REVIEW

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Role of antibiotics in sinusitis

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Purpose of review
Sinusitis is a leading reason for outpatient antibiotic use, but symptoms are nonspecific. We review potential methods that might enhance the ability to appropriately prescribe antibiotics.

Recent findings
The evidence base for antibiotic use in acute rhinosinusitis is strongest in studies with stringent entry criteria. In less restrictive studies antibiotics and placebo perform equally. Bacteria from nasopharyngeal swabs in adults correlate with sinus cultures. A recent study showed that antibiotics shortened the duration of acute rhinosinusitis (ARS) symptoms in children. Tellingly, over 2000 children with symptoms were screened to enroll less than 10% who fulfilled the study's stringent criteria. In chronic rhinosinusitis (CRS), two grade 1 studies on efficacy of long-term macrolide therapy showed conflicting results. Odontogenic sinusitis is underappreciated and frequently fails to grow on culture because of presumed difficulty in growing anaerobes.

Summary
There is currently no grade 1 evidence to support antibiotic use in CRS; however, studies to date have not been conducted in patients with isolated purulent sinusitis. Future use of cultures to direct antibiotic therapy, such as nasopharyngeal swabs in adults with ARS or endoscopically guided cultures, may aid in targeting antibiotic therapy more effectively.

Keywords
antibiotics, chronic rhinosinusitis, endoscopically directed cultures, nasopharyngeal culture, sinusitis

INTRODUCTION

Sinusitis, also known as rhinosinusitis, is commonly categorized by duration of symptoms. Symptoms less than 4 weeks are considered acute and designated as acute rhinosinusitis (ARS). The usual causes of ARS are viral illness, occasionally complicated by bacterial infection. In patients with symptoms of sinusitis for more than 12 weeks, the term chronic rhinosinusitis (CRS) is used. The pathogens associated with CRS are diverse and it is unclear whether or which have pathologic significance. To date, the best evidence for antibiotic usage is in ARS, as long as stringent criteria are employed. It is quite difficult for the clinician to distinguish the symptoms of a viral ARS from a bacterial ARS in an individual patient. Intriguingly, the use of nasopharyngeal cultures may help the clinician appropriately determine who might benefit from antibiotics in the setting of ARS.

The evidence for antibiotic use in CRS either short term or long term is even less than for ARS. The literature is reviewed, and the case is made for future studies utilizing culture in patients with mucopurulent discharge to study the effect of antibiotic therapy in this subset of patients with CRS.

Although dental infections have long been known to cause sinusitis, in recent years appreciation of this cause has waned. The advent of sinus computed tomography (CT) allows the clinician to appreciate periapical dental abscesses that may not be apparent to the dentist, and to accurately diagnose the cause of maxillary sinusitis in odontogenic sinusitis. If diagnosed, successful therapy must usually entail treatment of the affected infected tooth.

ACUTE BACTERIAL RHINOSINUSITIS

ARS is a commonly encountered ailment afflicting up to 20 million individuals each year and carries significant healthcare burden both in terms of patient distress as well as financial expenditures,

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KEY POINTS

- Evidence for the role of antibiotics in acute rhinosinusitis is limited; however, nasopharyngeal cultures may offer a practical solution for treating patients with the best antibiotic choice if bacterial pathogens are identified.
- Currently, there is no evidence for antibiotic efficacy in chronic rhinosinusitis; however, no studies have been conducted to date that are limited to patients with culture directed antibiotics for pathogen positive purulence.
- One third of patients with chronic rhinosinusitis symptoms have a normal sinus computed tomography (CT); therefore, objective verification of sinusitis is recommended before embarking on prolonged courses of antibiotics.
- Odontogenic maxillary sinusitis may be missed by dental examination and panorex, but is apparent as a periapical lucency on cone beam CT or sinus CT.

