REVIEW

Rhinology, 46, 3-14, 2008

Treatment alternatives for chronic rhinosinusitis persisting after ESS: What to do when antibiotics, steroids and surgery fail*

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SUMMARY

Background: *It is estimated that over 500.000 individuals in the United States currently suffer from chronic rhinosinusitis (CRS), which has persisted or recurred despite maximal medical therapy and endoscopic sinus surgery (ESS). Management of these individuals remains uncertain, as recent published guidelines on CRS do not extend to this population.*

Our ***objective*** *is to provide a framework for the management of patients who fail standard therapy for CRS while providing recommendations based on the strength of the evidence for alternative medical therapies that can be used for the treatment of recurrent CRS. This guideline targets ENT physicians and allergists managing this increasingly frequent clinical situation and attempts to assist them in selecting from the increasing array of potential therapies available. To this end, factors contributing to the pathophysiology of post-ESS CRS are reviewed to identify method of action of existing and potential therapies and recommendations are made for their use.*

Results: *Given the accessibility of the sinus cavities after ESS, topical therapies are privileged. Saline spray or irrigation is recommended for all patients. Corticosteroids in oral or topical forms are recommended for controlling the inflammatory component, while the use of a short term course of oral or topical antibiotics are recommended mainly for the treatment of exacerbations. Long-term therapy with oral macrolides is also recommended as an alternative therapy. Desensitization with acetylsalicylic acid (ASA) for individuals with documented ASA sensitivity is recommended where available, while revision surgery, anti-leukotriene agents and intravenous immunoglobulins are options in management in selected patients. Antifungal therapy is not recommended. No recommendations for potentially experimental strategies are made in the absence of published experience and safety data in human subjects.*

Key words: biofilms, recurrent chronic sinusitis, endoscopic sinus surgery, Staphylococcus aureus, Pseudomonas aeruginosa, Coagulase-negative staphylococci, Haemophilus influenza, nasal irrigation, biofilm therapy, antibiotic therapy, antifungal therapy, alternative medecine

INTRODUCTION

Chronic rhinosinusitis (CRS) is among the three most common chronic diseases in North America, affecting approximately 31 million people in the United States each year [(1)]. Patients with CRS report a significantly lower quality of life index in measures of bodily pain and social functioning than do patients with congestive heart failure, angina, chronic obstructive pulmonary disease, and back pain [(2)].

Once the diagnosis is established, the medical management of CRS centers around the judicious use of a combination of an oral antibiotic with topical or oral corticosteroids [(2)]. Surgery is reserved for those not responding to medical therapy. The aim of surgery is to remove presumably irreversibly diseased tissue obstructing sinus drainage passages harbouring infection, consequently restoring normal sinus function [(3)]. Curiously, despite the frequency of the disease, there are no randomized, prospective trials validating this approach [(4)]. The cause and mechanism of disease remain unknown, and curative treatment does not exist.

While endoscopic sinus surgery (ESS) has been shown to improve the signs, symptoms and quality of life in individuals with chronic rhinosinusitis [(5)], particularly lacking are recom-

List of Abbreviations

CF: cystic fibrosis; CNS: coagulase negative Staphylococcus; CRS: chronic rhinosinusitis; CSLM: confocal scanning laser microscopy; ESS: endoscopic sinus surgery; H. influenza: Hemophilus influenza; INCS: intranasal corticosteroids; P. aeruginosa: Pseudomonas aeruginosa; RCT: Randomised clinical trial; RCRS: recurrent chronic rhinosinusitis; S. aureus: Staphylococcus aureus; TLR: toll-like receptors MIC: Minimally Inhabitory Concentration

*Received for publication January 21; accepted: January 31, 2008

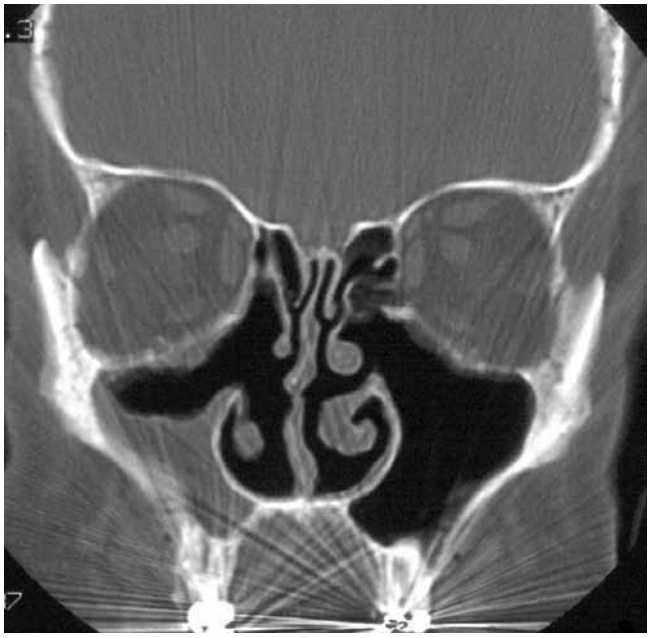

Figure 1. Persistent disease of the maxillary sinus despite widely patent maxillary sinus ostium post ESS.

mendations for patients who fail to respond to ESS, with persistence or recurrence of disease despite technically adequate surgery [6]. These individuals are deemed to have refractory chronic rhinosinusitis (RCRS) [7] (Figure 1).

