

# Topical antimicrobials in the management of chronic rhinosinusitis: A systematic review

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## ABSTRACT

**Background:** Chronic rhinosinusitis (CRS) is a common disease that can significantly impact health. The mainstay of medical treatment is topical steroids and oral antibiotics, but little is known about the efficacy of topical antibiotics. The purpose of this study was to identify evidence for the use of topical antibiotics in the treatment of CRS and exacerbations of CRS.

**Methods:** Systematic review of literature with a search of the MEDLINE, EMBASE, and CINAHL databases; Cochrane Central Register of Controlled Trials (Third Quarter 2007); and Cochrane Database of Systemic Reviews (3rd Quarter 2007) databases were performed. The dates of search were from December 1, 1949 to September 30, 2007.

**Results:** Fourteen studies that fulfilled the inclusion criteria were identified: seven were controlled trials and of these, five were double blinded and randomized. Only one of the randomized studies showed a positive outcome. Overall, there was low-level corroborative evidence for the use of antibacterials. No definite conclusions could be made regarding the use of antifungals. Currently, there is evidence for the use of nasal irrigation or nebulization rather than delivery by nasal spray. For the antibacterial studies, the highest level of evidence currently exists for studies that have used postsurgical patients and culture-directed therapy. Both stable and acute exacerbations of CRS appear to benefit from topical antimicrobials.

**Conclusion:** Topical antibiotics appear effective in the management of CRS. Given the combination of low-level evidence (level III, with inherent potential confounders of natural progression of disease and placebo effect) and the level IIb evidence being limited to the cystic fibrosis group of patients, topical antibiotics should not be first-line management but may be attempted in patients refractory to the traditional topical steroids and oral antibiotics. Larger and better-designed randomized double-blind placebo-controlled trials are required to more fully evaluate this emerging modality of treatment.

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**Key words:** Antibiotics, antifungal, antimicrobials, culture-directed, irrigation, nasal, nebulizer, rhinosinusitis, spray, topical

Chronic rhinosinusitis (CRS) is a common condition affecting 14.2% of the population in the United States.<sup>1</sup> It significantly impacts health<sup>2</sup> and has a considerable economic burden on society.<sup>3</sup> Recently, the management of CRS has improved tremendously, especially with the advent of functional endoscopic sinus surgery. The mainstay of medical treatment has been the use of topical steroids (level of evidence Ib) and oral antibiotics (level Ib).<sup>4</sup> However, little is known about the efficacy of topical antibiotics.

The purpose of this study was to identify evidence for the use of topical antibiotics in the treatment of CRS and to determine if evidence exists for the various CRS subgroups. These subgroups are characterized by (1) method of delivery (nasal spray, irrigation, and nebulizer), (2) type of antimicrobial treatment, (3) the presence or absence of previous surgery, (4) stable CRS (versus an acute exacerbation), (5) presence or absence of cultures with which to select antibiotics.

## METHOD

A search of the MEDLINE, EMBASE, CINAHL databases, Cochrane Central Register of Controlled Trials (Third Quarter 2007), and Cochrane Database of Systemic Reviews (Third

Quarter 2007) databases were performed for the period of December 1, 1949 to September 30, 2007. All articles published in peer-reviewed journals in any language were eligible for review. A publication was not deemed eligible for review if (1) all subjects within the study also used concomitant nasal steroids and/or (2) the study compared a topical antimicrobial with combination topical antimicrobial and nasal steroid. In these instances no definitive conclusions about the true effect of the antimicrobial *per se* could be made. Medical subject headings and main key words used in the database searches were "topical," "nasal," "antibiotics," "antifungal," "antimicrobials," and "rhinosinusitis."

## RESULTS

Fourteen studies that fulfilled the inclusion criteria were identified (Tables 1–3). Seven studies were controlled trials,<sup>5–11</sup> including five double-blind and randomized trials.<sup>5,6,8,9,11</sup>

Levels of evidence are summarized in Table 4. Only one of the five randomized controlled trials (RCTs) established a successful effect and was categorized at level Ib. This was the double-blind RCT by Ponikau *et al.*, which showed a successful effect with the empiric nonculture directed use of amphotericin B irrigations.

