Acute Community-Acquired Bacterial Sinusitis: The Value of Antimicrobial Treatment and the Natural History

Jack M. Gwaltney, Jr.,1 Barbara A. Wiesinger,2,* and James T. Patrie2

Departments of †Internal Medicine and ‡Health Evaluation Services, University of Virginia School of Medicine, Charlottesville, Virginia; and ‡Somerset, New Jersey

Two areas of investigation were reviewed: (1) placebo-controlled trials of antimicrobial treatment involving patients with a clinical diagnosis of acute community-acquired bacterial sinusitis (ACABS) for whom pre- and posttherapy sinus aspirate cultures were not performed, and (2) uncontrolled trials of antimicrobial treatment involving patients with ACABS for whom pre- and posttherapy sinus aspirate cultures were performed. The clinical diagnostic criteria in the controlled trials were not correlated with sinus aspirate culture results and, thus, were of questionable validity. Most of the populations probably included patients with viral rhinosinusitis.

In 10 uncontrolled studies, the posttreatment, weighted, pooled mean bacterial resolution rate (± standard error) at 7–10 days, based on sinus aspirate culture results, was 91% ± 10%. In 9 controlled trials, the weighted pooled mean rate of clinical improvement (± standard deviation) at 7–14 days for placebo recipients was 52% ± 18%. In 1 controlled trial in which diagnosis was based on duration of unimproved illness, 57% of placebo recipients and 85.5% of treated patients were healthy or had improved by day 10. Additional studies of ACABS are needed.

Acute community-acquired bacterial sinusitis (ACABS) has been reported to complicate 0.5%–2.0% of common colds and influenza-like illnesses in adults [1, 2] and 5%–10% of such cases in children [3]. In the United States, which has a population of >250 million people and an average incidence of colds in adults and children of ~4 colds each per year [1], this represents ~20–30 million cases of ACABS per year. Although its microbial etiology has been established by sinus puncture studies [4–9], there is little information on the natural history of the disease, and placebo-controlled trials of antimicrobial treatment have not been performed with patients for whom the diagnosis and proof of cure were established by sinus aspirate culture.

In this article, 2 areas of investigation are reviewed: (1) placebo-controlled trials of antimicrobial treatment involving patients with a clinical diagnosis of ACABS for whom pre- and posttherapy sinus aspirate cultures were not performed, and (2) uncontrolled trials of antimicrobial treatment involving patients with ACABS for whom pre- and posttherapy sinus aspirate cultures were performed. Using these data, the article examines the effectiveness of antimicrobial therapy for ACABS and the natural history of the disease.

ETHICAL CONSIDERATIONS IN TREATMENT AND FUTURE STUDY

Although most cases of ACABS are self-limited when treatment is not provided [10], ACABS can be complicated by bacterial meningitis, brain abscess, and infection of and around the eye. The role of ACABS in the pathogenesis of chronic sinus disease is open to
question but may also be important. In the past, ACABS was treated with irrigation and drainage [9], but these methods have been replaced by antimicrobial treatment, which remains the standard of practice. However, because the findings of controlled trials involving pre- and posttreatment sinus aspirate cultures were not reported when antibiotics became available, the standard of proof on the question is not ideal. Because of rising medical care costs, the value of using antimicrobials that cover the usual pathogens for ACABS has been questioned, and inexpensive antimicrobials to which resistance has developed have been recommended [11, 12].

This raises the question of whether there is sufficient scientific support to continue the use of antimicrobials for treating ACABS or whether controlled trials in which patients with ACABS receive no antimicrobial treatment are needed. Untreated subjects would be put at risk, although small, of developing serious or potentially fatal complications and of possibly developing chronic sinus disease. Therefore, it is important to evaluate the quality of published information on the effectiveness of antimicrobial treatment to determine whether current practices are acceptable and whether additional studies are needed.

METHODS

Two databases were used: Ovid and MEDLINE. The search used combinations of the terms “placebo-controlled trials,” “controlled clinical trials,” “antimicrobial therapy,” “bacterial sinusitis,” “sinusitis,” “acute-community acquired bacterial sinusitis,” and “acute sinusitis.” Nine placebo-controlled clinical trials of antimicrobial therapy were identified.