Existing algorithms do not address disease persisting after ESS [8]. It often seems to the patient that the physician has little to offer beyond antibiotics, corticosteroids, or further surgery. For individuals with chronic courses or on the lookout for a new therapeutic approach, this may open them to misleading claims from proponents or suppliers of alternative therapies.

GOALS OF THIS REVIEW

This review article seeks to provide the health-care practitioner with information regarding available alternative therapies for the management of CRS of patients 'refractory' to ESS, so as to enable them to better meet the needs of this chronically ill population. The existing treatment options and the evidence supporting them are reviewed in the context of the current knowledge on the pathogenesis of CRS.

As CRS has only recently been accepted as a clinical entity by the regulatory authorities in the United States [9], double-blind, placebo controlled trails of therapy for post-ESS disease are rare and those that have been performed have rarely been validated by a second trial. Therapy is then often based either on an extension from first principles (the identification of a strategy based on pathophysiology) or based upon the observed response in other diseases such as acute bacterial sinusitis or unoperated nasal polyposis. Results are also often reported anecdotally, in limited series, retrospectively, and without a valid control group. Nevertheless, CRS now affects a large number of patients globally, and though evidence is limited, guidance is required to enable a practitioner, whom is less experienced in the management of these patients, to offer rational care.

PROCESS DESCRIPTION

A team of two tertiary rhinologists reviewed available literature on post-ESS disease and therapy using an English language Medline® and Google™ search in the areas of chronic sinusitis and polyposis (limited to the adult population, human, clinical trials, items with abstracts) was conducted and further refined based on the individual topics. Only articles published after January 1997 were included. Any peer-reviewed publications captured in a Medline® search but not in the other two software applications, yet deemed important, were also included.

Articles were graded for strength of evidence according to AAP SCQIM (American Academy of Pediatrics Steering Committee on Quality Improvement and Management)guidelines.[87]

Recommendations for management were established by drawing upon strategies adapted from the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) grading system, which classifies strength of recommendations according to the balance of the benefits and downsides after considering the quality of the evidence (10), and from the recently published AAO-HNS guidelines in sinusitis which uses a similar strategy.[8]

These systems address the disadvantages inherent to other grading systems, such as a lack of separation between the quality of the evidence and the strength of recommendations, the lack of transparency about judgments, and the lack of explicit acknowledgement of values and preferences. This type of system is particularly useful in areas that are controversial or where recommendations are clear but only observational studies or expert opinion are available.

Recommendations were formulated based on the strength of the evidence and its potential risk/benefit ratio. As many therapies have not been subjected to safety evaluation in a clinical trial setting, the potential for harm was assessed for each therapy and weighs in the recommendation. Recommendation options were to recommend weakly, moderately or strongly; offer as an option for therapy; or to not recommend a given therapy as either clinical trial data did not support its use or a concern for toxicity was noted.

SCOPE OF THE PROBLEM

It is estimated that approximately 6 billion dollars is spent in the U.S. annually on therapy for rhinitis and sinusitis [11]. It is unknown what percentage of this is for post-ESS disease, but the plethora of web sites and physicians specifically targeting this market is a testimonial to the interest and the potential expense associated with it.

While the number of individuals with persistent disease after ESS cannot be precisely tracked, the numbers can be estimated from published studies on the success of ESS for CRS with or without nasal polyposis. ESS remains one of the most common surgical procedures, with over 500.000 performed yearly in the U.S. alone [12]. It enjoys a reported success rate ranging from 50 to 90% [13] suggesting that at least 10% of patients will have persistence or recurrence of disease post-surgery. However, in cases with more severe disease or when objective criteria are used to assess outcomes, this failure rate can increase to as high as 50% persistence [14]. Even using the conservative figure of a 10% failure rate, this leaves 50.000 individuals yearly undergoing ESS with an unfavourable post-operative result, at least for the past 10 years. As these relatively young patients do not die of their disease, cases tend to be cumulative over time. Thus, over 500.000 individuals in the United States can be estimated to have chronic sinusitis unresponsive to medical therapy, with the actual number probably considerably higher.

These chronic sufferers now make up a significant portion of most rhinology practices, and a growing number of commercial services now cater to them specifically. The direct cost of these services and medications and the loss in productivity is inestimable. World-wide surveys of ENT physicians have confirmed that CRS refractory to medical and surgical therapy is now a global problem. The proliferation of internet-based discussion groups and web sites catering to sinus sufferers is a testament to the fluency and desperation of this affected population.

Pathophysiology

The management of these patients is difficult because the pathophysiology of CRS has not been clearly established. Numerous etiologies for this heterogeneous disease have been posited including anatomic factors leading to osteal obstruction, ciliary dysfunction, bacterial or fungal infection, superantigen stimulation of the immune system, allergy, and immune deficiency. What is currently evident is that CRS is an inflammatory disease, and that the etiology for persistent inflammation in an individual patient is often indiscernible.

In a population of individuals with persistence of disease following ESS, high rates of asthma, ASA intolerance, and allergies have been identified suggesting links with these other inflammatory disorders [15,16]. Histologically, biopsy specimens of CRS demonstrate an accumulation of activated inflammatory cells that are mainly eosinophils, with loss of apoptosis (preprogrammed cell death) [17]. Numerous pro-inflammatory cytokines and chemokines, both Th-1 and Th-2 profiles, are over expressed in CRS. These include IL-2, IL-4, IL-5, IL-6, IL-8, IL-13 and IL-16 [18].

