Palliative Care for the Patient with Refractory Chronic Rhinosinusitis

Elizabeth J. Mahoney, MD[a,*], Ralph Metson, MD[b]

KEYWORDS

• Rhinosinusitis • Refractory • Palliative

Chronic rhinosinusitis (CRS) is a chronic condition affecting 14% to 16% of the United States population.[1] Patients with CRS have been shown to have a significant decrement in their quality of life, including domains of physical and social functioning.[2] Although well-established therapeutic options are available for the treatment of CRS, there remains a subset of patients with this disorder who fail to demonstrate symptomatic improvement following conventional therapy. For the patients who have failed to achieve relief of symptoms of CRS after both medical and surgical treatment, often there is a need for some kind of continuing care and usually the otolaryngologist is the member of the health care team to whom the responsibility falls for providing this continuing care, especially for those patients who have already had sinus surgery. In a sense, perhaps unwittingly, the otolaryngologist is providing palliative care when continuing to care for the patient who is having symptoms of CRS after medical and surgical management has been tried. By definition, palliative care attempts to help a patient live reasonably well with a medical condition that cannot be completely eradicated. To provide such care to the CRS patient, the otolaryngologist needs to be creative in devising treatment regimens customized to the unique needs of each patient.

THE SINUSITIS SPECTRUM

CRS has been defined by the Sinus and Allergy Health Partnership as a group of disorders characterized by inflammation of the nasal and paranasal sinus mucosa of at least 12 consecutive weeks' duration.[3] This chronic disorder can be viewed as a spectrum of pathology, ranging from localized processes to systemic disorders. Understanding this ''sinusitis spectrum'' may be helpful in identifying those patients at

[a] Department of Otolaryngology—Head and Neck Surgery, Boston University School of Medicine, F.G.H. Building, 820 Harrison Avenue, One Boston Medical Center Place, Boston, MA 02118, USA
[b] Department of Otology and Laryngology, Harvard Medical School, Zero Emerson Place, Boston, MA 02114, USA
* Corresponding author.
E-mail address: Elizabeth.mahoney@bmc.org (E.J. Mahoney).

Otolaryngol Clin N Am 42 (2009) 39–47
doi:10.1016/j.otc.2008.09.009 **oto.theclinics.com**
0030-6665/08/$ – see front matter

increased risk for failing conventional therapies, and in tailoring the treatment approach to fit a patient's individual needs.

At one end of the sinusitis spectrum is the patient with ''local'' disease. These patients tend to have clear anatomic factors predisposing toward sinus infection. Anatomic obstructions, such as conchae bullosae and septal deviations, are examples of local factors that may obstruct normal mucociliary flow. Additionally, patients with an isolated polyp or neoplasm may be classified as having local disease. Such local factors can usually be readily identified on nasal endoscopy or sinus imaging, and can be routinely addressed with conventional endoscopic surgical approaches.

At the other end of the sinusitis spectrum are those patients with ''systemic'' disease. These patients have an underlying systemic disorder leading to diffuse inflammation of the sinonasal mucosa, often with polyp formation, which places them at heightened risk for recurrent sinus infections. Individuals who may be classified in this category include those with triad asthma, granulomatous disease, cystic fibrosis, immunodeficiency, and primary ciliary dyskinesia. These systemic patients are at highest risk for failing conventional medical and surgical therapies used to treat CRS.

Within this sinusitis spectrum, there are a large number of patients who fall somewhere in the middle, between locals and systemics. This group of patients is referred to as ''intermediates.'' They may have a combination of localized and systemic disease. Many of these patients, however, when treated with standard medical and surgical therapies, fare quite well (**Fig. 1**).

