Chronic Rhinosinusitis

13

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Introduction

Chronic rhinosinusitis (CRS) is a disease characterized by chronic inflammation of the sinonasal mucosa [1–3]. The clinical manifestations include not only chronic sinonasal symptoms but also symptoms of acute exacerbations and any comorbid pulmonary diseases [4–6]. Chronic rhinosinusitis impacts quality of life to a degree comparable to asthma or heart disease [4, 7], causes significant losses in productivity from missed days at work and school [7, 8], and leads to billions of dollars in direct and indirect costs every year [9, 10]. The impact of CRS is not only on afflicted individuals but also on society as a whole.

As discussed below, CRS is a complicated and heterogeneous disease. The exact pathophysiology likely differs from patient to patient, but recent studies suggest that CRS results from a dysregulated interaction between external stimuli and the host immune response. This chapter will review the diagnosis, pathophysiology, and treatment of CRS.

Diagnosis

Chronic rhinosinusitis is defined clinically based on consensus guidelines incorporating both subjective and objective criteria. Guidelines by the American Academy of Otolaryngology—Head and Neck Surgery, as shown in Table 13.1, recommend at least 12 consecutive weeks of symptoms including at least two of the following four major symptoms of CRS (nasal obstruction, drainage, facial pain/pressure, and hyposmia/anosmia), in addition to objective evidence of sinusitis on nasal endoscopy or sinus computed tomography (CT) [1]. Very similar diagnostic guideline criteria have been adopted throughout the world [2, 11]. Because CRS is defined clinically, there are likely many different pathophysiologic processes that converge upon the final clinical phenotype defined by consensus diagnostic criteria. In fact, multiple inflammatory mechanisms are believed to contribute to the development and persistence of CRS [3, 12].

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Table 13.1 Clinical consensus guidelines criteria for the diagnosis of CRS from the American Academy of Otolaryngology—Head and Neck Surgery[a]

Diagnostic criteria for CRS
Subjective
At least 12 continuous weeks of at least two out of four symptoms of:
• Nasal obstruction
• Nasal drainage
• Facial pain/pressure
• Hyposmia or anosmia
Objective
• Nasal endoscopy findings
– Mucupurulent drainage, edema, polyps
Or
• Radiographic findings
– Mucosal thickening, sinus opacification, air-fluid levels

[a]Adapted from reference [1]

Pathophysiology

Genetic basis. There is ample evidence that dysregulated host inflammatory responses to various extrinsic inflammatory stimuli contribute to the pathophysiology of CRS [13]. In many cases, there appears to be a genetic basis for the host response that is inherited as a complex genetic trait. The heritability of CRS has been suspected for decades. Patients with cystic fibosis may have significant CRS and the association of CRS with mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which cause cystic fibrosis, represents a special case of CRS [14, 15]. However, a genetic basis for CRS in other patients has been suspected for many years because CRS patients often relate a positive family history of CRS, even in the setting of dissimilar environment exposures [16, 17]. Recent studies of a large genealogical database linked to medical charts of almost ten million individuals have shown an increased risk for the development of CRS in individuals with family members who have CRS [18, 19]. There was an increased risk of developing CRS in adults with a first-degree relative with CRS (two to four-fold increased risk) and in siblings of pediatric CRS patients (>50-fold increased risk) [18, 19]. Genetic linkage studies have identified numerous gene loci that appear to be associated with the development of CRS [12].

Innate immune response. Supporting the important role of the host inflammatory response in the development of CRS is the identification of genes involved in the innate and adaptive immune responses associated with CRS. The immune system is comprised of an innate and an adaptive immune system. The innate immune system is more primitive and present in both animals and plants, while the adaptive immune system is only present in vertebrates. The innate immune system is a rapid response system and serves as the first line of defense against invading microbes. It also activates the adaptive immune response to provide a secondary response. The ability of the innate immune system to rapidly recognize pathogens is linked to the presence of Toll-like receptors (TLRs) in the cell membranes of various types of white blood cells (e.g., macrophages, dendritic cells) as well as epithelial and endothelial cells. These TLRs recognize molecules that are broadly shared by viruses, bacteria, and fungi. Several studies have identified polymorphisms in TLRs and their downstream signaling molecules that appear to be associated with CRS [20–23]. Another receptor that plays a role in the innate immune system is the bitter taste receptor T2R38, which helps protect the upper airway. This receptor is found in human sinonasal epithelial cells and when activated by certain molecules (quorum-sensing) produced by bacteria, T2R38 causes the epithelial cells to release nitric oxide, which in turn triggers bactericidal activity and increased mucociliary clearance. Several recent studies have identified polymorphisms in T2R38 that are associated with medically refractory CRS [24, 25].