Overall, there was no evidence for the use of topical antimicrobials delivered as a nasal spray. With regards to the nasal irrigation studies, six out of seven studies showed a positive outcome, with levels of evidence ranging from Ib to IV.<sup>7,8,12–15</sup> For the five publications that presented nebulized

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Table 1 Nasal spray antimicrobials in the treatment of chronic rhinosinusitis (CRS)

| Study and Design                                 | n  | Stable CRS or Exacerbation/ Postsurgical | Arms in Study                                | Culture Directed/ Posttreatment Reculture | Treatment Regime (Follow-Up)                                      | Outcome Measures   | Success Rates (Side Effects)  | Evidence |
|--|----|--|--|---|---|--|---|----------|
| Sykes 1986 <sup>5</sup><br>Double-blind<br>RCT   | 50 | Stable/no                                | N, D, T vs<br>D, T vs<br>propellant<br>alone | *No/Yes                                   | 4×/day for<br>2 weeks<br>(2 weeks)                                | Symptoms; mucociliary<br>clearance; nasal<br>airway resistance;<br>sinus x rays;<br>intranasal<br>bacteriology;<br>intranasal appearance | N/D/T: 14/20<br>improved; D/T:<br>12/20 improved;<br>Placebo: 2/20<br>improved (no side<br>effects mentioned)               | None     |
| Weschta 2004 <sup>6</sup><br>Double-blind<br>RCT | 78 | Stable/no                                | Amphotericin<br>B vs<br>saline               | *No/Yes                                   | 200 µL/nostril,<br>3 mg/mL,<br>4×/day for 8<br>weeks<br>(8 weeks) | CT score; symptom<br>score; QOL score;<br>endoscopy scores   | Symptom scores worse<br>after amphotericin;<br>no difference in other<br>outcome measures<br>(no side effects<br>mentioned) | None     |

\*Cultures performed but not culture directed.

D = dexamethasone; N = neomycin; QOL = quality of life; T = tramazoline.

antimicrobials, four of these studies concluded a positive effect, with level of evidence ranging from IIb to III.<sup>10,16–18</sup>

Eight studies focused on post-functional endoscopic sinus surgery surgical patients.<sup>7,9–13,15,18</sup> Of these studies, only the study by Desrosiers *et al.*<sup>9</sup> and Ebbens *et al.*<sup>11</sup> did not show a positive outcome. The remaining studies showed a beneficial effect for both irrigated and nebulized antimicrobials, with levels of evidence ranging from IIa to IV.<sup>7,10,12,13,15,18</sup> Two of six nonsurgical studies did not show any positive effect. Both of these studies also used the nasal spray as the mode of delivery.<sup>5,6</sup> The remaining four studies showed beneficial effect with level of evidence ranging from Ib to III.<sup>8,14,16,17</sup>

There were a total of 10 publications that presented empiric (*i.e.*, nonculture-directed) therapy.<sup>5,6,8,9,11,13,14,16–18</sup> Only 6 of these studies<sup>8,13,14,16–18</sup> showed efficacy with topical antimicrobials, as opposed to the 4 culture-directed studies, all of which showed efficacy in using topical antimicrobials, with varying levels of evidence (level IIa–IV).<sup>7,10,12,15</sup>

All studies except for two<sup>10,15</sup> looked at patients with stable CRS. The studies by Vaughan *et al.*<sup>10</sup> and Solares *et al.*<sup>15</sup> showed a successful outcome for the use of nebulized and irrigated antibiotics, respectively, in the treatment of acute exacerbation of CRS, rather than stable CRS.

Both subjective and objective outcome measures were used in the studies examined. Subjective methods included assessment of symptom and quality-of-life scores. Objective methods used were measurements of nasal airway resistance, endoscopy findings and scores, sinus x-ray findings, CT scores, and intranasal inflammatory markers.

## DISCUSSION

### Use of Topical Antimicrobials in Otolaryngology

Within the realm of otolaryngology, topical antibiotics have been used in the treatment of otitis externa and media.<sup>19,20</sup> Until the early 1990s there was little evidence for the treatment of CRS with topical antimicrobials,<sup>21</sup> although over the past 10 years topical CRS antimicrobial treatment has gathered greater attention.