PATHOPHYSIOLOGY

Traditionally, CRS was understood to be the end stage of a disease process characterized by multiple acute bacterial infections. This theory, however, has been supplanted by the recognition that CRS is characterized by an aberrant inflammatory response in the sinonasal mucosa.[3] Although initiating events may vary, it is well understood that inflammation causing mucosal obstruction at sinus ostia triggers a cascade of events including impaired mucociliary clearance with stasis and bacterial overgrowth. In the absence of systemic disease, such as cystic fibrosis or an immune deficiency, a number of different paradigms have been postulated to explain the heightened sinonasal inflammatory response seen in CRS.

Although controversy exists as to whether bacteria play a direct or indirect role in the pathophysiology of CRS, antibiotic therapy remains a mainstay of treatment. Theories to explain how the presence of bacteria within the paranasal sinuses may trigger a noninfectious inflammatory process include the superantigen and biofilm theories.

It has long been recognized that certain bacteria secrete proteins called exotoxins, which are damaging to the host organism. A superantigen is a highly potent exotoxin that has been associated with dramatic disease processes, such as the toxic shock syndrome triggered by *Staphylococcus aureus'* production of superantigen. Recent

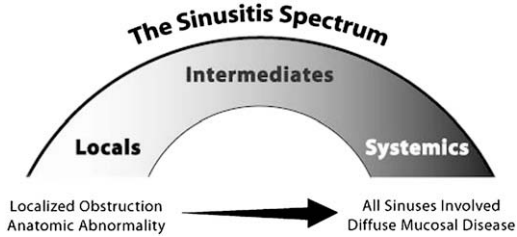

Fig. 1. The sinusitis spectrum.

interest has focused on the potential role of superantigens in triggering sinonasal inflammation. A recent study by Bernstein and colleagues[4] demonstrated toxin-producing *S aureus* in the nasal mucus adjacent to polyps in 55% of patients with chronic hyperplastic sinusitis and nasal polyposis. The corresponding variable β T-cell receptor site was also noted to be up-regulated. Although an understanding of the superantigen link to CRS continues to evolve, it seems that microbial superantigens bind to T-cell receptors and major histocompatibility complex II molecules in a fashion that bypasses the typical route of antigen presentation, resulting in an enhanced activation of the host T-cell population.[5] This cascade results in massive cytokine release and eosinophilic activation with consequent mucosal insult and inflammation.

The biofilm theory has also been postulated to explain the pathologic role of bacteria in the CRS process. Biofilms are created when bacteria bind to a surface and generate a community of microorganisms in a matrix attached to a surface. Bacteria in a biofilm state have a reduced metabolic state and do not provoke the exuberant systemic response elicited by free-floating bacteria. They demonstrate decreased susceptibility to systemic and local antibiotic therapy. In addition, they intermittently release free-floating bacteria that can serve as a continuous nidus of infection. Although biofilms have been identified on the surface of sinus mucosa of patients with CRS, the significance of these biofilms remains a subject of continued investigation.[6,7]

Atopic disease is also recognized as playing a key role in the pathophysiology of CRS. Although the epidemiologic association between CRS and allergy is well established, a causal relationship remains more elusive. In one study that examined the presence of allergy among patients undergoing functional endoscopic sinus surgery, 80% of patients were noted to have elevated specific IgE levels.[8] These epidemiologic observations, however, fail to provide an explanation of the causal relationship between allergy and CRS. One mechanism that may help to explain such a causal relationship is the induction of mucosal edema and sinus ostia obstruction through the release of allergic mediators and cytokines. Additionally, it has been shown that in patients undergoing sinus surgery, surgical outcomes are enhanced by treatment of underlying inhalant allergy.[9]