Adaptive immune response. Although innate immunity is critical to the initiation of the immune response, the adaptive immune response often plays a more important role in chronic inflammatory conditions such as CRS. While the innate immune response is static—hard-coded in the genome to respond to specific microbial antigens—the adaptive immune system is variable from person to person and can evolve over the course of days to maximize its efficacy against

targeted antigens. The adaptive immune system, which confers long-term immunity, creates an initial response to a pathogen and then an enhanced response with each subsequent encounter with the same pathogen. The central regulators of the adaptive immune response are T lymphocytes, and these respond to pathogens once these are presented to them on the surface of a host antigen presenting cell (e.g., dendritic cell). To "present" these pathogens to T lymphocytes, the pathogens or components of pathogens must be combined with the cell's major histocompatibility complex (MHC), also called the human leukocyte antigen (HLA) complex in humans. The MHC (or HLA) is a set of cell surface proteins present on nearly all cells of the body that enables the immune system to recognize "self" from "non-self," and recognize invading pathogens such as bacteria. Presentation of HLA-antigen (e.g., bacteria or bacterial component) complex activates T lymphocytes, which in turn activate the adaptive immune system response. Numerous studies have now found that the genes responsible for these HLA proteins are strongly linked to CRS [26–30], and this in turn suggests that the pathophysiology of CRS is related to an antigen-driven inflammatory response. Figure 13.1 illustrates various actions of the innate and adaptive immune systems (and their interactions) that may play a role in CRS.

Cytokines and other inflammatory mediators. Cytokines and other inflammatory signaling molecules have been associated with CRS [12, 31]. Many of the cytokine genes associated with CRS can be classified as pertaining to specific T-helper lymphocyte (Th) inflammatory responses, with the prototypical responses being Th1 and Th2 [32]. The Th1 response, which mediates the immune response to intracellular bacteria and viruses, is characterized by interferon-γ and interleukin-12 production as well as recruitment of cytotoxic $CD8^+$ T lympho-

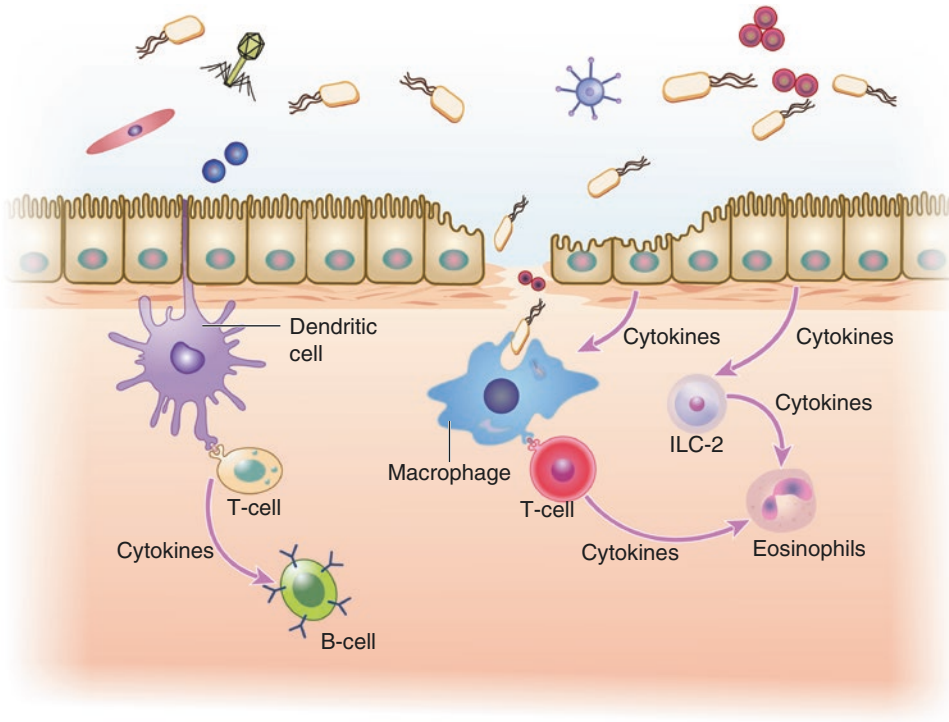

Fig. 13.1 Schematic of the contributions of—and interactions between—innate immunity (including epithelium, macrophages, dendritic cells, ILC-2s, and eosinophils) and adaptive immunity (including T cells and B cells) in the inflammation of the paranasal sinus mucosa in the setting of chronic rhinosinusitis