### Rationale for the Use of Antibiotics in CRS and Exacerbations

The role of microbial infections in the etiology of stable CRS is currently unclear.<sup>4</sup> Although there are documented differences in flora spectrum in healthy versus CRS subjects, isolation of microbes from nasal and sinus cultures do not necessarily imply causation. A strong case for causation can only be made when clinical improvement of a subject is coupled with a negative repeat culture. It is important to remember that microbes may exist in biofilms; thus, culture results may be less meaningful. Notwithstanding these uncertainties, there currently exists evidence for the usage of oral antibiotics in the treatment of stable CRS.<sup>22–24</sup>

By contrast, the overwhelming differences in microbial spectrum between healthy versus acute rhinosinusitis subjects make it clear that in ARS, viral and bacterial infections are pathoetiologic agents. It is not unreasonable to assume that acute exacerbations in CRS are because of the same causes and may benefit from antibiotic treatment. Indeed, there are var-

ious studies showing the effectiveness of oral antibiotics in treating such exacerbations.<sup>25,26</sup>

### Rationale for the Use of Topically Applied versus Oral Antibiotics

Despite uncertainty surrounding the pathogenesis of CRS, the effectiveness of oral antibiotics in the treatment of CRS and its exacerbations suggests that topical antibiotics may be effective also. Although satisfactory antibiotic concentrations have been achieved in the sinus mucosa with oral administration,<sup>27,28</sup> topical antibiotics have the theoretical advantage of acting directly on the site of infection and producing a higher concentration of antibiotic at the target site. Such increased concentration of topical antibiotics have also been shown to be effective in killing bacteria in biofilm form.<sup>29</sup> Topical usage may also produce less systemic side effects and avoids selection of resistant gut microflora.

### Difficulties in Deriving Evidence by Comparison of Studies

In analyzing the various studies under review, direct comparisons cannot strictly be made because the studies under review differ in various aspects, including study designs, patient characteristics, outcome measures, and quality of the studies. Outcome measures used by some of the studies also may not be clinically meaningful. The Food and Drug Administration have produced guidelines in regulating the quality of studies examining the use of antimicrobial drugs to treat sinusitis.<sup>30</sup> The studies analyzed in our review do not uniformly follow these guidelines. Additionally, it is not possible to determine if all the studies use the same standard definitions for CRS. Notwithstanding these difficulties, many of the studies used multiple outcome measures with overlap of “core” outcome measures between studies, allowing sensible, rationale conclusions to be drawn in performing our review.

### Evidence for Topical Antimicrobials by Mode of Delivery

In examining the evidence by mode of delivery, there is no evidence for the use of topical antibiotics delivered as a nasal spray, although there were only two studies in this category. The study by Weschta looked only at amphotericin, and questions have been raised as to whether the dose of neomycin used in the Sykes study was sufficient.<sup>12</sup> In contrast, there are seven studies in the nasal irrigation group<sup>7,8,11–15</sup> and five in the nebulizer group,<sup>9,10,16–18</sup> almost all (except two studies<sup>9,11</sup>) of which showed varying degrees of evidence. These delivery methods have the advantage over the nasal spray in that they do not rely on mucociliary clearance (which may be impaired in CRS) to effect drug distribution. In addition, nasal sprays achieve a smaller deposition surface area than that covered by nebulization.<sup>31</sup>

With reference to the irrigation studies, the highest level of evidence (level Ib) was established in the study by Ponikau *et al.*, which looked only at antifungal irrigation.<sup>8</sup> Among the remaining irrigation studies, the highest level of evidence (level IIa) was exemplified by Moss *et al.*, which showed a statistical decrease in repeat surgery in the combined irrigated tobramycin and surgery group versus surgery alone group ( $p = 0.03$ ).<sup>7</sup> However, it is important to note that the group of

CRS subjects under study here were specifically patients with underlying cystic fibrosis.

In further examining the seven studies using nasal irrigation, evidence exists for the irrigation of the nasal cavities alone<sup>11–15</sup> or both the sinus and nasal cavities.<sup>7,8,12–14</sup> Efficacy from nasal irrigation alone may be caused by improvement in mucosal edema and hence sinus drainage rather than direct action on sinus pathology. This concept has also been elegantly shown in the study by Kobayashi.<sup>16</sup>

When analyzing the studies using nebulized antibiotics, the study with the highest level of evidence (level IIb) was the study by Vaughan *et al.*,<sup>10</sup> which examined the effect of six different culture-directed antibiotics (mostly levofloxacin) and showed a significant increase in infection-free period versus standard therapy (IV or oral antibiotics). Optimal particle size in treating sinus infections by nebulization should be  $<5 \mu\text{m}$ .<sup>32</sup> In the five studies reviewed, particle size was mentioned only in the study by Vaughan, with an average particle size of  $3.2 \mu\text{m}$ .<sup>10</sup>

