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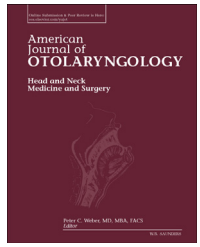

Original contribution

Endoscopic culture-directed antibiotic therapy: Impact on patient symptoms in chronic rhinosinusitis

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ABSTRACT

Background: Endoscopically guided cultures are frequently employed to guide antimicrobial therapy in refractory chronic rhinosinusitis (CRS) patients. The objective of this study was to determine the impact of culture-directed antibiotics on patient symptoms.

Methods: Retrospective review was conducted of 105 adult CRS patients undergoing evaluation in the ambulatory clinic of tertiary care academic medical center.

Results: The most common microbes were *Staphylococcus aureus* (29.5%), *Pseudomonas aeruginosa* (23.8%) and methicillin-resistant *S. aureus* (11.4%). Normal respiratory flora or no growth was found in 19% of patients. Culture results changed antibiotic choices in 77% of patients. Statistically significant change in total SNOT-20 scores and all 4 subdomains was noted, with improvement being clinically meaningful in the rhinologic subdomain (–1.10, $p < 0.0001$). Repeat purulence was only noted in 5 cases (4.8%). Multivariate regression analysis demonstrated that concurrent use of oral steroids was independently associated with improvement in the rhinologic subdomain ($p = 0.0041$). The mean length of follow-up was 37 days. Length of follow-up (14–30, 31–60, 61–90 days) did not statistically impact SNOT-20 scores.

Conclusion: Endoscopic-derived sinus cultures are associated with clinically meaningful change in the rhinologic subdomain of SNOT-20 scores, and repeat purulence was infrequently noted at follow-up. Further prospective studies are needed to better delineate the role of cultures in CRS management.

Level of evidence: 4.

1. Introduction

Chronic rhinosinusitis (CRS) represents an inflammatory disorder of the nose and paranasal sinuses characterized by sinonasal symptoms with evidence of disease by endoscopy or radiographic imaging of greater than 12 weeks duration [1]. A variety of environmental and host mechanisms have been implicated in the etiology of CRS including presence of microbes (bacteria, fungus), allergy, ciliary dysfunction, derangements in innate and adaptive immunity, biofilm formation, and osteitis [2]. The exact role of bacterial pathogens remains to be fully elucidated to date.

The utility of antibiotics in the management paradigm of CRS has been a cause of significant debate. Nonetheless, they

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are frequently employed to treat infectious exacerbations of CRS [3]. The microbiology of CRS, especially in the post-sinus surgery setting can be quite disparate, with frequent presence of *Staphylococcus aureus*, coagulase negative *Staphylococcus* (CNS), and gram negative rods [4]. Thus, endoscopically guided cultures (EGC) are commonly used to guide antimicrobial therapy, with one previous study noting EGCs resulting in change in antibiotic choice in 51.4% of cases [5]. However, there is a paucity of data addressing the essential question if antibiotics derived from EGCs impact objective symptom scores. The present study was conducted to better ascertain the impact of endoscopically driven antibiotic therapy on patient symptoms and endoscopic findings in CRS patients.

2. Materials and methods

The study was conducted at the University of Texas Southwestern Medical Center from July 2010 to October 2012. Patients for inclusion were identified from the senior author's (PSB) clinical practice using ICD-9 codes for CRS (473.0, 473.1, 473.2, 473.3, 473.8, and 473.9). The patient list was then cross-referenced to the central microbiology registry to identify patients that underwent sinus cultures. Institutional review board approval was obtained from UT Southwestern Medical Center prior to commencing the study.