cytes and IgG-producing B lymphocytes [32]. The Th2 response, which mediates anti-parasitic and allergy immune responses, is characterized by interleukin-4, -5, and -13 production as well as recruitment of eosinophils and IgE-producing B lymphocytes [32]. Whether Th1 or Th2 cytokines predominate in the sinonasal mucosa of CRS patients correlates with nasal polyps: Th2 is predominant in patients with polyps and Th1 in patients without polyps [33–35]. It is not surprising that genetic linkage studies have identified polymorphisms in Th2-specific cytokines that are associated with the presence of nasal polyps in CRS patients [36, 37].

The dysfunctional sinonasal epithelium. Genetic studies and immunologic profiling studies of CRS patients have pointed to the importance of antigen recognition and the subsequent host immune response in the development of CRS [35]. These findings naturally lead to the subsequent question: what are these antigens and why do they drive chronic inflammation resulting in CRS in some patients but not in others? The answer to this question likely lies, at least in part, with the state of the sinonasal epithelium in CRS. In the setting of CRS, histologic evaluation of the sinonasal mucosa has shown the sinonasal epithelium to be frequently damaged and at various stages of healing with regeneration often occurring in a suboptimal manner (Fig. 13.2) [38]. This damage may be due to the direct impact of inflammatory cytokines as well as microbial products, allergens, and airborne irritants that can lead to breakdown of tight junctions and epithelial cell apoptosis [39–43]. The end result is that the sinonasal epithelium is highly porous, allowing leakage of allergens, environmental irritants, microbes and microbial products into the deeper layers of mucosa [44, 45]. These foreign substances may all serve as inflammatory stimuli that chronically activate the mucosal immune system in the paranasal sinuses.

Mechanical factors. The normal paranasal sinus mucosa, lined with pseudostratified epithelial cells that each have 50–200 cilia and mucus-producing goblet cells. The sinus mucosa continuously produces mucus that is moved up and out of the natural sinus ostia through the

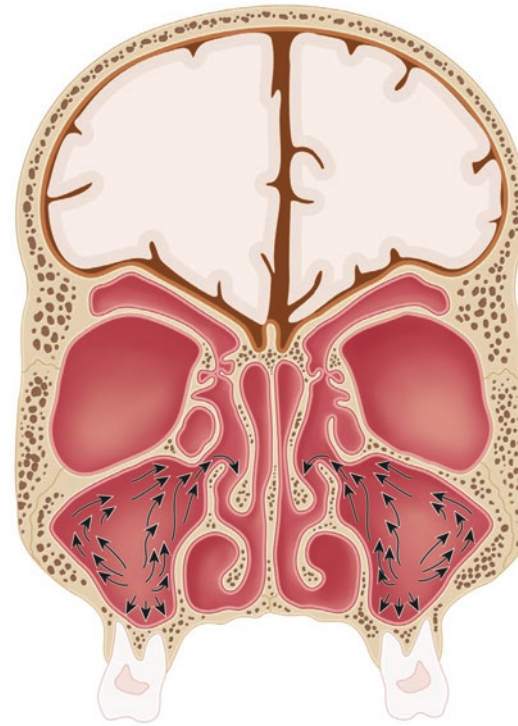

Fig. 13.2 Schematic of mucociliary clearance. A coronal section through the skull, including the paranasal sinuses. Mucociliary clearance from the maxillary sinus is represented by the arrows showing directional sweeping to move mucus out of the sinus by the ciliated sinonasal epithelium

action of the synchronized beating of cilia on sinonasal epithelium (Fig. 13.2) [46, 47]. Chronic inflammation may lead to a change in the composition of the sinus mucosa in CRS, with drop out of ciliated cells and an increase in mucus-producing goblet cells (Fig. 13.3). The cilia on the sinonasal epithelium, which normally beat in concert at 12–15 Hz, beat not only slower but also beat dyssynchronously in the setting of CRS (Fig. 13.4) [46, 47]. The sinus ostia may also be obstructed by inflamed mucosa, polyps, or inspissated secretions, which can further delay the natural movement of mucus out of the sinus (Fig. 13.5). The end result is that there is chronic mucus stasis in the sinuses, which can serve as a chronic inflammatory stimulus through accumulation of microbes and microbial products.