KEY FEATURES OF EXPERIMENTAL DESIGN

Content validity. The most challenging problem in clinical trials of ACABS is to ensure that patients in the study population actually have the disease (table 1). Various signs and symptoms used in the diagnosis of ACABS have been evaluated [13–15]. None have been correlated with sinus aspirate culture results, and none have shown both high sensitivity and high specificity, nor have various combinations. Also, it is not possible to obtain uncontaminated samples of the contents of the sinus cavity for culture without needle aspiration. The natural ostium of the maxillary sinus is hidden in the ethmoid infundibulum behind the uncinate process [16]. This makes it difficult to visualize and impossible to enter, even with angled telescopes.

An alternative is to collect specimens from the middle meatus of the nose. Limited data from samples obtained from this site by endoscopy have shown only fair correlation with sinus aspirate culture results. In a study of 47 patients with intact sinuses undergoing simultaneous maxillary sinus aspiration and endoscopic sampling of the middle meatus, endoscopic sampling had a sensitivity of 65%, a specificity of 40%, a positive predictive value of 38%, a negative predictive value of 67%, and an accuracy of 49% [17]. For Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae alone, the accuracy was 85%, but this ignores other relevant pathogens including β-hemolytic streptococci, pus-forming α-hemolytic streptococci, anaerobic bacteria, and Staphylococcus aureus. Also, endoscopic cultures may not reflect conditions in the sinus cavity after treatment. Endoscopic sampling is not sufficiently accurate for establishing diagnosis and proof of bacteriologic cure in research. Sinus aspirate culture remains the gold standard.

It has been proposed that a history of a cold or influenza-like illness that is no better or worse after 7–10 days is an acceptable standard for the clinical diagnosis of ACABS. Although this is not as accurate as sinus aspirate culture, it is now considered a better criterion than selected signs and symptoms for establishing the diagnosis of ACABS [18, 19].

Statistical power. End points used in evaluating antimicrobial treatment in ACABS are eradication of infection, duration and severity of illness, imaging study findings, and incidence of complications. Pre- and posttreatment sinus aspirate culture results had a weighted, pooled mean resolution rate (±SE) of infection of 91% ± 10% among patients who received a 7–10-day course of antimicrobial treatment (table 2) [20–22]. To detect an effect size for resolution of infection that

Table 1. Key features in the experimental design of clinical trials of acute community-acquired bacterial sinusitis.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content validity</td>
<td>Pretreatment sinus aspirate culture for bacteria, with quantitative culture preferred and simultaneous Gram stain desirable</td>
</tr>
<tr>
<td>Positive history of a common cold or influenza-like illness that is not better or worse after 7–10 days</td>
<td></td>
</tr>
<tr>
<td>Sample size calculations</td>
<td>Sample size calculations are reported and are adequate for effect sizes specified</td>
</tr>
<tr>
<td>Randomization</td>
<td>Patients are randomized by an accepted method to experimental and control groups</td>
</tr>
<tr>
<td>Blinding</td>
<td>Patients and investigators are blinded to treatment status</td>
</tr>
<tr>
<td>Completion rate</td>
<td>Completion rate of subjects is given</td>
</tr>
<tr>
<td>Compliance</td>
<td>Compliance in taking medications is measured</td>
</tr>
<tr>
<td>End points</td>
<td>Bacteriologic eradication: posttreatment sinus aspirate culture for bacteria, with quantitative culture preferred and simultaneous Gram stain desirable</td>
</tr>
<tr>
<td>Clinical response</td>
<td>Clinical response: pre- and posttreatment standardized measurements of duration and severity of signs and symptoms</td>
</tr>
<tr>
<td>Imaging response</td>
<td>Imaging response: pre- and posttreatment sinus imaging examinations with CT preferred in most instances</td>
</tr>
<tr>
<td>Functional status</td>
<td>Functional status: work, daily activities, quality of life</td>
</tr>
<tr>
<td>Data analysis</td>
<td>Data analysis: reporting of methodology</td>
</tr>
</tbody>
</table>

Pretreatment sinus aspirate culture for bacteria, with quantitative culture preferred and simultaneous Gram stain desirable.
is $\geq 20\%$ less than this standard, a sample size of 57 patients
with positive pretreatment sinus aspirate culture results is
required in both the experimental and control groups to have a
1-sided hypothesis test with a type I error rate of $\leq 0.05$ and
type II error rate of $\leq 0.20$ (statistical power of $0.80$).

