

The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: A fifteen-year experience at the University of Virginia and review of other selected studies

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Pretreatment sinus puncture was performed on 339 patients with acute community-acquired sinusitis (ACAS) between 1975 and 1990. Bacterial species recovered in titers of $\geq 10^4$ colony-forming units per milliliter (CFU/ml) from 383 sinus aspirates included Streptococcus pneumoniae, 92 (41%); Haemophilus influenzae, 79 (35%); anaerobes, 17 (7%); streptococcal species, 16 (7%); Moraxella catarrhalis, 8 (4%); Staphylococcus aureus, 7 (33%); and other, 8 (4%). Viruses (rhinovirus, parainfluenza virus, and influenza virus) and fungi (Aspergillus, zygomycoses, Phaeohiphomyces, Pseudallescheria, and Hyalohyphomycis) have also been reported to cause ACAS. Posttreatment sinus puncture was performed on 220 of the 339 patients in six studies to evaluate efficacy of selected antimicrobial agents in producing bacteriologic cure. Ampicillin, 500 mg four times daily; amoxicillin, 500 mg three times daily; trimethoprim-sulfamethoxazole, twice a day; cefaclor, 500 mg four times daily; bacampicillin, 800 mg twice a day; cycloacillin, 500 mg three times a day; cefuroxime axetil, 250 mg twice daily; amoxicillin-clavulanate, 500/125 three times daily; and loracarbef 400 mg twice daily, given in 10-day courses, produced bacteriologic cure in more than 90% of patients. Early studies were done before β -lactamase-producing strains of H. influenzae were a frequent cause of ACAS in Charlottesville. Management of therapeutic failures is a difficult problem for which diagnostic and therapeutic sinus puncture and lavage, prolonged antimicrobial therapy, steroid therapy, and evaluation of allergy, immunodeficiency, and surgically correctable lesions of the osteomeatal complex are recommended. (J ALLERGY CLIN IMMUNOL 1992;90:457-62.)

Key words: Acute sinusitis, microbial etiology, antimicrobial therapy

The paranasal sinuses are sterile under normal conditions,^{1,2} whereas the upper airway is continuously colonized by microorganisms, including a variety of pathogenic bacterial species. Therefore to study the microbial cause of sinus disease, it is necessary to perform sinus puncture and aspiration to obtain specimens for culture that are not contaminated by the resident microbial flora of the nasal passages. The investigations that form the basis of the information

Abbreviations used

ACAS: Acute community-acquired sinusitis
MRI: Magnetic resonance imaging

compiled in this article were done by means of sinus punctures or in a few instances direct surgical exposure to obtain specimens for culture.

Studies of ACAS that use sinus puncture were begun by Urdal in 1949.³⁻⁷ More recently, a series of studies of community-acquired sinusitis in adults with the use of sinus puncture has been done at the University of Virginia in Charlottesville.^{1,8-16} Available information is mainly limited to cultures of specimens from the maxillary sinus because of its accessibility to sampling

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1/0/38496

TABLE I. Bacterial cause of acute maxillary sinusitis from 383 aspirates in Charlottesville from 1975 to 1990*

Cause	No.	%
<i>Streptococcus pneumoniae</i>	92†	41
<i>Haemophilus influenzae</i>	79	35
Anaerobes	16	7
Streptococcal species	16	7
<i>Moraxella catarrhalis</i>	8	4
<i>Staphylococcus aureus</i>	7	3
Other	8	4

*The 383 sinus aspirates were obtained from 339 patients, some of whom had multiple infections. The bacterial recovery rate from all of the specimens was 59%.

†A culture was considered positive when it yielded a concentration of $\geq 10^4$ colony-forming units of bacteria on quantitative culture.

by puncture. Extrapolation of the maxillary sinus findings to the other paranasal sinuses may not be warranted, although there is currently no reason to believe that the bacterial cause of infection in the frontal, ethmoid, and sphenoid sinuses is substantially different from that in the maxillary sinus.

In addition to the bacteria, respiratory viruses have been implicated as having a role in the pathogenesis of ACAS. In particular, it appears that acute viral infections are a frequent precipitating event in the development ACAS. Recent studies with the rhinovirus challenge model have shown sinus abnormalities detected by MRI and increased volumes of nasal secretions in some volunteers with experimental rhinovirus colds.¹⁷ Also, several fungal species have now been associated with ACAS in otherwise healthy people.