which are estimated as high as US$ 3 billion in the United States alone [1]. The management strategy of ARS is complicated by the inability of the symptom complex or radiographic findings to differentiate between viral and bacterial causes. The role of antibiotics in acute bacterial rhinosinusitis (ABRS) is controversial because of inconsistent and often contradictory studies in the literature. ARS, both viral and bacterial, is common, with the potential for serious morbidity/mortality from bacterial complications. Better tools are needed to assess patients for appropriate antibiotic therapy. Up to 25–30% of patients with a cold are co-colonized with nasopharyngeal pathogens and it is this subset of patients with rhinitis who are most likely to benefit from antibiotics, whether or not there is also bacterial presence in the sinuses. In fact, patients colonized with pathogenic nasopharyngeal bacteria, even in the absence of documented sinusitis, have more severe symptoms than patients with a cold without pathogenic colonization. A bacterial sinus infection is estimated to complicate only 2% of colds, which is far less than the number of patients with nasopharyngeal colonization. Yet groups with pathogenic bacteria present would benefit from antibiotics, whereas those without bacterial presence would not. This section reviews evidence for and against antibiotics for acute presumed bacterial sinusitis, as well as studies on nasopharyngeal bacterial infection and response to antibiotics.

The recent European Position Paper on Rhinosinusitis (EPOS) 2007 provides the most comprehensive review of the evidence base for therapy of acute sinusitis [2]. To summarize the EPOS document, the diagnosis of ARS in the primary care setting remains symptom based. Plain radiography is neither useful nor warranted in the acute workup of suspected rhinosinusitis. General criteria for diagnosis of ARS include nasal blockage, obstruction, congestion, or nasal discharge in addition to facial pain/pressure or reduction/loss of smell. Symptoms lasting less than 5 days or improving thereafter can be treated symptomatically without antibiotics. Symptoms increasing or persistent after 5 days that are moderate in nature can be treated with topical steroids and observed for clinical improvement in 48 h. However, patients with the aforementioned symptoms with a severe presentation (fever $>38^{\circ}$C, severe pain) persisting/increasing after 5 days should receive oral antibiotics in addition to topical steroids. Moderate symptoms that persist without improvement for 48 h should be treated with oral antibiotics. CT imaging should be obtained in patients with severe symptoms and no improvement after 48 h of treatment, or patients with impending complications such as orbital infection or change in cognition or severe headache suspicious for intracranial infection. Intravenous antibiotics are rarely required, but are implemented for complicated sinusitis or progression despite oral antibiotics. The vast majority of patients with bacterial or viral sinusitis resolve spontaneously without therapy; however, antibiotics probably speed the time to recovery in bacterial sinusitis.

The gold standard for establishing ABRS is a maxillary sinus or antral sinus tap. Interestingly, even in pharmaceutical sponsored trials that used antral taps in comparative antibiotic trials in the past, the endpoint was not just an analysis of the bacterial positive patients, but all enrolled patients. Rarely does the incidence of positive bacterial pathogens in acute maxillary sinusitis exceed 50% of those patients enrolled. Antral tap is certainly not available as routine care of sinusitis in the primary care setting and is usually reserved for research purposes or for patients refractory to initial medical therapy. In the 1960s, in Scandinavia, antral tap with lavage repeated over several days, was the primary treatment of bacterial sinusitis, without use of antibiotics. Nasopharyngeal culture may provide a suitable alternative for identification of pathogenic bacterial rhinosinusitis. A study by Kaiser *et al*. [3] identified bacterial growth (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*) from nasopharyngeal secretions in the early course of upper respiratory tract infection. In this study, 265 patients were randomized into either placebo or azithromycin arms. Of those patients identified with positive nasopharyngeal secretions (29%), resolution of symptoms by day 7 occurred in

73% of patients in the azithromycin arm, versus 47% in the placebo arm ($P = 0.007$). Furthermore, prior studies have also shown that positive maxillary sinus tap was concordant with 98% prevalence of pathogenic nasopharyngeal bacteria, whereas negative tap was associated with a 50% presence of bacteria on nasopharyngeal swab [4]. Lindbaek *et al.* [5] conducted a study with 427 patients, correlating positive CT findings (air fluid level or total opacification) with positive nasopharyngeal culture in the diagnosis of acute bacterial sinusitis. Two hundred and fifty-two patients had positive CT findings versus 175 with negative imaging studies. The proportion of specimens with normal nasal flora or no growth was significantly higher in the nonsinusitis imaging group as opposed to those with positive sinus imaging studies.