Allergic fungal sinusitis has emerged as a clinically distinct subset of CRS, and merits special consideration in this discussion. Diagnostic criteria for allergic fungal sinusitis include eosinophilic mucin-containing noninvasive fungal hyphae and Charcot-Leyden crystals on microscopic examination. Patients with this disorder typically present with nasal polyposis, characteristic radiographic findings, immunocompetence, and allergy.[10] Although theories to explain the phenomenon of allergic fungal sinusitis abound, the core principle is based on the premise that it is the inflammatory response to fungus, rather than the mere presence of fungus. In 1999, the concept of a nonallergic fungal inflammatory process was described by Ponikau and coworkers[11] who identified hyphae in over 90% of patients with CRS. Eosinophils were also noted to be migrating into the mucus in characteristic clusters. In this study population, allergy to fungus failed to correlate with CRS. The suggested terminology was changed from allergic fungal rhinosinusitis to eosinophilic fungal rhinosinusitis. Questions and controversy continue to surround the significance of fungi in CRS.

WHY PATIENTS FAIL TO FIND THE RELIEF THEY ARE SEEKING

Understanding pathophysiologic events that may lead to CRS helps the otolaryngologist to understand why certain patients may fail conventional therapy. Maximal medical therapy typically involves courses of antimicrobials, nasal steroid sprays, and

possibly systemic steroids. Antihistamines, decongestants, and mucous thinning agents may also be used in selected patients. Sinus surgery is typically offered to patients who fail to respond to these measures and excellent success rates ranging from 80% to 90% have been reported.[12,13] Despite the success noted with functional endoscopic sinus surgery, there exists a subset of patients who do not improve after one or more endoscopic sinus procedures, even when postoperative nasal endoscopy and CT scan show patent sinus ostia. For the purpose of this discussion, conventional therapy is defined as the use of the previously mentioned medical therapies and patient-appropriate surgical interventions.

Although it may seem obvious, possible anatomic explanations for such failure should be investigated. Areas of synechiae and cicatricial scarring should be sought on CT and nasal endoscopy. Patients with recurrent nasal polyposis are at high risk for failed therapy as the polyps continue to grow and become a source of anatomic obstruction. More radical surgery, such as a frontal sinus drillout or obliteration, may be necessary for the otolaryngologist to consider in select patients.

In addition to an anatomic evaluation, such patients should have a thorough medical evaluation, which may require a multidisciplinary approach. Patients should be evaluated for systemic disorders that may account for failed therapy, such as immunodeficiency, allergy, Samters triad, granulomatous disease, vasculitides, ciliary dyskinesia, and cystic fibrosis. It is this patient population with systemic disease that often becomes the most refractory to standard surgical and medical therapy. At this point, a change in focus toward palliative care may be helpful.

TREATMENT OPTIONS

Palliative care by no means implies avoidance of aggressive medical or surgical therapy. Rather, palliative care implies the provision of care that allows the patient to live with his or her disease in a state aimed at preservation of quality of life. Multidisciplinary therapies whose goal is symptomatic improvement, and novel and experimental therapeutic regimens, are reasonable to consider when a patient has exhausted conventional treatment options.

Immunomodulatory Therapy

An assessment for immunodeficiency should be performed in patients with CRS refractory to conventional medical treatment. Interestingly, among a group of 78 patients with refractory sinusitis at a tertiary care facility, 17.9% were noted to have low IgG and 16.7% were noted to have low IgA. Common variable immunodeficiency was diagnosed in 9.9% and selective IgA deficiency was found in 6.2%.[14] Sethi and colleagues[15] recommend that the minimum immunologic evaluation in patients with CRS refractory to conventional medical therapy should include measurements of quantitative immunoglobulin and IgG subclass levels, complete blood count with differential, and responses to immunization with protein and polysaccharide antigens. Such assessment for subtle immunodeficiency is important, because intravenous immune globulin infusions are often beneficial in patients with deficiencies of IgG. Nevertheless, extending the standard application of intravenous immune globulin therapy for the treatment of recalcitrant sinusitis remains controversial. One open-trial study of intravenous immune globulin in six patients suggested the efficacy of monthly intravenous immune globulin as an adjunctive treatment in patients with chronic sinusitis who failed conventional medical management. The protocol involved a 12-month trial of monthly intravenous immune globulin infusions (400 mg/kg). Five of six patients had decreased antibiotic use and the total number of sinusitis episodes also decreased.