The inclusion criteria included diagnosis of CRS with or without polyposis in patients with age ≥18 years. Acute exacerbation of CRS, defined by minimum SNOT-20 score of 1.0 on scale of 0 to 5, was required for inclusion. This was based on 0.8 being deemed a clinically meaningful change by Picirillo et al. and would afford the ability to detect a discernable difference post-treatment [6]. All patients used nasal saline irrigations and topical nasal steroid for maintenance therapy. Patients were excluded who received oral, topical and/or intravenous antibiotic therapy within one week of presentation or who did not have purulence on presenting nasal endoscopy. One week constitutes more than 4.5 half-lives for most antibiotics and, thus, it was assumed that after one week, the level of antibiotics in patient's serum and soft tissue would be clinically negligible. All initial and follow-up endoscopies were performed by the senior author. Patients with follow-up shorter than 2 weeks were excluded to ensure adequate time for antibiotic efficacy to manifest in clinical changes. Similarly, follow-up greater than 90 days were also excluded to minimize the likelihood that the clinical would be influenced by other factors.

All patients presented with acute exacerbation of sinonasal symptoms with evidence of purulent secretions on endoscopy. A rayon-tipped swab (Bactiswab®, Remel Products, Lenexa, KS) or Lukens trap (Cardinal Health, Dublin, OH) was used to collect secretions from the site of purulence on nasal endoscopy. The microbiology laboratory protocol involved special handling of the sinus cultures. The cultures were initially handled on broad spectrum media. Specific colonies of certain bacteria commonly seen in CRS, such as *S. aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Serratia marcescens*, and *Stenotrophomonas maltophilia*, were assayed and reported when present. If two or three microbes were equally present, then the results were reported as polymicrobial. Normal respiratory flora was reported if none of these bacteria were identified. For patients undergoing multiple cultures, only the initial culture result was included.

Other data collected included patient demographics, co-morbidities (asthma, inhalant allergy, aspirin exacerbated respiratory disease, polyps), surgical history, site of culture, key pathogens, and antibiotic choices. SNOT-20 scores were prospectively recorded at the initial visit and then on follow-up visit after completion of treatment. Evidence of purulence on follow-up endoscopy was also ascertained.

2.1. Statistical analysis

Descriptive statistics of the study population were performed with mean and standard deviation being calculated for continuous variables and frequencies with percentage being calculated for categorical variables. The change in overall and sub-scale (rhinologic, ear/facial, psychological, sleep) SNOT scores were determined by using the following formula: delta score = post-treatment score − pre-treatment score. Univariate analysis was conducted to determine the impact of age, gender, number of previous surgeries, smoking history, asthma, aspirin sensitivity, polyps, organism type, and use of concurrent oral steroids on SNOT-20 scores. Association between each risk factor and overall and sub-scale SNOT-20 scores was calculated using Pearson correlation for continuous variables and two-sample t-test for categorical variables.

Multivariate stepwise logistic regression model was used to identify significant independent risk factors impacting post-treatment SNOT-20 scores while adjusting for all other risk factors. ANOVA test was used to test the association between SNOT-20 scores and time interval between exams (14–30, 31–60, and 61–90 days). Two-sided significance level of 0.05 was used for all statistical analyses. All analyses were carried out using SAS version 9.2 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Demographics

A total of 105 patients were included based on the inclusion criteria. The mean age was 46.3 years and 43.8% were males. Polyps were noted in 53 (51.0%) patients. The presence of inhalant allergy, asthma, and ASA sensitivity was noted in 58 (55.2%), 39 (37.1%), and 5 (4.8%) cases, respectively. The mean number of previous endoscopic sinus surgeries (ESS) was 1.9 (range 0–8). Overall, 96 (91.4%) patients had undergone previous sinus surgery. The mean follow-up after initial antibiotic treatment was 37 days (range: 14–85 days).

3.2. Culture and treatment data

The location of the sinonasal cultures included middle meatus in 56 (53.3%), maxillary sinus in 32 (30.5%), nasal cavity in 7 (6.7%), sphenoid sinus in 3 (2.9%), ethmoid cavity in 3 (2.9%), frontal recess in 2 (1.9%), and unspecified in 2 (1.9%) cases. The mean number of pathogens on the aerobic culture was 1.2 (range 0–3), with 32 (30.5%) cultures being polymicrobial (Table 1). No growth and normal respiratory flora was reported in 6 (5.7%) and 14 (13.3%), respectively.

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Table 1 – Most common pathogens assayed in this 105 patient group.