Recently, Han *et al.* [6▪▪] investigated the correlation of osteomeatal complex (OMC) culture with nasopharyngeal culture in patients presenting with upper respiratory illness (URI) symptoms as well as in normal control patients. Their findings indicated a higher incidence of positive bacterial middle meatal culture in patients with URI symptoms versus healthy controls (31% versus 8%, $P = 0.008$); this correlated well to the presence of the same bacterial pathogen(s) in the nasopharynx in symptomatic versus healthy controls (47% versus 14%, $P = 0.02$). All cases of positive middle meatal culture were found to have positive nasopharyngeal bacterial culture as this serves as the presumed reservoir for the bacterial pathogen. Although it should be acknowledged that these data show that not all cases of positive NP culture imply positive middle meatus culture, the propensity for bacterial superinfection from the positive NP reservoir still exists. This may explain the significant improvement in the antibiotic-treated patients seen in the study by Kaiser *et al*. discussed previously.

Even in the absence of detectable maxillary sinus bacterial infection, the presence of nasopharyngeal bacterial colonization carries significant consequence in the development of secondary bacterial sinusitis. Early in the course of viral rhinosinusitis, inflammation of the mucosal lining of the paranasal sinus ensues, causing a functional obstruction of the osteomeatal complex. It is thought that oxygen within the sinus is depleted as molecular oxygen is absorbed, resulting in a decreased partial oxygen pressure within the paranasal cavity. This resultant negative pressure promotes the aspiration of bacterial pathogens from the nasopharynx into the paranasal sinus cavity with subsequent bacterial colonization. Another mechanism by which the otherwise sterile paranasal sinus could be inoculated with bacteria is by nose blowing, which forces pathogenic bacteria into the sinus cavity, which can result in bacterial super infection as well. This phenomenon was illustrated by Gwaltney *et al.* [7], who showed that contrast dye from the nasopharynx was forced into the sinus cavity after vigorous nose blowing. Thus, identification of nasopharyngeal bacteria by culture is important for two reasons. Adults with pathogenic acute bacterial infection of their nasopharynx have a greater severity of symptoms and will improve faster with antibiotics than patients without nasopharyngeal pathogenic bacteria, and second, the presence of these bacteria is probably the source of potential sinusitis and nasopharyngeal cultures should thus appropriately direct antibiotic therapy for patients if they develop or also have sinusitis.

The use of antimicrobial agents for the treatment of acute sinusitis is controversial. Many studies show a significant clinical benefit from the use of antibiotics in acute bacterial rhinosinusitis [8–13], whereas other studies show an insignificant or marginal benefit with the use of antibiotics [14–16]. However, the majority of these studies showing no benefit did not make use of strict and appropriate exclusion criteria for patients treated with antibiotics and most likely represented primarily the more common viral cause of rhinosinusitis, also known as the common cold, which would explain failure of antibiotic responsiveness. Wald *et al.* [17] conducted a study in 2009 in which strict inclusion criteria were utilized prior to randomization to antibiotic versus placebo arms. Out of a total of 2135 children, 1982 were excluded from the study on the basis of a failure to meet the following inclusion criteria: first, persistent symptoms (nasal discharge or cough for 10 days without improvement), second, acutely worsening symptoms (nasal discharge or daytime cough worsening after 6 days with new onset fever or worsening in nasal discharge after transient improvement), and third, severe symptoms (temperature of at least 102°F and purulent nasal discharge for 3 consecutive days). The study was able to demonstrate a statistically significant rate of cure or improvement with use of oral antibiotics (amoxicillin clavulanate) in this specific patient population (64 versus 32% with placebo, $P = 0.01$).

This underscores the importance of appropriate identification of patients with symptoms more consistent with acute bacterial sinusitis. The findings of Wald *et al.* have demonstrated a clear benefit in terms of reducing duration of symptoms with the use of antibiotics in patients meeting specific inclusion criteria. These inclusion criteria may also one day incorporate the use of nasopharyngeal culture given the success seen in previously mentioned

studies. Therefore, we advocate the use of oral antibiotics with the addition of nasopharyngeal culture in patients meeting sufficient inclusion criteria in order to reduce the significant morbidity and healthcare costs associated with bacterial rhinosinusitis. Nasopharyngeal cultures are not recommended in children, as at baseline the adenoidal pad of children grows pathogenic bacteria in about 70% of children. In adults, pathogenic bacteria are normally present around 5% of the time.