These findings correlated with radiographic improvement in sinus disease.[16] More recently, subcutaneous IgG replacement therapy has been introduced, allowing for administration of similar cumulative doses at home.[17] Preliminary data suggest similar efficacy in protection against infection; however, this modality of treatment has yet to be evaluated in patients with CRS.

Leukotriene inhibitors including montelukast, zafirlukast, and zileuton have been shown to reduce both peripheral blood eosinophil counts and tissue eosinophilia in asthmatics. The same effect is believed to occur in CRS patients.[18] Leukotriene inhibitors have been shown to be effective in the treatment of CRS in open-label studies, particularly in patients with nasal polyposis and asthma. In a small prospective study, a statistically significant benefit for montelukast treatment in patients with nasal polyposis was observed both by symptom scores and polyp eosinophil counts.[19]

Aspirin desensitization has also been shown to down-regulate the cysL1-receptor expression and may have a role in the treatment of patients with refractory nasal polyposis and aspirin sensitivity. More specifically, aspirin desensitization may be indicated for patients who have aspirin-exacerbated respiratory disease and rhinosinusitis refractory to inhaled corticosteroids and leukotriene inhibitors. After initial desensitization, the maintenance of aspirin desensitization requires daily aspirin typically given at 650 mg twice-a-day doses. The daily dosing is very important, because subsequent desensitization is recommended if aspirin is missed for more than 48 hours.[20] The efficacy of aspirin desensitization therapy is supported by objective measures, which show a reduction in the number of sinus operations per year and sinus infections per year in patients who receive this treatment.[21]

Systemic Antibiotic Therapy

Consultation with an infectious disease specialist may be of benefit for consideration of less conventional antibiotic dosing regimens in refractory CRS patients. In one study, Anand and colleagues[22] demonstrated improved infection control in a group of patients with severe sinusitis who received up to 6 weeks of intravenous antibiotics based on pretreatment and posttreatment endoscopic culture results. Because of the difficulty in maintaining peripheral intravenous access for long intervals, oral antibiotics are more commonly used when treatment for several months is anticipated. To reduce the incidence of side effects and microbial resistance, the use of a lower than usual antibiotic dosage for long-term therapy has been advocated. Amoxicillin-clavulanate prescribed as a single daily dose of 500 mg, rather than the usual twice-a-day dosing, is practiced by some physicians. Although there is limited evidence to support the use of these regimens for chronic sinusitis, several studies have demonstrated the efficacy of low-dose, long-term antimicrobials for the treatment of recurrent episodes of otitis media in children.[23,24]

Long-term low-dose macrolide therapy may also be considered for its anti-inflammatory effect. Distinct from their antimicrobial properties, macrolides have been shown to have an anti-inflammatory effect and recent studies have shown that they may be effective in treating chronic airway inflammation, including the inflammation seen in CRS. Although the mechanism of macrolides' anti-inflammatory effects is not entirely understood, they seem to down-regulate proinflammatory cytokines and inhibit migration of inflammatory cells.[25] A recent study by Wallwork and colleagues[26] supports the practice of prescribing daily macrolides in patients with recalcitrant CRS. In a double-blind, randomized, placebo-controlled trial, patients who received 150 mg roxithromycin daily were found to have a statistically significant improvement in Sinonasal Outcome Test-20 scores and nasal endoscopy.