Pathogen	Frequency (%)
S. aureus	31 (29.5%)
P. aeruginosa	25 (23.8%)
MRSA*	12 (11.4%)
Staphylococcus epidermidis	6 (5.7%)
Streptococcus pneumoniae	6 (5.7%)
E. coli	6 (5.7%)
S. maltophilia	4 (3.8%)

MRSA: methicillin-resistant *S. aureus*.

Empiric antibiotic therapy was initiated in 55 (52.4%) cases, most commonly being amoxicillin/clavulanate in 21, quinolones in 14, and clarithromycin in 12 patients. Antibiotic therapy was changed based on culture in 81 (77.1%) patients. Monotherapy and dual therapy was used after the culture in 72 (88.9%) and 9 (11.1%) cases, respectively. Most common antimicrobial therapies instituted were doxycycline in 24, quinolones in 24, trimethoprim/sulfamethoxazole in 14, and second-generation cephalosporins in 9 patients. Typical duration of therapy was 2 to 3 weeks in most cases. A total of 62 (59.0%) patients received concurrent steroids for frank polyps or sinonasal polypoid edema.

3.3. *Outcomes data*

Table 2 demonstrates the pre- and post-treatment SNOT-20 and subdomain scores for the entire group. Univariate analysis did not identify any specific factors associated with a statistically significant change in total SNOT-20 scores (Table 3a). However, in the rhinologic subdomain, concurrent oral steroids (−0.72 vs. −1.38, p = 0.005) were associated with a statistically significant change in SNOT-20 scores (data for subdomains not shown). Multivariate analysis illustrated concurrent oral steroid usage was an independent predictor of improvement of the rhinologic subdomain (Table 3b). The time interval to follow-up after treatment was not found to be statistically associated with change in SNOT-20 scores (Table 4). Five (4.8%) patients had evidence of purulence on repeat endoscopy after treatment.

Table 2 – Total and subdomain SNOT-20 scores pre- and post-treatment [a].

Outcomes [*]	Pre-treatment score	Post-treatment score	Change of score (Post – Post)	p-Values [*]
Δ Total SNOT	2.23 (±0.81)	1.17 (±0.96)	−0.56 (±0.74)	<0.0001
Δ Ear-facial	1.85 (±1.23)	1.48 (±1.15)	−0.38 (±0.88)	<0.0001
Δ Rhinologic	2.90 (±1.28)	1.80 (±1.16)	−1.10 (±1.20)	<0.0001
Δ Sleep	2.50 (±1.33)	1.93 (±1.47)	−0.57 (±1.37)	<0.0001
Δ Psychological	2.13 (±1.32)	1.50 (±1.28)	−0.62 (±1.07)	<0.0001

[a] Total and subdomain scores were scaled from 0 to 5 in each outcome category to facilitate comparison across categories. A change of 0.8 per category represents a clinical significance threshold.
[*] p-Value calculated from two sample t-test.

Table 3a – Univariate analysis of impact of key variables on total SNOT-20 scores.

Variable	Δ SNOT-20 Absent	Δ SNOT-20 Present	p-Value [*]
Age [**]			0.03 (0.75)
Number of surgeries [**]			0.08 (0.40)
Male	−0.54 (±0.85)	−0.59 (±0.57)	0.7630
Smoker	−0.59 (±0.79)	−0.47 (±0.55)	0.4620
Asthma	−0.49 (±0.70)	−0.68 (±0.80)	0.2239
Allergy	−0.42 (±0.63)	−0.67 (±0.81)	0.0866
Aspirin sensitivity	−0.54 (±0.71)	−0.97 (±1.21)	0.2021
Polyps	−0.51 (±0.62)	−0.61 (±0.84)	0.5071
S. aureus	−0.64 (±0.77)	−0.38 (±0.64)	0.1114
MRSA	−0.57 (±0.77)	−0.47 (±0.44)	0.5137
S. epidermidis	−0.53 (±0.72)	−1.04 (±1.01)	0.0982
P. aeruginosa	−0.59 (±0.78)	−0.48 (±0.58)	0.5256
S. pneumonia	−0.56 (±0.73)	−0.62 (±0.91)	0.8445
Concurrent oral steroids	−0.48 (±0.59)	−0.62 (±0.82)	0.3003

[*] p-Values for two-sample t-tests.
[**] For continuous variables, correlation (p-value) was calculated; i.e. the Pearson correlation between age and delta SNOT-20 was 0.03 and the p-value for the association between the two variables was 0.75.