Although culture-directed antibiotics are the ideal, in the absence of cultures, reasonable choices of empiric antibiotic therapy for presumed acute bacterial sinusitis depend on the resistance patterns of the usual pathogens: *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* (Table 1) [18]. The incidence of β-lactamase production of *H. influenzae*, and *M. catarrhalis* is around 40 and 90%, respectively. Thus, antibiotics that cover β-lactamase producing bacteria are reasonable choices if initial antibiotics, such as amoxicillin, trimethoprim–sulfamethoxazole or doxycycline fail to improve symptoms. Examples of antibiotics with excellent coverage for both *S. pneumoniae* and β-lactamase producing bacteria include cefuroxime, cefpodoxime and amoxicillin clavulanate (Table 2) [19]. High levels of penicillin resistance of *S. pneumoniae* vary geographically and often coexist with resistance to other antibiotics, underscoring the usefulness of cultures. *S. pneumoniae* with high penicillin resistance can be overcome by increasing the dosage and frequency of amoxicillin, a well tolerated oral antibiotic. In the penicillin-resistant pneumoccocus, macrolide and even clindamycin pneumococcal resistance is not uncommon, whereas fluroquinolone resistance to levofloxacin and moxifloxicin is rare. Telithromycin, which no longer has an indication for the treatment of sinusitis, is an effective oral antibiotic available for penicillin-resistant pneumococcus. If an antibiotic is effective, then clinical improvement should be seen within 2–3 days of initiation of the antibiotic. If there is no improvement over that period, then the diagnosis of resistant bacteria or a nonbacterial cause of symptoms should be entertained.

Table 1. Common acute bacterial rhinosinusitis pathogens

Pathogen	Frequency (%)
Streptococcus pneumoniae	41
Haemophilus influenzae	35
Moraxella catarrhalis	4
Staphylococcus aureus	3
Anaerobes, streptococcal, and other species	18

Table adapted from [18].

Table 2. Common first-line and second-line antibiotic agents used in acute bacterial sinusitis

First-line agents	
Amoxicillin	500 mg b.i.d. 10–14 days
Trimethoprim–sulfamethoxazole	160/800 mg b.i.d. × 10 days
Doxycycline	100 mg b.i.d. × 10 days
Second-line agents	
Clarithromycin	500 mg b.i.d. × 14 days
Azithromycin	500 mg q.d. × 3 days
Amoxicillin/clavulante	875 mg b.i.d. × 10 days or two 1000 mg XR tablets b.i.d. × 10 days
Cefuroxime	250 mg b.i.d. × 10 days
Ciprofloxacin	500 mg b.i.d. × 10 days

Table adapted from [19].

CHRONIC RHINOSINUSITIS

CRS is diagnosed when symptoms of ARS persist for greater than 12 consecutive weeks and is the second most prevalent self-reported chronic condition in the United States, affecting approximately 15.5% of the population [20]. However, the prevalence of doctor-diagnosed CRS based on use of ICD-9 codes is approximately 2% [21], which highlights the heterogeneity and diagnostic inconsistencies associated with the condition. Moreover, in a recent prospective study, we found that a third of patients with CRS symptoms had no evidence of sinus disease by CT scan or endoscopy [22▪▪]. Symptoms of patients more likely to have sinus disease include decreased smell, whereas patients without sinus disease were more likely to complain of facial pain and pressure [22▪▪] (Fig. 1a and b). Patients with presumed CRS account for twice as many clinic visits as those patients without CRS and are prescribed five times as many prescription medications, of which many are antibiotics [23]; and as many as one third of these symptomatic patients lack objective sinus disease and thus antibiotics would not be appropriate. In the same study, we also found that approximately 25% of patients with objective CRS by CT had purulence present in the nose on endoscopic examination, and even more importantly, that all 50 patients, in this series of 125 patients, who had normal sinus CTs had no evidence of purulence in the nose [22▪▪]. This allows the clinician to increase the likelihood of appropriate antibiotic use in patients with sinus symptoms, if antibiotics are restricted to those with objective purulence in the nose. Even for patients with objective evidence of

