Chapter 2
Microbiology and Immunology of Rhinosinusitis

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Rhinosinusitis is one of the most common health care problems facing the primary care physician and results in significant heath care costs. With an increasing prevalence and incidence, it is believed that approximately 31 million Americans are affected by this condition annually [1–5]. Rhinosinusitis significantly impacts patients' quality of life and results in marked physical, functional, and emotional impairment. Thus, a good understanding of the pathogenesis, microbiology, and immunology of this illness is needed for accurate diagnosis and proper treatment.

Rhinosinusitis represents a group of disorders characterized by inflammation of the nasal and paranasal sinus mucosa [6]. As such, it is presently thought that rhinosinusitis is initiated with an inflammatory insult (allergic rhinitis exacerbation, viral upper respiratory tract infection, rhinitis medicamentosa, etc.), followed by bacterial or fungal superinfection. Mucociliary clearance is the sinonasal cavity's most powerful protective mechanism through its expeditious removal of offending organisms. Once cleared from the sinonasal cavity, organisms enter the nasopharynx, which is an area devoid of mucociliary clearance, thus resulting in bacterial colonization and the possibility of retrograde sinonasal infection [7]. Bacterial colonization of the nasal vestibule with staphylococcus species (*Staphylococcus epidermidis, Staphylococcus aureus)* is quite common and can affect the quality of sinonasal cultures. Viruses are not considered part of the normal flora of the sinonasal cavity and are considered precursors to bacterial sinusitis. Because specific treatment approaches are crucial for the different types of rhinosinusitis as well as their different pathogens, the microbiology and immunology of rhinosinusitis are now reviewed.

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E.R. Thaler, D.W. Kennedy (eds.), *Rhinosinusitis*, DOI: 10.1007/978-0-387-73062-2_2,

Microbiology

Viral Rhinosinusitis

Viral rhinosinusitis is widespread and is what most people identify as the "common cold." With the exception of herpes simplex and adenoviruses, viruses are not usually part of the normal flora of the nose and paranasal sinuses. Consequently, inoculation of the mucosa of the nose and paranasal sinuses by viruses leads to significant inflammation with subsequent obstruction of the ostiomeatal complex and impaired mucociliary clearance [8,9]. Because of the multitude of viral strains that can cause nasal and paranasal sinus inflammation, viral rhinosinusitis is quite prevalent. Pathogens in viral rhinosinusitis include more than 100 strains of rhinovirus, as well as influenza, parainfluenza, coronavirus, adenovirus, and respiratory syncytial virus. Rhinovirus is the predominant etiology of the common cold and is capable of survival on surfaces for up to 4 days. When inoculation of the nasal cavity occurs with a virus-contaminated finger, infection will result in the majority of cases [7]. Clinically, patients experience a self-limiting illness lasting 3 to 7 days. Treatment is usually supportive with adequate hydration and nasal decongestants. Unfortunately, by creating ostiomeatal complex obstruction, impairing mucociliary clearance, and weakening mucosal integrity, viral rhinosinusitis predisposes patients to invasion of their nasal and paranasal sinus mucosa by trapped facultative aerobic bacteria and the development of acute bacterial rhinosinusitis [10–13].

Acute Bacterial Rhinosinusitis

Acute bacterial rhinosinusitis is a clinical condition characterized by nasal congestion and rhinorrhea for 7 to 14 days, but no more than 4 weeks. This diagnosis is based on symptomatology, clinical signs, and duration of symptoms [13]. Specific diagnostic criteria can be elicited through a detailed history and physical examination without the need for endoscopy or computerized tomography, which are often used as adjuncts in the clinical management. Acute bacterial rhinosinusitis usually starts with marked mucosal inflammation from a viral upper respiratory tract infection or allergic rhinitis exacerbation. The mucosal inflammation, combined with retained secretions, constitutes an ideal medium for bacterial overgrowth. When bacterial superinfection occurs, a diagnosis of bacterial rhinosinusitis is established.