Persistent inflammation seems associated with a poor response to surgery. Lavigne reported that outcomes at 1 year after ESS were significantly worse in a sub-group of patients with asthma and in those expressing high levels of IL-5 mRNA in biopsy specimens taken at the time of surgery [19].

Dysfunction in various components of innate immunity are increasingly thought to play an important role in the pathogenesis of CRS [20]. As the first point of contact between the airway and external environment, the nasal mucosa possesses an elaborate arsenal of defenses against potential pathogens in inspired air. The non-specific mechanisms of the innate immune system in the nose and sinuses include mucociliary clearance – primarily determined by ciliary beat frequency and mucus properties – as well as secreted antimicrobial molecules such as lysozyme, lactoferrin, defensins, cathelicidins, and surfactant proteins.

Other important molecules that impart considerable specificity at recognizing pathogens are the pattern recognition receptors. The most extensively studied and characterized of these are the toll-like receptors (TLRs). Gene expression studies have shown that levels of TLR-2 and TLR-9 mRNA in the ethmoid mucosa from patients with early recurrence of polyps after surgery are significantly reduced as compared to surgery-responsive patients [21].

The role of bacteria in CRS has been difficult to understand as bacteria have been cultured in only 50% of patients undergoing primary ESS [22]. Additionally, the flora recovered is different from that in acute bacterial sinusitis, with high recovery rates of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The effect by which these known pathogens exert their effect is only beginning to be explained. *S. aureus* has been suggested as a pathogen in CRS with nasal polyposis, via a superantigen-driven mechanism [23-25], interference with tissue metalloproteinase function [26], or via induction of the low-affinity steroid receptor GR-beta [27]. *P. aeruginosa* is a frequent colonizer of the diseased respiratory tract and it is almost ubiquitous in adult patients with cystic fibrosis (CF). Its action is via a number of toxins and proteases. *Haemophilus influenza*, a respiratory pathogen previously believed to be important mainly in acute infections, may also be involved. In a study of bacterial biofilms in CRS using confocal scanning laser microscopy (CSLM) with fluorescent in-situ hybridization (FISH), the principal pathogen identified was *H. influenza*, despite the fact that it was not recovered in any of the simultaneously performed conventional sinus cultures [28]. However, it was also recovered in 2/5 of the asymptomatic control specimens, reinforcing the importance of other factors such as host susceptibility to the development and persistence of inflammation in CRS.

Bacterial resistance may occur, as may be expected in a group of individuals with multiple courses of antibiotic therapy, however, it alone is not sufficient to explain the persistence of disease. Persistence of these bacteria intracellularly or as bacterial biofilms may provide some answers to this perplexing clinical problem, by furnishing what seems to many as the 'missing link' between bacterial presence and inflammation in CRS. The intracellular persistence of *S. aureus* has been shown to

occur between exacerbations of disease in patients colonized with this agent [29]. The presence of bacterial biofilms has been demonstrated in CRS patients in several studies, by a variety of methodologies [30-32]. Arguing for a functional link between bacterial biofilms and CRS, our group has previously demonstrated a poor outcome in post-ESS patients harboring *S. aureus* or *P. aeruginosa* with the capacity to form a biofilm in-vitro [33]. This was not the case for coagulase negative *staphylococcus* (CNS), reinforcing the concept that it is not the presence of the biofilm itself but the specific pathogenic bacterium that is responsible for this phenomenon. This finding was confirmed by a separate group of investigators [34].

Infection of the sinus cavities with a fungal organism has recently been heralded as the key to understanding the disorder. However, evaluation of the published evidence suggests that the fungal cultures may have to be interpreted as those for bacteria. In the original findings by Ponikau et al. [35], a high number species of fungal organisms can be identified in individuals with CRS. However, the same number and type of organism can also be identified in normal subjects. Further publications have suggested that it is the host response to fungus which differs in CRS. Exposure of peripheral blood mononuclear cells (PBMCs) to suspensions of fungus or fungal antigens leads to the production of pro-inflammatory cytokines only in individuals with CRS [36]. Trials of antifungal therapy have been disappointing, suggesting that the importance of this mechanism is somewhat limited.

While genetic studies of CRS offer a hope for a better insight into the pathogenesis of the disorder, so far these have shown limited results. Notably, only unreplicated studies have shown polymorphisms in markers for TGF-β [37], IL-1R [38], C4 [39], ALOX-5, ALOX-5AP, and CYSLT1 [40], but the functional significance of these findings remains unknown. A slightly higher frequency of CRS was noted in individuals heterogeneous for the CF Δ508 gene [41], but this limited effect is insufficient to explain all cases.

In a final consideration as to the uncertain aetiology of post-ESS disease, the influence of endoscopic sinus surgery (ESS) on the physiology and/or bacteriology of the paranasal sinuses remains largely unknown. Changes in the sinus environment after ESS may alter innate mechanisms of immunity or bring about excess stimulation of specific defences. In the normal situation, the tortuous drainage path of the sinus filters outs particulate matter and prevents its deposition in the sinus cavities. Removal of this mechanical barrier allows the external environment access to an area that was formerly protected from exposure [42]. Hence, the physiologic alterations produced by surgery might actually, in certain individuals, hamper the function of the sinuses.

