longer than 1 year.

3. Avoiding recurrence of nasal polyps

The patients of the study comparing nasalisation to ethmoidectomy were proposed to participate in a check-up 5 years later, including a self-administered questionnaire with 10-point visual analogue scales for symptom evaluation, and free endoscopic calibrated check up and CT at our hospital. After taking account of the patients lost to follow-up, the 5-year recurrence rate of nasal polyps was 58% in the ethmoidectomy group vs. 22% in the group that had undergone ethmoidectomy ($p<0.05$) [13].

4. Complications

No serious complications (death, meningitis, blindness) associated with the surgical procedure have been reported since 1987. No CSF leak or orbital haematoma has been observed since 1990. Minor complications (post-operative haemorrhage, ecchymosis, long-lasting crusting, etc.) are each less than 1%. The most frequent complication is mucocele formation [4]. The mean incidence rate of mucocele formation after nasalisation for NP was estimated to be of 2.5/100 patients per year. Most of the mucoceles were diagnosed during the first 6 years after nasalisation, with a peak incidence around year 2 and 3.

In summary, all these results together show that NP is a chronic disease which cannot be cured, but that the underlying chronic eosinophilic ethmoiditis disease seems to be better controlled after nasalisation than after ethmoidectomy.

30.5 Discussion: Controlling the Underlying Pathophysiological Mechanism

While the pathophysiology of NP is still unknown, there are some clue data which can help understand why nasalisation seems leading to a better control of the disease mechanisms.

Hotchkiss was the first to demonstrate in 1956 that systemic steroids were very effective in the treatment of NP [7]. The efficacy of topical steroids was shown in 1968 [15, 18]. Both treatments form the basis of the current medical treatment. We have observed in a retrospective study of polyp specimen collected during surgery [12] that: (1) the number of eosinophils was significantly and severely decreased in polyps of patients having received a short course of systemic steroids in the month before surgery compared to patients without treatment; (2) there was no difference in the number of eosinophils in polyps of patients without treatment and patients under topical steroids for more than 2 months before surgery, who actually were considered the failure of medical treatment and therefore needed to be operated. In polyps of patients responding to topical steroids, others have observed that the number of eosinophils was significantly decreased compared to the placebo group [3]. These results indicate that the disease can be controlled by decreasing the number of eosinophils in the polyp tissue. So, it seems that corticosteroids are clinically effective as long as they are able to reduce the number of eosinophils in the polyp tissue [17, 19], and it could be the same with surgery.

The ethmoidal mucosa seems to be the source of attraction for bone marrow eosinophils. On one hand, Wei et al. have shown in vitro that nasal tissue obtained from patients with chronic rhinosinusitis and asthma have the ability to attract peripheral blood eosinophils from both chronic rhinosinusitis patients and healthy control subjects, but that significantly more blood eosinophils were attracted by chronic rhinosinusitis patient tissues than healthy nasal tissue, suggesting that blood eosinophils in chronic rhinosinusitis patients are already specifically activated once they are in the blood stream on their way from the bone marrow to the sinus mucosa [20]. On the other hand, we have observed, in a retrospective study comparing the number of blood eosinophils in patients operated on NP and in a control group gathering patients without NP but operated on thyroidectomy or acoustic neuromas, that the number of blood eosinophils was twice more higher in the NP group, despite staying within the normal range. Linear multivariate analysis confirmed that NP was the main factor for this difference ($p<0.0001$) [8]. So, when the medical treatment with corticosteroids fails to stop the eosinophil attraction, the aim of the surgery should be to remove as completely as possible the ethmoidal mucosa, which seems to be the main attractant for eosinophils.

Our surgical experience of more than 20 years has shown that nasal polyps of the NP disease almost always originate from the ethmoidal labyrinth mucosa. We have never seen NP starting in the large sinuses but always in the ethmoidal labyrinths. We have even observed recently that when polyps are found in the olfactory cleft, they most of the time arise from the superior or supreme meati or turbinates, but that when they really originate into the olfactory cleft, their histology is that of respiratory epithelial adenomatoid hamartoma [21], which is a completely different entity [16]. Our hypothesis, already developed in the introduction, is that the current ethmoidal mucosa is a vestigial olfactory mucosa, which has lost its histological appearance but still has ancient biological properties, especially to attract eosinophils (one of the oldest cell of the innate immune system) to defend itself [8]. Our clinical experience also suggests that this vestigial olfactory mucosa could be diffusely spread in the ethmoidal mucosa in some patients, whereas in others, they could be present in a variable number of multiple spots. Asthma is found in more than 50% of patients with NP and the question of diffusion of this vestigial olfactory mucosa to the bronchus apparatus in patients with asthma can even be raised. Surprisingly, a paper reports that (1) asthma develops in healthy recipients after lung transplantation from mild asthmatic donors, despite complete neural disconnection and immunosuppressive therapy, and (2) that asthma disappears in an asthmatic recipient after lung transplantation from healthy donors [5]. So, some intrinsic signal seems to be located in the mucosa, both in asthma and in NP.

If the aim of surgery for NP seems to be to remove as completely as possible the ethmoidal mucosa, a far more important aim is not to harm the patient. It is far cleverer to leave a piece of mucosa than to provoke a complication. Incomplete ethmoidectomy has anyhow an efficacy, which can be very good in patients having polyps developed on multifocal areas within normal

respiratory mucosa in some ethmoidal cells. If we could know the location of the vestigial mucosa in every case, only those with diffuse vestigial mucosa should be operated according to the nasalisation procedure. As we do not know the pattern of distribution of this vestigial mucosa in each individual patient and what is the physiological need of keeping some of the ethmoidal cells or compartments unoperated, we believe that nasalisation is the appropriate treatment for NP.

Take Home Pearls

- Nasal polyposis (NP) is a specific disease characterized by the presence, bilaterally, of non-infected white-oedematous polyps originating from the ethmoidal labyrinths.
- Ventilation/drainage or obstruction in the ostiomeatal complex is a minor pathogenic factor in NP disease. Our hypothesis is that NP is a disease generated by vestigial remnants of the olfactory mucosa.
- The aim of the nasalization procedure is to remove the ethmoidal mucosa as completely as possible without hazards, and to transform the ethmoidal labyrinth into a unique cavity opening into the nose.
- To achieve the nasalization procedure, it is more important to know the anatomy of the ethmoidal walls than the compartimentalisation inside the ethmoidal labyrinth.
- The technical key point to safely perform a nasalization procedure I to gently strip the mucosa to follow the bony structures of the medial orbital wall, ethmoidal roof and conchal lamina.

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Reasons for Failure and Complications of Surgery in Diffuse Nasal Polyposis

31

Metin Önerci

Core Messages

- The most important factor in classification systems is the presence of eosinophilia.
- All recent theories suggest that the stimulus comes from the nasal mucosal side.
- The aim of the surgical treatment is to relieve nasal blockage, to improve the symptoms of rhinitis and asthma, and the final target is to eliminate nasal polyps.
- To have a successful surgical result in recurrent diffuse nasal polyposis patients, all the cells and sinuses should be opened and drained. The mucus should not be allowed to collect in any unopened cells. These areas may serve as triggering points for asthma as well.
- The surgery should be radical in terms of opening all cells and functional in terms of protecting the nasal mucosa.
- Close follow-up is of paramount importance in order to prevent edematous mucosa from closing the ostia or cells and initiate the vicious circle again by allowing the mucus to collect between edematous mucosa.
- Although new technologies may help to lessen the incidence of complications, the safest way to avoid complications is to have enough anatomical knowledge and detailed preoperative evaluation of the patient. The operation should be performed step by step by identifying the landmarks after taking necessary preoperative and operative measurements.

Although nasal polyps have been known for a long time, they still remain one of medicine's unsolved problems. There is no consensus on the types and formation of polyps, and there are various surgical approaches to their treatment. Nasal polyps are not a single entity; they include different forms, both in growth pattern and response to different medications. Nasal polyposis is varied, encompassing a wide range, from mucosal edema and solitary polyps to diffuse and massive polyposis (Fig. 31.1). About 5% of the European population suffers from chronic sinusitis [8]. Nasal polyps account for 5% of referrals to ENT clinics and 4% of referrals to allergy clinics [21]. In other studies, the prevalence of nasal polyps was found to be between 1.3 and 5.6% [11, 25, 32]. Davidson [3] found the annual polyp incidence to be 0.43/1,000. Nasal polyposis occurs in about 0.6% of adults, but increases to 15% in patients suffering from bronchial asthma [12]. Up to 95% of patients with the bronchospastic type of analgesic intolerance will develop chronic polypoid sinusitis [19, 33]. Larsen and Tos [20] found polyps in 42% of autopsy specimens. Polyps are more common in male nonasthmatic atopic patients whereas in asthmatic patients, there is no

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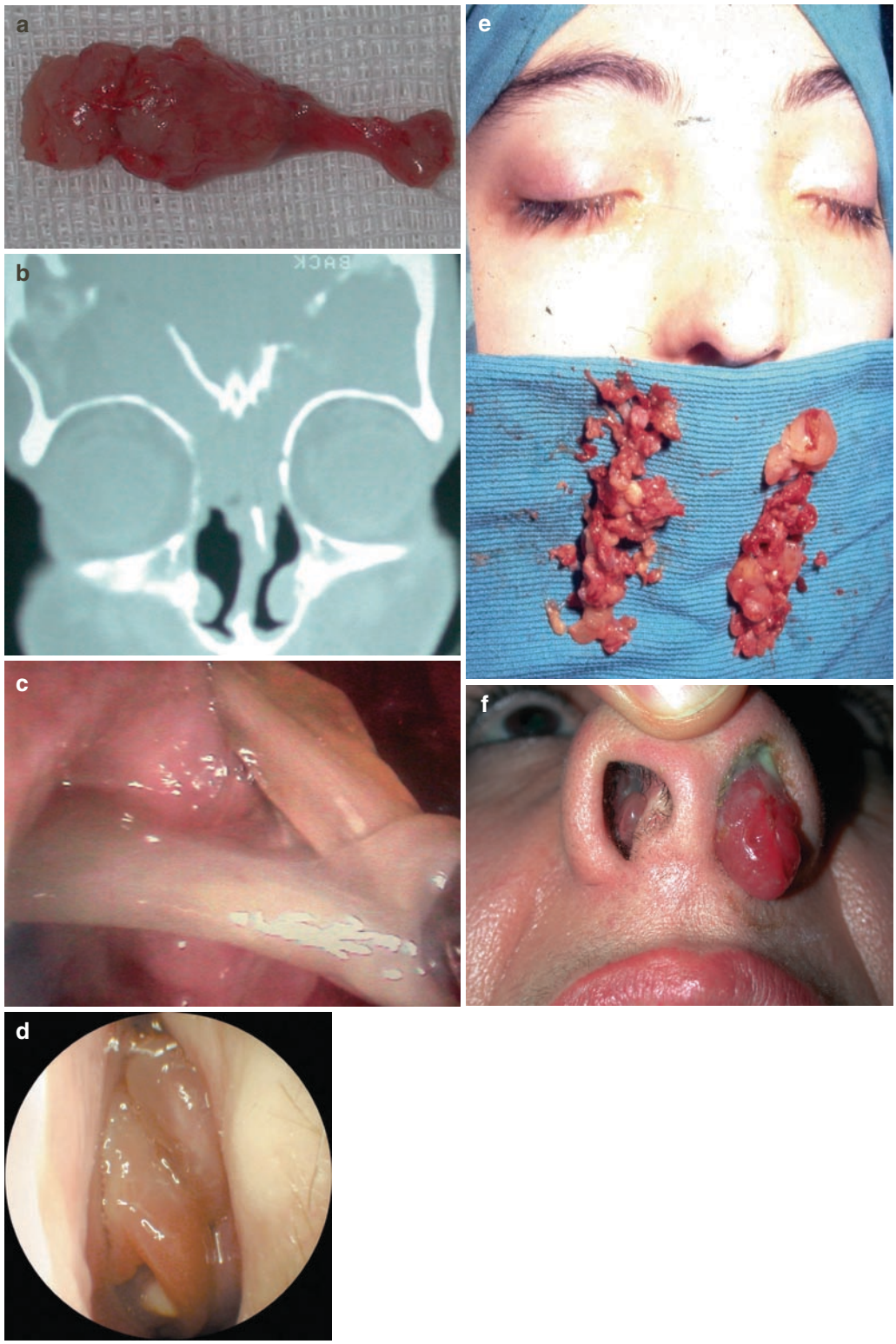

Fig. 31.1 (**a**) Solitary polyp deriving from uncinate process, (**b**) coronal CT, diffuse nasal polyposis, all sinuses are opaque, (**c**) thick and viscous secretion in a patient with NARES, (**d**) endoscopic intranasal view of diffuse nasal polyposis, completely filling the nasal passages, (**e**) polyps removed during surgery in a patient with diffuse nasal polyposis, (**f**) on the left side, nasal polyps protrude out of nostril. The patient did not accept the operation because of her fear of anesthesia

difference in prevalence between males and females [34]. Eosinophil-dominated diffuse nasal polyposis behaves differently from the noneosinophil-dominated nasal polyposis. The eosinophil-dominated polyp has a very close relationship with asthma and analgesic intolerance [32, 34, 39]. Nasal polyposis exacerbates asthmatic symptoms and its treatment is known to have a positive effect on asthma. In some cases, where only nasal polyposis is present, asthma or aspirin intolerance may develop up to 10 years later [32, 33]. Conversely, nasal polyposis may follow asthma and aspirin intolerance. Fifteen percent of patients with nasal polyps have the bronchospastic type of analgesic intolerance, which increases to 60% in patients who require follow-up surgery for major regrowth of polyps following initial surgery [5, 26]. Nasal polyposis may cause serious complications if not treated (Figs. 31.2–31.4).