It is interesting to note that with the exception of the studies by Ponikau and Ebbens,<sup>8,11</sup> all irrigation and nebulizer studies did not use an equivalent irrigated or nebulized control group, thus raising the possibility of a significant placebo effect in these studies. The study by Moss had surgery as a control group,<sup>7</sup> and the study by Vaughan had i.v. or oral antibiotics as a control group.<sup>10</sup> The possibility of a “nebulizer placebo” effect is further raised in the study by Desrosiers, which could not differentiate the beneficial effect of nebulized tobramycin versus saline.<sup>9</sup> Notwithstanding these questions, taken together, there currently exists low-level evidence for either irrigated or nebulized antimicrobials but no evidence exists for delivery by nasal spray.

### Evidence for the Type of Topical Antimicrobial

Of the 14 studies reviewed 9 studies explored the use of antibiotics,<sup>5,7,9,10,12,15–18</sup> 4 studies investigated the use of antifungals<sup>6,8,11,13</sup> and 1 study investigated the use of a broad-spectrum antimicrobial.<sup>14</sup>

For the antibiotic studies, only the study by Sykes (which may have used an insufficient a dose) did not show any positive effect.<sup>5</sup> The study that showed the highest level of evidence (IIa) was the study by Moss *et al.*<sup>7</sup> Overall, there seems to be a significant amount of mainly lower-level evidence (IIa–IV) pointing to the efficacy of topical antibacterials.

The 2005 study by Ponikau was performed with the hypothesis that fungi may be the antigenic stimulus driving the eosinophilic inflammation found in CRS.<sup>8</sup> This was a level Ib study with placebo irrigation as control. The findings from this study concur with an earlier single arm cohort study performed by the same author. However, two other studies, both RCTs performed in separate centers, did not find any evidence for the use of topical amphotericin.<sup>6,11</sup> In fact, the study by Weschta showed that symptoms worsened with it. However, a recent *in vitro* study has concluded that concentration of commercially available amphotericin B ( $100 \mu\text{g}/\text{mL}$ , the dose also used in the Ebbens study) may be insufficient to eradicate fungi.<sup>33</sup>

An argument against the use of antifungals is the fact that fungi are ubiquitous in sinonasal cavities, including normal subjects.<sup>34</sup> However, it has been argued that there may be a specific immune response driven by fungal antigens in pa-

Table 2 Nasal irrigation antimicrobials in the treatment of chronic rhinosinusitis (CRS)

| Study and Design   | n  | Stable Exacerbation/ Postsurgical | CRS or Exacerbation/ Postsurgical     | Arms in Study | Culture Directed/Post Treatment Reculture   | Treatment Regime (Follow-Up)  | Outcome Measures   | Success Rates (Side Effects) | Evidence |
|--|----|-----------------------------------|---------------------------------------|---------------|---|---|--|------------------------------|----------|
| Moss 1995 <sup>7</sup><br>Controlled study, no randomization | 51 | Stable/yes                        | Tobramycin + surgery vs surgery alone | Yes/no        | 40 mg/mL, 3 times/day for 7–10 days and monthly as necessary antral irrigation (monthly and 1 yr) | Decrease in repeat surgery  | Combined group decrease in repeat surgery at 1 yr, 10% vs 47% (not mentioned)  | IIa                          |          |
| Leonard 1999 <sup>12</sup><br>Report of clinical experience  | 50 | Stable/yes                        | Ceftazidime                           | Yes/no        | 300 mg/mL, 3 times/day nasal and sinus irrigation (1 and 2 wk)                                    | Symptoms; endoscopy   | Yes, based on clinical experience (1 pt, intranasal stinging sensation)  | IV                           |          |
| Ponikau 2002 <sup>13</sup><br>Single arm cohort study        | 51 | Stable most                       | Amphotericin                          | No#/no#       | 100 µg/mL, 80 mL/day nasal and sinus irrigation (3–17 mo)   | Subjective symptoms; endoscopic findings; CT findings   | 75% improvement in symptoms and endoscopic findings; statistically significant improvement in CT scan findings (20% burning sensation) | III                          |          |
| Ponikau 2005 <sup>8</sup><br>Double-blind RCT                | 30 | Stable/no                         | Amphotericin B vs placebo             | No#/no#       | 250 µg/mL, 20 mL 2 times/day for 6 mo nasal irrigation (6 mo)                                     | Primary: decrease mucosal thickening on CT; secondary: endoscopic patient symptom scores; intranasal inflammatory markers | Statistically significant improvement in CT scan findings (20% burning sensation)  | Ib                           |          |

