Title
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Journal
Current Opinion in Otolaryngology & Head & Neck Surgery, 23(1)

ISSN
1068-9508

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Publication Date
2015-02-01

DOI
10.1097/moo.0000000000000122

The role of antibiotics in endoscopic sinus surgery

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Purpose of review
To review and discuss recent literature regarding the use of antibiotics in relation to endoscopic sinus surgery (ESS), including perioperative antibiotics, postoperative antibiotics, and antibiotic usage in the setting of postoperative packing.

Recent findings
Perioperative antibiotics are not recommended by the American Society of Health-System Pharmacists. The necessity of antibiotics following ESS is a heavily debated topic. Most studies show little to no improvement in outcomes. Significant improvement in quality-of-life outcomes and endoscopic scoring appears limited to the early postoperative period using conventional postoperative antibiotics. Prolonged macrolide therapy may improve long-term outcomes. There is no convincing evidence to show the need for antibiotics in the setting of postoperative packing.

Summary
The available evidence regarding antibiotic use in relation to ESS overall fails to demonstrate routine benefit; however, the studies have various limitations. Overall, future, well designed, large-scale prospective studies would be beneficial to direct appropriate antibiotic use, whether systemic or topical, in relation to ESS.

Keywords
antibiotics, biofilm, chronic rhinosinusitis, endoscopic sinus surgery, packing

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory process involving the paranasal sinuses in which symptoms last longer than 12 weeks, and it is a debilitating medical condition affecting 12.5% of the US population [1,2]. Antibiotics are a mainstay of treatment for acute infections and disease exacerbations, but are problematic for many reasons. Major side effects may occur including allergic reactions and gastrointestinal symptoms with subsequent change in or cessation of therapy [3]. Additionally, bacterial resistance or unintended alteration of the existing flora of the nasal cavities may develop [4▪]. Liu *et al.* showed that treatment with oral antibiotics in patients with CRS significantly decreases microbiota diversity and evenness, and the bacteria become less susceptible to antibiotics. Finally, there is significant cost associated with repeated and prolonged antibiotic use. It is estimated that the healthcare system spends an average of $772 per patient per year on antibiotics, nasal sprays, and over-the-counter remedies [5].

Endoscopic sinus surgery (ESS) is indicated in CRS recalcitrant to medical therapy, and has been shown to significantly improve quality of life (QOL) and reduce long-term antibiotic utilization [6–8]. The necessity of antibiotics during or after ESS is not well established, and current practice exhibits wide variation. Given the above-mentioned concerns regarding antibiotic use, it is preferable to prescribe antibiotic therapy in a cost-effective and evidence-based fashion. This review discusses the recent pertinent literature regarding the utilization of antibiotics in the period surrounding ESS, including perioperative antibiotics, postoperative antibiotics, and the need for antibiotics with postoperative nasal packing.

EVIDENCE FOR PERIOPERATIVE ANTIBIOTICS

In 2013, an expert panel assembled to revise the ASHP Therapeutic Guidelines on Antimicrobial

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Curr Opin Otolaryngol Head Neck Surg 2015, 23:47–52
DOI:10.1097/MOO.0000000000000122

KEY POINTS

- As of the most recent guidelines, the ASHP does not recommend perioperative antibiotics at the time of ESS.
- Antibiotic use following ESS is highly debated. Most studies show little to no improvement in outcomes with the use of postoperative antibiotics. Statistically significant improvements have been limited to early postoperative outcomes.
- Prolonged postoperative macrolide therapy may improve long-term outcomes following ESS. These antibiotics may also have anti-inflammatory properties.
- There is no convincing evidence to show the need for antibiotics while packing is in place.

Prophylaxis in Surgery [9▪▪]. These guidelines are important to provide physicians with a standardized, rational approach to the use of perioperative antimicrobials to prevent surgical site infections with evidence-based recommendations. The previous guidelines from 1999 recommended antibiotic use in all clean-contaminated procedures of the head and neck, which includes ESS [10]. This decision was reversed in the most recent 2013 guidelines, which recommended antimicrobial prophylaxis in clean-contaminated procedures except for tonsillectomy and ESS. The decision was reversed due to a perceived lack of evidence showing that antibiotics change surgical outcomes.