The introduction of nasal endoscopy to rhinology has made it possible to detect even small asymptomatic polyps. The site of origin of the polyps is generally identifiable. The majority originate from narrow clefts of the ethmoidal cells. Contact areas may contribute to the formation of polyps. The extent of polyps may be misleading when endoscopically examined. Like the tip of an iceberg, in some patients, there appear small polyps behind the middle turbinate, whereas the whole ethmoid sinus may be full of polyps [37, 38]. Radiological studies show the extent of polyposis (Fig. 31.1b). However, since CT cannot differentiate between nasal polyps and secretion, the extent

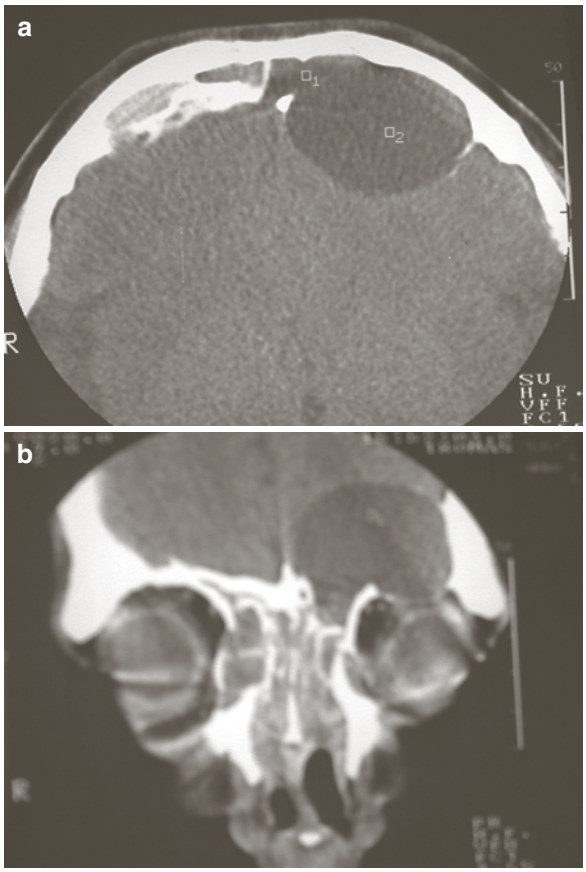

Fig. 31.2 Mucocele in a patient with Samter syndrome with destruction of the posterior table of frontal sinus and superior orbital wall (**a**) Axial CT scan, (**b**) Coronal CT scan

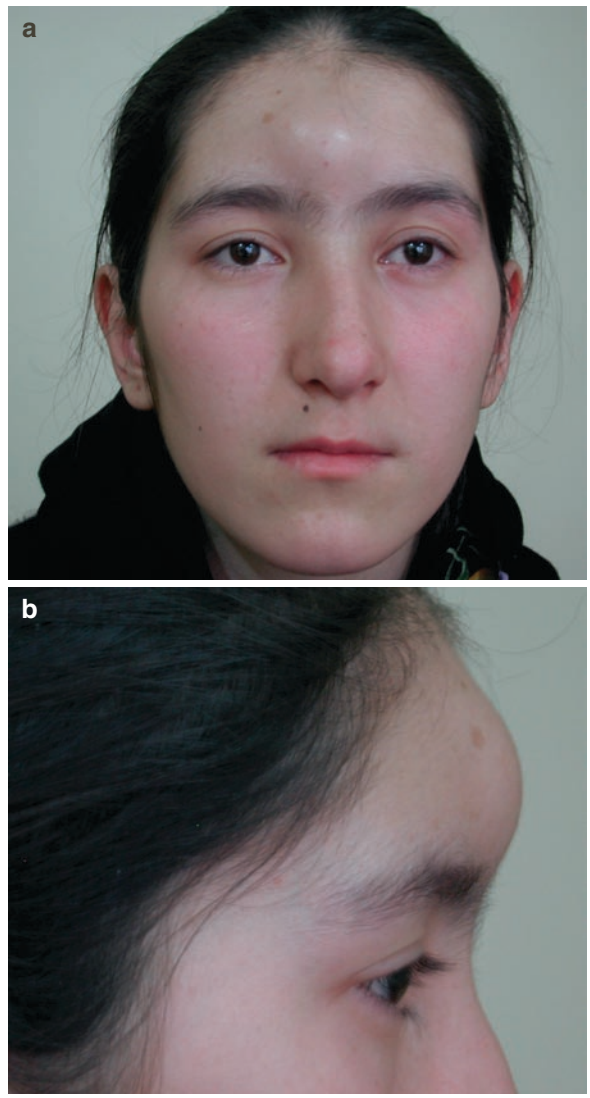

Fig. 31.3 Potts Puffy tumor in a patient with diffuse nasal polyposis (**a**) Front view, (**b**) Side view

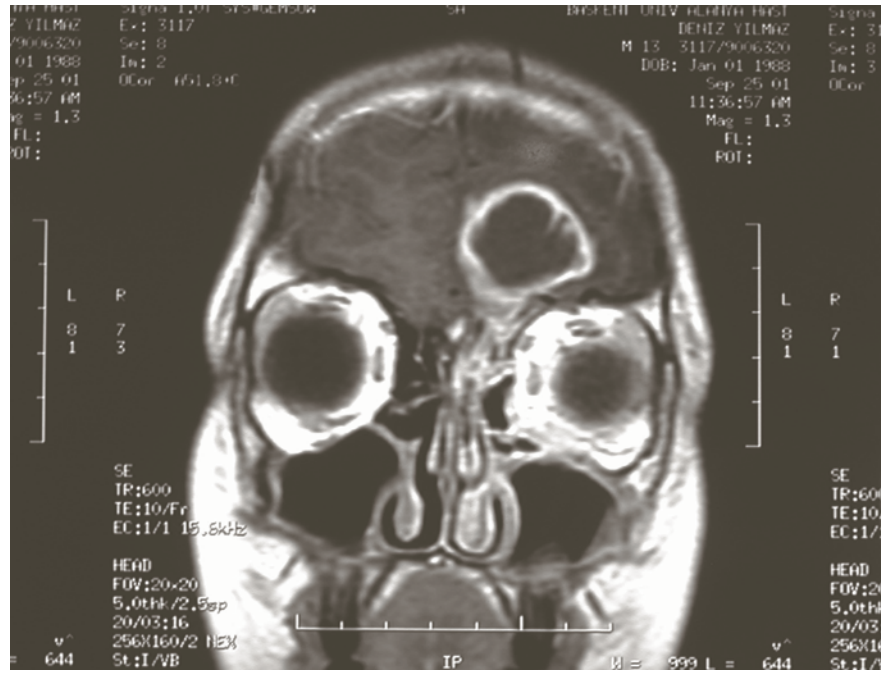

Fig. 31.4 Brain abscess in a case with unilateral polyp and sinusitis

of surgery necessary should be decided during the surgery and radical surgery should be avoided whenever possible.

There are different classification systems according to histology, site of origin, and the most common inflammatory cells of the polyps. In recent years, eosinophils are the cells that have drawn the most attention. A distinct eosinophilia in the nasal secretions is characteristic of diffuse eosinophilic nasal polyposis cases. The presence of eosinophils in the tissue and the mucus does not appear to be related to allergy or IgE-mediated hypersensitivity. The eosinophils are upregulated by cytokines, IL-3, GMCSF, and most importantly IL-5. IL-5 appears to have the most dynamic effect on the long-term survival of the eosinophils. In addition to these cytokines in the epithelium and the endothelium of the nasal polyp, the eosinophil itself can produce similar cytokines [2]. In nasal biopsies, there is an intense infiltration of eosinophils (Fig. 31.5), with ruptured granules dispersed in the tissue. Numerous theories implicating fungi and superantigens were suggested to explain the presence of eosinophils. Bachert et al. [1] detected staphylococcal superantigen-specific IgE antibodies to the superantigens SEA and SEB in nasal polyp tissue. Microbial persistence, superantigen production, and host T-lymphocyte response are fundamental components of all common chronic eosinophilic–lymphocytic respiratory mucosal disorders [1]. According to fungi theory, the eosinophils are attracted to a stimulus (fungus) in the mucus in patients who are immunologically sensitive to

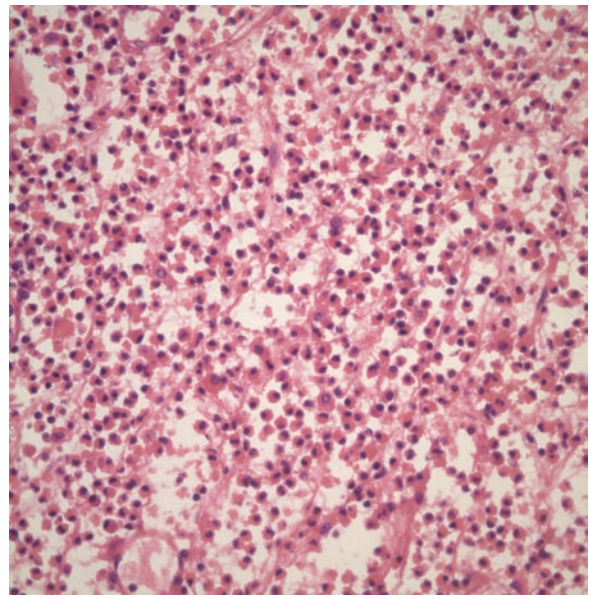

Fig. 31.5 Diffuse eosinophilia in polyp tissue (H+Ex230)

fungus. Since 40% of the contents of the eosinophils consist of major basic protein (MBP), the secretion of MBP kills the microorganism but also causes epithelial damage from the mucus side, causing secondary bacterial infection.

The aims of the treatment are to relieve nasal blockage, rhinitis symptoms, asthma, and to improve sinus drainage, whereas the final target is to eliminate nasal polyps and sinus pathology and to prevent recurrences. Solitary and noneosinophilic polyps are not difficult to manage and generally do not recur after surgery. Ostiomeatal unit surgery to remove defined microanatomical narrow passes around this functional key area of the middle nasal meatus, which facilitates drainage and ventilation of the dependent paranasal sinuses, may help recover the circumscribed hyperplastic changes of the remote paranasal sinuses. Even severe changes in the peripheral sinus mucosa may heal subsequently without being specifically treated [36, 41]. The patients with eosinophil-dominated diffuse nasal polyposis present a challenge to the clinician and the surgeon. Although it is possible to improve nasal breathing, olfaction, rhinitis symptoms, and asthma, it is not always possible to eliminate nasal polyps and sinus pathology in these cases. Treatment may help the patient live more comfortably with their disease, but in most cases, does not eliminate the disease entirely [17]. Therefore, the success of the treatment is dependent upon a careful evaluation of whether or not there are polyps causing symptoms, obstructing sinus drainage, and requiring revision surgery.

Irregardless of a medical or surgical approach to treatment, most polyps do recur after treatment. The literature is very scarce regarding comparative studies of medical or surgical treatment of nasal polyposis. These studies generally suggest medical treatment and reserve surgery for patients who respond poorly to medication. The treatment of eosinophil-dominated diffuse nasal polyposis includes topical and systemic corticosteroids (CS), topical diuretics, leukotriene antagonists, immune stimulants, and antifungal agents. Aspirin desensitization and intranasal lysine aspirin [9, 29] have also been suggested for Samter's triad patients. No treatment modality gives a complete cure, and varying success rates have been reported. The best results are with systemic corticosteroids. Although polyps regress with CS therapy, they may recur. Recurrent uses of CS may not be effective due to CS resistance. Some patients cannot use CS because of some medical problems. It is not possible to know in advance which patients will respond favorably to CS therapy and those who will not. Although surgical treatment is an adjunct for medical treatment and should not be considered as the first-line treatment of eosinophil-dominated diffuse nasal polyposis, it is unavoidable in some cases.

There are different surgical options described in the literature, ranging from simple polypectomy to nasalization, i.e., complete removal of all sinonasal mucosa [6]. Although FESS, which is the standard surgery for sinusitis today, may help patients with primary and limited polyps by improving ventilation, drainage, and by opening defined anatomical narrow passages, this surgery does not give satisfactory results in recurrent and advanced diffuse nasal polyposis, since the disease diffusely affects the whole sinus mucosa [22, 27, 28]. The success rates of surgical approaches are variable among reports. Schapowal [30] reports 90% recurrence within weeks or months after surgery, whereas Jankovski [13] reports a 91% success rate. In diffuse polyposis patients, a more extensive procedure ("pansinus surgery") is needed. Polypectomy may cause irregular scars that mask anatomical landmarks. Inevitable follow-up procedures are, therefore, rendered more difficult and the accompanying risks increase [14]. The surgeon must be aware of the anatomical abnormalities and possible risks (Fig. 31.5). Wynn and Har-El [42] reviewed 118 patients with asthma (50%) and documented allergy (79%). All patients underwent extensive bilateral nasal polypectomy, complete anterior and posterior ethmoidectomy, and maxillary sinusotomy. One hundred (85%) also had frontal or sphenoid sinusotomy. Follow-up ranged from 12 to 168 (median 40) months. Despite pre- and postoperative nasal and systemic steroid treatment in the majority of patients, 71 (60%) developed recurrent polyposis, 55 (47%) were advised to undergo revision surgery, and 32 (27%) underwent revision surgery. History of previous sinus surgery or asthma predicted higher recurrence and revision surgery rates. History of allergy also predicted recurrence and need for revision.

In recent years, otorhinolaryngologists have realized that recurrent polyp formation in eosinophil-dominated nasal polyposis patients is not a true recurrence, but the result of an ongoing immunological inflammatory reaction. This response may be a reaction to deposits of fungi in the nose [36]. The main pathology lies in the mucus. In other words, the stimulus comes from the mucus, and some patients react

differently due to their genetic makeup. The secretions are also very thick and viscid and ciliary activity is not capable of removing this thick mucus (Fig. 31.1c). Therefore, the aim of surgery should be to create a cavity, which allows this thick mucus to drain. Any collection or stagnation of the mucus should be prevented, and this extramucosal stimulus burden should be removed.

