Microbiology of Chronic Rhinosinusitis

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Key Take-Home Points

- Thorough understanding of the microbiology of chronic rhinosinusitis is a requisite in the management of CRS patients.
- The most common cultured organisms in chronic rhinosinusitis are *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, and gram-negative rods.
- *S. aureus* is the most common organism seen in chronic rhinosinusitis. Its presence at the time of endoscopic sinus surgery has been demonstrated to be a strong predictor of postoperative *S. aureus* infection and impaired mucosal healing.
- *Pseudomonas aeruginosa* is the most commonly cultured gram-negative rod and can be associated with biofilm formation.
- *Stenotrophomonas maltophilia* is a multidrug-resistant gram-negative bacteria seen in patients with previous FESS and prior antimicrobial treatment.

Introduction

Chronic rhinosinusitis (CRS) represents one of the most common healthcare problems in the United States, afflicting approximately 31 million Americans [1]. CRS is a clinical syndrome associated with persistent inflammation of the mucosa of the nose and paranasal sinuses for 12 weeks or longer [2, 3]. It is known to cause significant physical impairment, adversely impacting patient quality of life and psychosocial well-being. Despite its prevalence, CRS remains a challenging and, at

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P.S. Batra, J.K. Han (eds.), *Practical Medical and Surgical Management of Chronic Rhinosinusitis*, DOI 10.1007/978-3-319-16724-4_2

times, controversial disease entity. The etiologic mechanisms of CRS continue to be a source of much debate, and as such, different schools of thought exist on the optimal management strategy. The purpose of this chapter is to describe the different proposed pathophysiologic mechanisms of CRS, with a focus on the microbiology associated with CRS.

Accurate diagnosis of CRS rests on the ability to identify signs and symptoms associated with the disease process, such as nasal obstruction, purulent discharge, and/or facial pain, as well as objective evidence of mucosal inflammation, either by nasal endoscopy and/or computerized tomography [4]. However, it is also important to recognize that this is a heterogeneous disease spectrum, subject to further subclassifications. Patients with CRS may be divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). This distinction leads to both clinical and pathologic differences. CRSwNP is predominantly mediated by eosinophils, as well as increased levels of histamine, interleukin (IL)-5, and IL-13 [5]. In contrast, CRSsNP seems, at first glance, to be predominantly mediated by neutrophilic inflammation [6]. However, some CRSsNP cases may also exhibit extensive eosinophilic infiltration. Therefore, the distinction between CRS with and without polyps is not as clear as originally thought. In addition, CRS must be clearly differentiated from systemic processes that lead to sinonasal mucosal inflammation. Clinical entities, such as cystic fibrosis, sarcoidosis, Wegener's granulomatosis, and primary immunodeficiency (PID), may present with sinus involvement as a component of the multisystem process. Some cases of PID can be relatively mild and manifest primarily as sinusitis without pneumonia or other more serious systemic infections. The prevalence of PID in patients with recalcitrant CRS varies widely in the literature, from 0 to 19 %. Furthermore, secondary CRS may arise as a result of local, discrete processes such as tumor, mycetoma, and foreign-body reaction. A recent study even suggests a potential causal relationship between tobacco smoke exposure and the development of CRS [7]. The primary focus of this review is to discuss CRS as a primary disease process in the absence of systemic or local predisposing factors.

Etiology of CRS

Bacteria likely represent the main underlying cause of acute rhinosinusitis (ARS), with the most commonly identified bacteria being *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae* [8]. In contrast, the central pathophysiology of CRS remains elusive to date. A variety of possible etiologic mechanisms have been proposed, including microbes (viruses, bacteria, fungi), allergy, osteitis, biofilm formation, staphylococcal superantigen, and derangements in innate and adaptive immunity. Though the exact role of bacteria in the disease process remains to be fully elucidated, it is likely that bacterial infection plays an important role in CRS, either as a causative or an exacerbating factor [9].