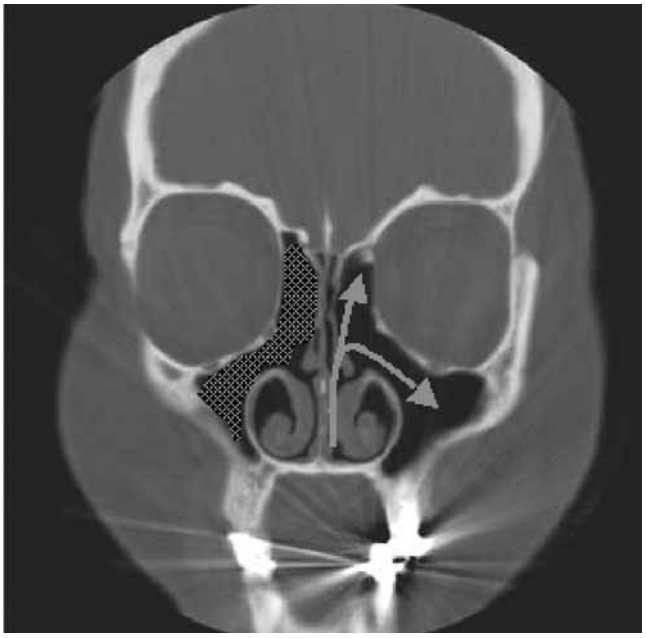

Figure 2. Persistent disease of the maxillary sinus despite widely patent maxillary sinus ostium post ESS.

THERAPIES FOR POST-ESS DISEASE

Topical therapy as a treatment strategy for post-ESS disease: moderate recommendation, moderate evidence.

Rationale: In post-ESS disease, topical therapy reaches sinus mucosa directly and avoids systemic side effects of oral administration of medication, however, not insignificant risks of absorption, local toxicity and sensitization to the medication should be considered.

Delivery of topical medication is based on therapies used for rhinitis and to observations taken initially from cystic fibrosis [43-45] Regardless of the agent selected for management of post-ESS disease, topical therapy should be considered as a route of administration because of the widely patent sinus ostia present post-ESS which afford excellent access for medications deposited intranasally to the diseased sinonasal mucosa (Figure 2). This allows for delivery of high concentrations directly at the site of disease while reducing the risk of systemic side effects. Less frequently considered are the optimal means of ensuring delivery to the intended site (deposition) and potential risks. Care must be taken to avoid developing cutaneous sensitisation to instilled agents.

The optimal means for depositing these substances in the sinus cavity has yet to be determined. The transfer of nebulized and liquid substances to the sinus cavity from the nasal passages is a function of particle size, sinus osteal diameter and pressure [46]. While nebulization is commonly used for delivery of medications to the lower respiratory tract, nebulizers used for the lungs may not necessarily be adaptable to the upper respiratory tract. For nasal deposition, particle size should be between 5 –10 microns.

Presently, several systems for the delivery of topical medica-

tions to the nasal mucosa are available. A study of their effectiveness at deposition has unfortunately been done on unoperated sinuses rather than patent, post-surgical ones [47]. In unoperated sinuses, penetration for nebulised particles is rather poor [48], with nasal irrigation affording better deposition. Based on mathematical models, deposition is however probably much enhanced after widening of the ostia after ESS. Penetration of pulsatile-type devices such as the Water-Pik have not been evaluated in this setting. Direct intrasinus deposition via indwelling catheter offers higher rates of deposition but may be too invasive in some settings or for long-term use.

Saline: Strong recommendation, moderate evidence.
Rationale: Saline irrigation has been shown to improve signs and symptoms of rhinosinusitis post-ESS in one prospective study. The risk of therapy is negligible and the potential benefit considerable.

Irrigation with saline remains an important part of the therapeutic arsenal, and has been recommended in a recent Cochrane review on this subject [49]. Theoretical advantages are that it improves mucociliary flow, hydrates the mucosa, and flushes away toxic and or irritative substances from the surface of the mucosa. The optimal concentration of saline has not been determined, but irrigation with hypertonic solutions may cause irritation in susceptible individuals.
Nasal irrigation has been used since ancient times [50]. Recent designs have sought to improve on the method by recommending and instructing on a more convenient head positioning (water squirted into the passages with the head flexed forward) and on the use of means for getting the solution into the passages (bulb and syringe techniques) at a higher pressure. For example, interesting adaptations of the Water-Pik system used for removal of dental plaque are available. This method uses pulsatile irrigation delivered via a variety of adapters to improve cleaning. Their use may theoretically be more effective at reducing bacterial load in situations where secretions are tenacious. Low-tech solutions such as sniffing water out of the palm of the hand should be discouraged, as they may increase the risk of contamination of the nasal passages.