Mucosa should be preserved as much as possible to avoid scarring, crusting, stenosis, and osteitic bone. However, preserving the normal mucosa is not always feasible, because it is sometimes very difficult to differentiate normal mucosa from the polypoid one. Moreover, thick mucus may stay in the folds of polypoid mucosa, which, in turn, starts the vicious circle again. Therefore, all polyps or severe polypoid mucosa that could hide thick mucus should be cleaned as far as access to all the anatomic areas of the nose is permitted. Nasalization makes sense in that it prevents microbial colonization and the foci of stimulants such as fungi in the folds of edematous or polypoid mucosa. However, unnecessary tissue destruction, increased scarring, stenosis, rhinitis sicca, and crusting are the disadvantages of this type of radical surgery. Nasalization should be reserved mainly for the tumors of the nose, and removal of all of the sinonasal mucosal covering should be avoided [12].

The main cause of recurrence is the areas that have not been opened or drained. If the ethmoidal cells are not opened completely, the polyps stay in these insufficiently opened cells (Fig. 31.6). These cells act as a pool for thick mucus. Topical drops cannot reach a sufficient concentration in these cells. Bone inflammation and obliteration of the Haversian system may contribute to the persistence of disease in localized areas, causing irregular bony thickening until such underlying bone is removed [18, 23]. Therefore, all the ethmoid partitions should be opened and removed. A smooth cavity should be created, which can be seen, examined, and cleaned, and to which medicine can reach. If there are any pathologies in the agger nasi, these cells should also be addressed. If necessary, the bony prominences should be drilled until no hidden area remains. No free bony spicles should be allowed to remain in the operation field so as to avoid both granulation tissue and polyp recurrence (Table 31.1).

Regarding the major sinuses, the foremost issue is to have a sufficient opening, which allows the sinus to drain and ventilate sufficiently. Stenosis should be prevented. Normal ostia should remain untouched. If there

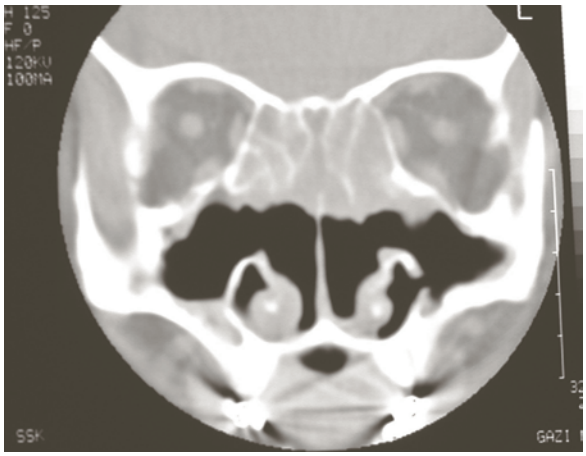

Fig. 31.6 A diffuse polyposis case after operation; ethmoid cells were not opened in the previous surgery

Table 31.1 Reasons for failure in surgery of diffuse nasal polyposis

Insufficient ethmoidectomy
Insufficient removal of septa
Insufficient drug concentration behind the septa
Insufficient cleaning of the polypoid mucosa behind the septa
Pool for collection of secretions
Insufficient surgery of the frontal sinus
Polyps at the frontal recess and frontal ostium area
Polyps and mucoceles in the frontal sinus
Stenosis of frontal ostium
Insufficient surgery of the maxillary sinus
Insufficient maxillary sinus ostium
Reclosure of the ostium
Decreased ventilation and drainage
Insufficient drainage due to thick secretions
Insufficient cleaning preop and postop
Insufficient opening of anterior wall of sphenoid sinus
Decreased ventilation
Decreased drainage
Insufficient drug concentration
Insufficient cleaning preop and postop
Free bony spicles
Granulation tissue and polyp recurrence

are polyps in the frontal recess, they need to be cleaned without damaging the mucosa and without touching the frontal ostium area. However, in recurrent cases, it is not sufficient only to drain the sinus, but also to have the possibility of irrigating, cleaning, and examining the inside of the sinus, as well as to apply medication. In these cases, the surgeon needs to have a very big ostium of the involved sinuses. The maxillary sinus ostium may be connected to the nasoantral window in the inferior meatus. Sphenoid sinus ostium is widened to the extent that the bottom and lateral aspects of the sinus can be seen. If the frontal sinus is opaque and the ostium is blocked, it may be necessary to widen the frontal ostia, to perform Draf type II or III (Draf) ostioplasty, and to remove the polyps and mucoceles from the frontal sinus, especially in recurrent cases [4] (Figs. 31.7 and 31.8a). Although osteoplastic frontal sinus operation is used rarely, in complicated diseases, trauma, tumor, or CSF fistula cases of the frontal sinus it provides a wide exposure. The anterior table of the frontal sinus is elevated. The periosteum is not separated from the anterior table and pedicled on the bone. After cleaning the pathology, the anterior table is placed back into the original position inside the frontal sinus (Fig. 31.8b).

Some authors advocate partial resection of the middle turbinate to expand the surgical approach [40], while others modify it only in case of abnormalities and leave as much as possible of the middle turbinate intact as a landmark in case revision surgery is needed [36, 37]. In a retrospective evaluation including 100 FESS patients, Giacchi et al. [7] preserved the middle turbinate on one side and partially resected it on the other

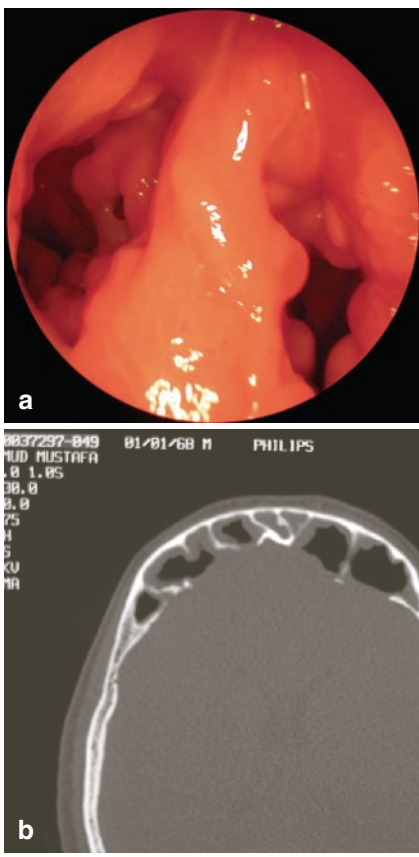

Fig. 31.7 Six months following surgery with polypoid mucosa of the frontal sinus; (**a**) polyps in the frontal sinus, (**b**) axial CT

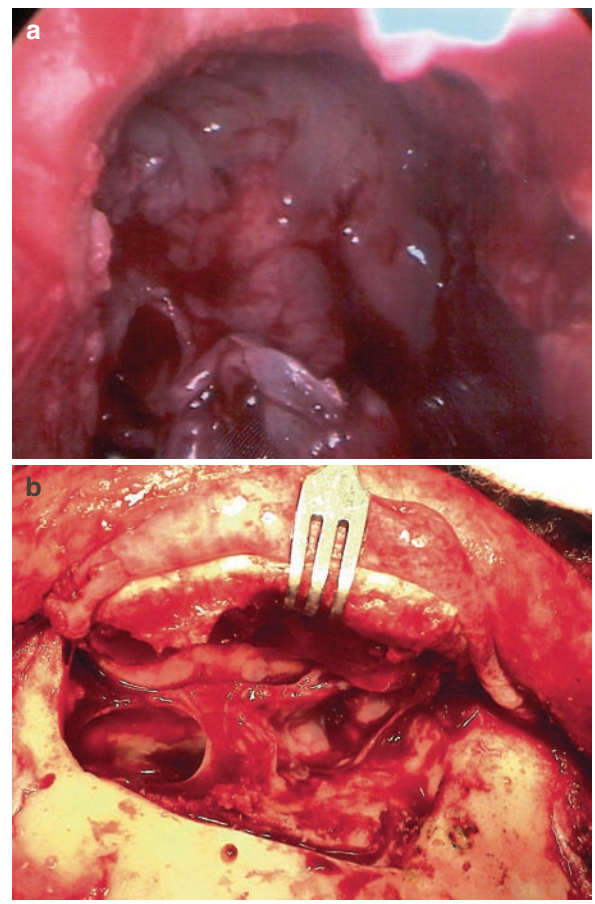

Fig. 31.8 (**a**) Inside of the frontal sinus after Draf type III ostioplasty procedure. (**b**) Osteoplastic frontal sinus operation. Although it is used rarely, in complicated diseases, trauma, tumor, or CSF fistula cases of the frontal sinus, it provides a wide exposure. The anterior table of the frontal sinus is elevated. The periosteum is not separated from the anterior table and pedicled on the bone. After cleaning the pathology, the anterior table is placed back into the original position

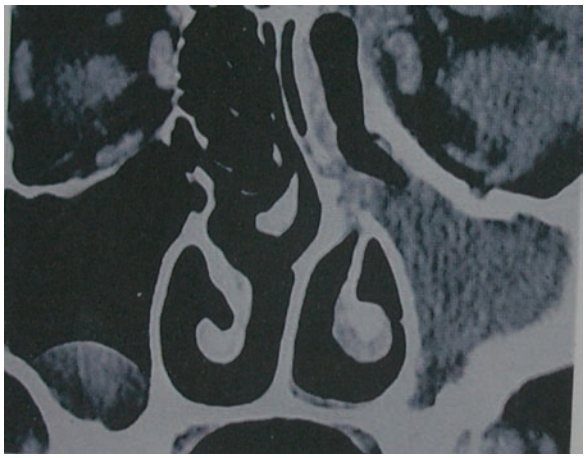

Fig. 31.9 Septal deviation with adhesion of the middle turbinate to the lateral nasal wall resulting in failure of the surgery

side. The authors observed no side effects in the studied outcome parameters. In a randomized trial, 1,106 matched CRS patients with and without polyps, who underwent similar functional endonasal sinus surgery with (509 patients) or without (597 patients) partial middle turbinate resection [10]. Partial middle turbinate resection was associated with less synechia formation ($p<0.05$) and less revision surgeries ($p<0.05$) than middle turbinate preservation. Complications particularly caused by partial middle turbinate resection were not observed [6]. In recurrent cases, the inferior 1/2 or 2/3 of the middle turbinate can be removed to get better access to the polyps behind the middle turbinate and sphenoid sinus ostium. The possibility that the middle turbinate bone may be osteitic lends support to the removal of the lower half of the middle turbinate. If necessary, septal deviation should be corrected (Fig. 31.9). Septal deviation may cause an insufficient exposure of the surgical field in addition to adhesion of the middle turbinate to the lateral nasal wall, resulting in failure of the surgery [31].

31.1 Postoperative Care

Long-term follow-up is very important. The debris in the nasal cavity should be cleaned by irrigation. Antibiotics and topical steroids (when necessary, systemic steroids) should be continued. The patients must be followed-up very closely and early polypoid tissues, which contain serous fluid, need to be drained. Any unnecessary trauma should be avoided, since this may activate the granulation tissue. Any persistent disease should be treated prior to becoming symptomatic since localized persistence of polyp disease eventually leads to diffuse recurrence.

31.2 Nasal Polyposis in Children

The incidence rate of nasal polyposis in children is very low. Symptomatic nasal polyps are generally bilateral and associated with a systemic disease. Children under 16 with bilateral nasal polyposis should be evaluated for cystic fibrosis [32]. Symptomatic diffuse nasal polyps are seen in 20–25% of pediatric patients with cystic fibrosis; in 10% of those with nonsteroidal anti-inflammatory drug intolerance; and in 5% with primary ciliary dyskinesia (Fig. 31.10) [16, 24]. They found that

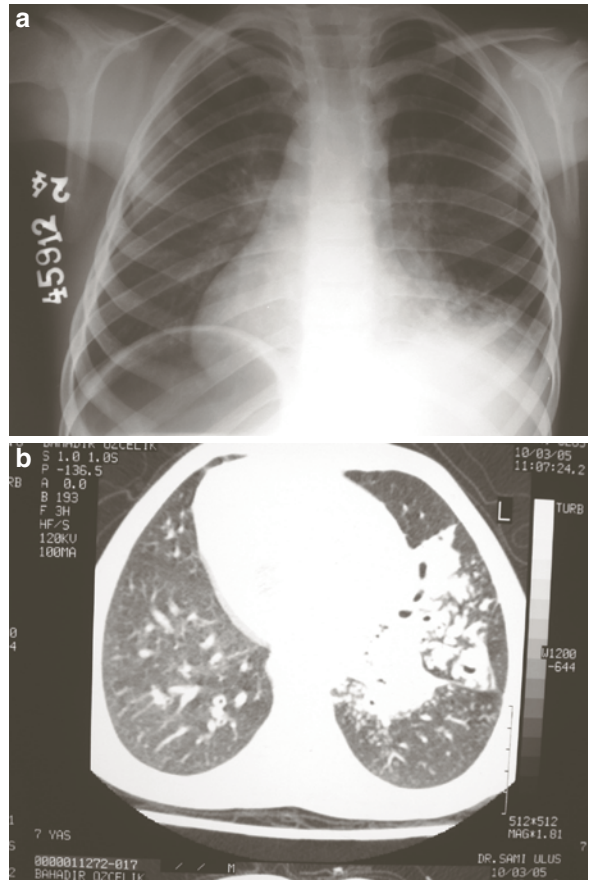

Fig. 31.10 Kartagener syndrome, (**a**) dextrocardia on chest X-ray, (**b**) diffuse bronchiectasia on axial CT scan

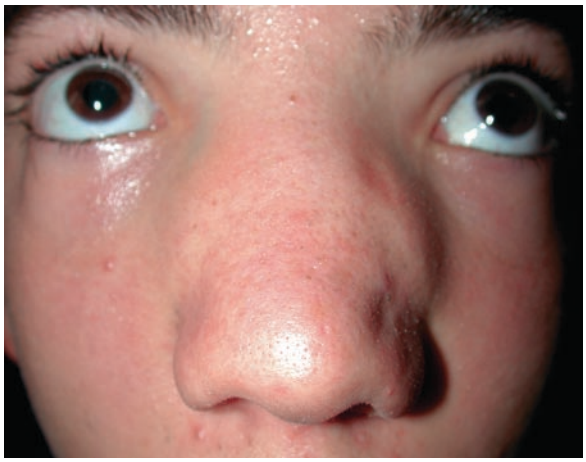

Fig. 31.11 Nasal bone expansion due to extensive diffuse nasal polyposis in the younger patient. Rhinoplasty is needed to restore the appearance

50% of children with nasal polyps have a positive family history for polyps, suggesting a genetic role in the development of the disease. The histological structure of the polyps in children is different from that of the polyps found in adults. Eosinophilic polyps do not occur as frequently in children as they do in adults. This may be related to frequent URT infections due to systemic diseases such as cystic fibrosis and primary ciliary dyskinesia.