Topical Antibiotic Therapy

Topical antibiotics delivered to the nasal and sinus cavities have been widely used for the palliative treatment of patients with refractory sinusitis. These medications are typically delivered in liquid form as saline irrigations or in aerosolized droplets by a handheld nebulizer. The potential advantage of topical therapy is that the antibiotic can be delivered in relatively high concentrations locally to the affected tissues, reducing the potential for systemic side effects. One noncontrolled study demonstrated the efficacy of culture-directed nebulized antibiotics in the treatment of acute sinusitis exacerbations in patients with CRS who had previously undergone functional endoscopic sinus surgery.[27] In a more recent review of clinical and basic science literature on the treatment of CRS with antimicrobial washes, Elliott and Stringer[28] recommend that topical antimicrobials be used in a culture-directed fashion. Normal saline is the typical delivery vehicle. Topical antibiotics are most commonly used in patients with a history of sinus surgery, because it is believed that the ability of topical antibiotics to reach the interior of sinus cavities may be contingent on the presence of surgically opened sinus ostia.

A number of antibiotic agents, including levofloxacin, tobramycin, and ceftazidime, are commercially available in preparations suitable for nebulized delivery. Although no topical antibiotics are approved by the Food and Drug Administration (FDA) for delivery into the nasal cavity, many such preparations have been compounded by local pharmacies for years. Antibiotic powder dissolved in saline for intravenous administration can be placed in a spray bottle for nasal applications. This liquid medication can also be squirted directly into the nose and sinuses by a soft plastic bulb syringe or squeeze bottle.

Neurologic Evaluation

For the patient with persistent headache and facial pain following CRS therapy, involvement of a neurologist or pain specialist as part of the treatment team may prove helpful. It is important for the consultant to rule out comorbid diagnoses, such as migraine, atypical facial pain syndrome, fibromyalgia, and neuralgia. Failure to recognize these diagnoses may confuse the otolaryngologist's interpretation of the patient's symptoms and lead to suboptimal patient care. Depending on the neurologic diagnosis, various treatment options are available to mitigate the patient's discomfort. In addition to a variety of available antimigraine medications, the use of antiepileptic medications, including gabapentin and topiramate, and antidepressant medications, such as amitriptyline, has demonstrated efficacy for treatment of patients with neuropathic pain. Although not FDA-approved for such use, the use of botulinum toxin (Botox) injected subcutaneously into pain trigger points in the head and neck has been shown to be effective in the treatment of select patients with atypical facial pain.[29]

Saline Irrigations

Maintenance of proper nasal hygiene with nasal saline irrigations is a mainstay of treatment in the patient with CRS and can be particularly beneficial when palliative therapy is needed. Cleansing the sinonasal membranes with salt water solution has been shown to facilitate mucociliary clearance and improve quality of life in such patients.[30] A recent Cochrane Review concluded that there is adequate evidence to support the use of saline irrigations as both a sole modality of treatment and adjunctive treatment for CRS.[31]

A variety of products and brands are commercially marketed for such use, including NeilMed Sinus Rinse, ENTSOL spray, and Saltaire. Most devices use a squeeze bottle,

which is filled with saline solution. By gently squeezing the bottle, the solution is directed out a hole in the top of the bottle and into the patient's nostril. The solution then runs back out of the nostril as it carries with it mucus and debris that may be obstructing the nasal passages and sinuses. Most preparations contain isotonic saline solution, although some patients find hypertonic solutions to be more effective, particularly when the mucus is very thick. It is recommended that most patients irrigate twice a day, although more frequent usage is not harmful.

A saline solution can be prepared at home; however, many patients find the commercially available preparations to be more convenient, improving compliance with the prescribed regimen. The NetiPot is another means of nasal washing, which involves instillation of warm saline solution by a spouted pot. The spout of the pot is inserted into one nostril; the position of the head and pot are adjusted to allow the water to flow out of the other nostril. This technique is usually best suited for patients with thinner clear mucus and may not be as helpful in patients with thick tenacious mucus as is often seen in CRS.