Complete resolution of illness is the ideal clinical end point,
but there are problems with this because of tailing off of
minimal complaints at the end of illness. Individual signs and symp-
toms present the problems of variations in incidence, duration,
and variance. In one study that used the end points of maxillary
sinus pain, C-reactive protein level, and erythrocyte sediment-
tation rate, a total sample size of 133 patients yielded a type I
error of $\leq 0.05$, a type II error of $\leq 0.10$, and a minimum
detectable effect size of 25% [23]. In a study that used the end
point of selected signs and symptoms, a sample size of 98
patients in each trial arm detected an improvement of cure rate
from 75% to 90% with a 2-sided hypothesis test with a type I
error of $\leq 0.05$ and a type II error of $\leq 0.20$ [24]. In a study
that included patients with both ACABS and the common cold,
a total sample size of 90 patients detected a 35% difference in
cure rate on the basis of selected signs and symptoms, with a
power of 90% and a significance level of 5% [25]. To assess a

difference of 1 day of illness ($\alpha = 0.05; \beta = 0.10$) on the basis
of pain and daily activity required a sample of 84 subjects in
each treatment group for a type 1 error rate of $\leq 0.05$ and type
II error rate of $\geq 0.10$ [26].

Imaging, especially sinus CT examination, provides another
end point for calculating sample size, but problems exist in its
use. Of 6 studies that compared sinus imaging findings with
sinus puncture findings, only 2 performed bacterial cultures of
the aspirate specimen, and neither used a positive culture result
for the diagnosis of ACABS. Validated criteria are not available
to distinguish abnormalities in ACABS from those of viral rhino-
sinusitis. Imaging abnormalities clear rapidly in viral rhino-
sinusitis [27] but may persist for up to a month in treated
cases of ACABS [28]. If the patient sample is contaminated
with cases of viral rhinosinusitis, imaging end points will be
affected. Also, the imaging abnormalities of chronic sinus
disease may not be distinguishable from those of ACABS
without serial examinations or the accompaniment of bony
abnormalities.

The incidence of intracranial and orbital complications is
not practical as a therapeutic end point, because their low in-
cidence requires very large samples to provide adequate statis-
tical power. The development of chronic sinus disease is an
important and neglected end point that also requires large sam-
ple sizes.

Randomization, blinding, and compliance. Clinical trials
of ACABS present no special problems in randomization, blind-
ing, and compliance.

Measurement of treatment effect. With the intact sinus,
noninvasive sampling of the sinus mucosa for histologic ex-
amination is not possible. As discussed above, measurement of
treatment effect has focused on bacterial eradication, resolution
of signs and symptoms, and changes noted by imaging studies.
Current US Food and Drug Administration regulations for clin-
ical trials of ACABS do not require negative posttherapy sinus
aspirate culture results as proof of bacterial eradication. Some
investigators have applied the term “presumed bacterial erad-
ication” to cases showing clinical response to antimicrobial
therapy. This preserves that clinical improvement correlates
chronologically with resolution of infection. However, there are
no data to show that this relationship is valid. In fact, inves-
tigators who perform sinus puncture studies have observed
patients who reported clinical improvement at a time when the
sinus aspirate specimen showed marked inflammatory changes
and yielded high titers of bacteria. In one study, 39% of 44
placebo recipients with presumed ACABS (determined on the
basis of illness duration) reported some degree of clinical im-
provement by day 3 of observation, and 89% reported this by
day 10, although only 11% had returned to normal by the latter
date [10]. Patients with clinical improvement would be con-
sidered to have had a “presumed bacteriologic cure,” but with-

Table 2. Bacterial infection resolution rates based on pre- and
posttreatment sinus aspirate cultures for patients with acute com-