(Table continues)

Table 2 Continued

| Study and Design  | n  | Stable CRS or Exacerbation/ Postsurgical | Arms in Study  | Culture Directed/Post Treatment Reculture | Treatment Regime (Follow-Up)  | Outcome Measures  | Success Rates (Side Effects)   | Evidence |
|---|----|--|--|---|---|---|--|----------|
| Neher 2005 <sup>14</sup><br>Single arm cohort study         | 12 | Stable/ no                               | N-chlorotaurine  | No§/no§                                   | 10–20 mL N-chlorotaurine 3 lavages/wk, 4 wk nasal and paranasal irrigation (smell, days 1,6, and 12; CT scan, wk 8) | Nasal breathing; smell; mucosa swelling; CT scan scoring      | 9/12 improved nasal breathing and smell; 12/12 improved mucosa swelling; no statistical improvement in CT scan scores (moderate pain, 5 cases)   | III      |
| Solares 2006 <sup>15</sup><br>Single arm cohort study       | 24 | CRS with acute exacerbations/ some       | Mupirocin ± doxycycline or trimethorpin-sulfamethoxazole | Yes/yes (most)                            | 22 g of 2% mupirocin in IL 0.9% of NaCl 50 mL b.i.d. 4–6 wk (3–27 mo)   | Symptomatic improvement; clinical and endoscopic findings     | Clinical and endoscopic resolution → 12 patients, symptomatic improvement with endoscopic evidence of disease → 13 patients, repeat cultures in this group none MRSA + ve, though 8 cultures + ve for other bacteria (not mentioned) | III      |
| Ebbens 2006 <sup>11</sup><br>Double-blind RCT multicentered | 51 | Stable CRS/ yes                          | Amphotericin B vs placebo                                | No/no                                     | 25 mL of amphotericin B (100 µg/mL) for 3 mo (2, 6, and 13 wk)  | VAS; endoscopic findings; RSOM-31; SF-36; PNIF; polyp scoring | No statistically significant difference in outcome measures (1 drug-related asthma attack)   | None     |

\*Study based on clinical experience, various facets of study exemplified by single case study.

#Quantification of *Alternaria* fungi performed, but treatment was not based on cultures.

§Cultures for fungi were performed, but treatment was not based on cultures.

MRSA = methicillin-resistant *Staphylococcus aureus*; PNIF = peak nasal inspiratory flow; VAS = visual analog scale.

Table 3 Nebulized nasal antimicrobials in the treatment of CRS

| Study and Design  | n   | Stable CRS or Exacerbation/ Postsurgical | Arms in Study  | Culture Directed/Post Treatment Reculture | Treatment Regime (Follow-Up)   | Outcome Measures   | Success Rates (Side Effects)  | Evidence |
|---|-----|--|--|---|--|--|---|----------|
| Kobayashi 1992 <sup>16</sup><br>3-arm cohort study          | 208 | Stable/no                                | DKB (aminoglycoside) fosfomycin cefmenoxime  | No*/no                                    | DKB, 5, 10, and 20 mg; fosfomycin, 30 and 50 mg; cefmenoxime, 20 and 40 mg (wk 8)  | Subjective symptoms x-ray findings                                       | DKB (50–62%) fosfomycin (43–71%) cefmenoxime (58–72%; not mentioned)  | III      |
| Desrosiers 2001 <sup>9</sup><br>Double-blind RCT            | 20  | Stable/yes                               | Tobramycin/saline vs saline only   | No*/no                                    | 80 mg# of Tobramycin 3 times/day for 4 wks (wk 8)                                  | Symptoms QOL endoscopic findings   | Statistically significant improvement in all outcome measures in both groups (but no significant difference between saline and tobramycin groups) | None     |
| Kamijyo 2001 <sup>17</sup><br>Single-arm cohort study       | 28  | Stable/no                                | Fosfomycin   | No*/no                                    | 2 mL of 3% Fosfomycin 3 times/wk for 4 wk (wk 4)                                   | 4 subjective and 5 objective symptoms as well as cytokine concentrations | Overall 78.6% improvement of symptoms (not mentioned)   | III      |
| Schienberg 2002 <sup>18</sup><br>Multiple-arm cohort study  | 41  | Stable/yes                               | 4 different nebulized antibiotics  | No/no                                     | Antibiotics nebulized for 3–6 wk (not mentioned)                                   | 5 subjective symptoms  | 82.9% excellent or good response (dry skin, throat irritation, cough)   | III      |
| Vaughan 2002 <sup>10</sup><br>Multiple-arm controlled study | 42  | CRS with acute exacerbations/yes         | 6 different culture-dependent nebulized antibiotics vs standard therapy (oral or IV) | Yes/yes                                   | Antibiotics nebulized for 3 wk (every 1–2 wk initially and for 3 mo after therapy) | RSOM –31; endoscopy findings   | Infection-free period average 17 wk vs 6 wk for standard therapy of oral/IV antibiotics (sore throat, cough, tinnitus, joint pain)                | IIb      |