BACTERIOLOGY

The findings of sinus puncture studies from the various laboratories have been in good agreement, although some differences have been observed in the relative importance of the different species.^{1, 3-16, 18} Thus the bacterial cause of ACAS is well defined. The importance of the various bacterial species has not changed during the past several decades, although individual species have changed in their susceptibility to antimicrobial agents. Most prominent has been the development of antimicrobial resistance by some species associated with the production of β -lactamases.

Streptococcus pneumoniae and *Haemophilus influenzae* have been the major causes of ACAS in the 339 adults who were studied in Charlottesville during the past 15 years (Table I). These two species have accounted for 76% of bacterial isolates. In a small proportion of patients, both organisms have been recov-

ered from the same sinus aspirate which indicates a dual infection. In the Charlottesville studies, *S. pneumoniae* and *H. influenzae* accounted for a relatively equal proportion of isolates, 41% and 35%, respectively. In a recent study of 238 young adults in Finland, *H. influenzae* accounted for 50% and *S. pneumoniae* for 19% of the cases.¹⁸ From 1975 through 1985 in Charlottesville, none of 53 strains of *H. influenzae* isolated from the sinuses produced β -lactamase, whereas from 1986 through 1989, 15 (52%) of 29 strains of *H. influenzae* were β -lactamase producers.

Next in frequency in Charlottesville have been infections caused by anaerobic bacteria and other streptococcal species, which have each accounted for 7% of isolates. Some of the anaerobic infections, which often originate as dental root infections, have had mixtures of various species of streptococci, *Bacteroides*, and *Fusobacteria*. In the Finnish study, when specimens containing only strains of *Propionibacterium acnes* were excluded, only 2% of the sinuses were considered to have true anaerobic infections.¹⁸ *Moraxella catarrhalis* caused 4% of the Charlottesville infections and is of special importance because of its antimicrobial susceptibilities that are influenced by the β -lactamase production of the bacterium. Previous studies of *M. catarrhalis* have shown that approximately 40% of strains recovered from patients with various infections produce β -lactamase. Seventy-four percent of the Charlottesville strains of *M. catarrhalis* recovered from the sinus were β -lactamase producers.

Staphylococcus aureus, which represented 3% of the bacterial strains recovered, although not a frequent cause of ACAS, is important because of its virulence and its usual resistance to the ampicillins and increasing resistance to methicillin. In studies in which sinus punctures are not used to provide culture specimens, the frequency of *S. aureus* as a cause of ACAS is overestimated because the nasal specimens reflect the baseline nasal carriage rate of this bacterium. *Streptococcus pyogenes* also accounts for a small proportion of cases of ACAS. The *Enterobacteriaceae*, *Pseudomonas* species, and other gram-negative bacteria, although occasionally recovered from sinus aspirates in the community setting, are not considered among the usual causes of ACAS in otherwise healthy individuals. Therefore, in selecting initial antimicrobial therapy for ACAS infection, it is not recommended that coverage be routinely extended to these organisms.

Acute sphenoid sinus infection was examined in one study from Boston,¹⁹ in which specimens for culture were obtained by sinus puncture and from sinus

tissue collected at surgery. The organisms recovered included streptococcal species in 41%, *S. aureus* in 29%, and *S. pneumoniae* in 17% of cases. The high recovery rate for the streptococcal species and *S. aureus* may indicate that there was some specimen contamination by indigenous nasal flora; however, antimicrobial coverage for *S. aureus* is recommended in all patients who have sphenoid sinus infection.