The primary pathogens in acute bacterial rhinosinusitis of the maxillary, ethmoid, and frontal sinuses are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Additional pathogens include other streptococcus species, *Staphylococcus aureus*, and anaerobes (Fig. 2.1) [14]. In contrast to the other sinuses, acute sphenoid sinusitis tends to have *Staphylococcus aureus* as one of its most common pathogens [15]. When patients present with acute maxillary sinusitis of odontogenic origin, the primary pathogens are anaerobic bacteria such as anaerobic streptococci, *Bacteroides*, *Proteus*, and coliform bacilli, and appropriate antibiotic treatment as well as proper dental referral is warranted (Fig. 2.2) [16,17].

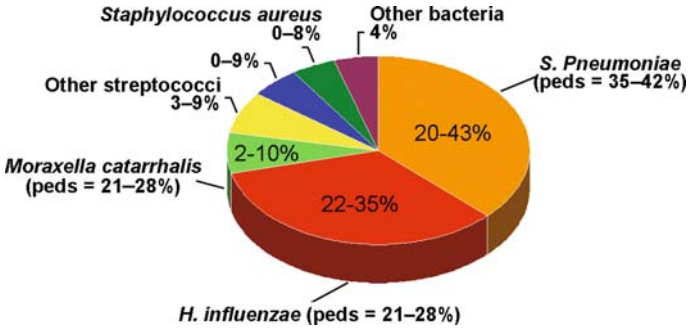

Fig. 2.1 Pathogens in acute bacterial rhinosinusitis. *peds*, pediatric. (Reprinted from James A. Hadley, MD, and David J. Osguthorpe MD. *Rhinosinusitis,* Fifth Edition, 2006, with permission of the American Academy of Otolaryngology–Head and Neck Surgery Foundation, copyright © 2006 [14]. All rights reserved.)

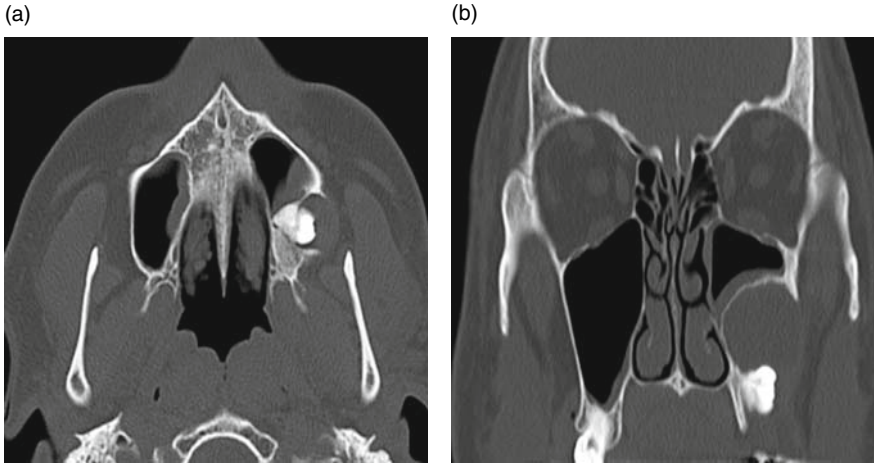

Fig. 2.2 Axial (**a**) and coronal (**b**) computed tomography (CT) scanning of a patient with left maxillary sinusitis from odontogenic origin

Children with acute bacterial rhinosinusitis usually have the same pathogens as previously listed, which tend to parallel those seen in acute otitis media (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*) [17].

Treatment of acute bacterial rhinosinusitis is based on restoration of sinus drainage and eradication of the offending organism(s). Most acute bacterial rhinosinusitis patients can be treated medically with topical vasoconstrictors, systemic decongestants, and appropriate antibiotics directed toward the previously listed three most common organisms. It should be noted that those patients with unilateral sinusitis should be appropriately evaluated for an odontogenic source of infection, or, in the case of children, for a foreign-body impaction. Without adequately

addressing the underlying cause, these patients will continue to suffer from chronic or repetitive infection.

Subacute Rhinosinusitis

Subacute rhinosinusitis is similar to acute bacterial rhinosinusitis but is present for more than 4 weeks and less than 12 weeks. The microbiology of subacute rhinosinusitis is believed to be similar to acute bacterial rhinosinusitis with the addition of more resistant organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Treatment consists of topical vasoconstrictors, systemic decongestants, and adequate antibiotic coverage. Complete and long-term resolution of symptoms is expected after appropriate medical therapy.