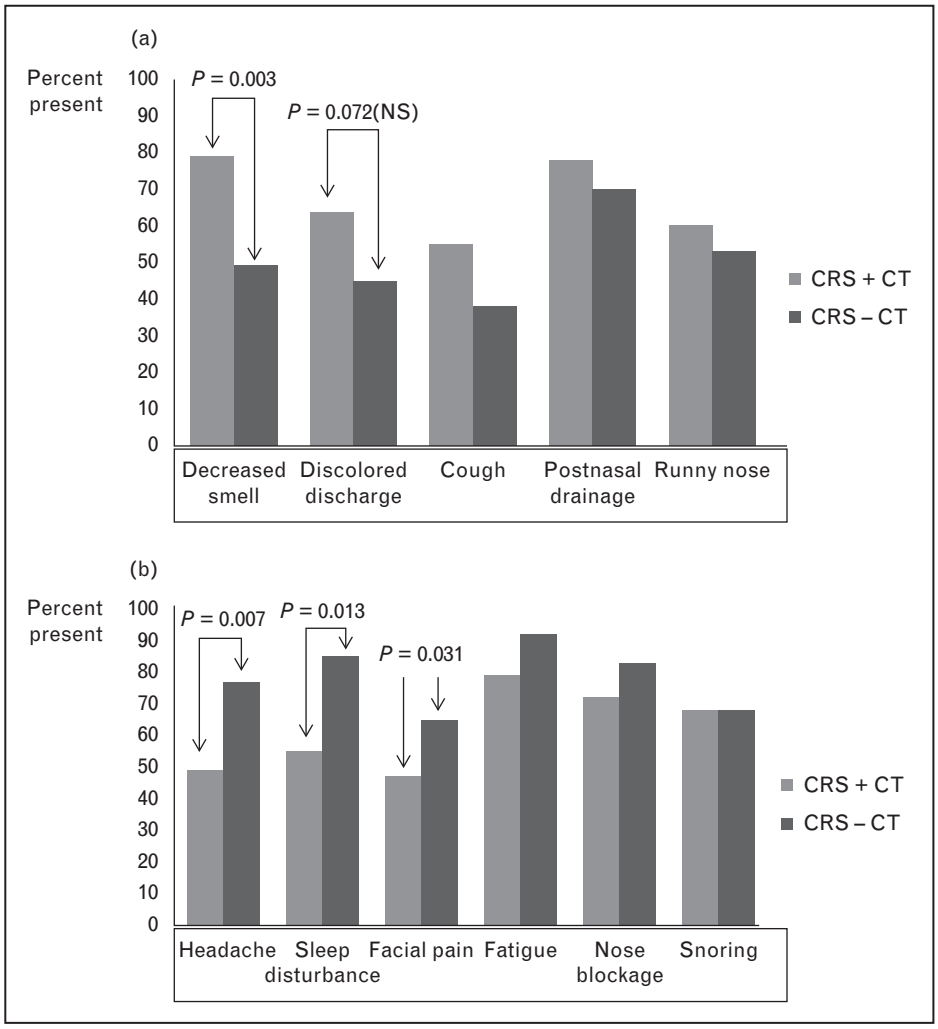

FIGURE 1. Symptoms most common in chronic rhinosinusitis (CRS) patients with a positive sinus computed tomography (CT) compared with CRS patients with a normal sinus CT. (a) Only loss of smell was found significantly more frequently in CRS patients with positive CT than in those with negative CT. (b) Headache, facial pain and sleep disturbance were reported more frequently by CRS patients with normal CT scans than by CRS patients with positive CT scans. Overall most of the symptoms used to diagnose CRS overlap those with objective evidence of sinusitis and those with objective evidence of no sinusitis. Adapted with permission from [22▪▪].

sinusitis on CT, the role bacteria play and the importance of antibiotics remains unproven.

CRS is a multifactorial disease attributed not only to bacterial infection but also to allergy, immune dysfunction, sinonasal mucosal inflammation, impaired ciliary function and/or anatomic obstructions within the sinonasal cavity [24–29]. Thus, treatment for CRS is aimed at correcting several of the contributing factors and includes topical and/or systemic corticosteroids, saline lavage, surgery, as well as antibiotics. Bacterial isolates from patients with CRS are nearly always polymicrobial with both aerobic and anaerobic species present. However, polymicrobial specimens have also been isolated from nondiseased sinuses in patients with CRS, suggesting that bacterial presence alone is not the most significant cause of CRS [30]. Antibiotic therapy comprises a significant component of medical treatment of CRS [31]. A recent survey showed that 94% of US otolaryngologists prescribe prolonged courses (minimum of 2 weeks) of oral antibiotics for the treatment of CRS [32]. However, the efficacy of antibiotic therapy is dependent on a wide variety of factors such as the class of antibiotic, dose and duration of therapy, as well as whether a significant bacterial infection is present. Furthermore, studies examining the effect of various antibiotic therapies frequently lack a control group, vary in the diagnostic criteria for CRS, and often have different outcome measures. An accurate diagnosis of CRS with positive endoscopic and/or radiologic studies and the use of