Virology

A long-standing clinical observation has been that ACAS is frequently preceded by a common cold. This connection is supported by epidemiologic evidence; ACAS is observed to occur after 0.5% of colds in a prospective study of minor illnesses in families.²⁰ Direct evidence of viral involvement in the pathogenesis of acute sinusitis comes from the finding of members of several virus families in sinus aspirates from patients with ACAS.^{1, 11} Viruses that have been cultured from the sinus cavity include rhinovirus, influenza virus, and parainfluenza virus. In some patients, a virus and bacteria were cultured from the same specimen. New information from studies of volunteers with experimental rhinovirus colds has shown that sinus MRI abnormalities consisting of mucosal thickening and fluid accumulation, which are associated with increased volumes of nasal secretions, occur during some rhinovirus infections.¹⁷

Mycology

Fungi have been increasingly recognized as playing a role in community-acquired sinusitis of an acute and in some cases more chronic nature.²¹⁻²⁴ Sinus infection in patients with diabetes and impaired immunity have long been associated with strains of *Aspergillus* and zygomycoses. Other causes of fungal sinus infection include strains of *Phaeohiphomyces*, *Pseudallescheria*, and *Hyalohyphomycis*.

Community-acquired fungal infections may be subacute and present over several weeks, with resultant pressure effects and sometimes bony destruction. Characteristically some of these infections produce a peanut butter-like exudate in the sinus cavity. Treatment of these infections in the immunocompetent patient has primarily been surgical.

Chronic sinus disease

When mucociliary clearance and other local host defenses are sufficiently impaired, the sinus cavity becomes chronically damaged as evidenced by persistent abnormalities seen by imaging. Under this condition, the sinus cavity is chronically invaded by bacteria, which results in the loss of the normal state of sterility.^{25, 26} This condition, which has also been re-

ferred to as chronic sinus "infection," is not truly an infection but the result of anatomic abnormalities that cause obstruction to sinus drainage and/or damage to the mucosal lining of the sinus cavity. Although episodes of recurrent acute infection are believed to play a major role in the development of chronic sinus disease, the condition, once established, is best thought of as one of structural damage and not as a chronic infectious process that can be cured by treatment with antimicrobial agents. Experience has shown that prolonged treatment with broad-spectrum antimicrobial agents is usually not effective in curing the disease, whereas appropriate surgical treatment directed at relief of the obstruction and removal of redundant mucosa is effective in minimizing symptoms and in some cases returning the sinus cavity to its premorbid condition. Antimicrobial therapy is not recommended for the treatment of chronic sinus disease per se; however, patients with this condition may have acute exacerbations of infection with the usual bacterial species that cause ACAS in which case antimicrobial therapy is indicated.

Antimicrobial treatment

Bacteriologic response. The effectiveness of several antimicrobial agents has been tested in the Charlottesville studies in which pretherapy and posttherapy quantitative cultures of sinus aspirates have been obtained to provide proof of bacteriologic cure (Table II).^{8, 9, 12, 14-16} Antimicrobial agents that have been tested and shown effective in producing bacteriologic cure rates of more than 90% include several drugs in the ampicillin group (with and without clavulanic acid), trimethoprim-sulfamethoxazole, two second-generation cephalosporins, and a carbacephen. The earlier studies, which are summarized in the table, were done at a time when the prevalence of β -lactamase production in *H. influenzae* species in the Charlottesville area was low, and thus cure rates for drugs such as the ampicillins, which are susceptible to β -lactamase, are not applicable to the current situation in many areas of the United States in which β -lactamase-producing strains of *H. influenzae* are more common. Another recent study with pretreatment and posttreatment sinus puncture culture was done in Sweden, Finland, and Iceland comparing cefixime to cefaclor.^{27, 28} Sufficient posttreatment culture results were available only to determine efficacy in the twice-a-day dosing schedule for cefixime.

A 10-day course of treatment was sufficient to achieve bacteriologic cure as defined by a follow-up sinus puncture, which showed a negative culture or a $\geq 5_{\log 10}$ fall in bacterial titer from the pretherapy puncture result. Patients with persistent low titers of bac-

TABLE II. Results of therapeutic studies of acute maxillary sinusitis

	No. of bacteriologic cures/No. evaluations	Cure (%)
Charlottesville, Va. 1975-1981		
Ampicillin, 500 qid	12/13	92
Amoxicillin, 500 tid	14/14	100
TMP/SMX DS, bid	18/19	95
Cefaclor, 500 bid-qid	1/5-15/17	88
1983		
Bacampicillin, 800 bid	18/19	95
1986		
Cyclacillin, 500 tid	23/26	88
Amoxicillin, 500 tid	25/27	93
1989		
Cefuroxime axetil, 250 bid	36/38	95
Cefaclor, 500 tid	15/21	71
1990		
Amoxicillin-clavulanate, 500/125 tid	11/12	92
Loracarbef, 400 bid	13/14	93
Nordic Multicenter Trial 1990		
Cefixime, 200 mg bid	105/115	91
Cefaclor, 500 mg bid	37/50	74

Pretreatment and posttreatment sinus aspirates were obtained by sinus puncture on all patients. Cure was defined as no growth on the posttreatment culture of a $\geq 5_{\log 10}$ fall in bacterial titer between pretreatment and post-treatment cultures.