Glucocorticosteroids: Strong recommendation, moderate evidence.
Rationale: Topical corticosteroids have been shown to reduce inflammation in CRS and to be associated with a reduction of recovery of *s. aureus* in patients undergoing revision ESS. Their effectiveness in reducing nasal polyposis has been demonstrated in RCT's, and they have been shown effective in reducing signs and symptoms of post-ESS disease when applied directly into the sinus via indwelling catheter. Risk appears minor as no effect on pituitary-adrenal axis has been shown in a small prospective trial.
Corticosteroids in various forms have long been used in the management of chronic sinusitis and nasal polyposis, both pre- and post-operatively, and represent the mainstay of therapy for individuals with post-ESS disease. The mechanism of action of corticosteroids is to prevent binding of transcription factors in the nucleus thereby modulating the transcription of a large number of genes on cells involved in immune and inflammatory responses. They are also able to influence the translational and post-translational mechanisms by which proteins are synthesized, processed and exported from cells. This inhibits the expression of inflammatory genes, mainly chemoattractants, thereby reducing both the recruitment and the activation of inflammatory cells. Steroids are thus beneficial in controlling inflammation associated with CRS with and without nasal polyposis [51].
Furthermore, as they do not inhibit the epithelial cell genes important for innate immunity, corticosteroids may even augment the innate immune response by increasing the expression of TLR's on the epithelial surface and enhancing the production of its effectors such as collectins, complement and acute-phase proteins, among others [52].
Oral corticosteroids are effective in managing recurrences of AFS after ESS, but their systemic side effects preclude long-term use [53]. Documented effects of topical INCS on post-ESS disease include retarding the rate of recurrence post-ESS in subjects with nasal polypois. While there is some concern that they may facilitate colonization and possible superinfection of the neo-sinus cavities post-operatively, this is probably unwarranted as the use of INCS is associated with a reduction in recovery of *S. aureus* in patients undergoing revision surgery [54].
Supporting the efficacy of corticosteroids for post ESS disease, twenty-one days of direct deposition of topical budesonide to the maxillary sinuses via an indwelling catheter improves signs, symptoms and radiologic apppearance of individuals with disease persisting or recurring after ESS [55]. Given that this technique may be too invasive or impractical for long-term use, physicians have struggled to find alternative means of improving deposition to the sinuses.
Intranasal and sinus deposition of INCS may be improved by using different application methods instead of that of the standard multidose dispenser (MD). Fluticasone propionate drops, applied in a head down position, are thought to improve deposition in the frontal recess and middle meatus [56-58]. Irrigations done with a mixture of budesonide and saline are widely used in the management of refractory disease and are also thought to improve deposition to the sinus areas. While no prospective study with corticosteroid irrigation has been done, a retrospective review in our institution has suggested that these improved 62% of patients referred for post-ESS disease.
Care must be taken in formulating solutions to minimize the risk of development of systemic effects, as absorption via this means of administration may differ from experience with nasal and pulmonary inhalers, which have proved to be safe. Hence, the clinician must use corticosteroids with low bioavailability, use the lowest dosage possible, and to remain cautious to the

development of systemic side effects. However, the safety of irrigation with 0.5 mg of budesonide BID has been confirmed by Wright who showed no effect on the HPA axis as determined by measures of serum cortisol and response to ACTH stimulation in a small group of patients [59].

Short-term courses of oral, topical and IV antibiotics are recommended for acute exacerbations of symptoms: Moderate recommendation, weak evidence based on trials of antibiotic therapy for acute bacterial sinusitis and bacteriology of CRS.
Rationale: No studies of effectiveness in CRS and risk of side effects of antibiotics and development of resistance.
Oral antibiotics: By definition, individuals with RCRS do not respond to oral antibiotics. Given their lack of proven efficacy in the long-term management of patients with chronic disease and the potential for development of resistance, they should probably be reserved for exacerbations with short-term courses [60,61]. Care must be taken to select an antibiotic with coverage for those pathogens expected in RCRS. Consideration should be given to obtaining endoscopically guided cultures of the sinus cavities at the time of evaluation as this may help guide selection of antibiotic or identify individuals with resistant organisms.
Nebulization of topical antibiotics has a long history in the management of patients with cystic fibrosis. However, nasal nebulisation has not been as successful in RCRS. In a RCT comparing saline with tobramycin administered BID for 21 days, a 30% improvement in symptoms was recorded and there was no additional benefit conferred by the addition of antibiotic [62]. This trial highlighted the importance of nasal irrigation in the management of RCRS. However, in a review, Vaughn et al described effectiveness of a variety of nebulised antibiotics (mainly ceftazidime and tobramycin) in a group of patients with exacerbations of RCRS [63]. Taken together, these studies suggest that the usefulness of antibiotics in this patient population is of limited effectiveness on the evolution of chronic disease, and should probably be reserved for acute exacerbations, if at all.
Intravenous antibiotics have been proposed for management of RCRS. Again, they are not effective in long-term eradication of the disease process and appear most beneficial in acute exacerbations.
Flaws in all of these studies are that little attention was given to selection of optimal dosages, intrasinus deposition, and concentrations used. For example, topical moxifloxacin showed in-vitro effectiveness against biofilms formed from clinical isolates of *S. aureus* only at concentrations 1000 times the minimally inhibitory concentration [64], suggesting that further study using different concentrations of antibiotics is required.

Antibiotics long-term: Moderate recommendation, moderate evidence:
Rationale: Prospective trials of long term, low-dose macrolide therapy have been beneficial in CRS.
It has been suggested that long term use of low dose erythromycin and its derivatives may have an immunomodulatory effect. This was first described in studies of panbronchiolitis conducted in Japan [65]. Since then, its application has been extended to other respiratory disorders, with good results in selected cases. This appears to be principally in individuals with neutrophilic infiltration, such as cystic fibrosis, rather than in the eosinophilic inflammation that characterises RCRS. Response to long-term administration in chronic sinusitis has been described by Koyabashi in Japan [66], by the group of Cervin in Sweden [67]. This may be a promising area as identification of the type of patient most likely to benefit from therapy becomes clarified.