Surgery for nasal polyposis in children should be reserved only for patients with complete nasal obstruction and facial skeletal deformity (broadening of the nasal dorsum, high arched palate) that negatively affects quality of life. Minimally symptomatic patients should not undergo surgery (Fig. 31.11) [2].

31.3 Complications

Mosher stated in 1912 that intranasal ethmoidectomy is one of the most dangerous of all surgical operations. The introduction of endoscopes made intranasal ethmoidectomy even more dangerous and the incidence of complications increased. The majority of complications are minor complications without any irreversible organ damage or any loss of function and do not have any life-threatening consequences.

Although uncinectomy is the basic step in endoscopic sinus surgery, it is potentially the most important cause for penetration of orbit. Even minor damage of the orbital periosteum may cause periorbital ecchymosis. Blowing after such minor penetration may lead to periorbital emphysema (Fig. 31.12). However, damage to the periosteum and prolapsus of fat medially will not create any major problem except periorbital ecchymosis unless the orbit is not entered further. However, removal of fat may result in enophtalmus, ptosis, and diplopia. If the damage to the periosteum is not recognized and deeper penetration to the orbit occurs, medial rectus muscle may be injured. The injury of the medial rectus muscle is very difficult to treat even in the very experienced hands of the strabismus surgeons (Fig. 31.13). Optic nerve injury results in permanent loss of vision. Preoperative evaluation of the CTs for the presence of Onodi cell or prominent optic nerve or any other anatomic abnormality is important to avoid the complications (Fig. 31.14) [15].

Transection and retraction of ethmoidal arteries into the orbit, where they may continue to bleed, may cause orbital hematoma. Intraorbital hematoma in the presence of visual loss must be treated with urgency (Fig. 31.15). The visual loss may be irreversible if not treated within 90 min. The ophthalmology consultation is important to follow the intraocular pressure. The aim of the treatment should be to decrease the intraocular pressure. The head should be elevated.

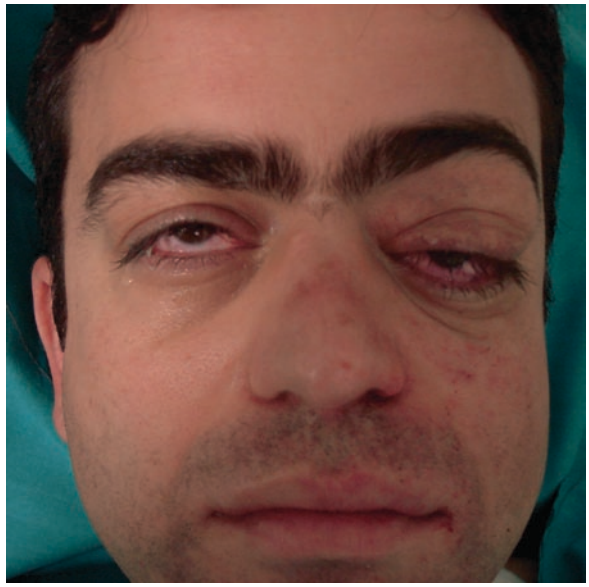

Fig. 31.12 Left periorbital emphysema due to blowing the nose just after endoscopic sinus surgery

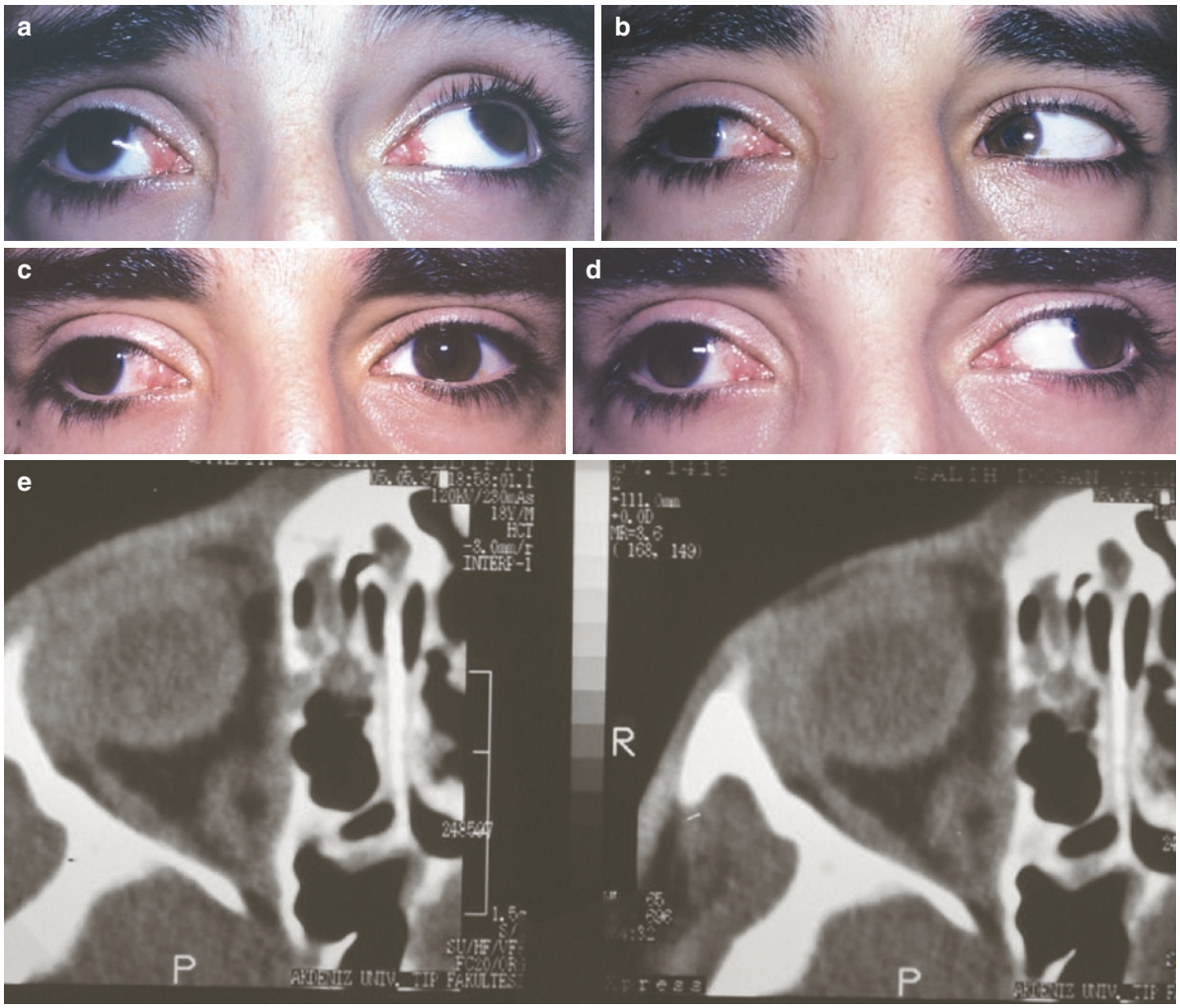

Fig. 31.13 (**a–d**) Left medial rectus muscle injury on the right side during endoscopic sinus surgery. There is strabismus to the lateral side and impaired mobility of the eye. (**e, f**) Axial CT scans show the injury (courtesy of Şener)

Nasal packs should be removed. If periorbita is exposed, it should be incised longitudinally, to allow both the blood to extravasate and to allow the intraorbital space to expand. Acetazolamide (500 mg) and mannitol (0.5–1.0 g/kg) may be given intravenously. If needed, lateral canthotomy and inferior cantholysis should be performed to increase orbital volume by allowing the eye to expand 4–5 mm anteriorly. If elevated intraocular pressure persists, external ethmoidectomy can be performed only to decompress the orbit more, and trying to identify the bleeding ethmoidal arteries should be avoided since it is never possible [15, 35] (Table 31.2).

Damage to internal carotid artery requires prompt action (Fig. 31.16). After packing of the sphenoid sinus to stop the bleeding, the patient should be immediately taken to the interventional radiology department for angiography and balloon occlusion, or stenting of the carotid artery should be performed if necessary.

The thinnest area of the skull base is adjacent to where the anterior ethmoid artery enters the anterior skull base at the lateral lamella of the cribriform plate. If the skull base is penetrated, clear fluid coming from the defect can be seen (Fig. 31.17). It is important to recognize the entrance into the

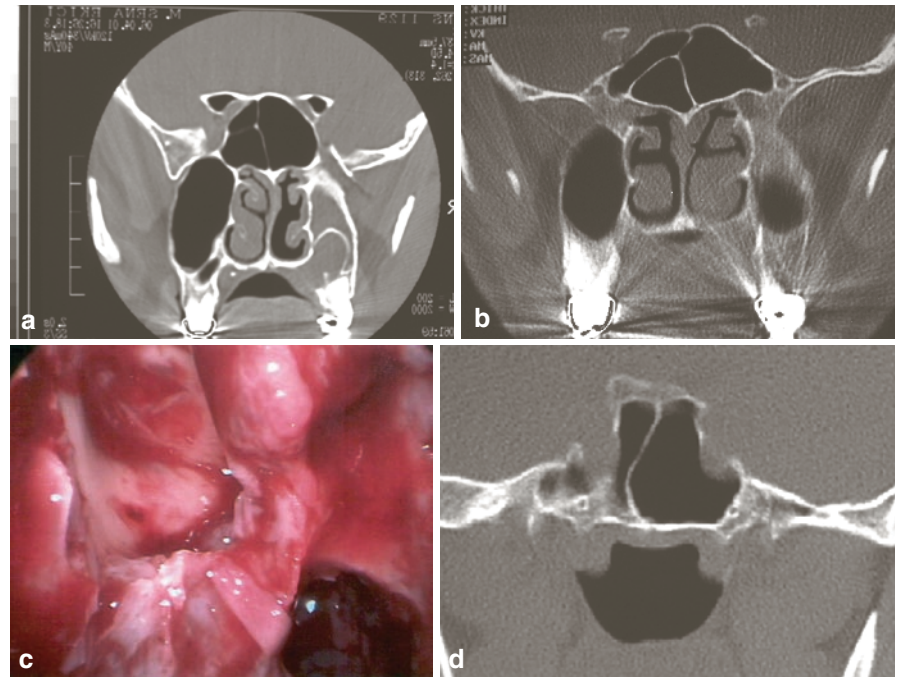

Fig. 31.14 (**a**) Optic nerve in the sphenoid sinus, coronal CT scan, (**b**) Onodi cell, coronal CT scan, (**c**) Onodi cell located superolateral to sphenoid sinus and optic nerve canal, (**d**) a carotid artery bulging into the sphenoid sinus and lacking the bony covering

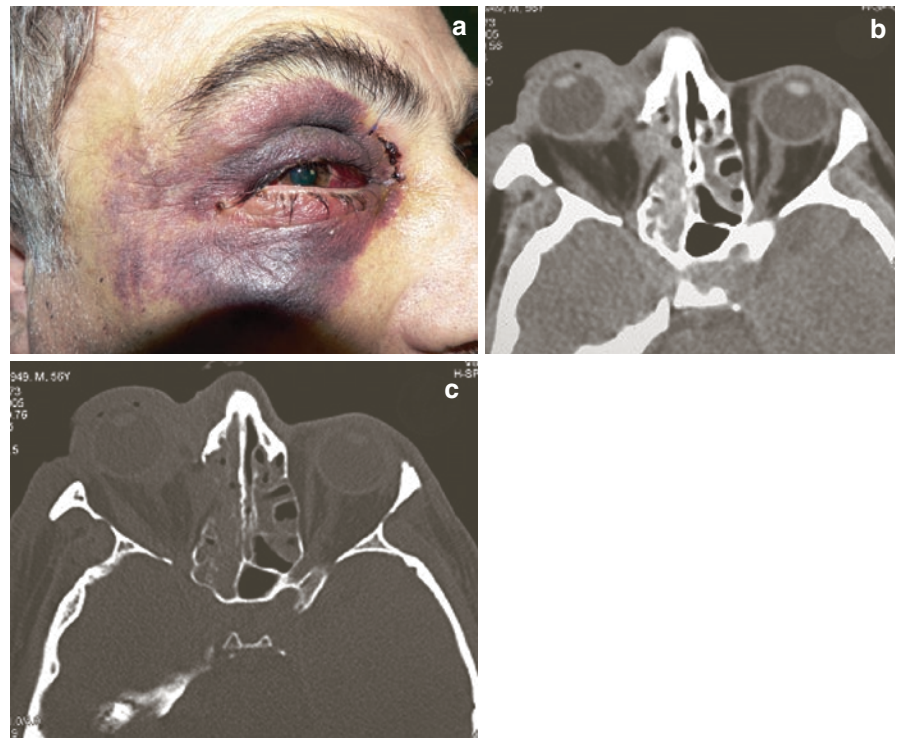

Fig. 31.15 Total loss of vision on the right side due to transection of the anterior ethmoid artery. (**a**) Dilated papilla without any light reflex. Lateral canthotomy and decompression of the orbit through external approach were performed. (**b**) Axial CT scan, penetration of lamina papyrecea, (**c**) MR, damage to the lamina papyrecea, periorbita, and orbital contents. Vision returned to normal