Bacteria

The microbiology of CRS varies greatly from ARS. Nadel et al. evaluated 507 endoscopically guided cultures in 265 patients [10]. The predominant organisms identified include *Staphylococcus aureus* (*31.3 %*), coagulase-negative *Staphylococcus* (SCN) (44.2 %), and gram-negative rods (34.3 %). A multitude of gram-negative organisms were cultured, with the most common being *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Escherichia coli*, and *Serratia marcescens*. Kingdom and Swain analyzed 182 total cultures with 257 isolates in 101 patients at the time of sinus surgery. The microbiologic yield was similar; the most common isolates were SCN (45 %), gram-negative rods (25 %), and *Staphylococcus aureus* (24 %) [11]. Comparative analysis between primary and revision sinus surgery cases demonstrated no differences in the bacterial yield or types. Bhattacharyya and Gopal have demonstrated that while approximately half of the bacteria cultured in CRS are found in isolation, the rest exhibit polymicrobial growth, with two or more bacterial species present [12]. See Table 2.1 for key bacteria and fungi identified in CRS.

Staphylococcus aureus

S. aureus is a ubiquitous microorganism, occupying the nasal vestibule of nearly one-third of the human population at any given time. *S. aureus* has emerged as an important pathogen in community- and hospital-acquired infections, resulting in sepsis, bacteremia, endocarditis, and soft tissue infections. *S. aureus* is commonly assayed in cultures performed for CRS [10, 11, 13, 14]. Nadel et al. and Kingdom and Swain reported its presence in 23.1 and 25 % of sinus cultures, respectively [10, 11]. Though the exact role in pathogenesis is a matter of debate, the presence of *S. aureus* infection at the time of sinus surgery has been demonstrated to be a strong predictor of postoperative *S. aureus* infection and impaired mucosal healing.

A variety of novel mechanisms of pathogenicity have also been implicated, including biofilm formation and intracellular residency [15]. Foreman et al. characterized bacterial biofilm by fluorescence in situ hybridization in 50 CRS patients. Biofilms were detected in 36 of 50 patients, with *S. aureus* being the most common biofilm-forming organism [16]. The capacity to form biofilms may confer the ability to create a recalcitrant infectious state unresponsive to conventional antimicrobial therapies.

Table 2.1 Key microbes cultured in chronic rhinosinusitis [8]

Aerobic	Anaerobic	Fungus
Staphylococcus aureus	*Fusobacterium* spp.	*Aspergillus fumigatus*
Coagulase-negative *Staphylococcus*	*Pigmented Prevotella* and *Porphyromonas* spp.	*Aspergillus niger*
Pseudomonas aeruginosa	*Peptostreptococcus* spp.	*Aspergillus flavus*
Stenotrophomonas maltophilia		
Haemophilus influenzae		
Streptococcus pneumoniae		

An increase in the recovery of methicillin-resistant *Staphylococcus aureus* (MRSA) has recently been noted in acute and chronic rhinosinusitis and anterior nares of normal individuals [17]. Brook et al. compared MRSA rates in chronic maxillary sinusitis between two time periods. *S. aureus* was found in 15 (15 %) of the patients between 2001 and 2003, four (27 %) of which were MRSA. *S. aureus* was cultured in 23 (20 %) of the patients between 2004 and 2006, with 14 (61 %) being MRSA. Indeed, MRSA represents a treatment challenge in the setting of CRS, given paucity of optimal treatment options. Oral antibiotics that may be effective include doxycycline, trimethoprim/sulfamethoxazole, and clindamycin. Topical mupirocin irrigations may also serve as an important adjunct in the postoperative CRS patient [18].

Staphylococcal Superantigens

The superantigen hypothesis proposes that *S. aureus* secretes high molecular weight proteins known as enterotoxins. These enterotoxins have significant stimulatory activity that can foster the characteristic tissue response seen in patients with nasal polyps. Approximately 50 % of CRSwNP patients show lymphocyte responses consistent with superantigen exposure [19]. In addition, staphylococcal toxin-specific IgE antibodies have been detected in 18 of 23 patients with nasal polyps [20]. It is unclear, however, whether *S. aureus* superantigens represent an etiologic agent or a disease modifier. The link between superantigens and CRSsNP has not yet been established.

Coagulase-Negative *Staphylococcus*

The exact role of SCN in CRS remains to be determined, as its reported incidence varies widely [11]. It has been posited to be a contaminant, supported by previous work that found CNS in the middle meatus of 56 % of healthy patients and in only 20 % of patients with CRS [21]. Moreover, the microbe is ubiquitous on human skin; thus, contamination may occur readily without proper sterile precautions during culture technique. However, different strains of CNS may have differing abilities to cause disease. Recent studies evaluating CNS in indwelling devices have shown that bacterial pathogenicity is dependent on genes associated with biofilm formation, which are only found in certain strains [22]. The mere presence of SCN may not indicate infection, as a specific strain may be necessary for such an infection to develop. Nonetheless, endoscopically acquired cultures have consistently identified SCN in multiple studies in CRS. Bolger found SCN in 17 %, Hsu et al. in 42 %, and Nadel et al. in 35 % of cultures [10, 13, 14]. One possible method to ascertain significance of SCN culture is based on the quantitative growth on culture, along with presence of leukocytosis on the gram stain result. Scant or light growth, especially with a paucity of gram-positive rods or white blood cells (WBCs) on gram stain, likely represents contamination. In contrast, moderate to heavy growth, with large number of WBCs on gram stain, should alert the clinician of the possibility of a true infection.