4. Discussion

The role of bacterial pathogens in the pathophysiology of CRS, and, hence, the role of antibiotics has been a source of significant controversy in rhinology. The preponderance of particular bacteria on culture does not imply causation of CRS but merely an associated factor in this experimental design. Despite the paucity of robust data to support their efficacy, an American Rhinologic Society survey of 308 members revealed that majority of respondents use antibiotics as a component of maximal medical therapy "almost always (>90%)" [7]. Indeed, in this study, all patients received some form of antibiotics, regardless of culture results. A systematic review recommended short-

Table 3b – Multivariate stepwise linear regression model for independent risk factors for total and subdomain SNOT-20 scores.

Outcome [a]	Factor [b]	Estimate (± STE) [c]	p-Value
Δ Total	NA	NA	No independent risk factor identified
Δ Ear-facial	NA	NA	No independent risk factor identified
Δ Rhinologic	Concurrent oral steroids	−0.68 (±0.24)	0.0041
Δ Psychological	NA	NA	No independent risk factor identified
Δ Sleep	NA	NA	No independent risk factor identified

NA: not applicable.
[a] Post-treatment score – pre-treatment score.
[b] Factors entered into the multivariate model were allergies, polyps, smoking, *S. aureus*, *S. epidermidis*, concurrent oral steroids (univariate p-value <0.2 for at least one of the outcome).
[c] Estimate (±STE): Parameter estimate (±standard error).

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Table 4 – Association between days in between visits with total and subdomain SNOT-20 scores.

Outcome [a]	Days in between SNOT			p-Value [*]
	14–30 (n = 45)	31–60 (n = 50)	61–90 (n = 10)	
Δ Total	−0.64 (±0.81)	−0.52 (±0.69)	−0.39 (±0.68)	0.5617
Δ Ear-facial	−0.39 (±0.82)	−0.36 (±0.94)	−0.38 (±0.94)	0.9829
Δ Rhinologic	−0.69 (±1.31)	−0.84 (±1.32)	−0.50 (±0.74)	0.6956
Δ Sleep	−0.74 (±1.50)	−0.41 (±1.34)	−0.73 (±0.95)	0.4716
Δ Psychological	−0.99 (±1.03)	−0.94 (±0.97)	−0.55 (±1.13)	0.4608

[a] Outcomes = post-treatment score – pre-treatment score.
[*] p-Values from ANOVA test.

term non-macrolide oral antibiotics (less than 3 weeks duration) as a potential option in adult patients with CRS with or without polyposis [8]. Nevertheless, a recent Cochrane review found "limited evidence from one small study to support the use of systemic antibiotics for the curative treatment of chronic rhinosinusitis in adults" [9]. The disparity between the available evidence base and existing clinical practice served as an important impetus for the current series.

The preponderance of *S. aureus* and *P. aeruginosa* in this series has been observed in previous series [5,10]. Cincik and Ferguson noted prevalence of *S. aureus* and *P. aeruginosa* in 33% and 18.5% of patients presenting with acute exacerbation of CRS [5]. Not surprisingly, 77.9% of their patients had undergone previous ESS. Bhattacharyya and Kepnes performed 290 cultures in 125 post-ESS patients, with most common pathogens being *S. aureus*, CNS, and *P. aeruginosa* [10]. Previous studies have demonstrated increased antimicrobial resistance rates in CRS patients [11,12]. Thus, given the significant microbiologic diversity and increased rates of antibiotic resistance encountered in the CRS population, especially in the post-ESS setting, EGCs are frequently warranted to guide optimal management of acute exacerbations of CRS.

