The Risk of Development of Antimicrobial Resistance in Individual Patients With Chronic Rhinosinusitis

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Objective: To determine if individual patients with chronic rhinosinusitis (CRS) demonstrate an increasing prevalence of antimicrobial resistance over time.

Patients: A prospectively maintained database of microbiologic culture results for adult patients with CRS was sequentially analyzed, extracting patients who underwent multiple serial sinus cultures over time. Antimicrobial resistance patterns were identified and quantified for each bacterium. Sequential culture results were compared for individual patients to determine if increasing overall bacterial resistance, gram-positive resistance, gram-negative resistance, or a shift toward gram-negative organisms was manifested within individual patients.

Results: During a 7-year period, 90 adult patients were identified with 224 serial cultures (mean, 2.5 cultures per patient) obtained, with a median time between cultures of 157 days. Four hundred twenty-nine organisms were isolated from these serial cultures, consisting of 255 gram-positive organisms, 120 gram-negative organisms, 48 anaerobes, and 6 fungi. Pairwise analysis of sequential cultures revealed no significant trend toward increasing bacterial resistance within individual patients (P=.57, runs test). Similarly, no significant trend toward increasing gram-positive or gram-negative resistance was demonstrated. There was no shift toward gram-negative organisms (P>.15 for all).

Conclusions: Individual patients with CRS do not necessarily develop increasing levels of bacterial resistance over time. The use of culture-directed antimicrobial therapy may “protect” against the development of sequentially increasing antimicrobial resistance for patients with CRS.

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Although the cause of chronic rhinosinusitis (CRS) remains controversial, most investigators agree that at least one component of the pathogenesis of CRS is microbial infection. Substantial information exists in the literature implicating bacterial infection as one of the microbial pathogens in CRS. Because of the putative role of bacterial infection in CRS, most treatment guidelines recommend extended courses of antibiotics in the medical management of CRS before consideration of surgical therapy. In addition, despite adequate surgical therapy, typically with endoscopic sinus surgery (ESS), a small but significant number of patients may continue to experience acute bacterial exacerbations of their CRS, often requiring antibiotic therapy. Investigators have analyzed microbiologic patterns of bacterial infection in CRS before and after surgery. Results have confirmed a substantial prevalence of gram-negative organisms and perhaps increasing microbiologic resistance patterns to antibiotics.

However, the time-dependent pattern of the development of antimicrobial resistance for individual patients with CRS has not been previously studied, to our knowledge. Although the overall prevalence of increasing antimicrobial resistance may be identified in populations studied over the course of years, it is not clear as to the specific origin of increasing antimicrobial resistance. Whether individual patients are experiencing increasing rates of antimicrobial resistance for their bacterial pathogens of CRS as sequential infections are treated has not been determined. This study was conducted to determine if, as they are treated for CRS exacerbations, patients individually develop increased levels of antimicrobial resistance during the course of their disease. Phrased another way, do individual patients acquire increasing rates of bacterial resistance as they are treated repeat-
edly for acute exacerbations of CRS over time? This would have important repercussions for the treatment of individual patients if indeed serious increases in antimicrobial resistance were demonstrated in patients during the course of their disease.

**METHODS**

This study was approved by the Committee on Clinical Investigations at Brigham and Women’s Hospital. We analyzed a prospectively maintained electronic database of sinus culture results for January 1997 through December 2003. This database consists of all sinus cultures submitted from our hospital for adult patients with a diagnosis of CRS and includes date of culture, site of culture, isolated organism, gram stain characteristic, and sensitivity analysis. Sensitivity analysis is determined and coded according to the National Committee Clinical Laboratory Standards break points for each bacterial species.

From this prospective database, patients who underwent 2 or more sinus cultures during the study period were identified and extracted. Demographic and microbiologic culture data were retrieved. Data were tabulated and exported to Microsoft Excel (Redmond, Wash). After preliminary demographic analysis, the database was further restricted to cases for which multiple positive cultures were isolated for each patient on separate calendar days during the study period. Therefore, each remaining case had 2 or more sinus cultures (serial culture data) with an identified organism on each of the bacterial cultures, allowing comparative analysis among cultures by isolated organism. Data were imported to SPSS version 10.0 (Chicago, Ill).