Pseudomonas aeruginosa

Gram-negative rods are often identified in CRS cultures, more commonly in patients who have undergone endoscopic sinus surgery [10, 13, 14]. However, their role in patients with CRS without previous surgery should also not be underestimated. Kingdom and Swain found GNRs in 31 % of cultures in a group of patients at the time

of primary sinus surgery [11]. Nadel et al. found GNRs in 9.5 % of cultures taken from patients without previous sinus surgery [10]. *P. aeruginosa* has long been recognized as an important pathogen in the upper and lower airway in cystic fibrosis patients. It also represents a common and problematic organism in CRS. Rates of assay in CRS cultures have been reported between 9 and 16 % [10, 11]. Nadel et al. noted that *P. aeruginosa* was most commonly cultured in patients with previous FESS and irrigation usage [10]. *P. aeruginosa* also has the capability of biofilm formation which may in part contribute to its refractory nature in CRS patients. Further, the presence of *P. aeruginosa* biofilm has been associated with poor evolution after FESS [23]. Fluoroquinolones are the only orally administered antibiotic group with efficacy against *P. aeruginosa*. Quinolone resistance has become more problematic, with limited alternate proven oral antimicrobial therapies for *Pseudomonas* rhinosinusitis.

Stenotrophomonas maltophilia

Stenotrophomonas maltophilia is a multidrug-resistant gram-negative bacillus most often encountered as a nosocomial pathogen in immunocompromised and intensive care unit patients. Infection with *S. maltophilia* most frequently involves the respiratory tract, bloodstream, wounds, and genitourinary tract. *S. maltophilia* has also been cultured from the paranasal sinuses, often in the setting of prior antimicrobial treatment and sinus surgery. The exact implication of *S. maltophilia* cultures in the paranasal sinuses is unclear. Whether this represents a true infection by an atypical microorganism or colonization that surfaces after eradication of other microbes by antimicrobial therapy merits additional research. Despite its multidrug-resistant nature, trimethoprim/sulfamethoxazole and fluoroquinolone monotherapy has been employed with improvement of symptoms and endoscopic findings in CRS patients [24].

Viruses

Patients with CRS frequently report that their symptoms initially started after an acute viral event [25]. Furthermore, viruses can cause multiple changes on a cellular level, facilitating an infectious and inflammatory milieu of CRS, such as increase in bacterial adhesion and production of inflammatory mediators by nasal epithelial cells [26, 27]. Multiple studies have evaluated the presence of respiratory viruses in samples taken from patients with CRS. Ramadan and colleagues found RSV present in 20 % of samples collected from patients with CRS [28]. However, this study did not report a control group or the timing of the specimen collection, as the presence of RSV is much greater in the winter months in the general population. Jang et al. reported a similar study with a control group and collected specimens during the summer months [29]. Rhinovirus was identified in 21 % of samples from CRS patients and 0 % in the control group. However, these samples were taken from the inferior turbinates and not the paranasal sinus mucosa. In contrast to the above studies, Wood et al. collected sinus mucosa samples from 13 CRS patients and 2 controls [25]. No respiratory viruses, including RSV and rhinovirus, were identified in any of the samples. While viruses may be implicated in the initial or ongoing stimulus of inflammation, their exact role in CRS is not clearly defined.