\*Cultures performed but not culture directed.

#Additional 21-day course of antibiotic therapy was administered to all patients before their entry into this study.

DKB = dibekacin; QOL = quality of life; RSOM = rhinosinusitis outcome measure.

**Table 4 Levels of evidence**

|                            |   |
|----------------------------|---|
| Category of evidence       |   |
| Ia                         | Evidence for meta-analysis of randomized controlled trials  |
| Ib                         | Evidence from at least one randomized controlled trial  |
| IIa                        | Evidence from at least one controlled study without randomization   |
| IIb                        | Evidence from at least one other type of quasi-experimental study   |
| III                        | Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies |
| IV                         | Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both                   |
| Strength of recommendation |   |
| A                          | Directly based on category I evidence   |
| B                          | Directly based on category II evidence or extrapolated recommendation from category I evidence                                |
| C                          | Directly based on category III evidence or extrapolated recommendation from category I or II evidence                         |
| D                          | Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence                    |

tients with CRS.<sup>13</sup> In light of these conflicting results, it is difficult to draw any definitive conclusions for the use of topical antifungals at present.

### Evidence for Surgical and Nonsurgical Patients

In theory, the postsurgical patient offers unparalleled access for delivery of medication to the sinuses, as compared to the non-surgical patient. A study by Kobayashi has demonstrated that in non-surgical patients high concentrations above minimal inhibitory concentration are achievable in the nasal cavities but not in the maxillary sinus.<sup>16</sup>

In practice, the widened openings postsurgery may scar or become obstructed with mucosal edema or mucous. Optimal delivery to the sinuses can be achieved by placing a catheter directly within the sinus or by irrigating it intraoperatively. Nebulization or irrigation soon after the operation may also avoid the obstructing effects of possible postoperative scarring.

Among the eight postsurgical studies in our review,<sup>7,9–13,15,18</sup> the study by Desrosiers reported antibiotic nebulization for patients at least 8–12 weeks postsurgery<sup>9</sup> and the study by Moss described antibiotic irrigations for patients immediately after surgery using a catheter.<sup>7</sup> It was not clear from the remaining six studies how soon postoperatively the patients were treated.

In fact, both surgical and nonsurgical studies show efficacy

for the use of topical antimicrobials; however, currently, the level of evidence is higher in the postsurgical group. Specifically, the highest levels of evidence for the postsurgical studies are presented by Moss *et al.*<sup>7</sup> (level IIa) and Vaughan *et al.*<sup>10</sup> (level IIb). The publications focusing on nonsurgical patients, with the exception of the study by Ponikau,<sup>8</sup> present mainly level III evidence only.

### Evidence for Topical Antimicrobials in Stable and Acute Exacerbations of CRS

The rationale for the use of antimicrobials in the treatment of both acute exacerbations and stable CRS have been discussed previously in this article. It is not surprising then that the studies reviewed show evidence for the use of topical antimicrobials in the treatment of both subtypes, although there were only two studies (Solares<sup>15</sup> and Vaughan<sup>10</sup>) that examined acute exacerbations of CRS.