Chronic Rhinosinusitis

Chronic rhinosinusitis is defined as rhinosinusitis of at least 12 consecutive weeks duration. Therefore, it represents a group of disorders characterized by inflammation of the nasal and paranasal sinus mucosa for at least 12 consecutive weeks [6]. Chronic rhinosinusitis is typically diagnosed in association with predisposing conditions such as asthma, allergy, dental disease, cystic fibrosis, polyposis, and immunodeficiency syndromes. While there is little debate regarding an association between bacteria and acute rhinosinusitis, the role of bacteria in the pathogenesis of chronic rhinosinusitis is still unclear.

The bacteriology of chronic rhinosinusitis is considerably different than acute bacterial rhinosinusitis [18]. Pathogens such as *Staphylococcus aureus*, coagulase-negative staphylococcus, and anaerobic and gram-negative bacteria replace the pathogens commonly found in acute bacterial rhinosinusitis (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*). One theory is that prior repeated use of antibiotics in patients with frequent rhinosinusitis accounts for the observed difference in pathogens.

Chronic rhinosinusitis also involves significant osteitis from the prolonged inflammation and remodeling occurring within the bone of the paranasal sinuses. This phenomenon, which seldom occurs in acute bacterial rhinosinusitis, can lead to distal submucosal spread of the infectious process in other parts of the paranasal sinuses and render medical and surgical treatment more difficult [19]. A recent prospective clinicopathological study showed that more than 50% of patients undergoing sinus surgery for chronic rhinosinusitis had pathological evidence of osteitis [20]. Although the direct impact on treatment has not yet been determined, many experts believe that this finding will influence future treatment approaches for chronic rhinosinusitis [19,20].

An important factor in the pathogenesis of chronic rhinosinusitis is the role of bacterial biofilms [21]. Bacterial biofilms are aggregates of bacteria with special properties secondary to their group structures (Fig. 2.3). One of these properties

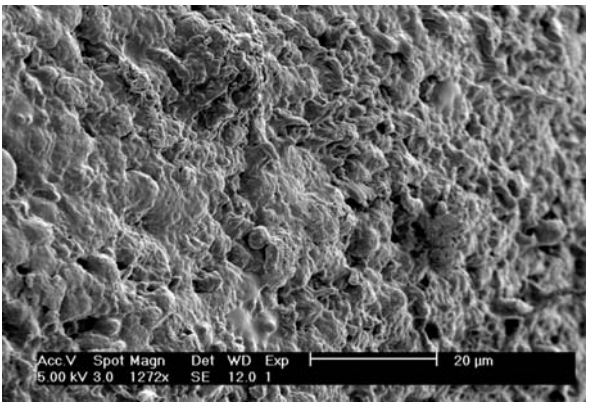

Fig. 2.3 Electron microscopy of *Pseudomonas aeruginosa* biofilms

involves significant increased resistance to antibiotics. Bacterial biofilms have previously been cultured in patients with chronic rhinosinusitis. In fact, strains from two of the most common bacterial isolates in chronic rhinosinusitis (*Pseudomonas aeruginosa* and *Staphylococcus aureu*s) have been proven to form biofilms [21]. This finding may explain why a subgroup of patients fails to improve or has frequent recurrence after medical and surgical management for chronic rhinosinusitis [21,22]. Studies are ongoing to determine the utility of topical therapies to penetrate the bacterial biofilms, thus rendering them more susceptible to antibiotic therapy.

Treatment of chronic rhinosinusitis involves the identification and appropriate management of possible underlying conditions causing rhinosinusitis. Intranasal steroid sprays, decongestants, and systemic steroids, with appropriate antibiotic coverage, have all been used with some efficacy. Nevertheless, there are no randomized clinical trials supporting the use of antibiotics in this condition. When medical management fails, surgical intervention is needed to provide sinus drainage and to remove predisposing anatomic obstruction.