Table 31.2 Treatment of intraorbital hematoma

Ophthalmology consultation
Measure intraocular pressure
Head elevation
Nasal packing removal
Acetazolamid and mannitol
Lateral canthotomy and cantholysis
Medial decompression
External decompression

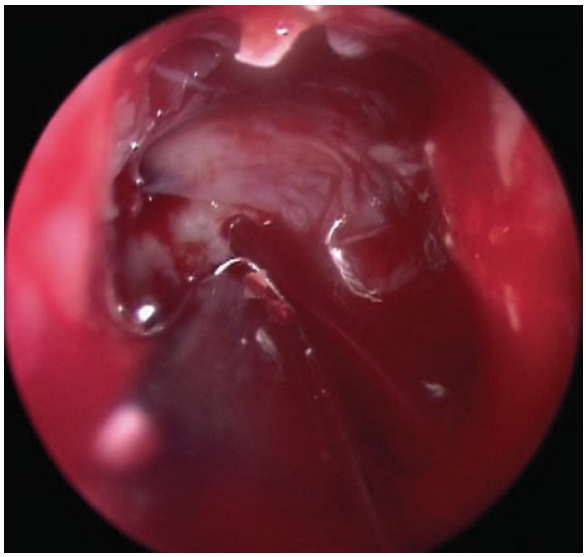

Fig. 31.16 Internal carotid artery injury during pituitary gland surgery

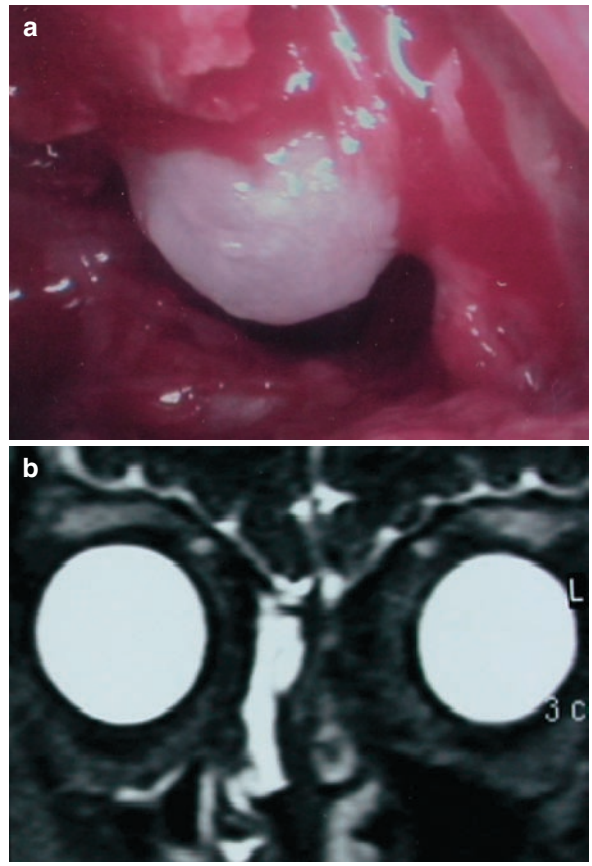

Fig. 31.17 (**a**) CSF fistula with herniation of dura, (**b**) MR cisternography showing leakage of CSF into the nasal cavity

intracranial cavity to avoid further damage to the intracranial structures. After the introduction of powered instruments, suction can easily remove the tissues and should not be used in cases with suspicion of complications (Fig. 31.18). The defect can be repaired by fat, fascia, mucosal grafts, or flaps [35]. Endoscopic sinus surgery became more popular in the recent decade and the incidence of complications increased. Preoperative evaluation and careful surgery taking care for landmarks may reduce the rate of complications.

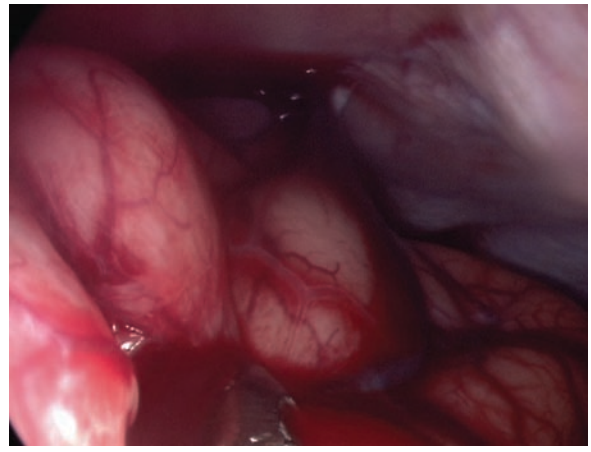

Fig. 31.18 Penetration of anterior skull base and damage to the brain (courtesy of TESAV)

31.4 Conclusion

Recovery does not mean complete relief from polyps or polypoid mucosa, but improvement in the symptoms and relief with the help of topical drugs. The mucosa should be preserved to the fullest extent possible. However, in recurrent cases, more extensive surgery is needed. All the ethmoidal cells require opening and the bony partitions need to be removed. This, in turn, results in access to the whole ethmoidal cavity, allowing topical medication to reach and make contact with the mucosal surfaces. No pooling in the sinuses should be allowed, since stasis and stagnation of the mucus in these areas continue to stimulate the immune reaction. All entrances of the major sinuses should be cleaned and mucociliary activity restored. If the major sinuses are involved and the lining is completely polypoid, the sinus drainage should be restored or, if this is not possible, the ostia should be made wide enough (megaostium) for the sinus to be cleaned. In recurrent cases, Draf type II or III osteoplasty for frontal sinus may be an option. For maxillary sinus, the nasoantral window may be opened and the middle meatal antrostomy may be connected to the nasoantral window. Sphenoid sinus deserves close attention due to the critical structures involved, but the ostia can be widened as much as possible. Surgery for eosinophil-dominated diffuse nasal polyposis should be completely radical in terms of opening all the cells, therefore creating an open and smooth cavity, but it must also be completely functional in terms of preserving the functioning mucosa. Complications of endoscopic sinus surgery are an important issue. Preoperative evaluation, awareness of the possible dangers of the endoscopic technique, and careful surgery taking care for landmarks may reduce the rate of complications (Table 31.2).

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Nasal Polyposis: Aggressive Sinus Marsupialization Including the Endoscopic Modified Lothrop Procedure

32

Erik Kent Weitzel, Harshita Pant, May Thwin, and Peter-John Wormald

Core Messages

- Symptomatic polypoid chronic rhinosinusitis (CRS) that fails an adequate medical trial responds well to endoscopic sinus surgery (ESS).
- More aggressive (extensive) ESS leads to better clinical outcomes with polypoid CRS.
- Successful surgical management of the frontal sinus is the most challenging aspect of the management of nasal polyposis.
- In patients who develop recurrent polyps after surgery, the modified endoscopic Lothrop procedure, Draf III or frontal drillout produces better outcomes, and in some cases a cure, than standard revision ESS.

32.1 Introduction

Polypoid chronic rhinosinusitis (CRS) consists of a diverse group of patients whose clinical course ranges from mild to severe and recurrent disease. Endoscopic sinus surgery (ESS) plays an important role in providing symptomatic relief for these patients, including those with persistent disease [1, 2, 4]. The surgical management of the frontal sinuses affected by polypoid CRS has traditionally posed significant challenges, especially in providing long-term control for patients in whom recurrence of polyps is almost inevitable. Recent advances in endoscopic frontal sinus surgery have led to the development of new techniques to adequately manage these complex areas. The main surgical procedures include the Draf I, IIA, IIB, and III operations. The Draf III, also known as the endoscopic modified Lothrop procedure (EMLP) or frontal drillout, was developed to maximally enlarge the frontal recess and frontal sinus ostium. Compared to the more conservative approaches to the frontal sinuses, including the Draf I and Draf II operations, the EMLP has shown to significantly delay the time to symptomatic recurrence of polypoid frontal sinus disease in a select group of patients [12].

32.2 Polypoid Chronic Rhinosinusitis with a Poor Surgical Prognosis

- Eosinophilic mucus and increased Lund and MacKay CT scan scores can predict patients that may require further surgical interventions.
- EMLP or the frontal drillout procedure has a significantly lower rate of recurrent polyposis than a frontal recess clearance in select cases.

A retrospective review of our practice was performed with the intention of evaluating the outcomes of different frontal surgical approaches for polypoid CRS

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patients (Thwin et al., unpublished data). Our surgical algorithm involves a staged and progressive approach moving initially from a complete frontal recess clearance to an EMLP in recalcitrant cases. We found two major factors that identified patients who were likely to require further procedures: the presence of eosinophilic mucus in the sinuses and a higher Lund and MacKay score. Patients with eosinophilic mucus in their sinuses, termed eosinophilic mucus chronic rhinosinusitis (EMCRS), include the allergic fungal sinusitis (AFS) patients and nonallergic fungal sinusitis patients [5]. In our series, 53% of patients requiring revision surgery had eosinophilic mucus in their sinuses compared to 21% of patients who did not require revision surgery ($p=0.001$). Additionally, the Lund and MacKay score was significantly greater in patients with recurrent disease (average 15.3) compared to those that did not (average 10.9) ($p<0.001$). The most important surgical outcome from the preliminary analysis of our data showed that EMLP has a significantly lower rate of recurrent polyposis than revision FESS. Among those patients who had extensive polyposis and who underwent the EMLP, 67% had recurrent polyposis compared with 94% in patients who did not have the EMLP (Pearson Chi^2 3.715, $p=0.05$). This study complements previous findings that the presence of eosinophilic mucus, a marker of severe inflammation, is associated with extensive sinus disease and a more recalcitrant and recurrent clinical course compared to patients who do not have eosinophilic mucus in their sinuses [5, 7]. Failure rate for EMLP over a 5-year period has been 12%. All of these cases have responded to revision EMLP.

32.3 Rationale for the EMLP or Frontal Drillout

- More aggressive (extensive) FESS shows clinically important benefits in symptomatic control of CRS.
- Frontal dissection improves symptoms related to frontal CRS.
- Larger frontal ostia lead to better long-term outcomes (critical minimum size is 5 mm), with the best results noted in the Draf III procedure (EMLP or frontal drillout).

Several studies have shown a clear benefit from frontal recess dissection of the affected sinuses in polypoid CRS patients. Hosemann et al. retrospectively evaluated their outcomes of complete FESS with frontal recess clearance in 110 patients with CRS [2]. Overall, 70% of patients reported a significant improvement in their symptoms. By carefully analyzing their failures, they found that the frontal ostium stenosis rate was affected by the extent of ostial enlargement and the severity of the underlying disease. Frontal ostia enlarged to a minimum dimension of 5 mm or greater became obstructed in 16% of cases, compared with obstruction in 30% of cases where the ostium was less than 5 mm. They additionally found that patients with Samter's triad and pronounced polyposis showed a trend toward a higher rate of ostium stenosis. In conclusion, these authors suggest that a greater frontal ostium size leads to better long-term outcomes.

A separate analysis suggests that more extensive FESS leads to better subjective, endoscopic, and radiological outcomes. Jankowski et al. carefully documented and evaluated two surgical techniques that involved a targeted approach to treat localized ethmoid disease vs. a more radical "nasalization" or complete FESS for similar disease states. This well-performed analysis shows clinically important improvements with the more radical FESS in the outcome measures of: need for revision surgery, recurrence rate, endoscopic exam, and nasal functional benefit (specifically in nasal obstruction, anterior and posterior rhinorrhea, although olfaction showed no difference) [3].

A retrospective study by Weber et al. supports the notion that a larger frontal sinus ostium provides a better outcome. This group analyzed 1,286 patients undergoing frontal sinus surgery, including Draf I, II, and III procedures. They found that there was a progressive improvement in the rate of subjective and objective outcomes as the surgeries become more extensive. The best results were seen with Draf III operations (equivalent to the EMLP) irrespective of poor prognostic status. The authors concluded that "it seems to be obvious that a bigger drainage procedure leads to a greater probability of an endoscopically open frontal sinus neo-ostium [11]."

These three well-performed articles by respected rhinologists build an important argument suggesting that larger ostial diameters result in less stenosis and

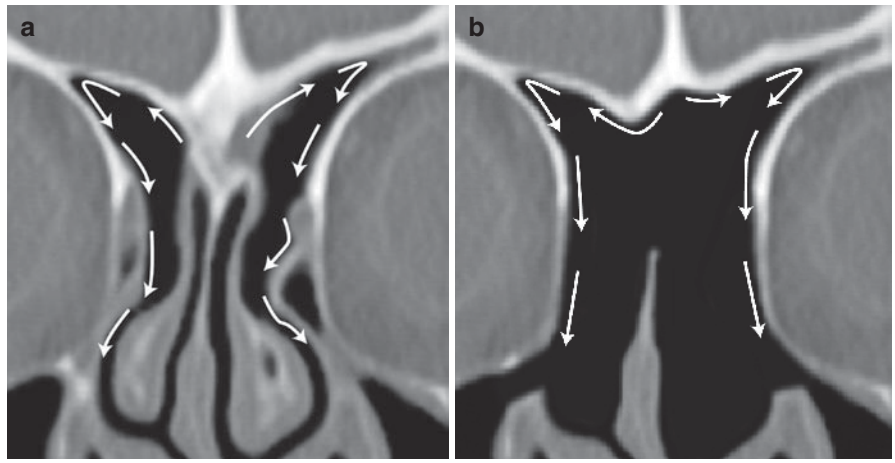

Fig. 32.1 In (**a**), normal mucociliary flow is shown in an unoperated frontal sinus. After frontal drillout (**b**), mucociliary flow remains similar to the preoperative condition

better long-term results. Additionally, more extensive FESS leads to significantly better outcomes, which is shown in terms of both ethmoidectomy and frontal sinus surgeries. These three articles essentially say, "more is better" when it comes to the surgical management of frontal sinus polyposis and complements our own research showing lower recurrence rates in patients who have undergone EMLP.