Topical anti-fungal therapy: Not recommended, moderate evidence.
Rationale: RCT's of topical antifungal therapy to date have been conflicting and have failed to show a consistent benefit as therapy in post-ESS disease.
Topical antifungals: Despite the interest in fungus as an etiologic agent in RCSR, prospective trials of antifungal therapy have not convincingly documented a beneficial effect [69-70]. In addition, the optimal agent, concentration, and optimal conditions for preparations of a topical solution have not been adequately described, suggesting that locally-prepared solutions may not be comparable to those touted as having clinical effects. A large multicenter clinical trial is underway which should settle this issue and if positive should lead to commercial availability of a prepared solution.
Oral antifungals: Oral antifungals in high doses are sometimes used as management of individuals where a fungal element can be demonstrated. Raines et al has described a protocol for the management of AFS using long-term high dose therapy [71]. As there is a potential toxicity of long-term use and significant risk of interactions with other drugs, the effectiveness of antifungals will have to be documented with placebo-controlled RCT's and safety concerns addressed before their widespread deployment.

Leukotriene modifiers: Option, weak evidence.
Rationale: Leukotrienes are involved in the disease process but there is no documented proof of efficacy of these agents in RCRS. Despite a good safety profile for monteleukast, there exists a potential for liver toxicity for 5-LO inhibitors.
Leukotriene antagonists have been used for the treatment of nasal polyposis. A limited number of case reports suggest a beneficial effect [72,73]; one using topical application being the most successful. However, this effect appears limited at best. No well-constructed trial has been performed, despite their availability on the market for several years now. It has been suggested that targeting the 5-lipoxygenase enzyme may be a more effective way of targeting the leukotriene pathway [74]. A 5-LO synthesis inhibitor is being explored in this aspect.

ASA desensitization: Weak recommendation, moderate evidence.
Rationale: ASA desensitization has been documented effective in reducing nasal polyps. Successes have been mostly reported by experienced groups and there is a risk of adverse reactions in unexperienced practitioners or where non-compliance is an issue.
ASA desensitization has been reported by several groups as reducing nasal polyps [75]. The mechanism of action is unknown. However, therapy must be taken daily and may need to be re-initiated if the patient misses a daily dose.

Intravenous immunoglobulin (IVIG): Option, weak evidence.
Rationale: Uncontrolled trial of IVIG for post-ESS has shown benefits in a selected population with post-ESS disease. Cost of therapy and risks from use of a blood-derived product suggest considering its use only in subjects not responding to other therapies.
Classical common variable immunoglobulin deficiency is occasionally associated with recurrent or refractory sinusitis, and will be detected by low serum *IgG or IgG*-subclass levels. However, a study by Chee et al. described altered cellular immune responses in individuals with refractory CRS with normal IgG levels who responded to a six-month trial with IVIG [76]. There is thus little evidence to support the use of intravenous immunoglobulins in this setting, and this therapeutic approach should only be considered in the most refractory of cases.

Surgery as a strategy for post-ESS disease: Option, weak evidence.
The decision to re-operate a patient with sinus disease is centered principally on the demonstration of a symptomatic obstruction to sinus drainage or the presence of significant disease load [77]. A maxim to guide the surgeon is that the patient can never truly be deemed a failure of therapy until all obstructions to drainage and ventilation (or irrigation) have been corrected. In the sinuses this must be tempered by the clinician's judgment, experience, and comfort level.

Table 1. Pathophysiology of post-ESS disease.

Purported pathogenic factor	Identified in at least 2 studies	Targeted therapy impacts evolution
Bacterial presence	Yes	Yes
Th2 inflammation	Yes	Yes
Bacterial biofilms	Yes	Yes
Fungal presence	Yes	No
Superantigen	Yes	?
Non-HIV immune deficiency	Yes	?
Respiratory allergy	No	?
Defects in innate immunity	Yes	?
Genetic factors	Yes	?

ALTERNATIVE THERAPIES
Not recommended, weak evidence.
Rationale: While some results are interesting, they must be considered experimental until mechanism of action proposed therapies supported by additional clinical trials will be required prior to any recommendation.

Numerous therapies exist depending upon the stream of alternative medicine that is consulted. Some are experimenting with irrigation additives, including tea tree oil, as it has been described as possessing germicide, fungicide, and antiseptic properties. A potential issue when applying oil-based products to the sinonasal cavities is the possibility of lung contamination and a resultant lipoid pneumonia.
Other alternative medicines include acupuncture, whose performance is believed to help to balance fluid circulation and to alleviate sinonasal congestion. A homeopath may suggest taking silica and Kali bichromicum daily for the symptoms of sinusitis. Meanwhile, individuals who use aromatherapy would consider inhaling the aromas of eucalyptus, lavender, lemon and tea tree oils mixed in a bowl of boiling water in order to attain relief from sinonasal symptoms. None of these therapies have any proven benefit, but physicians treating patients who are using these alternative therapies should encourage sharing of this information so that advice can be given if there appears to be a clear health threat from the selected therapy, and to better understand potential confounding factors to medically prescribed therapy.

Antiseptics
N-chlorotaurine (NCT), an oxidant produced by stimulated granulocytes, has been previously demonstrated to possess a bactericidal effect at various concentrations in vitro. NCT has been successfully used in an irrigation solution for the treatment of sinus infection in immunocompromised patients. A 1% solution used in an uncontrolled, prospective cohort caused a decrease in mucosal edema, improved olfaction, and decreased nasal obstruction while being well tolerated. Other 'natural' products that are referred to as having antiseptic properties include tea tree oil, grapefruit seed extract, and eucalyptus oil.