culture-directed antibiotic therapy may help in clarifying the true role of antibiotic therapy in CRS, but, to date, such studies have not been performed. For these reasons, the use of antibiotics in the medical management of CRS remains widely debated. Despite the widespread use of antibiotics for CRS, only one randomized placebo-controlled trial, utilizing a macrolide antibiotic for several months, showed efficacy [33]. Recently, a similarly designed study showed no improvement in the macrolide therapy arm compared with placebo [34▪▪]. Despite the paucity of evidence supporting antibiotic use in CRS, it remains important in our armamentarium and the remainder of this CRS section will discuss aspects of antibiotic use with review of trials and variations in aspects of the trials.

Antibiotic therapy in CRS is utilized for both reducing the bacterial burden and also for antiinflammatory effects of the medications. Studies of antibiotic efficacy in chronic and acute exacerbations of CRS vary in the study methodology, definition of CRS, duration of therapy and outcome measures, which makes definitive conclusions difficult to reach. An illustration of representative, poorly designed studies in the literature is given in Table 3. For example, two retrospective studies concluded that a 4-week course of systemic antibiotic therapy led to subjective improvement in greater than 90% of patients with CRS [35,36]. However, these two studies included patients treated with multiple other medications in addition to systemic antibiotics, including topical or systemic corticosteroids, and the sample sizes differed significantly between the two studies. Additionally, only one of the two studies commented on the duration of symptom improvement, which lasted at least 8 weeks in only 60% of patients [36].

COMPARISONS OF ANTIBIOTIC THERAPIES

Prospective, comparative studies between two different antibiotic therapies for CRS lack a placebo arm, precluding interpretation of antibiotic efficacy in the absence of any antibiotic showing superiority over the antibiotic comparator. A large prospective trial comparing ciprofloxacin versus amoxicillin/clavulanic acid (AMX/CA) therapy for 9 days revealed similar rates of clinical cure and bacterial eradication with the two different therapies [37]. Although the ciprofloxacin therapy was significantly better tolerated with a higher rate of prolonged bacterial eradication when examined at 40 days posttreatment (83.3 versus 67.6%), there was no significant difference in symptom improvement between the two antibiotics. Interestingly, only 56.2% of patients had positive middle meatus cultures at the beginning of the study, which may indicate that almost half the patients did not have a bacterial cause of CRS.

A prospective, multicentre, open randomized clinical trial (RCT) comparing the safety and efficacy of AMX/CA versus cefuroxime axetil (second-generation cephalosporin) for 14 days showed a similar clinical response and rate of bacterial eradication with a significantly lower relapse rate with AMX/CA compared with cefuroxime (0 versus 8%) [38] (Table 3).

LONG-TERM MACROLIDE THERAPY

Long-term antibiotic therapy, particularly with macrolides, has been reported to improve symptoms in patients with CRS refractory to surgery and corticosteroid therapy [40–43]. The mechanism behind these effects may be reduced virulence and tissue damage without eradication of the bacteria. Macrolide therapy increases mucociliary transport, reduces goblet cell secretion and enhances neutrophil apoptosis in animal models, which may reduce the effects of chronic inflammation in CRS patients. A RCT of 90 patients with CRS revealed similar symptom resolution with a 3-month course of macrolide therapy when compared with surgery for at least 1 year after treatment [44].

A randomized, placebo-controlled trial by Wallwork *et al.* [33] in 2006 demonstrated significant improvements in both symptom scores and clinical findings after 3 months of oral roxithromycin therapy for CRS. Until recently, this study remained the only placebo-controlled, RCT studying the effects of systemic antibiotic therapy in patients with CRS diagnosed with both subjective and objective criteria [45]. Earlier this year, the Macrolides in Chronic Rhinosinusitis study by Videler *et al.* [34▪▪] revealed no significant difference in symptom scores or objective measures after a 3-month course of azithromycin in a placebo-controlled RCT. Although both studies had a similar sample size, the study by Wallwork *et al.* did not include patients with nasal polyps. Additionally, there are variations in the dosing of the macrolides as well as the specific outcome measures between the two studies (Table 3).