The success of the EMLP is most likely due to two main factors: maintenance of the physiologic mucociliary clearance and the large size of the frontal sinus neo-ostium. The mucociliary clearance is largely unaffected following an EMLP because the lateral and medial portion of the frontal ostium where the normal pattern of mucociliary clearance occurs remains intact [6, 11]. Hence, following an EMLP, mucosal secretions from the frontal sinuses are moved superiorly toward the lateral walls of the frontal sinuses, and then moved inferiorly onto the floor before passing through the neo-ostium and onto the osteomeatal complex and common drainage pathway (Fig. 32.1).

At the conclusion of an EMLP, the largest possible diameter of the frontal ostium is achieved in contrast to frontal recess clearance. The maximum neo-ostium size may be the most important factor in the success of an EMLP, even in the patients with poor surgical prognosis. As noted previously, recurrent disease is first seen in the region of the frontal sinus ostium following a frontal recess clearance. Despite full clearance, the region of the frontal recess is still relatively narrow and predisposes to early obstruction. This is manifested initially by edema followed by mucosal cobblestoning and culminating in polyp formation. Although the exact pathogenesis is not understood, it is conceivable that the obstruction may result in colonization with bacteria and fungi, thereby leading to biofilm formation. These factors may lead to an exacerbation of the mucosal inflammation by several methods that may involve secondary infection and immunological mechanisms including innate and superantigen-driven responses. The intense inflammatory response may recruit more lymphocytes and eosinophils, resulting in further epithelial injury and ineffective wound healing and remodeling. Hence, the beneficial effect of a large neo-ostium with an EMLP may be twofold. First, the large neo-ostium minimizes the fluctuations in mucosal thickness that would otherwise obstruct the mucociliary drainage from the sinus. Second, the large neo-ostium allows for effective postoperative debridement and irrigation with saline and topical medications. Together, these measures may be the key to help control the inflammation and be responsible for the reduced recurrence rates seen in polyp patients following an EMLP.

32.4 Surgical Plan and Surgical Technique

- Two techniques are utilized at our institution to surgically manage medically recalcitrant chronic frontal sinusitis.
- The frontal recess clearance maximizes the natural ostium of the frontal sinus without enlarging it.
- The frontal drillout or EMLP creates the largest possible frontal ostium diameter for individual anatomical constraints.

Sinus surgery is offered to polypoid CRS patients who have failed an adequate trial of maximum medical management. This includes a course of topical and oral corticosteroids and when infection is present, a 3-week course of culture-directed oral antibiotics. The preoperative surgical assessment of the frontal sinus includes (a) the extent of frontal sinus and recess involvement (b) size of the natural frontal ostium, (c) presence of osteitis and neo-osteogenesis, (d) the anatomy of the frontal recess and cells obstructing the course of the drainage pathway, and (e) coexisting pathology, including frontal osteoma.

The surgical algorithm begins with a thorough endoscopic clearance of polyps and mucus from all affected sinuses. This includes specific attention to the frontal recess, frontal ostium and frontal sinus, complete clearance of the maxillary and ethmoid sinuses, and creating a large sphenoidotomy. The aims of surgery are to remove polyps and mucus from the diseased sinuses, preserve mucosa, and to provide an anatomically patent and functional sinus ostia and drainage pathways.

In patients who have complete opacification of the maxillary sinuses, canine fossa trephinations may also be required. This procedure has been shown to have almost no significant long-term morbidity, superior access to the anterior half of the maxillary sinus, and potential for complete debridement without mucosal stripping [7–9]. Preservation of the mucosal lining is critical for rapid regeneration of a functional epithelial lining and minimizing the formation of synechiae.

In patients with frontal sinus involvement, special attention is given to meticulous clearance of the frontal recess by removal of any obstructing polyps, mucus, and cells so that the frontal ostium and frontal sinus is visualized adequately. When polypoid CRS patients have recurrent frontal sinus disease (Fig. 32.2) despite having a full frontal recess clearance and maximum medical treatment, these patients are then offered an EMLP, There is little to be gained from further conservative surgery as it can be assumed that the pathological process causing ongoing nasal polyp formation is not capable of being managed with the size of the natural ostium achieved with frontal recess clearance.

Several anatomical considerations also play a role in the decision to perform an EMLP, which may be contemplated early in the treatment algorithm in select patients. Patients who have extensive disease with a naturally very narrow frontal ostium will often do poorly with "standard FESS." When the ostium is less than 3 by 3 mm, obstruction occurs easily in the postoperative period (Fig. 32.3).

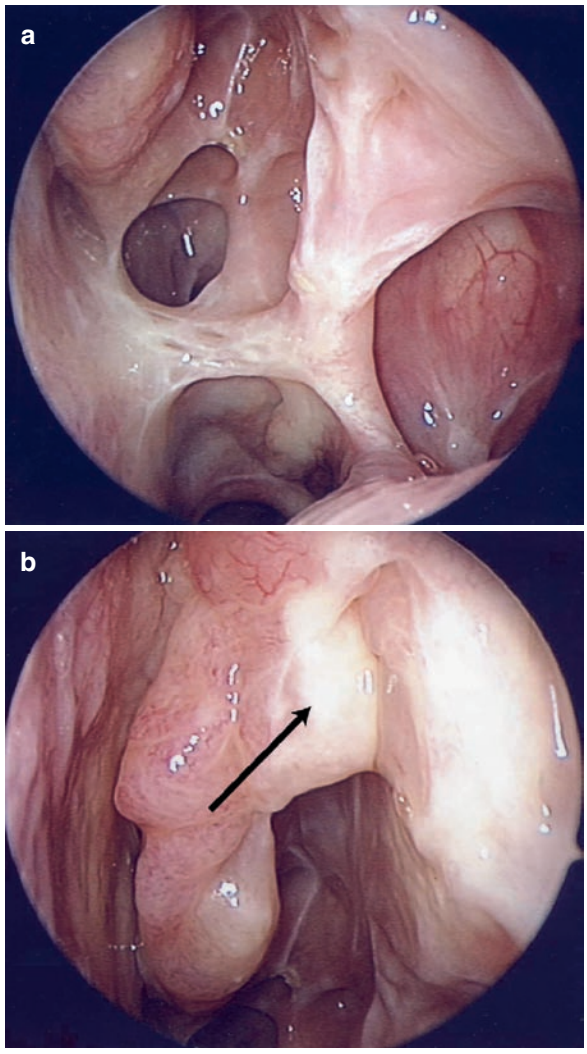

Fig. 32.2 (**a**) Healthy maxillary sphenoid and posterior ethmoids without polyp formation after "standard FESS" surgery. (**b**) Edema and early polyp formation (*arrow*) in the frontal recess and around the frontal ostium

In addition, the EMLP may be the best option to adequately manage patients with complex frontal recess cell configurations that narrow the natural frontal ostium, including an intersinus septal cell, Type 3, and Type 4 fronto-ethmoidal cells. An example of an intersinus septal cell with a firm cell roof that could not be fractured is presented in Fig. 32.4. This will often push the ostium laterally and significantly narrow it (Fig. 32.4b). Furthermore, neo-osteogenesis in the region of the frontal ostium does very poorly in polypoid CRS and is also best managed by an EMLP (Fig. 32.5).

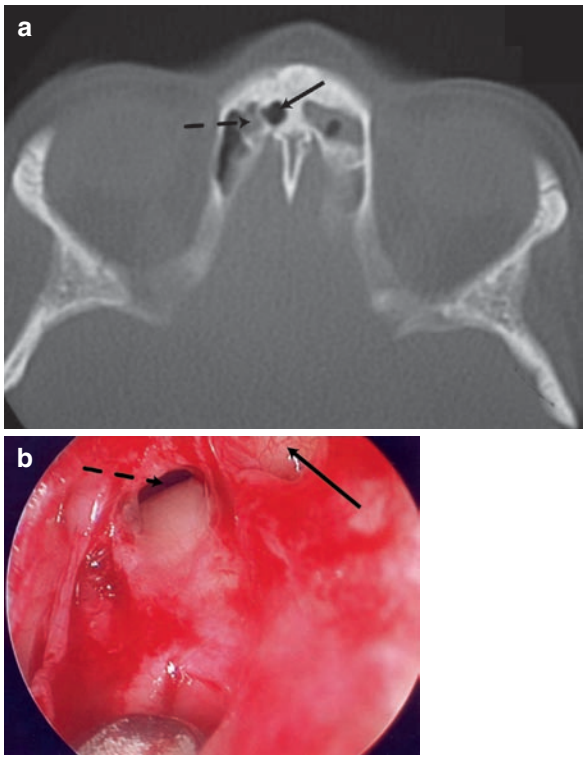

Fig. 32.3 (**a**) Shows the very small antero-posterior diameter of the frontal ostium in an axial scan and (**b**) shows the right frontal ostium (*dashed arrow*) narrowed by an intersinus septal cell (*solid arrow*) after clearance of the frontal recess. Compare the size of the instrument (which measures 3×3 mm) seen at the *bottom* of the picture with the frontal ostium

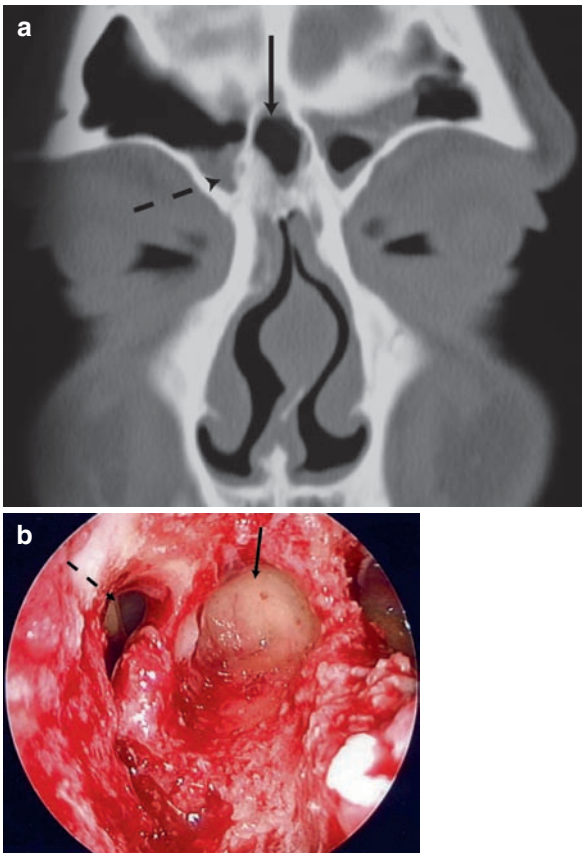

Fig. 32.4 (**a**) Coronal CT scan shows a large intersinus septal cell (*solid arrow*) narrowing and pushing the frontal ostium laterally (*dashed arrow*). (**b**) The intraoperative picture shows how this cell (*solid arrow*) obstructs and narrows the right frontal ostium (*dashed arrow*)

1. Frontal recess clearance

The frontal recess clearance begins by developing an axillary flap. The anterior wall of the agger nasi cell is removed with a Hajek–Koeffler punch flush with the frontal bone. The remaining frontal recess dissection includes a complete removal of all cells that encroach on the frontal ostium, thereby maximizing the natural ostium of the frontal sinus without enlarging it (Fig. 32.6).

If the frontal drainage pathway is not visualized easily at this point then frontal sinus mini-trephination is also performed. This is often the case with severe mucosal disease, complex frontal recess anatomy, or where the operative field is very vascular. The fluorescein stained saline is flushed through the minitrephines and visualized as it passes into the frontal recess along the outflow tract. This allows for easy identification of the tract so that the instruments can be passed along the pathway delineated by the fluorescein flushes,

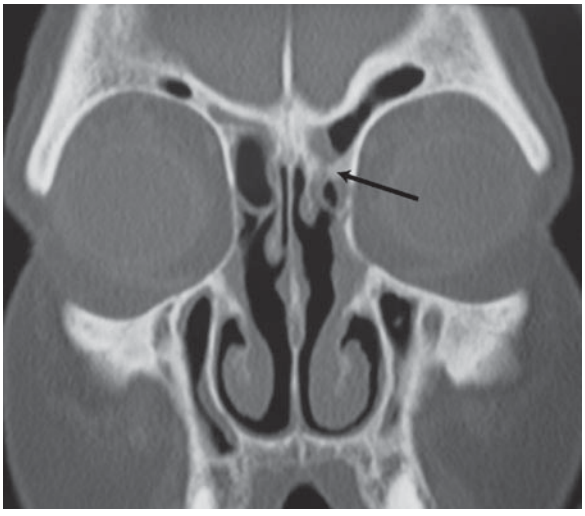

Fig. 32.5 Left frontal ostium has marked neo-osteogenesis (*arrow*) and would respond poorly to conventional FESS

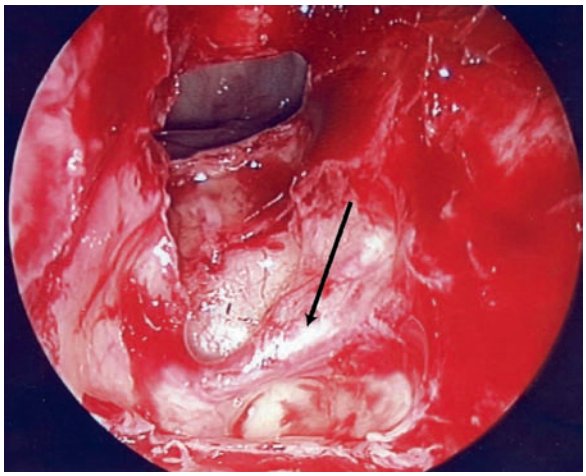

Fig. 32.6 Right frontal ostium after clearance of all obstructing cells and polyps with visualization of the frontal sinus. Note the anterior ethmoid artery (*arrow*) on the skull base

and the cells obstructing the frontal ostium can be safely removed with exposure of the ostium. At the end of the frontal recess dissection, the surgeon should be able to clearly visualize the skullbase, including the anterior ethmoidal artery, the frontal ostium, and the roof of the frontal sinus (Fig. 32.6). There should be no residual cell structures on the lamina papyracea or on the medial aspect of the frontal beak.