In contrast, a recent review article by Ottoline *et al.* [11] recommended the routine use of intravenous antibiotic prophylaxis in all otolaryngologic surgical procedures prior to anesthesia. However, there was no evidence cited to support this recommendation. Regarding preoperative antibiotics, these authors recommended the use of oral amoxicillin-clavulanate and prednisolone for 14 days, starting 7 days before surgery. This recommendation was based on a study from 2001 on pediatric patients under the rationale that the nasal cavities are a contaminated surface.

Inoshita *et al.* [12] showed that oral perioperative antibiotics were equally effective to intravenous antibiotics. Ninety-three patients were enrolled in the study comparing levofloxacin by mouth to flomoxef (second-generation cephalosporin) intravenously both 2 h before surgery and 6 h after surgery, followed by twice-daily administration for 2 days postoperatively. No patient was found to have a postsurgical infection. Further study comparing this to placebo would be beneficial.

At this stage, perioperative antibiotics are likely more widely used than what would be predicted by the standards set forth by the ASHP. The decision for perioperative antibiotics appears to be based largely upon expert opinion and surgeon preference. High-quality prospective trials might assist with establishing definitive recommendations.

EVIDENCE REGARDING POSTOPERATIVE ANTIBIOTICS

Historically, it was reported that the use of antibiotics in nasal surgery was increasing from the 1970s to the 1980s due to reports of toxic shock syndrome following nasal surgery with postoperative packing. The use of postoperative antibiotics was recommended in the following situations: active infection at the operative site, nasal packing in place longer than 24 h, the presence of hematoma, when alloplastic implants are used, and in the immunocompromised patient [13]. A survey of the members of the American Rhinologic Society (ARS) in 2009 with respect to intraoperative antibiotic use following ESS demonstrated that 57% of the respondents used antibiotic prophylaxis, but only 7% of these did so because they felt there was strong evidence supporting this decision. The other 93% used antibiotics despite their belief that there was no solid evidence to support the use of perioperative antibiotics [14]. In another survey study performed in 2012, it was estimated that 86% of otolaryngologists use postoperative antibiotics [15]. Other than the reasons mentioned above, antibiotics might intuitively be beneficial following ESS on the basis of the clean-contaminated wound class with close approximation with bacteria throughout surgery and the healing process.

There have been multiple studies in the past 10 years showing evidence both for and against postoperative antibiotics. In 2008, Jiang *et al.* [16] demonstrated no short-term benefit in either symptom or endoscopic scores to postoperative amoxicillin/clavulanate therapy at 3 weeks. Three years later, Liang *et al.* [17] showed that there was no difference amongst patients treated with Chinese herbal medicine, amoxicillin, or placebo in the postoperative period in the Chinese version of the Rhinosinusitis Outcome Measure (CRSOM-31) and endoscopic scores. On the contrary, in 2010, Albu and Lucaciu [18] were able to show improved endoscopic scores on postoperative day number 5 and 12 with postoperative antibiotic treatment.

Saleh *et al.* [19] conducted a meta-analysis in 2012 that included the studies by Albu and Jiang. These authors were unable to support the use of prophylactic antibiotics following ESS based on the four studies examined that met the inclusion criteria. This was attributed to the small number

of patients and studies. The main antibiotics used were cefuroxime and amoxicillin/clavulanate. Rudmik and Smith [20] also reviewed similar evidence over the same time period. This study concluded that antibiotic administration did improve symptoms and crusting as suggested by Albu and Lucaciu. They qualified these conclusions by stating that these benefits seemed to be limited to the early postoperative period. The variability in conclusions of these meta-analyses is likely a factor of different inclusion criteria of studies for analysis.

In a recent study by Lee *et al.* [21▪▪], patients were separated into three groups: normal flora, culture-positive, and culture-negative (i.e. no growth) based on intraoperative cultures. The most common bacterial species seen intraoperatively were *Staphylococcus epidermidis, Propionibacterium acne*, and *Corynebacterium* spp. [21▪▪]. All patients were treated postoperatively with clarithromycin for 2 weeks followed by ciprofloxacin for 1 week. At 3 weeks, the patients were then treated with oral steroids and topical nasal steroids. The postoperative endoscopic scores were statistically better at 6 months in the culture-negative patients when compared to the normal flora and culture-positive patients. These authors suggested surgical results were improved by using postoperative antibiotics that were found in retrospect to be culture-appropriate.