Recurrent, Acute Rhinosinusitis

A patient with at least four episodes of acute rhinosinusitis per year—with each episode lasting 7 to 10 days without intervening signs of chronic rhinosinusitis—has, by definition, recurrent acute bacterial rhinosinusitis [13]. These patients tend to have similar pathogens as acute bacterial rhinosinusitis and are usually treated with medical management. Sinonasal culture may be helpful in guiding antibiotic choice in this subgroup of patients (Fig. 2.4).

Acute Exacerbation of Chronic Rhinosinusitis

Acute exacerbations of chronic rhinosinusitis are characterized by sudden worsening of the dull and persistent symptoms of chronic rhinosinusitis. This condition

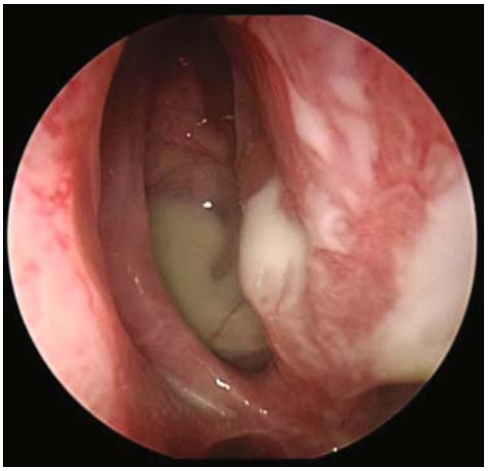

Fig. 2.4 Purulent nasopharyngeal discharge in a patient with recurrent acute rhinosinusitis

may be triggered by factors such as worsening allergic rhinitis or transient decrease in host immune response secondary to a viral upper respiratory infection. The bacteriology is usually similar to chronic rhinosinusitis. Treatment involves topical vasoconstrictors, systemic decongestants, and appropriate antibiotics. After appropriate medical management, these patients typically return to their baseline.

Fungal Rhinosinusitis

Fungi are ubiquitous organisms, and as expected, commonly colonize the nasal cavity and paranasal sinuses in both the normal and disease states. Fungal rhinosinusitis can be classified in five different manifestations: acute invasive, chronic invasive, fungal ball, allergic, and saprophytic. The prognosis and therapy for each histopathological form of fungal rhinosinusitis is different and is primarily based on the immunological status of the host (Table 2.1).

Table 2.1 Classification of fungal rhinosinusitis

Classification	Immunological status	Treatment	Prognosis
Acute invasive	Immunocompromised	Reversal of immunocompromise; surgery; antifungal agents	Guarded/poor
Chronic invasive	Immunocompetent	Surgery; antifungal agents	Fair/good
Fungus ball (mycetoma)	Immunocompetent	Surgery	Good
Allergic	Atopic	Surgery; steroids; immunotherapy	Excellent
Saprophytic	Immunocompetent	Removal	Excellent

Acute invasive fungal rhinosinusitis almost exclusively occurs in immunocompromised patients (organ transplant recipients, diabetic patients, and patients with primary or acquired immunodeficiency), and has a fulminant onset with high mortality. Diagnosis is made by histological evidence of invasive fungal hyphae (within the sinus mucosa, submucosa, blood vessels, or bone) in the nose and paranasal sinuses. Common pathogens causing this condition include aspergillus and fungi of Mucoraceae, of the order Mucorales, including *Rhizopus* and *Mucor* [23,24]. *Aspergillus* species are the most common pathogens identified in acute invasive fungal rhinosinusitis (Fig. 2.5). Although approximately 350 strains of this fungus have been identified, the three strains with pathological significance to humans are *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus niger*. The strain most commonly responsible for disease in the United States is *A. fumigatus* while *A.flavus* is most often associated with the indolent chronic invasive rhinosinusitis seen in the Sudan. Nonetheless, any of these *Aspergillus* species can cause fatal acute fulminant fungal rhinosinusitis. Treatment involves correction of the immunocompromised state, aggressive surgical debridement, and long-term systemic and topical antifungal agents. Recent reports suggest an increase efficacy of the antifungal posaconazole for fungal sinusitis refractory to standard antifungal therapy [25].