Antifungal Therapy

Experimental use of intranasal antifungal agents has been reported as successful in the treatment of patients with CRS and should be given consideration. The premise of topical therapy is based on the theory that reduction of fungal antigenic load reduces eosinophilic activation and the subsequent release of inflammatory factors, which can lead to sinusitis. In a double-blind, placebo-controlled trial of daily intranasal instillation of amphotericin B, Ponikau and colleagues[32] showed an objective improvement in radiographic and endoscopic findings of CRS. These findings were questioned by Ebbens and colleagues[33] when a subsequent multicenter study of similar design failed to show significant differences between amphotericin and placebo groups in either subjective or objective outcome measures. Clearly, controversy continues to surround the issue of antifungal treatment for CRS.

FUTURE DIRECTIONS

In the future, treatment of patients with refractory CRS likely will include the use of newer immunomodulatory medications. Omalizumab, a monoclonal anti-IgE agent, has been noted to be effective in treating allergic asthma and allergic rhinitis.[34] Because of concerns about anaphylaxis, omalizumab currently has limited indications and is restricted to use in persons greater than 12 years of age with moderate to severe asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have failed therapy with inhaled corticosteroids. The use of anti-interleukin agents, such as anti–interluekin-5, has also shown mixed results to date.[35,36]

Recent studies have begun to reveal a genetic basis for CRS through the use of DNA microarrays.[37,38] Genome-wide scanning of patients with sinusitis has identified the overexpression and underexpression of specific enzymes involved in the mucosal inflammation associated with CRS. The targeting of these aberrant genes and their protein products holds great promise for the future treatment of patients with sinusitis who remain symptomatic despite the best efforts of their treating physicians.

REFERENCES

1. Rosenfeld RM. Clinical practice guideline on adult sinusitis. Otolaryngol Head Neck Surg 2007;137(3):365–77.
2. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg 1995;113(1):104–9.

3. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology and pathophysiology. Otolaryngol Head Neck Surg 2003;129(3 Suppl):S1–32.
4. Bernstein JM, Ballow M, Schlievert PM, et al. A superantigen hypothesis for the pathogenesis of chronic hyperplastic sinusitis with massive nasal polyposis. Am J Rhinol 2003;17(6):321–6.
5. Seiberling KA, Grammer L, Kern RC. Chronic rhinosinusitis and superantigens. Otolaryngol Clin North Am 2005;38:1215–36.
6. Ferguson BJ, Stolz DB. Demonstration of biofilm in human bacterial chronic rhinosinusitis. Am J Rhinol 2005;19(5):452–7.
7. Sanderson AR, Leid JG, Hunsaker D. Bacterial biofilms on the sinus mucosa of human subjects with chronic rhinosinusitis. Laryngoscope 2006;116(7):1121–6.
8. Emaneul IA, Shah SB. Chronic rhinosinusitis: allergy and sinus computed tomography relationships. Otolaryngol Head Neck Surg 2000;123(6):687–91.
9. Nishioka GJ, Cook PR, Davis WE, et al. Immunotherapy in patients undergoing functional endoscopic sinus surgery. Otolaryngol Head Neck Surg 1994;110(4): 406–12.
10. Bent JP, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1994;111(5):580–8.
11. Ponikau Ju, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc 1999;74(9):877–84.
12. Senior BA, Kennedy DW, Tanabodee J, et al. Long-term results of functional endoscopic sinus surgery. Laryngoscope 1998;108(2):151–7.
13. King JM, Caldarelli DD, Pigato JB. A review of revision functional endoscopic sinus surgery. Laryngoscope Apr;104(4):404–8.
14. Chee L, Graham SM, Carother DG, et al. Immune dysfunction in refractory sinusitis in a tertiary care setting. Laryngoscope 2001;111(2):233–5.
15. Sethi DS, Winkelstein JA, Lederman H, et al. Immunologic defects in patients with chronic recurrent sinusitis: diagnosis and management. Otolaryngol Head Neck Surg 1995;112(2):242–7.
16. Ramesh S, Brodsky L, Afshani E, et al. Open trial of intravenous immune serum globulin for chronic sinusitis in children. Ann Allergy Asthma Immunol 1997; 79(2):119–24.
17. Gardulf A, Nicolay U, Asensio O, et al. Rapid subcutaneous IgG replacement therapy is effective and safe in children and adults with primary immunodeficiencies: a prospective, multi-national study. J Clin Immunol 2006;26(2):177–85.
18. Pizzichini E, Leff JA, Reiss TF, et al. Montelukast reduces airway eosinophilic inflammation in asthma: a randomized, controlled trial. Eur Respir J 1999;14:12–8.
19. Kieff DA, Busaba NY. Efficacy of montelukast in the treatment of nasal polyposis. Ann Otol Rhinol Laryngol 2005;114(12):941–5.
20. Macy E, Bernstein JA, Castells MC, et al. Aspirin challenge and desensitization for aspirin-exacerbated respiratory disease: a practice paper. Ann Allergy Asthma Immunol 2007;98(2):172–4.
21. Berges-Gimeno MP, Simon RA, Stevenson DD. Long-term treatment with aspirin desensitization in asthmatic patients with aspirin exacerbated respiratory disease. J Allergy Clin Immunol 2003;111(1):180–6.
22. Anand V, Levine H, Friedman M, et al. Intravenous antibiotics for refractory rhinosinusitis in nonsurgical patients: preliminary findings of a prospective study. Am J Rhinol 2003;17(6):363–8.