Silver extract
There continues to exist individuals who promote the use of nasal sprays and other products containing silver as the 'natural antibiotic' and treatment for sinus infections. However, this metal has been demonstrated to be toxic. It is difficult to endorse a product that has unproven antimicrobial qualities, yet places the health of any consumer at unnecessary risk.

Neutraceuticals: Probiotics
Probiotics are commonly regarded as 'friendly' or 'good' bacteria, whose consumption is thought to provide health benefit for a potential number of ailments including sinusitis.

Table 2. Available therapies for post-ESS disease.

Post-ESS therapy	Effect confirmed in RPCT	Level of evidence	Recommendation
Antibiotics, oral- short term	Yes, in ABRS	Weak	Recommendation, exacerbations
Antibiotics, oral long-term	Yes, in CRS	Moderate	Option, selected cases
Antibiotics, nebulised	No	Weak	Option, exacerbations
Steroids, oral	Yes	Weak	Recommendation, short term
Steroids, spray	Yes, in NP	Strong	Recommendation
Steroids, drop	Yes, in NP	Strong	Recommendation
Steroids, irrigation	No	Weak	Option
Saline, spray	Yes *	Moderate	Recommendation
Saline, irrigation	No	Weak	Option
Antifungal, oral	No	Weak	Not recommended
Antifungal, irrigation	No	Moderate	Not recommended
Leukotriene antagonist	No	Weak	Option
Leukotriene (5-LO) inhibitor	No	Weak	Not recommended
IVIG	No	Weak	Option
ASA desensitization	Yes	Weak	Option
Revision surgery	No	Weak	Option
Alternative approaches	No	Weak	Not recommended

* Marked saline effect in placebo-controlled RCT's

Table 3. Recommendations for management for post-ESS disease according to the GRADE system.

- Topical therapy: Moderate recommendation, moderate evidence: In post-ESS disease, topical therapy can attain sinus mucosa directly and avoid systemic side effects of oral administration of medication. Not insignificant risks of absorption, local toxicity and sensitization to the medication should be considered.
- Saline: Strong recommendation, moderate evidence. Saline irrigation has been shown in one prospective trial to have an effect on improvement of signs and symptoms of rhinosinusitis post-ESS. The risk of therapy is negligible and the potential benefit considerable.
- Corticosteroids: Strong recommendation, moderate evidence: Topical corticosteroids have been shown to reduce inflammation in CRS and to be associated with a reduction of recovery of staphylococcus aureus in patients undergoing revision ESS. Their effectiveness in reducing nasal polyposis has been demonstrated in RCT's, and they have been shown effective in reducing signs and symptoms of post-ESS disease when applied directly into the sinus via indwelling catheter. Risk appears minor as no effect on pituitary-adrenal axis has been shown in a small prospective trial.
- Short term courses of oral, topical and IV antibiotics recommended for acute exacerbations of symptoms: Moderate recommendation, weak evidence based on trials of antibiotic therapy for acute bacterial sinusitis and bacteriology of CRS. Risk of side effects of antibiotics and development of resistance.
- Antibiotics long-term: Moderate recommendation, moderate evidence: prospective trials of long term, low dose macrolide therapy have been beneficial in CRS.
- Anti-fungal therapy: Not recommended, moderate evidence. RCT's of antifungal therapy to date have not shown a benefit to therapy in post-EESS disease.
- Leukotriene modifiers: Option. Weak evidence. Leukotrienes involved in disease process but no documented proof of efficacy. Potential for liver toxicity for 5-LO inhibitors.
- ASA desensitization: Weak recommendation, moderate evidence: ASA desensitization has been documented effective in reducing nasal polyps. Successes have been mostly reported by experienced groups and there is a risk of adverse reactions in inexperienced practitioners or where non-compliance is an issue.
- Intravenous immunoglobulins (IVIG): Option, weak evidence. Uncontrolled trial of IVIG for post-ESS has shown benefits in a selected population with post-ESS disease. Cost of therapy and risks from use suggest considering its use only in subjects responding to no other therapy.
- Revision surgery: Option, weak evidence. Removal of obstructions to drainage and or access of medication to the sinus cavity may improve response to therapy.
- Alternative approaches: Not recommended, weak evidence. While some results are interesting, they must be considered experimental until mechanism of action and safety of proposed therapies supported by additional clinical trials will be required prior to any recommendation.

Typically, a probiotic consists of a strain of *Lactobacillus* species. In alternative medicine, the thought behind their use stems from the belief that their consumption helps to strengthen the immune system. There is some belief that probiotics may have a protective effect against the development of asthma and allergic rhinitis for children treated with antibiotics during their first year of life. No research currently exists in CRS to support their use.

Microbe extracts

These agents are less commonly employed in the treatment of sinusitis. In a double-blind placebo-controlled German study of post-operative chronic sinusitis, an autolysate of *Enterococcus fecalis* bacteriae of human origin was used as the treatment [82]. Patients were treated for 6 months and then followed for 8 months. They found that relapse of symptoms and clinically evident disease was about half of that which occurred

in the placebo group, and that relapse took significantly longer to occur post-operatively in the verum-treated group. They believe these group differences are related to immune-modifying characteristics of this treatment. In an earlier multicenter, randomized double-blind placebo-controlled study using a bacterial lysate for the treatment of patients with CRS, use of the study drug was associated with a significant improvement in the sinonasal symptoms from the first to sixth month of observation for the treatment group [83].