Chronic invasive fungal rhinosinusitis is often divided into granulomatous and nongranulomatous subtypes on the basis of histopathology. However, the diagnosis, management, and prognosis of these two subtypes are comparable. Chronic invasive fungal rhinosinusitis is rare in the United States, with most literature in this condition emanating from the Sudan. This condition usually occurs in immunocompetent or mildly immunocompromised hosts. The overwhelming majority of these cases have *Aspergillus flavus* as the offending organism. Other causative fungi include *Aspergillus fumigatus*, *A. mucor*, *A. alternaria*, *A. curvularia*, *Pseudallescheria*

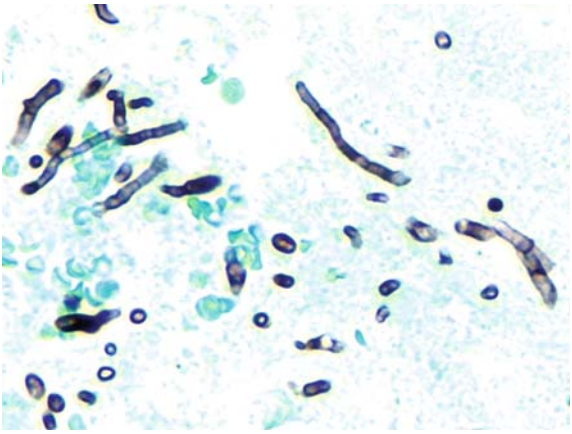

Fig. 2.5 Micrograph of septated hyphae typical of *Aspergillus*. (Grocott–Gomori methenamine-silver nitrate stain; × 400.)

boydii, *P. bipolaris*, and *Sporothrix schenckii* [26]. Chronic invasive fungal rhinosinusitis is treated with long-term systemic antifungal therapy and surgical debridement.

Mycetomas or fungal balls are common fungal infections found in the immunocompetent host. They can remain asymptomatic for years and be diagnosed incidentally, or present with symptoms mimicking chronic bacterial rhinosinusitis. The moist environment of the sinonasal cavity serves as an optimal medium for fungal proliferation. Common pathogens include *Aspergillus fumigatus*, *A. flavus*, *A. alternaria*, and *A. mucor* [27,28]. Fungal balls are treated by endoscopic surgical removal alone rather than systemic antifungal therapy. Recurrence is common.

Allergic fungal rhinosinusitis is a noninvasive disease characterized by atopy and a marked inflammatory response to certain fungal antigens. This entity was initially described by Millar et al. in 1981 [29]. The diagnosis of allergic fungal rhinosinusitis is made by histopathological analysis of allergic mucin. In 1994, Bent and Kuhn described five major criteria found in this condition, namely, atopy, nasal polyposis, eosinophilic mucin without fungal invasion into soft tissue, characteristic computed tomographic findings of serpiginous areas of high attenuation in affected sinuses, and positive fungal stain [30]. Organisms commonly found in allergic fungal rhinosinusitis are primarily dematiaceous and include species of *Alternaria*, *Bipolaris*, and *Curvularia* [31]. Treatment of allergic fungal rhinosinusitis is mainly endoscopic sinus surgery, as well as systemic and topical corticosteroids. Because of the strong influence of atopy in the development of this condition, immunotherapy has been used with significant success. Recurrence is very common, and patients with allergic fungal rhinosinusitis require long-term follow-up.

Saprophytic fungal infections are commonly seen after sinus surgery and occur when ubiquitous fungal spores land and germinate on mucous crusts and old hematomas. This condition can be prevented with proper office debridement and frequent sinus irrigation after sinus surgery. Treatment consists of simple removal of the crust and hematoma and appropriate nasal irrigation.

Immunology

The immune system plays a vital role in preventing rhinosinusitis, as well as being an integral component to its pathogenicity. The normal sinonasal mucous blanket contains secretory IgA, which serves as a barrier against certain microorganisms and decreases the incidence of infections. Likewise, cell-mediated immune response constitutes a major defense against viruses and fungi. Unfortunately, the numerous cytokines and chemokines released after a potentially self-limiting infection (such as the common cold) is a clear example of the possible deleterious effect of an overly stimulated response. In these cases, the released proinflammatory chemokines cause immunosuppressive effects on neutrophils, macrophages, and lymphocytes, therefore reducing the efficacy of cell-mediated immune response and raising vulnerability to infection by local bacteria.