2. Frontal drillout or EMLP

The effectiveness of the EMLP relies on the creation of the widest possible diameter of frontal neo-ostium. Preoperatively, the maximum diameter can be determined on an axial scan at the level of the olfactory bulb. In most patients, we are able to achieve a diameter of 22×18 mm. The surgical steps have been fully described elsewhere [13–16]. In brief, the procedure begins with an access septoplasty and septal window that removes the high anterior septal cartilage and bone. Using the fluorescein stained saline flushed via minitrephines as a guide; the frontal process of the maxilla is drilled to obtain the lateral limit of the dissection by exposing small areas of the undersurface of skin. Once the frontal sinus is entered bilaterally, the frontal beak is removed until the anterior wall of the frontal sinus runs smoothly into the nasal cavity without any ridge. This results in a thin anterior bony wall and maximizes the anterior–posterior dimension.

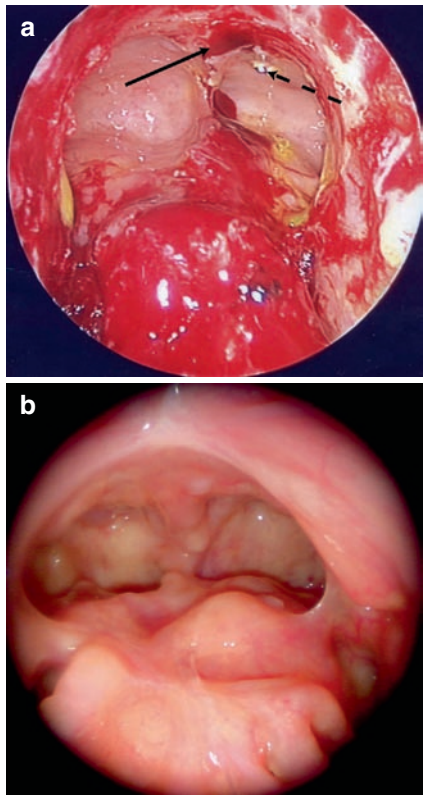

Fig. 32.7 The anterior walls of the frontal sinus move smoothly into the nasal cavity without a ridge as the beak has been completely removed (*solid arrow*), thereby maximizing the size of the neo-frontal ostium in (**a**). Note the left mini-trephine (*dashed arrow*) in place in the anterior wall of the left frontal sinus. (**b**) Shows the postoperative view after 2 years

There should be no bulge where the frontal beak previously existed (Fig. 32.7).

The posterior limit is maximally achieved in two steps. First, the olfactory mucosa is reflected posteriorly to identify the first olfactory neuron that forms the anterior boundary of the olfactory bulb (Fig. 32.8).

This step defines the posterior limit of the dissection. Second, drilling with the aid of image guidance allows for the gradual removal of bone overlying the olfactory bulb, thereby clearly defining the "T" shaped anterior projection of the cribriform plate (Fig. 32.8). Failure to achieve the maximum dimension of the frontal sinus ostium is generally due to inadequate reduction of the bone over the olfactory bulb and is predictable when a "banana" shape is evident instead

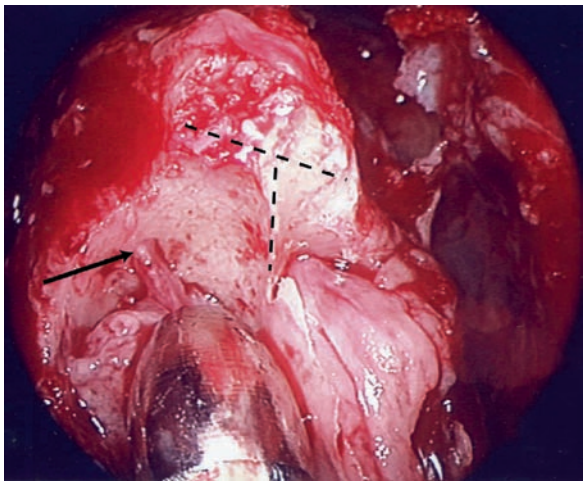

Fig. 32.8 The frontal "T" (*dashed lines*) is exposed and the olfactory mucosa reflected posteriorly to expose the right, first olfactory neuron (*arrow*)

of a more desirable oval shape. Studies in our department have shown that the average neo-frontal ostium stenosis narrows by about 33% in 1 year after which it is generally stable [10]. If a crescent-shaped ostium is created rather than an oval opening, the AP diameter is small and a narrowing of 25% is sufficient to cause obstruction and disrupt the mucociliary clearance.

Figures 32.9 and 32.10 demonstrate an example of a patient from our recent series who had severe

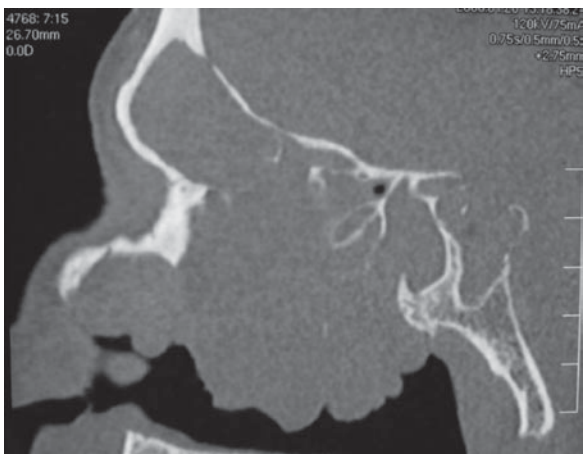

Fig. 32.9 Parasagittal CT scan showing complete opacification of all sinuses and massive nasal polyposis filling the nasal cavity in a patient with multiple previous standard FESS procedures

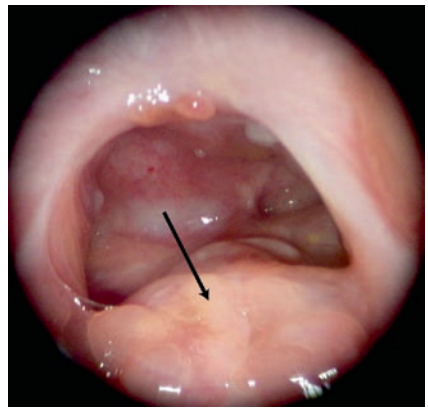

Fig. 32.10 Clinical picture of the patient in Fig. 32.8 at 12 months, showing a large frontal ostium with only mild edema of the mucosa on the posterior wall of the frontal sinus (*arrow*)

polypoid CRS that was successfully managed with an EMLP. This patient had eight previous ESS procedures before presenting to our department. Most recurrences in this patient were seen within the first 3 months of previous surgeries. The photograph in Fig. 32.10 was taken 12 months following an EMLP and shows mild mucosal edema but no significant regrowth of nasal polyps.

32.5 Conclusion

Effective surgical management of the frontal sinus in polypoid CRS depends on the complete removal of nasal polyps and by achieving a widely patent drainage pathway. In most situations, this goal is accomplished with complete clearance of the frontal recess. The EMLP is particularly beneficial in cases of recurrent polypoid disease and pathologically narrowed anatomical configurations of the frontal outflow tract. Furthermore, recognition of the high-risk subgroups of polypoid CRS patients enables appropriate risk stratification for recurrence and need for subsequent surgery. Patients with EMCRS, Samter's triad, and those with high Lund-MacKay scores would be more likely to benefit from EMLP and thus, deserve early consideration for this procedure when their disease recurs following an initial frontal recess clearance.

Take Home Pearls

- Medically resistant chronic rhinosinusitis with nasal polyposis is safely and effectively managed with extensive sinus surgery.
- Numerous studies support the use of more extensive sinus surgery with recalcitrant forms of sinusitis.
- The larger the frontal ostia, the better the long-term outcomes that will be achieved with sinus surgery.
- The endoscopic-modified Lothrop procedure creates the largest possible frontal ostium, and therefore, is the appropriate surgical choice for recurrent polypoid sinusitis after previous extensive sinus surgery.

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Evaluation of Surgical Treatments

33

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Core Messages

- Evidence-based medicine is also applicable for surgical treatment.
- The best treatment of CRS with NP is a sandwich therapy of medical, if necessary surgical, and medical treatment again.
- Predictors of outcomes of FESS in CRS with NP.
  - Age
  - Allergy
  - Asthma
  - ASA
  - Cystic fibrosis
  - Severity of disease
  - Previous surgery
  - Sex
  - Gastroesophageal reflux
- Functional endoscopic surgery is superior to minimal conventional procedures including polypectomy and antral irrigations, but superiority to inferior meatal antrostomy or conventional sphenoethmoidectomy is not yet proven.

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33.1 Introduction

Surgeons have traditionally made therapeutic decisions based on existing surgical dogma, personal experience, recommendations of surgical authorities, and thoughtful application of surgical basic sciences. The last decade has emphasized the need for evidence to base our practice on. Evidence-based surgery emphasizes the need to evaluate properly the efficacy of diagnostic and therapeutic interventions before accepting them as standard surgical practice. Essential for evidence-based surgery is a clear definition of the disease of the patient and standardized ways to evaluate surgical treatment [13].

33.2 Evidence-Based Surgical Treatment of Nasal Polyps

Evidence-based treatment is definitely not the same as treatment based on randomized controlled trials (RCT) [39]. Although in surgery it is often not ethical or possible to do RCT, it does not release us from the necessity of evaluating the available evidence to prevent us from giving our patients ineffective or even harmful treatments. However, evaluation of the available evidence is not always easy. Not only is surgery in general difficult to dose or standardize, particularly in multicenter trials, but especially in sinus surgery the patients included in the studies are usually variable in their signs and symptoms of the disease, further debilitating the drawing of conclusions from these studies. Despite these difficulties, sinus surgeons should critically evaluate published evidence and then adjust their practices accordingly.

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33.3 How Do We Measure the Efficacy of Sinus Surgery

The most relevant way of measuring the efficacy of sinus surgery is measuring the symptomatology of the patients. This can be done by measuring individual symptoms of the patient like nasal obstruction, rhinorroheoa, loss of smell, and facial pain or by measuring disease-specific or general quality of life.

The degree or strength of the symptoms can be estimated using many different grading tools recorded as severe, moderate, slight, and no symptom; by numbers from 0 to 4 or as many degrees as needed; or recorded as VAS score on a line giving a measurable continuum (0–10 cm) [13]. Terms such as mild, moderate or severe may include not only symptom severity estimation, but also an estimate of duration. A recent study has considered the relationship between subjective assessment instruments in chronic rhinosinusitis and has shown that "mild" equates to a visual analog score of 3 or less, "moderate" to >3–7 and "severe" to >7–10 [25] (Fig. 33.1). Various symptom scores have been used to show the efficacy of sinus surgery in nasal polyposis.

Traditionally, quality-of-life studies have focused on assessment of generic QOL. The generic HRQL questionnaires, such as the SF-36, allow comparison among patients with different diseases [44]. However, generic instruments may be unresponsive to small – but to the patient important – changes in HRQL. Piccirillo et al. [33] was the first to publish about the development of disease-specific HRQL instruments for rhinosinusitis. In recent years, multiple other HRQL questionnaires have been developed specifically for rhinosinusitis. A number of QOL questionnaires have shown that sinus surgery results in a significant improvement of QOL [44].

Fig. 33.1 VAS score to evaluate the severity of the symptoms compares well with mild, moderate, severe

33.4 Can We Predict the Outcomes of Sinus Surgery

A number of studies have looked at potential predictors of outcomes of surgery. Again the pathological case mix varies widely and is often poorly described. Sobol et al. described a 1-year retrospective analysis of outcome in endoscopic sinus surgery for chronic sinusitis in 393 patients. The most important prognostic factor was nasal polyposis [42]. Other factors affecting outcome were asthma, smoking, previous surgery, and pansinusitis.

Sil et al. [40] developed a composite model to find out the predictive values of various prognostic factors, using an outcome measure based on the need for postoperative medical intervention (augmentin and prednisone) in a prospective study in 109 patients with a 5-year follow-up. They showed that CT scan scores and polyp scores were the strongest predictors and that using their model the probability to predict correctly the need for postoperative systemic medication was found to be 81.7%.

Some other relevant predictors seem to be:

(a) Age

In two retrospective studies, functional endonasal sinus surgery outcomes in CRS patients >65 years were compared with adult patients under 65, and in one study, patients younger than 16 years [17, 36]. Both studies found that the geriatric group experienced a disproportionately larger share of operative complications, in particular, orbital complications. Outcomes were similar in all three groups [17].