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Caveats and dangers

It is to be remembered that none of these of these therapies have an indication for this purpose, and that no FDA-accepted demonstration of their effectiveness and or safety has been performed. These are all off label uses and the physician should proceed accordingly with caution.

POTENTIAL FUTURE THERAPIES

Therapies targeting biofilms: The recent surge of interest in biofilms [78] has led to interest in strategies targeting control of the biofilm matrix by chemical or mechanical means. There are numerous potential ways to eradicate a bacterial biofilm. These include ventilation of the sinus cavity, killing of the pathogenic bacteria, interfering with the quorum sensing of biofilms, and interfering with the biofilm structure, either mechanically or chemically [79].

To date, anti-biofilm strategies have only been tested using in-vitro models but these offer intriguing insights into effectiveness of conventional therapies. In an in-vitro model, we have shown that *S. aureus* in biofilm do not respond to antibiotics they are sensitive to at concentrations that can be attained orally [80]. Concentrations 1000x the MIC are required to effect a significant reduction, suggesting that topical therapies with antibiotics will need to be re-evaluated. Simple irrigation with saline has no effect on bacterial biofilms [80]. This is not enhanced with the addition of tobramycin (80mg/l), doxycyclin (80mg/l), or triclosan (an antiseptic), but reduction in bacterial load is noted with a combination of citric acid (a calcium sequestering agent) and a zwitterionic surfactant (a detergent). Biofilm removal is enhanced by using a hydrodebrider, (a device for pulsatile irrigation) for application, and increases the effect synergistically. Recently, the antibiotic muporicin has been suggested as an effective anti biofilm agent [81] but has not undergone testing in a clinical trial setting.

While obviously promising, these novel therapeutic approaches have yet to be translated into therapies for clinical practice. While the use of irrigations with a detergent such as baby shampoo have been suggested, this and other therapies have not been subjected to clinical trials to determine safety and efficacy.

Anti IL-5 monoclonal antibodies: Targeting individual cytokine with intravenously injected monoclonal antibodies is being done successfully in other inflammatory diseases. An antibody to IL-5 has undergone trials in humans and it is effective in reducing size of nasal polyps [84]. It is not commercially available at this time.

Phototherapy: Ultraviolet (UV) light applied to the nasal passages has been successfully used for the treatment of allergic rhinitis [85]. In one study, it was also shown that UV exposure increased eosinophil and T cell apoptosis in a dose-dependent way [86]. It may find a role in the management for post-ESS recurrences.

Vaccines: Anti-Staphyloccocal or other vaccines may eventually be available and may play a role in enhancing mucosal immunity.

Pharmacogenetics: As individual susceptibility factors become better characterized through genetic studies, predictors of severity and response to therapy will hopefully be developed. In the future, the physician will hopefully have available a diagnostic test allowing him/her to identify the factors responsible for the development of a particular patient's disease and to predict response to potential therapies, allowing them to target the disease more rapidly and effectively by selecting appropriate therapy.

IMPROVING PATIENT SATISFACTION WITH PATIENT CENTERED MANAGEMENT

The importance of establishing a significant and ongoing therapeutic relationship with these patients is paramount. These individuals are afflicted with a disease, which has significant impact on their physical and emotional state of health, with all of its attendant complications for hampering work, family, and social life. The physician should inquire into these so as to attempt to tailor therapy appropriately. Due to the ongoing nature of the disease, a complete remission with no medication or therapy is unlikely. Even in the well-managed patient,

exacerbations may be expected thus the patient must then be counseled as to what consists realistic expectations and therapeutic objectives mutually agreed upon.

The availability of information on the Internet makes it an increasingly frequent medical reference for individuals with CRS. The health care practitioner must be aware that patients do access these sites and are often confused by the information and /or therapies presented, which may conflict with the advice the practitioner offers. Use of alternative medications is also a concern as cultural traditions may increase a reliance on 'traditional' therapies and may vary according to beliefs in a given country or region. The physician should specifically inquire into their use, and attempt to persuade the patient to pursue these in conjunction with standard therapy.

Ensuring compliance with therapy is one of the biggest challenges the physician faces, and assessment of compliance should be part of each visit.

CONCLUSIONS

Rational management of severe disease

Severe sinus disease unresponsive to intense medical management and surgery remains an enigma to the clinician. Management remains largely based on clinical experience and novel concepts gained via new insights on the pathophysiology of CRS. Targeting inflammation remains a mainstay of therapy, but new found recognition of the role of bacteria in chronicity of this disorder require giving consideration to specific therapy, which may differ from the conventional short courses of wide spectrum antibiotics used in acute bacterial rhinosisnuistis.

Despite the severity and increasing frequency of refractory rhinosinusitis, limited Grade I evidence exists to support the medical therapies commonly used in its management. Selection among available options will thus require both knowledge of the pathophysiology of the disease and of the means of action of each therapy.

Given the multiple clinical presentations and the variable natural evolution it is probable that a given patient may require different therapies at different stages in their disease process. The challenge for the clinician remains to determine the stage of disease and select among therapeutic options. Thus astute clinical judgment will continue to play an important role in the management of this patient population.

In the absence of standardized definitions and of clinical trials, the clinician is still faced with a bewildering series of alternatives. There is an increasing recognition of the importance of topical therapies in the chronic management of this disorder, but clinical research in this area is still in its infancy. In order to avoid returning to the era of early 1900's era of patent medicines with unsubstantiated claims, new agents should be assessed prospectively in well-designed trials with appropriate controls to determine their effectiveness and safety profile prior to their adoption.

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