<table>
<thead>
<tr>
<th>Antimicrobial treatmenta</th>
<th>No. of bacteriologic resolutions/no. of patients evaluated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975–1981</td>
<td></td>
</tr>
<tr>
<td>Ampicillin, 500 mg q.i.d.</td>
<td>12/13 (92)</td>
</tr>
<tr>
<td>Ampicillin, 500 mg t.i.d.</td>
<td>14/14 (100)</td>
</tr>
<tr>
<td>TMP-SMX, 160/800 mg b.i.d.</td>
<td>18/19 (95)</td>
</tr>
<tr>
<td>Cefaclor, 500 mg q.i.d.</td>
<td>15/17 (88)</td>
</tr>
<tr>
<td>1983: Bacampicillin, 800 mg b.i.d.</td>
<td>18/19 (95)</td>
</tr>
<tr>
<td>1986</td>
<td></td>
</tr>
<tr>
<td>Cyclacillin, 500 mg t.i.d.</td>
<td>23/26 (88)</td>
</tr>
<tr>
<td>Amoxicillin, 500 mg t.i.d.</td>
<td>25/27 (93)</td>
</tr>
<tr>
<td>1989: cefuroxime axetil, 250 mg b.i.d.</td>
<td>36/38 (95)</td>
</tr>
<tr>
<td>1990</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanate, 500/125 mg t.i.d.</td>
<td>11/12 (92)</td>
</tr>
<tr>
<td>Loracarbef, 400 mg b.i.d.</td>
<td>13/14 (93)</td>
</tr>
<tr>
<td>Cefixime, 200 mg mg b.i.d.</td>
<td>105/115 (91)</td>
</tr>
<tr>
<td>1995: Levofloxacin, 500 mg q.d.</td>
<td>14/14 (100)</td>
</tr>
<tr>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanate, 500 mg t.i.d.</td>
<td>22/26 (85)</td>
</tr>
<tr>
<td>Cefdinir, 600 mg q.d., 300 mg b.i.d.</td>
<td>56/64 (87.5)</td>
</tr>
<tr>
<td>Total</td>
<td>382/418 (91)b</td>
</tr>
</tbody>
</table>

NOTE. TMP-SMX, trimethoprim-sulfamethoxazole.

a Received for 7–10 days

b Mean ± SE, 91% ± 10%.
out sinus aspirate culture results, it is not possible to know whether active infection was still present.

**REVIEW OF PUBLISHED LITERATURE**

The key features of controlled clinical trials of antimicrobial therapy for ACABS described above were used for the evaluation of published work (table 3).

**Placebo-controlled trials.** With a single exception, the placebo-controlled trials of antimicrobial treatment of ACABS used clinical criteria (and not sinus aspirate culture results) to ensure content validity [7, 10, 23–26, 29–31]. One investigator used the duration of illness criterion [10]. Otherwise, the quality of the studies was generally satisfactory, except that several studies lacked sample size calculations. However, it is not sufficient to meet the standards of adequate sample size, randomization, blinding, and standardized measurement of effect if a study population is composed of subjects who do not have the disease being investigated.

The following are examples of this problem. One study involved 247 patients with “nasal discharge of any quality, facial pain unrelated to trauma, or self-suspected sinusitis” [13]. Using the criterion standard of sinus radiograph abnormality to diagnose “sinusitis” (implied ACABS), they found that 95 (38%) of the patients met this standard. Another group of researchers studied patients whose primary physician had “made a clinical diagnosis of acute sinusitis and considered them to be in need of antibiotic treatment” [14]. Using the criterion standard of sinus CT abnormality for diagnosis, they observed that 127 (63%) of 201 patients had “sinusitis” (implied ACABS). With viral rhinosinusitis predominating by such a wide margin over ACABS, the predictive value of any clinical criterion will be low unless the criterion or criteria have high sensitivity and specificity, which is not the case. With the prevalence of viral rhinosinusitis at 90%–98% and that of ACABS at 2%–10%, and with the sensitivity of the diagnostic criteria at 38% or 63%, respectively, the chances of accurately diagnosing cases of ACABS are low. With the above examples, there is the more important problem that imaging abnormality, not sinus aspirate culture, was used as the diagnostic standard. Because the content validity of the controlled clinical trials cannot be assured, their findings are open to question.