Alterations in the sinonasal microbial flora. It has been established for several decades that

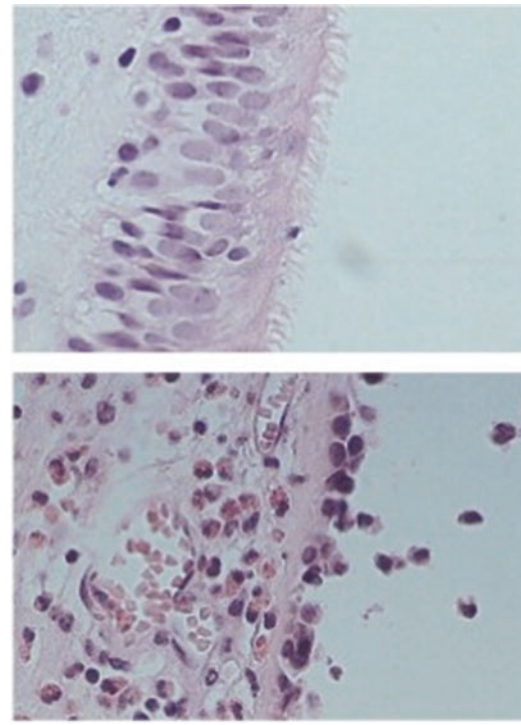

Fig. 13.3 Histologic images of normal healthy pseudostratified sinonasal epithelium (top panel) and sinonasal epithelium from a patient with CRS demonstrating complete erosion of the epithelium. Reproduced from Ponikau JU, et al. [121], with permission from Elsevier

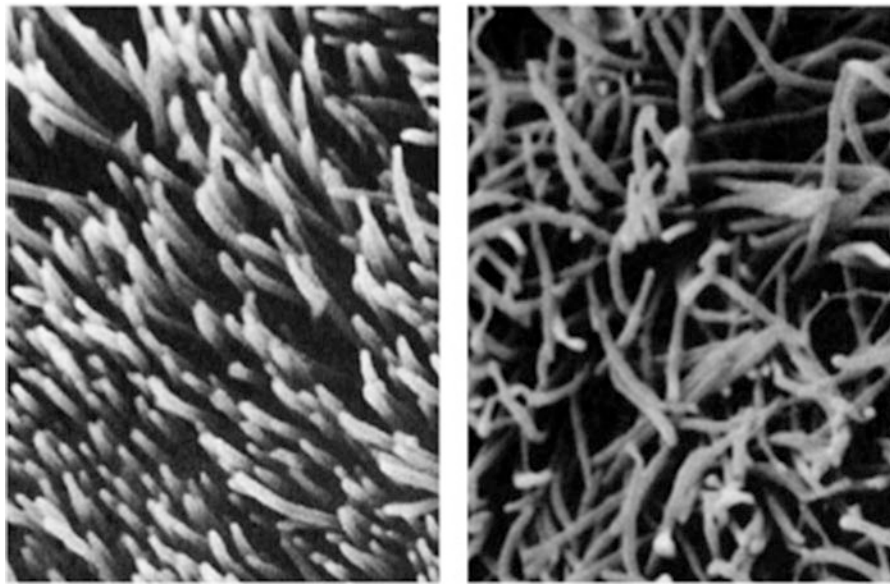

Fig. 13.4 Scanning electron microscope images (600×) nasal mucosa from patients with CRS, ranging from normal synchronous cilia beating at approximately 15 Hz (left) to complete ciliary beat disorientation at approximately 6 Hz (right). Reproduced from Joki S, et al. [122], with permission from John Wiley and Sons