Fungus

It is clear that fungus is responsible for some forms of sinusitis, in both invasive and noninvasive forms. Though a wide variety of fungi have been identified in the sinuses of CRS patients, the central etiologic role of fungus in CRS has not been clearly demonstrated. In 1999, positive fungal cultures from nasal mucus were used as the basis to posit that eosinophilic infiltration and fungal presence provided the main inciting event for CRS [30]. However, further studies found a similar percentage of positive cultures in normal control patients [31]. In addition, a double-blind, placebo-controlled randomized multicenter trial has failed to identify any benefit of topical antifungal therapy in objective and subjective outcome measures in patients with CRS [32]. A subset of CRS, allergic fungal rhinosinusitis (AFRS), is characterized by type I hypersensitivity to fungi, nasal polyposis, eosinophilic mucin, hyperdensities on CT imaging, and positive fungal stain or culture with the absence of diabetes, immunodeficiency, or an invasive fungal process [33]. Furthermore, patients with AFRS have been shown to have elevated levels of total serum IgE and IgG anti-*Alternaria* antibodies when compared to patients with CRS [34]. While fungus does play a role in specific subtypes of CRS, its role as a central pathophysiologic mechanism of CRS is not corroborated in the literature.

Osteitis

Osteitis is another possible etiologic factor for CRS. Patients with CRS often show areas of irregular bony thickening on CT imaging. It has been proposed that this irregular thickening and increased bone density may be a sign of inflammation in the bone, resulting in persistent inflammation of the overlying mucosa [35]. Osteitis is marked by varying degrees of osteoclast-osteoblast activity, leading to disruption of organized lamellar bone and formation of immature woven bone [36]. Entry of inflammatory infiltrate into the Haversian canal system may act as a potential pathway for spread of inflammation and, as such, mucosal disease. The prevalence of osteitis is estimated between 36 and 53 % in CRS patients, based on CT findings or pathologic evaluation [37]. This concept of osteitis, an inflammation of the bone, should be differentiated from osteomyelitis, as direct bacterial invasion of the bone in CRS has not yet been demonstrated in studies.

Innate and Adaptive Immune Dysfunction

The innate immune system provides the first line of defense against pathogens through both physical barriers, such as ciliated mucosa, and the expression of several antimicrobial molecules, including S100 and surfactant protein A. The data on these antimicrobial molecules has been somewhat inconsistent. Some studies have not shown consistent changes in these antimicrobial molecules in patients with CRS [38, 39]. Other, more recent studies have shown more consistent changes, specifically in the S100 proteins [40]. These have direct antimicrobial effects as well as aid

in recruitment of neutrophils and lymphocytes. These proteins are decreased in patients with CRS compared to controls. The dysfunction of the innate immune system remains a strong area of ongoing research to determine its true role in the pathophysiology of CRS.

Dysfunction in the adaptive immune system may also play a role in the development of CRS. The epithelium serves an important role in the adaptive immune system, mediating communication through cell surface molecules that regulate activation of T cells, as well as producing cytokines and chemokines that activate B cells and T cells and enable their migration. Dysregulation of the interaction between epithelial cells and the adaptive immune system may also play an important role in the development of CRS. Moreover, free light chains, which are thought to be involved in mast cell-dependent immune responses, have been found to be increased in nasal secretions and mucosal tissue of patients with CRS [41]. This increase is most prominent in CRSwNP. The increased free light chains suggest a possible role in mediating the local immune dysregulation in CRS.

Allergy

Allergy may represent a confounding factor in the development of CRS. Allergy often manifests as swelling of nasal mucous membranes, leading to sinus ostia narrowing and obstruction. Such obstruction can lead to retained mucus, decreased ventilation, and infection. Furthermore, positive allergy skin prick tests are highly associated with CRS. Benninger reported 54 % of patients with CRS had positive skin prick tests [42]. This is in keeping with multiple other studies, showing rates of positive skin prick tests in 50–84 % of patients with CRS undergoing sinus surgery [43, 44]. However, others studies point toward no increase in CRS in patients with positive allergic responses. Despite the lack of a clear etiologic role for allergy in CRS, it likely represents a contributing factor that should be addressed in the overall treatment strategy.

Anatomic Factors

Anatomic factors have been theorized to play a role in the development of CRS. These include a pneumatized middle turbinate (concha bullosa), septal deviation, and variations in configuration of the uncinate process. Despite the proposed mechanisms of anatomic variability leading to CRS, multiple studies have shown no difference in prevalence of anatomic variations between patients with and without CRS [45, 46]. In contrast, a systematic review on the role of septal deviation in CRS concluded that increasing angles of septal deflection were associated with a small, but significant, increasing prevalence of CRS [47]. Based on current information, the exact role of anatomic variations in CRS is unclear. It would seem that altered sinus ventilation may result from anatomic variants, but this alone is likely insufficient for the development and propagation of CRS.