Zhang *et al.* [22▪▪] recently studied whether culture-directed antibiotics improve long-term outcomes. In this study, all patients were treated with trimethoprim-sulfamethoxazole and clindamycin for 2 weeks postoperatively. On the basis of results of intraoperative cultures, only 7% of patients were found to have culture-inappropriate antibiotic therapy. Another 5% had culture-specific antibiotic adjustment. QOL outcomes were worse in patients with culture-inappropriate antibiotics at 1 and 3 months postoperatively. There was a slight improvement in outcomes when antibiotics were adjusted by 1 month postoperatively. By 6 months postoperatively, there was no statistical difference. These data suggest that culture-guided selection of postoperative antibiotics may improve short-term QOL, but long-term outcomes were equivalent.

Topical antibiotics

A biofilm is a group of microorganisms embedded within a self-produced matrix of extracellular polymeric substance (EPS). They have been found to be quite common, may be polymicrobial, can be extremely difficult to eradicate, and have been implicated in disease severity and recalcitrance in CRS [23,24]. With respect to antimicrobial therapy, topical therapies carry the benefit of mechanical debridement if administered by saline rinse and avoidance of systemic side effects when compared with oral antibiotics [23]. However, the use of topical antibiotics such as mupirocin irrigation has not historically shown significant benefit in patients with routine CRS or post-ESS recalcitrant patients [25,26▪]. Jervis-Bardy and Wormald [25] demonstrated that patients with *S. aureus*-positive CRS had subsequent reculturing of *S. aureus* in 73.7% of patients despite treatment with mupirocin irrigations twice daily for 4 weeks. The average time to the first positive culture was 144 days. On the contrary, when compared with normal saline sinus irrigations intraoperatively, mupirocin irrigations were recently found to statistically reduce the incidence of *S. aureus* found within the maxillary sinus 7–10 days postoperatively [27].

The eradication of *Pseudomonas aeruginosa* biofilm has been shown to be particularly difficult [28]. Topical tobramycin therapy has been utilized in this setting. A study by Chiu *et al.* [28] showed that irrigations are able to eliminate the bacteria within the lumen of the sinus, but were unable to break through the biofilm and remove the bacteria attached to the mucosa. No studies have been conducted on tobramycin irrigations in the immediate postoperative period to date.

Macrolide antibiotics

Macrolides are a specific class of oral antibiotics that deserve mention. These broad-spectrum antibiotics are commonly used to treat infections caused by gram-positive bacteria in addition to intracellular organisms such as *Mycoplasma* and *Chlamydia* spp. In addition to antimicrobial function, macrolides may also be beneficial due to anti-inflammatory properties involving suppression of promoters of neutrophilic inflammation and antibiofilm activity owing to interference with quorum sensing [29].

Nakamura *et al.* [30▪▪] recently showed that prolonged macrolide therapy (treatment for 6 months postoperatively) improved outcomes starting at 6 months after surgery. Additionally, following cessation of treatment at 6 months, outcomes continued to improve marginally. In the immediate postoperative period, no difference in outcome scores was noted. However, a recent meta-analysis by Pynnonen *et al.* [31▪] had conflicting conclusions, showing statistical significance at 24 weeks postoperatively. This study did not include data from the study by Nakamura *et al.* as they were published around the same time. As was previously suggested by Wallwork *et al.* [32], Pynnonen *et al.* emphasize that the subgroup of patients with low IgE levels demonstrate a greater response; however,

the meta-analysis was unable to show significance in this subgroup due to insufficient number of studies.

Comorbid conditions and antibiotic selection

It is known that certain comorbid conditions are associated with characteristic bacterial culprits. This knowledge may guide proper selection of postoperative antibiotics. In a retrospective study of patients with CRS with or without diabetes mellitus undergoing ESS, the patients with diabetes mellitus were much more likely to have cultures positive for *P. aeruginosa* and gram-negative rods [33]. Patients with diabetes mellitus had significantly worse postoperative sino-nasal outcome test (SNOT-22) at 6 months after adjusting for other risk factors. Future study is necessary to evaluate the response to specific antibiotics or no antibiotics in this patient population.