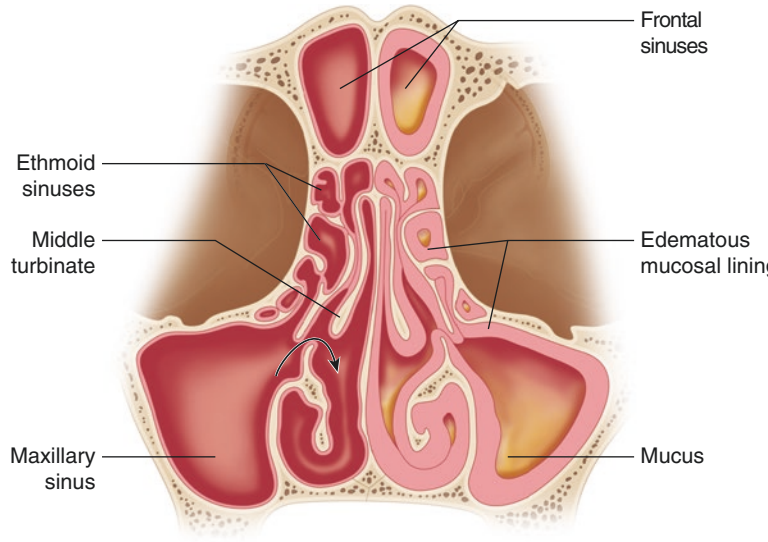

Fig. 13.5 Schematic showing obstruction of normal mucociliary clearance by sinonasal mucosal edema on a coronal section through the paranasal sinuses. On the left, there is normal mucociliary clearance of mucus through the natural opening of the maxillary sinus. On the right, edema of the sinonasal mucosa obstructs the natural opening of the maxillary sinus leading to resultant mucus stasis

the microbial flora colonizing the sinuses of CRS patients differs from that of non-CRS patients and from pathogens seen in acute sinusitis [48, 49]. Pathogens cultured from acute bacterial rhinosinusitis (ABRS) are primarily *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* [48–50] and these may be cultured in up to 15% of CRS patients as well, in some cases in the setting of an acute exacerbation [48, 49]. Sinus cultures from CRS patients, however, usually grow a mixture of aerobes and anaerobes, with aerobes consisting of *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), and/or Gram-negative bacilli such as *Pseudomonas* and Enterobacteriaceae (e.g., *Klebsiella*). Anaerobes may be cultured in up to two-thirds of CRS patients when careful anaerobic cultures are obtained.

Interpreting sinus cultures can be challenging because microbes that colonize the nares and nasal passages may readily contaminate "sinus" cultures obtained via the nose, including those obtained endoscopically. Coagulase-negative staphylococci colonize nearly 100% of the nares of the general population but these bacteria are not respiratory pathogens. *Staphylococcus aureus* colonizes the nares of 20–30% of the normal population and MRSA colonizes approximately 3% (up to 6% of healthcare workers and patients with frequent healthcare contact).

Although fungi can be cultured from the nasal secretions of almost all the CRS patients, the same is also true of healthy individuals. This reflects the ubiquitous nature of fungal spores in the ambient air and the entrapment of these spores in the mucus of the upper airway [48]. In both CRS and healthy individuals, *Aspergillus*, *Cladosporium*, *Candida*, and *Alternaria* are commonly cultured from the nasal cavity [51, 52]. The pathogenic role of these fungi is unclear and increasingly unlikely (except for special cases discussed later) as the prevalence of detectable fungi from the paranasal sinuses (in contrast to mucus of the nasal cavity) of CRS patients is extremely low [53].

Given the similarities between CRS and asthma, there has been interest in the role of viruses in CRS. Viral respiratory tract infections are well-known contributors to asthma pathophysiology. Respiratory syncytial virus (RSV) infection during infancy and childhood is a risk factor for the development of wheezing and asthma later in life [54–56] and viral respiratory tract infections (RSV as well as others such as Human Rhinovirus) are associated with asthma exacerbations [57]. Advances in DNA sequencing technology have made detection of viruses more convenient and these approaches have been applied to study the prevalence of viruses in the paranasal sinuses of CRS patients. In one study

of 13 CRS patients undergoing sinus surgery, RSV was not found in the sinus mucosa of any patient and the authors concluded that persistent RSV infection is not a pathophysiologic mechanism of CRS [58]. In another study, RSV was detected at high levels in the middle meatuses of both CRS patients and in healthy controls [59]. Another study found a higher prevalence of respiratory viruses, such as rhinovirus, parainfluenza virus, and RSV, in the nasal washes of CRS patients compared to healthy controls [60]. These reported differences in the detection of viruses from the sinonasal cavities of CRS patients may be related to the source material (nasal washing, epithelial scraping, whole tissue/sinonasal mucosa) as well as the timing of the sampling (e.g., time of year). Nevertheless, these inconsistent findings raise more questions than provide answers and the role of viruses in CRS pathophysiology is still unclear.