(b) Allergy

Most studies assessing the effect of atopy on surgical outcome included CRS patients with and without nasal polyps. Data on the effect of allergy on outcome of FESS in CRS are contradictory [28, 41]. In patients with extensive polyposis [49], allergy diagnosis predicted a worse outcome and increased recurrence rate (level IV). However, antiallergic treatment is suggested to compensate for the possible shortcomings of sinus surgery in allergic patients. Nishioka et al. compared postoperative middle meatal antrostomy patency, middle meatal synechia formation, and polyp recurrence in 211 nonallergic CRS patients and 72 CRS patients and suggested, for all three outcome parameters, that allergic patients

who undergo immunotherapy do better than those who do not undergo immunotherapy and, with the exception of recurrent polyps, do as well as nonallergic patients [32] (level IV).

(c) Asthma
Retrospective studies assessing the effect of asthma on sinus surgery outcomes in CRS patients with or without nasal polyps do not show consistent results [28, 41, 49]. In a recent prospective study assessing surgical outcomes in 21 asthmatics compared with 77 nonasthmatic patients [20], symptom scores improved significantly in both asthmatics and nonasthmatics postoperatively, although the group of patients suffering from asthma had significantly worse postoperative endoscopic outcomes. No difference was found in other outcome parameters between the two groups (level IV).

In three other studies on various predictors of treatment success of sinus surgery, asthma had no independent influence on outcome parameters [6, 18, 48]. In a prospective outcome analysis, 79 patients underwent endoscopic sinus surgery for CRS with polyps [12]. In the subgroup of 22 patients with concomitant asthma, more recurrences and less symptom score improvement was observed (level IV).

(d) ASA-intolerance
In most trials, ASA-intolerance was consistently found to adversely affect sinus surgery outcomes, including a higher number of repeat operations and less lower airway improvement [2, 3, 18, 41] (level IV).

(e) Cystic fibrosis
Several reports explicitly describe CRS with polyps in CF patients. From a cohort of 650 patients undergoing endoscopic sinus surgery for CRS, 28 patients suffered from cystic fibrosis [26]. Overall subjective improvement rate in the cohort as a whole was 91%, whereas only 54% of the cystic fibrosis patients derived significant benefit at 6-month follow-up (level IV). Rowe-Jones and Mackay performed endoscopic sinus surgery on 46 cystic fibrosis patients with chronic, polypoid rhinosinusitis [38]. Their mean age at first surgery was 23 ± 7.5 years. Follow-up ranged from 1 month to 6 years (mean, 28.2 months). Overall, 50% of the patients suffered either recurrence of preoperative severity or had to undergo second endoscopic sinus procedure (level IV).

(f) Severity of disease
Kennedy found a strong correlation between the extent of the disease and the surgical outcome [18]. This finding was supported by Marks, Wang and Sil who both showed that computed tomography stage of disease is correlated to poor outcomes after endoscopic sinus surgery [28, 40, 48]. Stewart on the contrary showed a better outcome after surgery in patients with more severe disease [43].

(g) Previous sinus surgery
Previous surgery, in a study in patients with severe CRS with NP, was shown to be a predictor of bad outcome together with a history of asthma [49]. Interestingly, this study shows a very high level of recurrence when only patients with severe CRS with NP are evaluated. In some other studies with mixed CRS populations, previous surgery was also a predictor of bad outcome [28].

(h) Sex
Improvement after FESS does not differ by sex, nor is sex predictive of postoperative outcome [30]. Despite similarities in objective disease measures, females report significantly worse QOL scores pre- and postoperatively, most likely reflecting sex differences in ASA intolerance and depression, both more prevalent in females.

(i) Gastroesophageal reflux
Chambers et al. [6] showed in 182 patients that only gastroesophageal reflux disease was statistically significant as a predictor of poor symptomatic outcome. It is unclear whether the patients had polyps or not.

33.5 Predictors of Outcomes of FESS in CRS with NP

- Age
- Allergy
- Asthma
- ASA
- Cystic fibrosis
- Severity of disease
- Previous surgery
- Sex
- Gastroesophageal reflux

33.6 Surgery as Part of Treatment of Nasal Polyps

Few studies compared sinus surgery, which was always combined with medical treatment, with medical treatment alone. The majority of studies show appropriate medical treatment to be as effective as surgical treatment, thus sinus surgery should be reserved for patients who do not satisfactorily respond to medical treatment [23]. Moreover, sinus surgery is almost always preceded and/or followed by various forms of medical treatment including nasal douches, nasal steroids, systemic steroids, and systemic antibiotics. The EPOS guidelines advise to always treat patients with medical treatment before surgery is used [13]. The medical treatment depends on the severity of the symptoms from nasal spray in mild nasal polyps to a combination of systemic corticosteroids and local corticosteroid treatment in patients with severe disease [1, 5, 24, 34].

33.7 Functional Endoscopic Sinus Surgery in Nasal Polyps

In a review, Dalziel et al. screened 444 articles and evaluated 33 articles published between 1978 and 2001 [10] on the effect of FESS on CRS with NP. Major reasons for exclusion were narrative character of the publication or less than 50 patients with polyps. The authors reviewed three RCT comparing functional sinus surgery with Caldwell Luc or conventional endonasal procedures ($n=240$), three nonrandomized studies also comparing different surgical modalities ($n=2{,}699$) and 27 case series studies ($n=8{,}208$). Consistently, patients judged their symptom "improved" or "greatly improved" in 75–95% (level IV). The percentage of overall complications was 1.4% for FESS compared to 0.8% for conventional procedures.

In 2000, the Clinical Effectiveness Unit of the Royal College of Surgeons of England conducted a National Comparative Audit of the Surgery for Nasal Polyposis and Chronic Rhinosinusitis covering the work of 298 consultants working in 87 hospital sites in England and Wales [15]. Patients undergoing sinus surgery were prospectively enrolled and followed up in this observational study at 3, 12, and 36 months postoperatively using the SNOT-22 as the main outcome measure. Two thirds (2,176) of the 3,128 patients participating in this study had CRS with nasal polyps. CRS patients with nasal polyps more frequently suffered from concomitant asthma and ASA-intolerance, had more previous sinonasal surgery, their mean CT score was higher, and their mean SNOT-22 symptom score was slightly lower than that of CRS patients without polyps. All forms of sinus surgery were considered though the majority were performed endoscopically. Overall, there was a high level of satisfaction with the surgery, and clinically significant improvement in the SNOT-22 scores was demonstrated at 3, 12, and 36 months [15]. Polyp patients benefited more from surgery than the chronic rhinosinusitics without polyps. Revision surgery was indicated in 3.6% at 12 months and in 11.8% at 36 months. Major complications were rare (level IIc).

In this context, a recent case series study of CRS patients with particularly extensive polyposis is worth mentioning [49]. Of the 118 patients reviewed, 59 (50%) had asthma, and 93 (79%) had documented allergy. All patients received extensive bilateral nasal polypectomy, complete anterior and posterior ethmoidectomy, and maxillary sinusotomy. One hundred (85%) also had frontal or sphenoid sinusotomy. Follow-up ranged from 12 to 168 (median 40) months. Despite pre- and postoperative nasal and systemic steroid treatment in the majority of patients, 71 (60%) developed recurrent polyposis, 55 (47%) were advised to undergo revision surgery, and 32 (27%) underwent revision surgery.

33.7.1 Conclusion

FESS is an effective way to treat nasal polyps, especially when combined with medical treatment.

33.8 Functional Endoscopic Sinus Surgery vs. Conventional Surgery

In the NHS R&D Health Technology Assessment Programme evaluation [10], polyp recurrence was 28% following functional endoscopic ethmoidectomy compared to 35% following intranasal polypectomy. The percentage of overall complications was 1.4% for

FESS compared to 0.8% for conventional procedures.

Hopkins et al. compared, in the National Comparative Audit of Surgery for Nasal Polyposis and Rhinosinusitis, the SNOT-20 supplemented with two additional items (SNOT-22) after simple polypectomy and after functional endoscopic sinus surgery in addition to medical treatment [15]. The SNOT-scores did not differ significantly between the two treatment arms after 12 and 36 months, if adjusted for relevant confounders. Revision surgery was carried out more frequently in the polypectomy only group in the first 12 months after surgery ($p = 0.04$), but this difference was not significant at 36 months. Complication rates did not differ significantly.

33.8.1 Conclusion

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

33.9 Extent of Surgery

Extent of surgery may vary from mere uncinectomy to radical sphenoethmoidectomy with middle turbinate resection. In several studies, the extent of sinus surgery on various outcome parameters was investigated in CRS patients, not differentiating between CRS with and without polyps. In a prospective trial, 65 CRS patients with and without polyps were randomized to undergo limited endonasal functional surgery (infundibulectomy) and a more extensive functional procedure, including sphenoethmoidectomy and wide opening of the frontal recess. Diseases extent was similar in both treatment arms. Outcome parameters included symptom scores, rhinoscopy scores, and nasal saccharin transport time [22]. Recall rates were below 60%. Outcome parameters revealed no relevant differences after 3, 6, and 12 months (level Ib).

In a randomized trial, 1,106 matched CRS patients with and without polyps, who underwent similar functional endonasal sinus surgery with (509 patients) or without (597 patients) partial middle turbinate resection [14]. Partial middle turbinate resection was associated with less synechia formation ($p < 0.05$) and less revision surgeries ($p < 0.05$) than middle turbinate preservation. Complications particularly caused by partial middle turbinate resection were not observed (level Ib).

The patency rate after large middle meatal antrostomy and undisturbed maxillary ostium in endoscopic sinus surgery for nasal polyposis was compared in 60 patients with bilateral nasal polyps [47]. A large middle meatal antrostomy was performed on one side, whereas on the other side, an uncinectomy preserving the natural maxillary ostium was done. The sides were chosen randomly. The patency rates of a large middle meatal antrostomy were significantly higher 3 months after surgery when compared with undisturbed maxillary ostium. This difference became insignificant after 12 months (level Ib).

Jankowski et al. retrospectively compared a case series of 37 CRS patients with extensive nasal polyps treated with FESS with a historical group of 36 patients with similar disease extent treated with radical sphenoethmoidectomy and middle turbinate resection [16]. Outcome parameters assessed 5 years following surgery included a mailed questionnaire on nasal symptoms, the number of patients with revision surgery, and nasal endoscopy scores at a follow-up visit. Recall was below 80% and differed significantly between the two groups. The radical surgical procedure yielded better symptom scores, less recurrence, and better endoscopy scores at the follow up visit (level IV).

33.9.1 Conclusion

Although not fully evidence based, the extent of surgery is frequently tailored to the extent of disease, which may appear as a reasonable approach. In primary paranasal surgery, surgical conservatism is recommended.

33.10 Revision Sinus Surgery

Approximately 10% of operated patients respond insufficiently to sinus surgery with concomitant medical therapy and eventually require a secondary surgical

procedure [4]. Middle turbinate lateralization, synechiae and scar formation in the middle meatus, an incompletely resected uncinate process, and retained ethmoid cells are frequent findings in patients undergoing revision surgery [31, 35, 37]. Previous revision surgery, extensive polyps, bronchial asthma, ASA-intolerance, and cystic fibrosis are predictors for revision surgery [7, 11, 21, 27–29]. Inflammatory involvement of underlying bone may also be of significance [19, 45, 46]. Technical issues of sinus revision surgery have recently been reported by Cohen and Kennedy [8]. A more extensive surgical procedure and also external approaches may be indicated [9, 16, 45, 46]. Success rates of revision endoscopic sinus surgery have been reported to range between 50 and 70% [18, 21] (level IV). Complication rates of revision surgery are higher when compared with initial surgery and approximate 1%, but may be as high as 7% [4, 7].

McMains and Kountakis also reported the results of 59 CRS patients with nasal polyps after revision surgery [29]. Consistent with the results of the National Comparative Audit [15] and the comparative study by Deal et al. [11], CRS patients with polyps had lower SNOT scores preoperatively (less severe symptoms), more previous surgeries, and a higher CT score preoperatively than CRS patients without polyps. However, the improvement of outcome parameters after revision surgery was significant and comparable with the improvement in CRS patients without polyps.

33.10.1 Conclusion

Revision endonasal sinus surgery is only indicated if medical treatment is not sufficiently effective. Substantial symptomatic improvement is generally observed in both, CRS with and without polyps, though the improvement is somewhat less than after primary surgery. Complication rates and particularly the risk of disease recurrence are higher than after primary surgery. Some patients still suffer from CRS symptoms after several extensive surgical procedures. CT scans frequently show mucosal alterations adjacent to osteitic bony margins in an extensively operated sinus system (Fig. 33.2). As a rule, revision surgery is not indicated in these patients but radical surgery can be an option [45, 46].

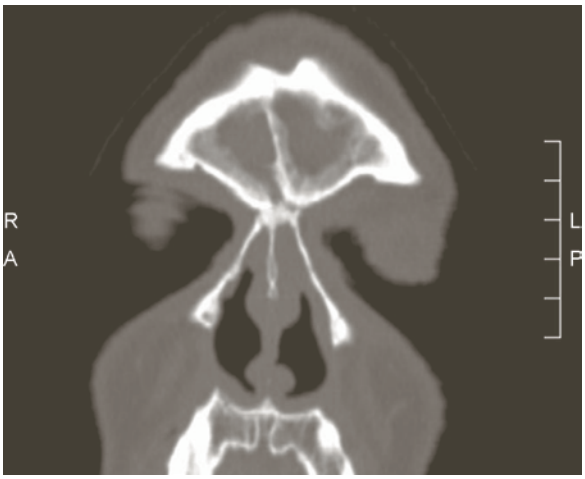

Fig. 33.2 CT scan showing neo-osteogenesis/osteitis

Take Home Pearls

- Nasal polyposis is a chronic disease. When treating nasal polyposis tailor the treatment to the disease.
- Do not overestimate the possibilities of surgery especially in treating smell disorders.
- Apply sandwich therapy as much as possible: medical treatment-surgery-medical treatment.

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