TMP/SMX, Trimethoprim-sulfamethoxazole; bid, twice daily; tid, three times daily; qid, four times daily.

teria in the posttherapy cultures did not have clinical or bacteriologic relapses.

Antimicrobial drugs, which combine completeness of spectrum for the bacteria that cause ACAS, low cost, and low rate of side effects, are currently unavailable. Among the antimicrobial agents that have shown effectiveness in sinus puncture studies and provide coverage for β -lactamase-producing bacteria are drugs with wide variations in cost. For example, in Charlottesville trimethoprim-sulfamethoxazole costs under \$5.00 for a 10-day course of treatment in recommended doses, whereas cefaclor costs more than \$100.00 for a 10-day course of treatment in recommended doses. Unfortunately, side effects, mainly skin rashes, are a problem with trimethoprim-sulfamethoxazole. Other drugs with satisfactory activity against the bacteria that cause ACAS, including the β -lactamase-producing strains but not methicillin-resistant *S. aureus*, have costs ranging from \$50.00 to \$75.00 for a 10-day course of therapy.

Thus selecting optimal therapy for patients with ACAS presents the clinician with a problem because of the related issues of antibacterial spectrum, cost, and side effects. Because the proportion of ampicillin-resistant bacteria that causes ACAS has increased in recent years, especially with *H. influenzae*, adequacy of coverage for β -lactamase production has become the primary consideration, leaving the physician to weigh the advantages and disadvantages of prescribing an inexpensive antimicrobial, trimethoprim-sulfamethoxazole, for which side effects are a problem versus selecting a considerably more expensive drug, such as cefuroxime axetil, which is better tolerated. Considerations, such as prior history of sulfa allergy, obviously must be weighed in the decision, as well as the economic status of the patient and the frequency of β -lactamase production among *H. influenzae* strains in the community.

Clinical response and general management. It should be emphasized that clinical improvement was seen in the face of bacteriologic failure in patients in whom the infecting bacteria was resistant to the antibiotic given. Particularly, facial and "sinus" discomfort tended to resolve despite continued high bacterial concentrations and exudate in the sinus cavity, presumably because these complaints were associated with the initial stretching of the sinus membrane in the early stages of the infection. Persistent nasal discharge and abnormal tonal quality of the voice appeared to be more sensitive signs of continuing active disease. Follow-up sinus transillumination and x-ray films were useful to determine resolution of ACAS, but these examinations are slow to return to normal over days and weeks. In patients suspected of having an unsatisfactory response to treatment, a sinus puncture is useful to obtain an aspirated specimen for quantitative bacterial culture and antimicrobial sensitivities and to provide the therapeutic benefit of sinus lavage.

Adjunct treatment with oral or topical vasoconstrictors has not been studied under controlled conditions in the treatment of ACAS but has support on a theoretical basis and was used in the Charlottesville patients. Patients suspected of having intracranial complications of ACAS require immediate diagnostic evaluation and should receive broad coverage with parenteral antimicrobial therapy and surgical intervention when indicated.