Microbiome. The collection of microbial species, also referred to as the *microbiome*, in paranasal sinuses is clearly different between CRS patients and healthy individuals based on culture data alone. These culture-driven findings and our knowledge of the microbial flora in CRS have been taken a large step forward through advances in high-throughput ribosomal RNA sequencing technology. This has allowed characterization of the paranasal sinus microbiome through identification of thousands of microbial species that may be present at levels that are too low to detect by cultures. Several studies have now characterized the microbiome of the paranasal sinuses in CRS patients and healthy controls [61–63]. The results of these studies have been inconsistent, with some studies identifying a decrease and others an increase in bacterial and fungal diversity in the paranasal sinuses of CRS patients compared with controls. Some differences in results may be explained by differences in methodology, but others may be due to the fact that the microbiome of the paranasal sinuses is not static and can instead change in response to, for example, acute bacterial superinfections or environmental exposures [64, 65].

Some studies have found a correlation between the sinonasal microbiome in CRS and clinical outcomes. Ramakrishnan et al. found that CRS patients whose sinus cultures had less microbial diversity had worse clinical outcomes after endoscopic sinus surgery but patients with abundant *Corynebacterium* species, particularly *C. tuberculostearicum*, had improved postoperative outcomes [61]. Abreu et al. found that, in comparison with CRS sinuses, the sinuses of healthy patients had more microbial diversity, more *Lactobacillus* species, and fewer *C. tuberculostearicum* [62]. Abreu et al. also demonstrated the pathogenic potential of their microbiome findings by animal experiments, producing histopathologic changes in the sinonasal mucosa of mice suggestive of CRS (e.g., goblet cell hyperplasia) through intranasal inoculation with *C. tuberculostearicum*, and protecting against those changes through co-inoculation with *Lactobacillus species* [62]. Aurora et al., in contrast with the studies by Ramakrishnan and Abreu, found that the microbiomes of CRS patients and controls were similar, but that CRS patients appeared to be hyperreactive to their colonizing flora [63].

Biofilms and antigenic stimulation. With CRS increasingly recognized as an inflammatory condition that is driven by an aberrant host immune response, the role of microbes in CRS is likely as a chronic inflammatory stimulus [13, 45]. Many of the bacterial species, such as *S. aureus* and *P. aeruginosa*, that are found in the paranasal sinuses of CRS patients can form biofilms which is one particularly robust mechanism of bacterial persistence. In contrast to the isolated or free planktonic bacterial forms that can be isolated from mucus, biofilms are adherent complexes of extracellular matrix composed of polysaccharides and proteins, within which bacteria are embedded. Biofilms may also serve as a mechanism for enhanced survival. Although biofilms may be found on the sinonasal mucosa of healthy individuals, some studies have found that biofilms are enriched on the sinonasal mucosa of CRS patients and so may serve as a reservoir for bacterial stimulation of the mucosal immune system [66]. Because microbes may easily penetrate into the subepithelial layers of the sinonasal mucosa in CRS patients, they may provide direct antigenic stimulation to the host mucosal immune

system. One study found that biofilms adjacent to breaks in the sinonasal epithelium in CRS patients were accompanied by a focal enrichment of T lymphocytes and macrophages [67]. Other studies have shown that CRS patients have higher numbers of memory and fungal-specific T lymphocyte responses, suggesting a greater history of antigenic exposure [68, 69]. Bacteria and fungi that are routinely found in CRS are agonists for TLRs which, as described above, activate cells of the innate immune response and also modulate the adaptive immune response [32]. Additionally, *S. aureus*, which is cultured in up to a quarter of CRS patients, produces a superantigen that is believed to be a major driver of nonspecific inflammation in the sinonasal mucosa of CRS patients [70]. In support of this, one study found evidence for oligoclonal expansion of T lymphocytes in the polyps of all 18 CRS patients studied, while another study showed that in CRS patients with polyps, there was evidence of significant enrichment of T lymphocytes responsive to staphylococcal superantigens in 35% of nasal polyps [71, 72]. However, these studies did not include analysis of sinonasal mucosa of non-CRS controls.

Treatment

Saline irrigation and corticosteroids. The mainstay of treatment for CRS is medical management consisting of nasal saline irrigation and topical intranasal corticosteroids [2, 3]. Randomized controlled trials (RCTs) have shown that low-pressure, high volume (240 mL) nasal saline irrigation alone may improve sinonasal symptoms in up to 50% of CRS [73–75]. These studies have also found that low-pressure, high volume irrigation is superior to intranasal saline sprays. While isotonic and hypertonic saline irrigations appear to be equally effective [76, 77]. hypertonic saline irrigations may lead to more patient discomfort (e.g., complaints of burning) [78]. Evidence for the clinical efficacy of intranasal topical corticosteroid sprays in CRS, both for patients with nasal polyps and for patients without, comes from numerous RCTs that have identified a clear benefit for improving CRS symptoms as well as objective sinonasal mucosal inflammation [79, 80].