### Evidence for Culture-Directed Therapy

Culture-directed therapy is the “gold standard” when treating CRS with antibiotics.<sup>35</sup> Although antibiotic therapy has traditionally been empiric in the treatment of sinusitis, the emergence of antibiotic resistance has increased the failure rate for empiric treatment.<sup>36</sup> This is particularly the case in postoperative patients.<sup>37</sup> In advocating culture-directed therapy, the American Academy of Otolaryngology–Head and Neck Surgery recommends irrigation or nebulization with ceftazidime, aminoglycoside, or quinolones if pseudomonas is cultured and the use of amphotericin B irrigation with proven fungal infections.<sup>38</sup> The minimal inhibitory concentration of each antibiotic is well established, allowing guidelines to be produced on the optimal preparatory concentrations of each antibiotic to be used in topical irrigation.<sup>39</sup>

The culture-directed antibacterial studies present a higher level of evidence compared with the nonculture-directed studies. This is because of the studies by Moss<sup>7</sup> and Vaughan,<sup>10</sup> which studied culture-directed, postsurgical patients. Thus, the highest level of corroborated evidence in our review was for this particular category of patients. The study by Vaughan, in particular, should be highlighted.<sup>10</sup> This was one of only two studies that correlated clinical evidence of infection-free status with a negative repeat culture, and the results from this study make a very strong case for the use of culture-directed therapy. The other study by Solares did not perform repeat cultures for all cases but showed some degree of correlation between symptomatic improvement and a negative repeat culture.<sup>15</sup> Interestingly, it should be pointed out that both studies dealt with acute exacerbations of CRS rather than stable CRS.

### Other Specific Subgroups

Other clinical subgroups for CRS are well recognized, although they are based on anecdotal observations that have not been universally accepted. Postoperative infections with methicillin resistant *Streptococcus Aureus* (MRSA) as well as pseudomonas and other Gram-negative rod organisms may be a unique category in which topical antibiotics may play a unique role. Solares *et al.* focused on MRSA exacerbations in a group with a high prevalence of previous surgery; however, they did not focus on MRSA in the immediate postoperative

period. No study explicitly examined topical treatments for postoperative pseudomonas and Gram-negative rod rhinosinusitis, although the American Academy of Otolaryngology recommends topical treatments for pseudomonas rhinosinusitis.

Some clinicians have emphasized the concept of eosinophilic inflammation as the driver behind CRS. Unfortunately, these studies have not addressed the impact of topical antibiotic treatments on eosinophilic CRS.

### Limitations of Literature Review

Rules for evidence-based medicine (EBM) provide a vigorous methodology for the evaluation of previous studies, which individually carry little impact, but, collectively, show clinically meaningful results. Unfortunately, systematic reviews of the literature are limited by the quality of previous publications. For instance, studies that point to a small but statistically significant impact of an intervention probably should carry less weight than studies that show a larger therapeutic effect. Similarly, it is problematic to compare outcomes from treatment groups from different studies, because patient characteristics and other parameters are not uniform across different studies. Thus, one can only assess the quality of conclusions reached in individual studies. This approach relies on the application of EBM principles that provide a robust and reproducible methodology for the assessment of clinical research conclusions from numerous individual trials. EBM is not a perfect solution but is a practical and widely accepted solution for clinical dilemmas with no other easy answer.

### CONCLUSION

Emerging evidence suggests that topical antibiotics may be useful as a treatment modality in CRS and its exacerbations. Current corroborating evidence, at a relatively low level of evidence, points to the efficacy of topical antibacterials rather than antifungals, and to nasal irrigation or nebulization rather than delivery by nasal spray. For the antibacterial studies, the highest level of evidence currently exists for studies that have used postsurgical patients and culture-directed therapy. No definite conclusions could be made regarding the use of antifungals, because Ponikau's initial reports<sup>8,13</sup> have been contradicted by other studies. Both stable and acute exacerbations of CRS appear to benefit from topical antibiotics.

Given the combination of low-level evidence (level III, with inherent potential confounders of natural progression of disease and placebo effect) and the level IIb evidence being limited to the cystic fibrosis group of patients, topical antibiotics should not be first-line management but may be attempted in patient's refractory to the traditional topical steroids and oral antibiotics.

Larger and better-designed randomized double-blind placebo-controlled trials are required to more fully evaluate this modality of treatment. In particular, the control group for these future studies should be an equivalent sinonasal placebo rather than alternative methods of therapy. Additional studies could also directly compare different delivery methods, antibacterials versus antifungals, surgical and nonsurgical patients, and culture-directed versus empiric treatment. Comparison may prove difficult because of inability to adequately blind subjects and observers.

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