TOPICAL ANTIBIOTIC THERAPY

Recently, there has been increased interest in the use of topical antibiotic formulations for CRS. Although oral and intravenous deliveries consistently achieve the therapeutic minimum inhibitory concentration (MIC) for the common pathogens of CRS in the sinonasal mucosa [46,47], topical administrations

Table 3. Illustrating representative studies of antibiotics in chronic rhinosinusitis

No of patients	Study	Study design	Therapy	Criteria	Effect on symptoms	Gram stain/mucopurulence	Culture and method	Imaging	Level of evidence
200	McNally *et al.* [35]	Retrospective review	4 weeks of various oral Abx, + nasal steroids, + saline lavage, + topical decongestants	Symptoms of chronic rhinosinusitis and endoscopic examination	Improved symptoms and examination findings in all patients	Gram stain not performed, mucopurulence evaluated on endoscopy (postnasal or anterior rhinorrhea)	None	Computed tomography scan initial and one-month follow-up after antibiotic therapy complete	III
40	Subramanian *et al.* [36]	Retrospective review	4–6 weeks of various oral Abx, + oral steroids, + adjunctive therapy	Symptoms of chronic rhinosinusitis and sinus computed tomography	Symptomatic +/− radiographic improvement in 90% of patients	None	In rare cases	Sinus computd tomography obtained before treatment and 6–8 weeks after antibiotic therapy, Lund Mackay score used for grading	III
251	Legent *et al.* [37]	Double blinded, double placebo-controlled trial	9 days of ciprofloxacin (500 mg b.i.d.) or AMX/CA (500 mg t.i.d.)	Endoscopic examination and/or sinus computed tomography	Clinical cure: 58.6% Cipro, 51.2% AMX/CA, bacterial eradication: 88.9% Cipro, 90.5% AMX/CA	Mucopurulence evaluated by rhinorrhea	Gram stain and culture performed	Sinus computed tomography scan performed at time of diagnosis	II
206	Namyslowski *et al.* [38]	Open, multi-center randomized control trial	14 days of cefuroxime (500 mg b.i.d.) or AMX/CA (875 mg b.i.d.)	Symptoms of CRS	Clinical response: 88% cefuroxime, 95% AMX/CA, bacterial eradication: 68% cefuroxime, 65% AMX/CA, clinical relapse: 7% cefuroxime, 0% AMX/CA	Culture performed on sinus aspirate or washout specimen. Mucopurulence is not a requirement for diagnosis	Pretreatment and posttreatment cultures	Pretreatment sinus radiography or ultrasound	II
64	Wallwork *et al.* [33]	Randomized, double blinded placebo-controlled trial	3 months of roxithromycin (150 mg daily)	Symptoms of chronic rhinosinusitis and endoscopic examination and sinus computed tomography	Treatment group with subjective improvement (SNOT-20 questionnaire) and endoscopic examination	Mucopurulence evaluated with endoscopy	Pretreatment and posttreatment Gram stain and culture	Sinus computed tomography scan performed at time of diagnosis	II
60	Videler *et al.* [34▪▪]	Randomized, double blinded placebo-controlled trial	3 months of azithromycin (500 mg daily for 3 days in week 1; then once weekly)	Symptoms of chronic rhinosinusitis and endoscopic examination and sinus computed tomography	No significant subjective improvement or endoscopic examination in treatment group	Presence of secretions evaluated with endoscopy	Pretreatment and posttreatment Gram stain and culture	Pretreatment computed tomography scan performed, Lund Mackay score used for grading	II
96	Huck *et al.* [39]	Double blinded, randomized controlled trial	10 days of cefaclor (500 mg b.i.d.) OR AMX (500 mg t.i.d.)	Symptoms of chronic rhinosinusitis and sinus radiography	Clinical improvement in 85% of ARS patients and 56% of recurrent ARS patients	Not specified	Pretreatment Gram stain and culture via antral tap	Sinus radiography (Waters view) performed to confirm diagnosis of rhinosinusitis	II

Few of these studies represent randomized placebo controlled trials (RPCT), and of the RPCT all but one fails to show antibiotic efficacy. Abx, antibiotics; AMX/CA, amoxicillin/clavulanic acid; ARS, acute rhinosinusitis; CRS, chronic rhinosinusitis; SNOT, Sinonasal Outcome Test.