Conclusion

This snapshot of etiologic information highlights the inherent difficulties in managing the infectious aspects of CRS. Though coagulase-negative *Staphylococcus*, *S. aureus*, and *P. aeruginosa* predominate in microbiologic studies, multitude of gram-negative rods and other atypical organisms may also be cultured in refractory CRS, especially in the setting of previous sinus surgery. Furthermore, other factors including immune derangements, osteitis, fungus, viruses, allergy, and anatomic factors may also play a role in the etiology of CRS. Ongoing research in pathophysiologic mechanisms and treatment schemes is absolute imperatives to continue to enhance patient care.

References

1. National Center for Health Statistics. National ambulatory medical care survey 1990–1995. Hyattsville: US Public Health Service; 1997. Series 13 [CD-ROM].
2. Fokkens W, Lund V, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. Rhinol Suppl. 2012;50:1–299.
3. Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. Mayo Clin Proc. 2011;86:427–43.
4. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology and pathophysiology. Otolaryngol Head Neck Surg. 2003;129:S1–32.
5. Drake-Lee AB, McLaughlan P. Clinical symptoms, free histamine and IgE in patients with nasal polyposis. Int Arch Allergy Appl Immunol. 1982;69:268–71.
6. Pawankar R, Nanoka M. Inflammatory mechanisms and remodeling in chronic rhinosinusitis and nasal polyps. Curr Allergy Asthma Rep. 2007;7:202–8.
7. Reh DD, Higgins TS, Smith TL. Impact of tobacco smoke on chronic rhinosinusitis: a review of the literature. Int Forum Allergy Rhinol. 2012;2(5):362–9.
8. Brook I. Microbiology of sinusitis. Proc Am Thorac Soc. 2011;8:90–100.
9. Biel MA, Brown CA, Levinson RM, et al. Evaluation of the microbiology of chronic maxillary sinusitis. Ann Otol Rhinol Laryngol. 1998;107:942–5.
10. Nadel DM, Lanza DC, Kennedy DW. Endoscopically guided cultures in chronic sinusitis. Am J Rhinol. 1998;12:233–41.
11. Kingdom TT, Swain RE. The microbiology and antimicrobial resistance patterns in chronic rhinosinusitis. Am J Otolaryngol. 2004;25:323–8.
12. Bhattacharyya N, Gopal HV. Microbiology of the ethmoid sinus following endoscopic sinus surgery. Ear Nose Throat J. 2002;81:558–61.
13. Bolger WE. Gram negative sinusitis: an emerging clinical entity? Am J Rhinol. 1994;8:279–84.
14. Hsu J, Lanza DC, Kennedy DW. Antimicrobial resistance in bacterial chronic sinusitis. Am J Rhinol. 1998;12:243–7.
15. Lowy FD. Staphylococcal aureus infections. N Engl J Med. 1998;339:520–32.
16. Foreman A, Psaltis AJ, Tan LW, Wormald PJ. Characterization of bacterial and fungal biofilms in chronic rhinosinusitis. Am J Rhinol Allergy. 2009;23:556–61.
17. Brook I, Foote PA, Hausfeld JN. Increase in the frequency of recovery of methicillin-resistant *Staphylococcus aureus* in acute and chronic maxillary sinusitis. J Med Microbiol. 2008;57:1015–7.
18. Solares CA, Batra PS, Hall GS, Citardi MJ. Treatment of chronic rhinosinusitis exacerbations due to methicillin-resistant Staphylococcus aureus with mupirocin irrigation. Am J Otolaryngol. 2006;27:161–5.