Recently, a prospective study was performed in patients with cystic fibrosis treated with ESS and postoperative topical antibiotic irrigations with colistimethate [34]. Colistimethate sodium is a polymyxin antibiotic effective against gram-negative bacilli. It can be used intravenously, aerosolized, or in nasal irrigations. Although its routine use is limited due to nephrotoxicity, it is still considered in cases of refractory, multidrug-resistant cystic fibrosis. In this study, 58 patients with cystic fibrosis with an intraoperative sinus culture positive for *P. aeruginosa*, *Achromobacter xylosoxidans*, and/or *Burkholderia multivorans* were initiated on a postoperative regimen consisting of nasal irrigations with normal saline mixed with colistimethate sodium, as well as systematic endoscopic cleansing. Sixty-seven per cent of patients had no growth of bacteria at 6 months postoperatively. This provides some evidence for efficacy of topical antibiotics that may be beneficial with respect to reducing use of systemic antibiotics and related significant drug resistance in this population.

EVIDENCE FOR ANTIBIOTICS WITH NASAL PACKING

One often cited reason for the use of antibiotics postoperatively is for prophylaxis while packing is in place. Recent meta-analyses failed to demonstrate significant difference in outcomes with absorbable packing, nonabsorbable packing, or no packing following ESS [35–37]. In a study by Verim *et al.* [38], patients with absorbable packing were shown to significantly improve in terms of pain, bleeding, nasal obstruction, and facial edema postoperatively, and healing was equivalent when compared to nonabsorbable packing. However, these studies did not comment on the necessity of antibiotic use with packing in place.

Antibiotic use in the setting of nasal packing has typically been studied in patients with anterior epistaxis. From 2009 to 2013, studies have failed to demonstrate improvement in outcomes or reduction in adverse events with routine use of oral antibiotics [39–41]. Nasal culture results at the time of packing removal have been overall similar to those of nonpacking nasal cavities [40]. A recent study by Biggs *et al.* [39] reviewed the use of antibiotics in patients with anterior nasal packs for epistaxis, showing that there were no difference in outcomes such as infective nasal symptoms, rebleeding, or readmission, even though antibiotic use fell 58% during the time period studied. These authors suggest that use of a topical antibiotic might be a more effective and cheaper alternative to oral antibiotics.

Wijewickrama *et al.* [42▪▪] recently discussed postoperative treatment with either 1 week of oral antibiotics and saline-soaked absorbable middle meatus sponge, or no oral antibiotics and the placement of a bacitracin-soaked absorbable sponge in the middle meatus following ESS. The addition of bacitracin is thought to provide sufficient protection against bacterial colonization and toxic shock syndrome. There was no significant difference in postoperative outcomes. These data would suggest that eliminating the risks of oral antibiotic treatment including side effects, drug–drug interactions, and medication compliance is not accompanied by worsened outcomes. Further study might include a group of patients who received no antibiotic therapy.

FUTURE DIRECTIONS

Currently, a randomized, double-blind, placebo controlled trial is in the enrollment stage at Massachusetts Eye and Ear Infirmary to determine the need for prophylactic antibiotics after ESS [43]. Participants are being divided into amoxicillin/clavulanate and placebo groups. The primary outcome tested is SNOT-22 scores. The secondary outcome measure is endoscopic scoring. Furthermore, the authors will measure the rate of postoperative infection. All of these outcomes will be measured up to 6 weeks postoperatively. Of note, one of the exclusion criteria is the presence of any postoperative foreign body such as absorbable or nonabsorbable packing. Recruitment is estimated to complete in December of 2014. It is anticipated that the results of this study will add to the evidence base regarding antibiotic use following ESS.

CONCLUSION

Current data remain inconclusive with regards to antibiotic use in the perioperative period. Perioperative prophylaxis is not recommended by the ASHP at this time. Regarding postoperative antibiotics, studies in general show little to no difference in outcomes and any improvement is limited to the early postoperative period. Studies to date have several limitations including small sample size, heterogeneous outcome parameters, and follow-up time periods, thereby limiting the feasibility of meta-analysis. Long-term macrolide therapy when used for 6 months postoperatively may be an exception, although improved outcomes may also be related to anti-inflammatory properties. The role of topical antibiotics requires further study. Overall, future well designed, large-scale prospective studies would be beneficial to direct appropriate antibiotic use, whether systemic or topical, in relation to ESS.

Acknowledgements

None.

Financial support and sponsorship

Financial disclosure: no financial disclosures.

Conflicts of interest

The authors have no relevant conflicts of interest or sources of funding to disclose.

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