can localize drug delivery to the sinonasal cavity and minimize the systemic effects of the antibiotics [48,49]. Recent technologic advances, such as nebulized drug delivery systems, have been shown to be effective drug delivery mechanisms in the sinonasal tract [50], with more effective drug deposition than spray formulations [51]. Additionally, common pathogens in CRS, such as *Staphylococcus aureus* and *P. aeruginosa*, are known to form biofilms, which have been found in up to 75% of CRS patients undergoing sinus surgery [52]. Bacteria present in a biofilm formation require higher antibiotic concentrations, up to 1000× the known MIC, in order to significantly reduce the bacterial count [53,54]. Topical antibiotic therapy may achieve the necessary drug concentrations to eradicate the common pathogens while minimizing systemic toxicity.

As with systemic antibiotic therapy, RCTs comparing topical antibiotic therapies are scarce in the literature and provide limited evidence regarding the efficacy of topical therapy. In a blinded placebo-controlled trial by Desrosiers *et al.* [55] of patients with CRS and open sinus cavities from prior endoscopic sinus surgery randomized to a tobramycin–saline nebulization or a saline-only group, both groups showed similar improvement in symptoms and endoscopic findings after 4 weeks of nebulized therapy. In a noncomparative observational study by Uren *et al.* [56], approximately 75% of patients with *S. aureus* cultured from their recalcitrant CRS had symptomatic and endoscopic improvement with mupirocin lavages.

ODONTOGENIC SINUSITIS

Odontogenic sinusitis, recognized since the 19th century as a cause of sinusitis, is usually a unilateral infection of the maxillary sinus from a maxillary dental infection, whose incidence has been underreported until recently [57–59]. This cause of recalcitrant sinusitis is typically overlooked due to a lack of sensitivity of dental examination and panorex in detection of dental infection and from lack of awareness amongst medical professionals [57]. Though the presenting symptoms of odontogenic sinusitis are rarely distinct from those of a nonodontogenic sinusitis, a high index of suspicion and careful evaluation of the maxillary dentition with computed tomography can aid in accurately diagnosing an odontogenic cause [57]. Longhini and Ferguson [57] and Ferguson *et al.* [22▪▪] showed that up to 47% of patients with odontogenic sinusitis will note a rotten smell and almost a third report upper teeth pain. Still half of patients with odontogenic sinusitis do not have these symptoms.

The bacterial pathogens implicated in odontogenic sinusitis are most commonly bacteria that comprise the normal oropharyngeal flora. Interestingly, these same bacteria are commonly isolated in patients with CRS without an obvious odontogenic source [60]. These isolates are predominantly anaerobic species within a polymicrobial population including aerobes as well [61]. Although many cases of odontogenic sinusitis persist until the infected dentition is addressed via root canal or extraction, appropriate antibiotic therapy may adequately control the acute exacerbation. Therefore, antibiotic therapy should consist of agents that have a spectrum of activity that includes anaerobic bacteria commonly found in the oropharyngeal flora. Culture-directed therapy by endoscopy is less useful in this setting due to the anaerobic nature of the bacteria, with many cultures showing no growth in the setting of odontogenic sinusitis, unless assessed by maxillary sinus tap of an unoperated, unventilated maxillary sinus. Therefore, when an odontogenic sinusitis is suspected the usual antibiotic recommendations are for clindamycin or amoxicillin/clavulanate.

CONCLUSION

The diagnosis of a bacterial cause for both ARS and CRS is difficult and antibiotics are only appropriate for those cases of sinusitis caused by bacteria. Nasopharyngeal swabs may aid the clinician in proper identification of bacterial causes of acute rhinosinusitis in adults and have the added benefit of providing antibiotic sensitivities, so antibiotic choice can be made accordingly, rather than as a guess of probabilities. The role of bacteria in CRS remains elusive, despite widespread use of antibiotics for this diagnosis. Up to one-third of patients with symptoms of CRS have no objective evidence of sinus disease. We recommend ancillary studies such as sinus CT or endoscopy before prolonged antibiotic courses are used in patients with CRS. Odontogenic sinusitis is often difficult to diagnose; however, close examination of the sinus CT for evidence of periapical lucencies has greatly increased our appreciation for the frequency of this finding.

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No conflicts of interest for R.M. or N P.
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Research – Genentech.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 232).

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