19. Bachert C, Zhang N, van Zele T, et al. Staphylococcus aureus enterotoxins as immune stimulants in chronic rhinosinusitis. Clin Allergy Immunol. 2007;20:163–75.
20. Tripathi A, Conley DB, Grammer LC, et al. Immunoglobulin E to staphylococcal and streptococcal toxins in patients with chronic sinusitis/nasal polyposis. Laryngoscope. 2004;114:1822–6.
21. Araujo E, Palombini BC, Cantarelli V, et al. Microbiology of middle meatus in chronic rhinosinusitis. Am J Rhinol. 2003;17:9–15.
22. Larson DA, Han JK. Microbiology of sinusitis: does allergy or endoscopic sinus surgery affect the microbiologic flora? Curr Opin Otolaryngol Head Neck Surg. 2001;19:199–203.
23. Bendouah Z, Barbeau J, Hamad WA, Desrosiers M. Biofilm formation by Staphylococcus aureus and Pseudomonas aeruginosa is associated with an unfavorable evolution after surgery for chronic sinusitis and nasal polyposis. Otolaryngol Head Neck Surg. 2006;134:991–6.
24. Grindler D, Thomas C, Hall GS, Batra PS. The role of *Stenotrophomonas maltophilia* in refractory chronic rhinosinusitis. Am J Rhinol Allergy. 2010;24:200–4.
25. Wood AJ, Antoszewska H, Fraser J, Douglas RG. Is chronic rhinosinusitis caused by persistent respiratory virus infection? Int Forum Allergy Rhinol. 2011;1(2):95–100.
26. Wang JH, Kwon HJ, Jang YJ. Rhinovirus enhances various bacterial adhesions to nasal epithelial cells simultaneously. Laryngoscope. 2009;119:1406–11.
27. Wang J, Watanabe S, Matsukura S, et al. Double-stranded RNA poly (I:C) enhances matrix metalloproteinase mRNA expression in human nasal polyps epithelial cells. Acta Otolaryngol Suppl. 2009;562:105–9.
28. Ramadan HH, Farr RW, Wetmore SJ. Adenovirus and respiratory syncytial virus in chronic sinusitis using polymerase chain reaction. Laryngoscope. 1997;107:923–5.
29. Jang YJ, Kwon HJ, Park HW, et al. Detection of rhinovirus in turbinate epithelial cells of chronic sinusitis. Am J Rhinol. 2006;20:634–6.
30. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc. 1999;74:877–84.
31. Braun H, Buzina W, Freudenschuss K, et al. Eosinophilic fungal rhinosinusitis: a common disorder in Europe? Laryngoscope. 2003;113:264–9.
32. Ebbens FA, Scadding GK, Badia L, et al. Amphotericin B nasal lavages: not a solution for patients with chronic rhinosinusitis. J Allergy Clin Immunol. 2006;118:1149–56.
33. Bent III JP, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg. 1994;111:580–8.
34. Hutcheson PS, Schubert MS, Slavin RG. Distinctions between allergic fungal rhinosinusitis and chronic rhinosinusitis. Am J Rhinol Allergy. 2010;24:405–8.
35. Kennedy DW, Senior BA, Gannon FH, et al. Histology and histomorphometry of ethmoid bone in chronic rhinosinusitis. Laryngoscope. 1998;108:502–7.
36. Giacchi RJ, Lebowitz RA, Yee HT, et al. Histopathologic evaluation of ethmoid bone in chronic sinusitis. Am J Rhinol. 2001;15:193–7.
37. Lee JT, Kennedy DW, Palmer JN, et al. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. Am J Rhinol. 2006;20:278–82.
38. Lee HM, Kang HJ, Woo JS, et al. Upregulation of surfactant protein A in chronic rhinosinusitis. Laryngoscope. 2006;116:328–30.
39. Psaltis AJ, Bruhn MA, Ooi EH, et al. Nasal mucosa expression of lactoferrin in patients with chronic rhinosinusitis. Laryngoscope. 2007;117:2030–5.
40. Tieu DD, Kern RC, Schleimer RP. Alterations in epithelial barrier function and host defense responses in chronic rhinosinusitis. J Allergy Clin Immunol. 2009;124:37–42.
41. Groot Kormelink T, Calus L, de Ruyck N, et al. Local free light chain expression is increased in chronic rhinosinusitis with nasal polyps. Allergy. 2012;67:1165–72.
42. Benninger M. Rhinitis, sinusitis and their relationship to allergies. Am J Rhinol. 1992;6:37–43.
43. Emanuel IA, Shah SB. Chronis rhinosinusitis: allergy and sinus computed tomography relationships. Otolaryngol Head Neck Surg. 2000;123:687–91.

44. Grove R, Farrior J. Chronic hyperplastic sinusitis in allergic patients: a bacteriologic study of 200 operative cases. J Allergy Clin Immunol. 1990;11:271–6.
45. Jones NS. CT of the paranasal sinuses: a review of the correlation with clinical, surgical and histopathological findings. Clin Otolaryngol. 2002;27:11–7.
46. Jones NS, Strobl A, Holland I. A study of the CT findings in 100 patients with rhinosinusitis and 100 controls. Clin Otolaryngol. 1997;22:47–51.
47. Orlandi RR. A systematic analysis of septal deviation associated with rhinosinusitis. Laryngoscope. 2010;120:1687–95.