Statistical analyses were conducted to answer 4 basic questions: (1) Is there a trend toward increasing degree of antimicrobial resistance for individual patients with CRS? (2) Are gram-positive organisms acquiring increasing resistance over time for an individual patient? (3) Are gram-negative organisms acquiring increasing resistance? (4) Is there a shift from gram-positive to gram-negative organisms within individual patients with CRS over time?

First, the development of increasing microbial resistance according to serial cultures for each patient was analyzed. For each patient, a sequence of pairs of cultures was constructed according to sequentially advancing dates of culture. For example, patient A may have had cultures done on January 1, 1997, July 1, 1998, and January 1, 1999. From this sequence of serial cultures, 2 pairs (1997-1998 and 1998-1999) exist for comparison with each other. From each pair of cultures obtained in a serial fashion for each patient, the degree of resistance for the maximally resistant bacterium (understanding that the culture results were commonly polymicrobial) was identified for the first culture and then compared with the maximally resistant bacterium isolated from the second culture. The degree of resistance for a given bacterium was defined as the number of antibiotics with microbial resistance divided by the number of total tested antibiotics. Intermediate antimicrobial resistance according to the National Committee Clinical Laboratory Standards break points was considered “resistant” for the purposes of this study. If the second culture’s bacterium exhibited a more severe degree of antimicrobial resistance, this paired sequence of cultures was considered as having demonstrated increasing bacterial resistance over time. If there was no increase in resistance severity for the second culture’s isolated organism vs the first culture’s organism, this pair was considered as not exhibiting increasing bacterial resistance over time. Ties (ie, equivalent resistance percentages between pairs) were considered as not showing increasing development of resistance. A comparison of proportions of increasing bacterial resistance vs lack thereof was conducted with the runs test for randomness of a sequence with the Monte Carlo exact method with significance set at $P<.05$.

This pairwise comparison method was then used to determine whether increasing sequential resistance could be demonstrated specifically for the subset of gram-positive organisms and again for the subset of gram-negative organisms. Finally, this pairwise comparison method was used to determine if a shift occurred within individual patients from gram-positive to gram-negative organisms over time. However, for the analysis of gram-negative shifts, persisting gram-negative organisms on cultures after the first culture were considered as demonstrating a shift toward gram-negative prevalence.

**RESULTS**

During the period under consideration, 834 positive sinus cultures were obtained, yielding 1074 organism isolates. Among these cultures, 90 adult patients had 2 or more cultures drawn on different days, comprising 224 serial cultures (mean, 2.5 cultures per patient). The median time between serial cultures was 137 days. Overall, 429 organisms were isolated from these serial cultures, consisting of 235 gram-positive organisms, 120 gram-negative organisms, and 48 anaerobes; 6 isolates were fungi. **Table 1** lists the organisms recovered by frequency. On average, gram-positive organisms demonstrated a mean number of 1.7 antimicrobial resistances per organism vs 5.0 antimicrobial resistances per organism for gram-negative organisms.

**Table 2** demonstrates results of the statistical analysis for the 4 hypotheses tested. No statistically significant increase in severity of antimicrobial resistance was demonstrated within patients as serial cultures were...
drawn. In fact, a general trend toward decreasing antimicrobial resistance was noted overall, with many patients showing reversion to lesser degrees of antimicrobial resistance over time. Similarly, no significant increase in antimicrobial resistance was demonstrated for subgroups of gram-negative organisms or gram-positive organisms. Again, a trend toward decreasing antimicrobial resistance was noted over time. Finally, no statistically significant shift toward increasing prevalence of gram-negative organisms was identified on an individual patient basis.

**COMMENT**

During the past decade, substantial interest and concern have surfaced regarding the increasing prevalence of antimicrobial resistance in medicine, prompting high levels of attention even at the governmental level. Several medical societies and federal agencies have cautioned the health care industry and the public, and they have called for more judicious, evidence-based prescribing rules for antibiotic treatment in an effort to stem what is believed to be a potential serious problem in the treatment of common infectious diseases. Many otolaryngologic conditions arise from or are in part due to chronic infections, and one of the most common of these entities is CRS. Therefore, the problem of antimicrobial resistance has a significant bearing on our specialty.