23. Marchisio P, Principi N, Sala E, et al. Comparative study of once-weekly azithromycin and once-daily amoxicillin treatments in prevention of recurrent otitis media in children. Antimicrobial Agents Chemother 1996;40(12):2732–6.
24. Paradise JL. Antimicrobial prophylaxis for recurrent acute otitis media. Ann Otol Rhinol Laryngol 1992;155:33–6.
25. Tamaoki J. The effects of macrolides on inflammatory cells. Chest 2004; 125(2 Suppl):41S–50S.
26. Wallwork B, Coman W, Mackay-Sim A, et al. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Laryngoscope 2006;116(2):189–93.
27. Vaughan WC, Carvalho G. Use of nebulized antibiotics for acute infections in chronic sinusitis. Otolaryngol Head Neck Surg 2002;127(6):558–68.
28. Elliott KA, Stringer SP. Evidence-based recommendations for antimicrobial nasal washes in chronic rhinosinusitis. Am J Rhinol 2006;20(1):1–6.
29. Borodic GE, Acquadro M. The use of botulinum toxin for the treatment of chronic facial pain. J Pain 2002;3(1):21–7.
30. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. Laryngoscope 2000;110(7):1189–93.
31. Burton MJ, Eisenberg LD, Rosenfeld RM. Extracts from The Cochrane Library: nasal saline irrigations for the symptoms of chronic rhinosinusitis. Otolaryngol Head Neck Surg 2007;137(4):532–4.
32. Ponikau JU, Sherris DA, Weaver A, et al. Treatment of chronic rhinosinusitis with intranasal amphotericin B: a randomized, placebo-controlled, double-blind pilot trial. J Allergy Clin Immunol 2005;115(1):125–31.
33. 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(5):1149–56.
34. Vignola AM, Humbert M, Bousquet J, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy 2004;59(7):709–17.
35. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic process. Lancet 2000;356(9248):2144–8.
36. Flood-Page PT, Menzies-Gow AN, Kay AB, et al. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in the asthmatic airway. Am J Respir Crit Care Med 2003;167(2):199–204.
37. Liu Z, Kim J, Sypek JP, et al. Gene expression profiles in human nasal polyp tissues studied by means of DNA microarray. J Allergy Clin Immunol 2004;114(4): 783–90.
38. Fritz SB, Terrell JE, Conner ER, et al. Nasal mucosal gene expression in patients with allergic rhinitis with and without nasal polyps. J Allergy Clin Immunol 2003; 112(6):1057–63.