The current analysis builds on earlier work by Cincik and Ferguson who also addressed this important issue [5]. A total of 68 consecutive patients with CRS and acute exacerbation of CRS with nasal secretions underwent endoscopic cultures in their study. Empiric antimicrobial therapy was initiated in 47%; therapy was changed in 66% based on the culture result. Similarly, in the present series, empiric antibiotic therapy was started in 52% of the cases; eventually being altered by the culture in 77.1%. However, the present study differed in several important respects from this previous data, as this study only included patients with symptomatic exacerbation with documented purulence on endoscopy. The exclusion of non-purulent secretions represented an important divergence from the previous data. The exact significance of non-purulent secretions remained unclear in the CRS group, with previous work demonstrating frequent colonization of CNS, diphtheroids, and *S. aureus* in asymptomatic CRS patients [11].

The initial antibiotics used in this series most commonly included amoxicillin/clavulanate, quinolones, and clarithromycin. The most common therapies instituted after culture were doxycycline, quinolones, and trimethoprim/sulfamethoxazole. Intuitively, initial choices were broad spectrum to cover common CRS organisms, being tailored by cultures to specifically target the cultured organisms. However, the rationale for the specific changes instituted is quite complex and multifactorial, carefully considering not only the culture and sensitivity results, but also accounting for patient preference, allergies, side effect profile, and cost. The ideal duration of the treatment is also not known, though typically 2 to 3 weeks was employed in this series. This is in congruence with recent recommendations from a systematic review, suggesting ≤3 weeks of non-macrolide antibiotics as an option for adult CRS patients [8]. Longer treatment courses should be discouraged given lack of strong efficacy data, increased risk of side effects, and potential for antibiotic resistance.

Univariate and multivariate analysis was performed to discern potential factors that may impact improvement in SNOT-20 scores. Interestingly, the use of concomitant systemic steroids was the only factor observed to be an independent predictor for improvement in the rhinologic subdomain of SNOT-20 scores. This suggested that the mere use of oral antibiotics alone may not be sufficient to address the exacerbation. It underscored the importance of oral steroids as an important component of the overall multimodality treatment, especially in patients with significant relapse of frank polyps or evidence of polypoid edema. This was also in accordance with a recent evidence-based review with strong recommendation for use of oral steroids for short-term management of CRS with polyps [12].

The other important factor that was identified was the presence of *S. aureus* in patients with persistent purulence despite treatment. The exact reasons for this association is not clear but could be related to the importance of *S. aureus* in contributing to the recalcitrance of CRS. The ability of *S. aureus* to form biofilms and to maintain intracellular residence are two potential mechanisms that may pose a significant challenge to achieve complete eradication of the infectious process [13]. Furthermore, enterotoxins derived from *S. aureus* have been implicated in the pathogenesis of CRS with nasal polyps, and may induce a pro-inflammatory environment and immune system dysfunction, rather than an actual infection itself [14]. It is important to note that, overall, majority of the patients had resolution of the purulence with the treatment. Further, bacterial species other than *S. aureus* have biofilm-forming abilities which may also be associated with persistent purulence. However, since only five patients had persistent purulence, this study was underpowered to detect these intricate associations.

Important limitations of this present study must be acknowledged. The retrospective, uncontrolled nature posed potential for recall bias in the data collection process, though all SNOT-20 data was collected prospectively. Further, the patient group represented a heterogeneous patient population with differing co-morbidities, though most patients in the group as a whole was a recalcitrant subset having undergone previous sinus surgery. Furthermore, the length of follow-up was not standardized. One would expect patients with more severe disease to have a propensity to follow-up sooner than scheduled; likewise, patients with greater improvement may have simply canceled or delayed their appointments. Future studies with preferably a prospective design with a standardized follow-up protocol, uniform treatment algorithm, and a control arm, with patients possibly receiving no antibiotics or broad-spectrum antibiotics not tailored to culture, would be required to better discern these issues.

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5. Conclusion

Endoscopically derived aerobic cultures to direct antibiotic therapy was associated with a change in antibiotic treatment in 77% of patients with acute exacerbations of CRS. This treatment strategy resulted in statistically significant improvement in total and subdomain SNOT-20 scores in the patient group, with the change being clinically meaningful in the rhinologic subdomain. The use of concurrent oral steroids appeared to an independent predictor of improvement of the rhinologic subdomain SNOT-20 scores.

Disclosures

PSB: Consultant (Medtronic), SAB (Merck).
ZYJ: none.
YFK: none.

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