Several potentially disturbing trends have emerged in the bacteriology and infectious epidemiology of CRS. Recently, several authors have identified increasing prevalence for gram-negative organisms in CRS in native and surgically treated cases. In a study of patients transitioning from acute to chronic rhinosinusitis, Broek et al demonstrated a microbiologic transition from common offenders such as Staphylococcus pneumoniae for acute rhinosinusitis to more refractory bacteria such as Staphylococcus aureus. Increases in β-lactamase activity were also demonstrated. In addition, patients experiencing acute exacerbations of CRS after ESS have been demonstrated to have a significant prevalence of gram-negative organisms, often with elevated levels of antimicrobial resistance.3

Recently, the Sinus and Allergy Health Partnership put forth recommendations for the antimicrobial treatment of acute bacterial rhinosinusitis. Because of the increasing prevalence of β-lactamase–producing strains of bacteria, recommendations have now shifted to more potent β-lactam–stable antibiotics with broader spectra of antibacterial action. These recommendations, when empirically followed for patients with CRS rather than acute bacterial rhinosinusitis, could lead to the formation of refractory antimicrobial resistance. Unfortunately, little attention has been paid to antimicrobial treatment guidelines for CRS. Two separate areas of debate exist. First, what is the appropriate-spectrum antibiotic for the initial treatment of CRS, and what is the appropriate treatment duration with antibiotic regimens before consideration of ESS? The second area of debate surrounds the treatment of acute exacerbations of CRS before or after ESS. Little scientific data exist concerning the appropriate use of antimicrobials in the medical management of CRS, especially in the preoperative state. Typically, authors recommend 4 to 6 weeks of broad-spectrum antimicrobials in the initial medical management of CRS. However, there are no specific randomized trials for extended-course antimicrobial therapy in CRS, and, to date, no specific antibiotic carries a Food and Drug Administration–approved indication for the treatment of CRS (as opposed to approval for the treatment of acute bacterial rhinosinusitis).

The problem of recurrent acute bacterial exacerbations of CRS, especially after ESS, has drawn some significant attention in the literature. We have previously demonstrated a somewhat concerning prevalence of gram-negative organisms in patients experiencing recurrent acute exacerbations of CRS after ESS. Other investigators have shown similar prevalences of gram-negative organisms and some trends toward increasing antimicrobial resistance in patients after ESS. In the postoperative setting, oral antibiotics are sometimes recommended, whereas topical antibiotics, some delivered by novel methods, have also demonstrated efficacy. The use of antibiotics for the treatment of postoperative acute exacerbations of CRS seems warranted given that recent data have shown that these infections occurring after surgery are due to growth of noncolonizing bacteria.

The use of culture-directed therapy has been proposed as one conceivable method for reducing the prevalence of antimicrobial resistance in patients with CRS. Advocates of culture-directed therapy suggest that, by obtaining cultures at the time of an acute exacerbation of CRS, likely organisms may be identified and targeted antibiotic therapy instituted, avoiding the need for empiric therapy with overly potent broad-spectrum antibiotics. As it is believed that overuse of broad-spectrum antibiotics may be a key step in the promotion of bacterial resistance, culture-directed therapy has been adopted by many investigators.

Unfortunately, culture-directed therapy requires significant cooperation on the part of the patient and is more expensive because of the costs of a physician’s visit and laboratory culture compared with empiric antibiotic therapy. Although empiric therapy may be less expensive in the short term, resulting antimicrobial resistance may have more serious implications in the long term for these patients.

We advocate culture-directed therapy for all patients after ESS and for patients not operated on after the failure of first-line antimicrobials. To some degree, we believe that the demonstrated lack of increase in antimicrobial resistance in the present patient population may be accounted for by our reliance on culture-directed therapy. In addition, in our clinical practice, a strong ef-
fort is made to avoid broad-spectrum antimicrobials when possible; this avoidance may have helped prevent a shift toward gram-negative organisms on serial culture for individual patients.

In conclusion, the present study demonstrates that, in patients undergoing serial culture and treatment for acute exacerbations of CRS, the risk of developing antimicrobial resistance over time remains small. Individual patients with CRS are not more likely to develop antimicrobial resistance as recurring infections are treated. Therefore, patients should not necessarily be more concerned about their individual potential development of antimicrobial resistance when culture-directed therapy is used.

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REFERENCES