Community-acquired sinus disease of uncertain duration. Adults who have symptoms compatible with community-acquired sinusitis of uncertain duration may present diagnostic and management problems, particularly when the patient is new and prior imaging studies are unavailable. In this situation the patient may represent a case of untreated or inadequately treated acute sinusitis or a case of chronic sinus disease

with an acute infectious exacerbation. If it is not possible to distinguish between the two possibilities by history, and after the presence of sinus disease has been confirmed by sinus imaging, either of two management strategies are acceptable. The more conservative strategy, particularly of the previously untreated patient, is to give a course of an antibiotic that provides coverage for the usual causes of ACAS and follow clinically and radiographically for clearing of disease. Patients so treated who do not show clinical and radiographic response should then receive sinus puncture for the diagnostic information provided by microbial culture and antibiotic sensitivities and the therapeutic benefit of sinus lavage. The alternative strategy of immediate sinus puncture with microbial culture and antibiotic sensitivities and therapeutic lavage may provide useful information for directing antimicrobial therapy and allow more rapid return of the sinus to normal if chronic sinus disease is not present. Patients managed in either of these two ways who fail to achieve a clinical response and radiographic normalcy of the sinuses are suspect of having sinus disease that is becoming or has become chronic. If a course of more prolonged antimicrobial therapy does not succeed, such patients should have allergic and immunologic evaluations and be seen for obstructive conditions that would make them candidates for corrective sinus surgery. How long medical treatment should be continued if the disease is not reversed before seeking surgical therapy is currently not well defined. Based on new concepts of relieving obstruction in the osteomeatal complex, traditional and endoscopic surgery in the nasal cavity, coupled with modern imaging techniques, is providing good results. Prolonged unsuccessful medical treatment is not justified if correctable surgical conditions are present.

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DISCUSSION

Dr. Spector. I wonder if either of you or both would comment on the advantages of culturing the mucosa obtained at the time of surgery. I only know of one study from Finland some years ago. What I remember was that they showed in cases with chronic sinus disease a very high incidence of anaerobic organisms that had never been suspected before. I wonder why more people do not do that.

Dr. Gwaltney. The question is, are they of any importance in the etiology of the condition? Nobody really knows.

Dr. Spector. Is there an advantage or disadvantage in

instilling saline solution in the sinus when you do the culture?

Dr. Gwaltney. If fluid cannot be obtained, we instill 1 ml of normal saline solution to obtain a specimen.

Dr. Wald. Probably the single most important thing is getting the specimen to the laboratory as fast as possible and then getting in on the right media I agree with Jack. I think that normal sinuses are bacteria free; on the other hand, the idea that they might be transiently contaminated with great frequency holds much appeal. I think quantitation is important for us to assess whether the organism is truly there in high number or it is just passing through.

Environmental control and immunotherapy for allergic disease

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Treatment for allergic disease can help prevent recurrent sinusitis. Removal of carpeting and feather bedding and use of acaricides can significantly improve symptoms caused by house dust mites or animal dander. To kill mites, wash-water temperature must be at least 58° C. Patients with severe allergy should use an air-filtering vacuum cleaner and an air cleaner with a HEPA filter. Humidity should be kept at under 50%. If other measures fail, pets may have to be removed. Subcutaneous immunotherapy is effective for patients with anaphylactic reactions to insect stings, allergic rhinitis, and allergic asthma. It is ineffective for food allergy or nonallergic rhinitis or asthma. In children, immunotherapy is reserved for generalized life-threatening airway reactions. Relative indications for immunotherapy include inability to avoid the allergen and poor results or significant side effects from pharmacologic treatment. Efficacy depends on dosage, duration of treatment, and allergen selection. Low initial doses are increased at a set rate until the dose induces appropriate antibody response without significant reactions. Patients should be much improved or symptom-free for 1 to 2 years before immunotherapy is discontinued. Pollen, house dust mite, cat, and some mold spore extracts reduce symptoms and sensitivity to nasal or bronchial provocation. When used appropriately, immunotherapy is safe and effective. (J ALLERGY CLIN IMMUNOL 1992;90:462-8.)

Key words: Allergy, animal, asthma, environment, extracts, house dust mite, immunotherapy, insect bites and stings, rhinitis

Because there is an apparent relationship between allergic rhinitis and sinusitis, it is likely that treatment for allergic disease will have the additional benefit of helping prevent recurrent sinusitis. Toward that end, patients with allergic rhinitis and recurrent sinusitis

Abbreviations used

Der p: *Dermatophagoides pteronyssinus*

Der f: *Dermatophagoides farinae*

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require an aggressive approach toward management of their allergic disease.

Today, IgE-mediated diseases such as allergic asthma and allergic rhinitis are managed by one or all of three approaches: allergen avoidance, drug therapy, and/or allergen-specific immunotherapy. Of the three,