Antibiotics. The role of antibiotics in treating CRS is unclear [48, 81]. Table 13.2 summarizes the evidence to date. Antibiotics have historically been used for CRS due to the belief of an underlying bacterial etiology. When used for CRS, the typical route of antibiotic administration for CRS is by mouth as there are no studies to date that show an advantage for intravenous or topical antibiotics, with these latter routes of antibiotic administration used on a patient-by-patient basis [2, 3, 48, 81]. There is, in fact, little evidence for the use of antibiotics for CRS in general [48, 81]. However, despite surprisingly scant evidence, antibiotics have traditionally been used as a component of maximal medical therapy [82]. Typically, endoscopically obtained culture-directed antibiotics are administered for up to 3 weeks in the treatment of CRS. This duration is based, in part, on a study that demonstrated a pla-

Table 13.2 Summary of the role of antibiotics in uncomplicated chronic rhinosinusitis

	Level of evidence	Result	References
Topical antibacterials	• RCTs (N = 14–50) • Cochrane review	No benefit vs. placebo	[81, 106–109]
Topical antifungals	• RCTs (N = 24–116) • Cochrane review	No benefit vs. placebo	[97, 99, 110–113]
Oral antibacterials	• RCTs (N = 43–66) • Cochrane review	Possible benefit of macrolides vs. placebo but high quality studies still needed	[81, 84, 88, 89, 114–118]
Oral antifungals	• RCT (N = 53) • Cochrane review	No benefit vs. placebo	[99, 119]
Intravenous antibiotics	• Retrospective reviews • Consensus statement	No clear benefit	[3, 120]

RCT = randomized controlled trial

teau of radiographic improvement of sinus disease after 3 weeks of treatment with antibiotics [83]. Unfortunately, RCTs to study antibiotics in the treatment of CRS are lacking. One small RCT has also shown that a 3-week course of doxycycline may reduce sinonasal symptoms and reduce polyp size in CRS patients [84]. However, these beneficial effects may have been due to the anti-inflammatory—rather than antibacterial—properties of doxycycline [85]. In support of this, one recent open label study showed that long-term low dose doxycycline, which is a dose that is subtherapeutic as an antibiotic but is used as an anti-inflammatory medication in a variety of diseases, was beneficial for improving subjective CRS symptoms and improving objective radiographic CRS severity [86].

The majority of studies on antibiotics for CRS have examined the effect of macrolide antibiotics. Macrolide antibiotics are also known to possess anti-inflammatory properties and it is these properties that have been the subject of much interest for the treatment of CRS [87]. Many retrospective or uncontrolled studies have reported macrolides to reduce sinonasal symptoms and polyp size when used as long-term medical therapy for CRS [88–90]. A recent meta-analysis of RCTs supported the use of long-term macrolide antibiotics in the medical management of CRS patients with polyps who have had endoscopic sinus surgery, stating that more high quality studies are still necessary to determine which additional CRS patients would most benefit from macrolides [91]. While macrolide antibiotics may benefit a subset of CRS patients, the possibility of adverse events—such as development of *Clostridium difficile* colitis—must also be considered. As such, long-term macrolide antibiotics are an option but not necessarily recommended for the long-term treatment of CRS [3].

Another role for antibiotics in CRS may be for acute exacerbations of CRS. However, there is no consensus agreement as to what represents an acute exacerbation of CRS. Instead, the diagnosis of CRS exacerbations is patient-driven and often described in the literature as, for example, "sudden worsening of symptoms with return to baseline after treatment" [2]. Presently, acute exacerbations of CRS are treated like episodes of acute rhinosinusitis using observation, and/or antibiotics [1, 2]. Chapter 11 discusses acute rhinosinusitis in detail. In fact, bacterial isolates from CRS with acute exacerbations are similar to those seen in ABRS, including, *M. catarrhalis*, *H. influenzae*, and *S. pneumoniae* [92]. However, bacterial isolates that are more consistent with CRS, such as anaerobes, are also found in acute exacerbations of CRS [92]. The only RCT to study the treatment of CRS exacerbations found no evidence for improved sinonasal symptomatology after 2 weeks of antibiotics compared to placebo [93]. This finding is analogous to a recent RCT of antibiotics for acute rhinosinusitis, which showed that although antibiotic therapy accelerated the resolution of symptoms, both the antibiotic and placebo groups had the same degree of improvement after 10 days of antibiotics [94]. It is therefore possible that antibiotics may accelerate the resolution of acute exacerbations of CRS, but it remains unclear if they have any other benefit over observation alone. It should be noted that the above findings apply only to acute exacerbations of CRS in which there is no evidence for a complication of sinusitis (e.g., no high fever, orbital cellulitis, bacteremia, central nervous system infection).