The incidence of ACABS as a complication of acute viral respiratory illness has not been established by sinus aspirate culture. In one study, 53 (0.5%) of 11,134 patients with colds had developing sinusitis (implied ACABS) diagnosed by clinical criteria [1]. Other investigators, who used a purulent character of the sinus aspirate, not culture, as the diagnostic standard, observed this finding in 2 (2%) of 100 adults with common colds [2]. In children, the incidence of ACABS after colds, determined on the basis of extended duration of illness, was reported to be 5% [3].

Acute exacerbations of chronic sinus disease can also be difficult to distinguish from ACABS. These patients may also contaminate the patient populations in clinical trials of ACABS. Invalid content of study populations affects the clinical response to antimicrobial therapy in several ways. Cases of viral rhinosinusitis will not respond to antibiotic treatment but will rapidly and spontaneously resolve, adding noise to the true signal of therapeutic response to antimicrobial therapy. Cases of chronic sinus disease may respond poorly, adding further noise. The duration of imaging abnormalities is also different for the 3 conditions.

**Uncontrolled trials with pre- and posttreatment sinus aspirate culture.**
pirate culture data. The number of patients in these studies ranged from 12 to 115 persons (table 2) [20–22]. Resolution of infection was judged to have occurred if the posttreatment aspirate culture result was negative or if the titer had decreased by \( \geq 4 \log_{10} \) from the pretreatment titer. The bacterial resolution rate ranged from 71% to 100% but was \( \geq 88\% \) in 11 of 13 instances. The 2 instances in which the resolution rate was lower were associated with the use of an inadequate dose of the antibiotic.

Two trials that used pre- and posttreatment sinus aspirate cultures compared different dosages or different antibiotics (table 4) [32, 33]. The bacteriological resolution rates were higher in patients receiving doses that were considered adequate, compared with those receiving doses that were considered inadequate, on the basis of in vitro MICs for the infecting bacteria. The effectiveness of antimicrobial treatment in eradicating infection in the sinus cavity is supported by the results of other puncture studies in which the use of inadequate doses of antibiotics was associated with a lower bacteriologic resolution rate than that seen in historical controls receiving an adequate dose [9, 20, 34].

**NATURAL HISTORY OF ACUTE COMMUNITY-AQUIRED BACTERIAL SINUSITIS**

Studies could not be located that described the natural history of untreated cases of ACABS. Thus, information on the clinical course of untreated disease comes from patients receiving placebo in the controlled trials reviewed above. Various parameters were used to determine the severity and duration of illness. Most studies used a combination of signs and symptoms, but one focused on severity of pain [26], and another focused on the inflammatory character of the sinus aspirate [7]. The number of patients receiving placebo varied from 18 to 106. The time of evaluation ranged from 7 to 14 days of observation. The percentage of placebo recipients who showed improvement at this time ranged from 37% to 85%. The weighted pooled mean recovery rate was 52%, but the SD was large (± 18%). The large variance in recovery rate may have resulted from a problem with the content validity of the populations, as discussed above, or from other unknown factors.

In the study that addressed content validity by duration of illness, only 5 (11%) of 44 illnesses in placebo recipients had completely resolved by day 10 (figure 1) [10], compared with a complete resolution rate of 38.5% (32 of 83) among patients treated with antibiotics. By day 10, a total of 25 patients (57%) in the placebo group had complete resolution or were much better, compared with 71 (85.5%) of those receiving antibiotics. At the end of a month, 75% of placebo recipients had completely recovered, compared with 90% of patients receiving antimicrobial treatment.