The immune mechanisms used at the mucosal level in the nose and sinuses can be divided into innate and adaptive immunity. These two immune mechanisms are different in their response time and specificity. While innate immune response is significantly less specific, it has a very short response time and acts as the initial defense mechanism after exposure to a potentially harmful pathogen. Conversely, adaptive immunity is very specific, but has to go through a cascade of cytokine activation before pathogens eradication can occur.

Innate Immunity

The continuous sinonasal mucous flow known as mucociliary clearance represents the primary mechanical innate defense of the sinonasal mucosa. The effectiveness of this process relies on the viscoelastic property of the mucus blanket as well as adequate ciliary beat frequency. When exposed to airborne irritants or bacteria, the Schneiderian epithelium of the sinonasal cavity increases its production of mucus, leading to suppression of bacterial overgrowth from the effects of the secreted antimicrobial products in the mucus, and increases mucociliary flow with the propulsion of trapped irritants and bacteria into the nasopharynx. A healthy and noninflamed sinonasal epithelium is paramount for optimal mucociliary clearance. In fact, many recent studies have demonstrated significant differences in mucociliary clearance between normal subjects and patients with rhinosinusitis [32–34]. In patients with poor mucociliary function, chronic mucous stasis leads to bacterial overgrowth and the development of bacterial rhinosinusitis.

The sinonasal mucous blanket contains numerous antimicrobial products such as immunoglobulins, enzymes (lysozyme, lactoferrin, secretory leukocyte proteinase inhibitor), opsonins, and defensins that help the host defend against pathological bacteria. These molecules, which are secreted by the sinonasal epithelial cells, are responsible for immobilization and destruction of microorganisms and play a vital role in immediate host defense against pathogens entering the body through the sinonasal mucosa. Lysozymes (secreted by macrophages, monocytes, and sinonasal epithelial cells) act against the peptidoglycan cell wall of bacteria and are highly effective against gram-positive bacteria. Lactoferrin (secreted and stored by serous mucosal glands) is a cofactor that enhances lysozyme activity against gram-negative bacteria. This antimicrobial acts as an iron-binding protein that inhibits bacterial growth through iron sequestration. Secretory leukocyte proteinase inhibitor, which is also found in the sinonasal mucous blanket, has been shown to have in vitro activity against gram-positive and gram-negative bacteria, as well as being able to inhibit neutrophil elastase [35–37].

Adaptive Immunity

Similar to other disease processes, the adaptive immunity observed in rhinosinusitis is mediated by T and B lymphocytes and has specificity and memory. $CD4^+$ helper

T cells represent the primary mediator of this process. These T cells are divided into two functionally different phenotypes: “Th1” cells, which are responsible for cell-mediated immune response (phagocytosis and cytotoxic killing), and “Th2” cells, which trigger a humoral response (antibody production). Th1 cells secrete cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), which in turn activate macrophages and cytotoxic T lymphocytes, leading to phagocytosis and cytotoxic cell death. In contrast, Th2 cells secrete the interleukins IL-4, IL-5, IL-9, and IL-13, which promote IgG and IgE secretion, eosinophil production, and proliferation and maturation of mast cells. Each of these two immune pathways exerts an inhibitory effect on the cytokines produced by the other and causes polarization of the immune response [36].

Summary

Rhinosinusitis is a very common medical condition with significant heath care costs. Many different forms of this condition, exist with very distinct microbiology. A thorough understanding of the different forms of rhinosinusitis, as well as their common pathogens, is paramount for appropriate antimicrobial therapy. The most common pathogens in rhinosinusitis are viruses, for which supportive therapy is sufficient. Acute bacterial rhinosinusitis is usually precipitated by viral rhinosinusitis. Antimicrobial therapy for acute bacterial rhinosinusitis should be directed at common pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Isolates in chronic rhinosinusitis typically show *Staphylococcus aureus*, coagulase-negative staphylococcus, and anaerobic and gram-negative bacteria. Although antimicrobials are commonly used in chronic rhinosinusitis, no clear role for antibiotic therapy has been determined in this condition. Bacterial biofilms and chronic osteitis are important factors to consider in the patient with chronic rhinosinusitis refractory to medical and surgical management.

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