Early studies that found fungi in the sinonasal cavities of CRS patients suggested that fungi might be a dominant driver of CRS [95, 96]. Additional smaller randomized clinical trials also seemed to show a benefit for the treatment of CRS with systemic and topical antifungals [97]. However, this line of investigation has since been disproven as studies have shown an equivalently high prevalence of fungi in the sinonasal cavities of non-CRS controls and several subsequent randomized clinical trials have found no benefit for antifungals in CRS [98]. At present, there is no evidence to suggest a role for antifungals in CRS [99].

Surgery. Endoscopic sinus surgery may serve as another treatment modality for CRS. There are absolute and relative indications for endoscopic sinus surgery in CRS. Absolute (or emergent) indications for endoscopic sinus surgery include orbital or intracranial complications of CRS

requiring surgical drainage procedures. These complications usually occur in the setting of an acute sinus infection, and are discussed in detail in Chaps. 11 and 12. In these cases, the goal of endoscopic sinus surgery is to gain source control of the infection, decompress any abscess, and obtain cultures for directed antibiotic therapy. Relative indications for endoscopic sinus surgery primarily include persistently decreased quality of life due to CRS despite appropriate medical management (i.e., medically refractory CRS). In the treatment of medically refractory CRS, the goals of endoscopic sinus surgery are to remove excessive inflammatory tissue (such as polyps), enlarge the natural drainage pathways of the paranasal sinuses for improved ventilation, and improve access to the paranasal sinuses for topical medications (e.g., saline irrigation or topical corticosteroids). Although there are no RCTs for the efficacy of endoscopic sinus surgery, one multi-center prospective observational cohort study has reported that endoscopic sinus surgery leads to a greater improvement of CRS symptoms and objective endoscopic findings than continued medical therapy in patients with medical refractory CRS [100].

Special Considerations

Because CRS is defined based on clinical criteria, many different pathologic processes, with distinct underlying pathologies, may be categorized as CRS. There are two special cases of CRS that are worth discussing in the context of infectious disease. The first is odontogenic CRS related to the upper teeth, the roots of which are in close proximity to the floor of the maxillary sinuses. There is usually a history of antecedent dental surgery or odontogenic infection (e.g., a periapical dental abscess) with secondary maxillary sinusitis that, if untreated, can progress to odontogenic CRS [101, 102]. Odontogenic CRS can usually be cured by eradicating the infection—usually oral flora—with antibiotics, addressing the odontogenic source and establishing drainage of the affected paranasal sinuses [101, 102].

The second special consideration is allergic fungal rhinosinusitis (AFRS). This is a special form of CRS, most common in warm and humid locales such as the southern United States, caused by an allergic response to fungi trapped in the paranasal sinuses [103]. In addition to the standard diagnostic criteria for CRS, a diagnosis of AFRS also includes type I hypersensitivity to fungi, nasal polyps, characteristic CT findings of serpentine areas of high density scattered within low density sinus opacification, and eosinophilic mucus within the paranasal sinuses that contain fungi on fungal stain or fungal culture but without evidence of fungal invasion [104]. The treatment of AFRS is much the same as standard CRS: intranasal saline irrigation, topical intranasal corticosteroids, and endoscopic sinus surgery—with meticulous removal of fungal mucin to lower the antigenic burden as much as possible—when medical management fails. Even though AFRS is hypothesized to be driven by allergic inflammation to fungi, antifungals and allergen immunotherapy are not a routine or standard treatment for AFRS due to only low quality evidence supporting their use [3, 105]. Allergic fungal sinusitis is discussed further in Chap. 14.

Conclusions

CRS is a complex disease that is likely driven by a combination of both aberrant host-specific inflammatory responses and extrinsic inflammatory stimuli, which likely interact with each other in a dysregulated manner within the paranasal sinus mucosa of affected patients. The role of microbes remains unknown but is most likely as a chronic inflammatory stimulus. No studies to date have demonstrated any benefit of treating CRS with antibiotics other than possibly those antibiotics with anti-inflammatory properties (e.g., macrolides). The treatment of CRS remains saline irrigations, topical corticosteroids, and surgery to remove obstruction of the natural sinus ostia and re-establish sinus drainage.

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