**DISCUSSION**

Much knowledge is lacking about ACABS, including the true incidence of ACABS after colds in adults and children; the severity and duration of illness; the incidence of acute suppurative complications; the percentage, if any, of cases progressing to chronic sinus disease; and the effectiveness, if any, of antimicrobial treatment. The reasons for the poor state of knowledge are understandable. Although ACABS is a relatively common disease, epidemiologic studies to measure its incidence require large populations [1] and, to measure suppurative complication rates, very large populations. Establishing an accurate diagnosis and obtaining evidence of bacteriologic cure in the investigative setting requires sinus aspirate culture. Although currently controversial and often not used, aspiration of the maxillary sinus is a well-established procedure in research and can be performed safely by experienced hands. The information obtained from studies of putative ACABS without aspirate culture results is always open to question. Some have questioned the ethics of conducting costly projects of antimicrobial treatment of ACABS without aspirate culture results to provide support from microbiological data [35]. Although it is essential in research, sinus aspiration is not recommended in routine clinical care because of its invasive nature, minimal but potential risk, cost, and poor acceptance by patients. The clinical diagnosis of ACABS is now made from a history of a cold

### Table 4. Comparative bacteriologic resolution rates (as determined by pre- and posttherapy sinus puncture findings) among patients with acute community-acquired bacterial sinusitis.

<table>
<thead>
<tr>
<th>Reference, comment regarding treatment</th>
<th>No. of bacteriologic resolutions/no. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carenfelt et al. [32]</td>
<td></td>
</tr>
<tr>
<td>Antibiotic concentrations(^a) were greater than or equal to the MIC for the causative bacteria</td>
<td>19/21 (90)</td>
</tr>
<tr>
<td>Antibiotic concentrations(^a) were less than the MIC for causative bacteria</td>
<td>15/33 (45)</td>
</tr>
<tr>
<td>Hamory et al. [34]</td>
<td></td>
</tr>
<tr>
<td>Appropriate antimicrobial and dose given(^b)</td>
<td>47/49 (96)</td>
</tr>
<tr>
<td>Inappropriate antimicrobial given(^b)</td>
<td>0/6</td>
</tr>
</tbody>
</table>
or “influenza-like” illness that has not improved after 7–10 days. An exception is the more severe case with the classic findings, such as fever, sinus pain, and inflammation and tenderness over the sinus.

Three facts about ACABS are well established: the paranasal sinuses are normally sterile [5, 8, 36, 37], ACABS is a bacterial infection of known etiology [9], and antimicrobial treatment for 7–10 days is associated with a resolution rate of infection in the maxillary sinus of ~90% [20–22]. Other knowledge about ACABS is limited. Data on the validity of clinical criteria in diagnosis are based on cases that were not diagnosed by sinus aspirate culture. Information on the natural history is limited, as is information on the effectiveness of antimicrobial treatment. However, the conclusion of the Lindbæk study [10]—that antimicrobial treatment is effective for ACABS—is supported by the results of studies comparing bacterial resolution rates in adequately and inadequately treated cases (table 4). Whether “resolution” equals “cure” in the uncontrolled pre- and posttreatment sinus aspirate studies cannot be determined with certainty, because these studies lacked a cohort of patients receiving placebo. The results of these studies can only be compared with historical control subjects with posttreatment aspirate cultures who received inappropriate or low doses of antibiotics.

With the current uncertainty and controversy surrounding ACABS, a well-designed placebo-controlled trial of antimicrobial treatment with pre- and postsinus aspirate cultures involving closely monitored patients may be justified. Placebo recipients with unresolved infection would be offered treatment. The scientific value of conducting additional studies of antimicrobial therapy in adults with ACABS for whom the diagnosis and proof of bacteriologic cure are not based on the results of sinus aspirate cultures is questionable.

The evidence reviewed above supports the effectiveness of antimicrobial treatment in eradicating infection and shortening illness. Antimicrobial treatment is recommended for a period of 7–10 days for patients with ACABS, and agents should be effective against the most common causes of ACABS, including antimicrobial-resistant S. pneumoniae, antimicrobial-resistant H. influenzae, and antimicrobial-resistant M. catarrhalis. Antimicrobials with such a spectrum of activity also provide coverage for the other streptococcal species and most of the anaerobic bacteria associated with ACABS. This has been the standard of practice. Changes in the practice, including eliminating or shortening the duration of antimicrobial treatment, should only be made when they are supported by scientific evidence that includes proof of bacteriologic cure.

References

17. Talbot GH, Kennedy DW, Scheld WM, Granito K. Rigid nasal endoscopy versus sinus puncture and aspiration for microbiologic docu-