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Evaluation of the Microbiology of Chronic Ethmoid Sinusitis

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In a prospective study, patients with the diagnosis of chronic ethmoid sinusitis were evaluated microbiologically by using biopsy specimens of the ethmoid sinus mucosa. Microbiology cultures were performed on 94 specimens from 59 patients. *Staphylococcus aureus* and members of the family *Enterobacteriaceae* were the most frequent classical pathogenic bacteria isolated. Coagulase-negative staphylococci were the most common overall isolates. *Streptococcus pneumoniae* and *Haemophilus influenzae* were infrequent isolates. No anaerobes, viruses, or *Chlamydia trachomatis* organisms were identified. Results of this study showed organism isolation frequencies different from those found in other studies of chronic sinusitis reported in the literature. The predominance of *S. aureus* and members of the family *Enterobacteriaceae* could have an effect on the antimicrobial therapy for chronic ethmoid sinusitis.

Chronic paranasal sinusitis is generally a mild disease. However, it is important to realize that it afflicts a significant percentage of the population and causes considerable long-term morbidity. Many patients with chronic sinus disease are subjected to multiple courses of antibiotics and surgeries, with little or no improvement in their condition. Despite the tremendous advances in medicine over the last few decades, there have been relatively few advances in the diagnosis and treatment of chronic sinus disease. Long-term results of medical and surgical therapies have resulted in cure rates that vary between 29 and 80% (14, 23, 25). We feel that this lack of progress is largely due to the paucity of knowledge on the microbiology and histopathology of chronic sinus disease available to us, and this was the impetus for our study.

The factors which are important in the pathophysiology of chronic sinusitis, and in particular, the role of allergy and infection in chronic sinus disease, are not well understood. The maxillary sinuses have always been considered the primary focus of disease, and they have been the focus of the majority of microbiological studies on chronic sinusitis (1, 2, 5, 6, 12, 13, 18, 20, 26, 32, 33). Ease of access may be a factor in this emphasis. The less accessible ethmoid sinuses were little studied until the development of the rigid endoscope, which provides improved visualization of the ethmoid sinus through the nasal cavity (19, 24, 29–31).

Recent studies, however, suggest that the ethmoid sinuses play a central role in the drainage and blockage of the frontal, maxillary, and sphenoid sinuses and are the key to the etiology and management of chronic paranasal sinusitis (11, 30). This is consistent with the embryology of the sinuses. The sphenoid sinus develops from the posterior ethmoidal cells, the frontal sinus develops from the anterior ethmoidal cells, and the maxillary sinus most likely arises as an extension of the middle meatus or middle ethmoid air cells (11).

Knowledge of the normal flora can help in the assessment of the significance of organisms isolated from the sinuses. No studies have examined the normal flora of the ethmoid sinuses. Bjorkwall (3) found normal healthy maxillary antra to be sterile in 54 cases; however, other studies have shown conflicting results (1, 3, 4, 32). It is difficult to extrapolate these results to the ethmoid sinuses.

We undertook this study to prospectively examine the microbiology of chronic ethmoid sinusitis. Our study is unique in that we examined a large number of patients with chronic ethmoid sinusitis, which is believed to be the focus of disease for the frontal and maxillary sinuses.

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MATERIALS AND METHODS

This prospective study was performed as a collaborative effort between St. Paul's Hospital, Metro-McNair Clinical Laboratories, and the British Columbia Center for Disease Control (Provincial Laboratory) over a 2.5-year period from 1987 to 1989.

Patient selection. Patients were selected by one of the authors (J.D.W.) from among a group of patients with a diagnosis of chronic sinusitis referred from otolaryngologists or family practitioners. Patients presenting with a history of chronic sinusitis of more than 6 weeks' duration, which was supported by X-ray and/or computed tomography scan findings and which was confirmed by office endoscopic findings consistent with chronic sinusitis, were included in the study. Specifically, the diagnosis had to include the following: (i) symptoms of nasal obstruction or purulent nasal discharge, discomfort or fullness over the sinuses, episodes of recurrent acute sinusitis, and/or disturbances in olfaction; (ii) signs of inflamed nasal mucosa; purulent exudate in the middle meatus, nasal cavity, or nasopharynx; and/or polyposis; and (iii) radiological evidence of thickening and/or opacification of the ethmoid sinus. It should be noted that these criteria do not differentiate infectious from allergic chronic sinus disease.

Patients meeting the criteria for entry into the study were placed on conservative medical therapy, consisting of nasal saline irrigations and steroid sprays. If the patients were taking antibiotics, the antibiotics were discontinued. Patients were reevaluated approximately 3 weeks after the initial visit. Those patients who experienced relief of their

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symptoms were removed from the study and were not evaluated further. Patients who did not respond to medical therapy were booked for a computed tomography scan and surgery.

This study was approved by the ethics committees of both St. Paul's Hospital and the University of British Columbia, and all patients signed an informed consent.

Collection of specimens. All study patients were taken to the operating room for endoscopic examination of the nasal cavity and the ethmoid sinus. If disease was present in the maxillary sinuses, the maxillary sinuses were also examined. Necrotic ethmoidal tissue was removed if it was present, and corrective nasal surgery was performed if necessary.

Surgery was performed under local-combined anesthesia or general anesthesia. The nasal cavity was exposed with a retractor; and the internal nares, septum, and nasal valve area were disinfected with a chlorhexidine solution. A nasal swab specimen was then taken from the area of the middle meatus, which was not disinfected, and this culture was considered representative of the background nasal flora.

The endoscopes were sterilized in a glutaraldehyde solution for 10 min and washed prior to use. The ethmoid sinus was entered through the area of the anterior middle meatus by performing an infundibulotomy. In order to decrease the risk of contamination, biopsy specimens were taken from within the ethmoid sinus air cells upon entering the sinus. Biopsy specimens for microbiological analysis were inserted immediately and aseptically into a modified Cary-Blair anaerobic transport medium (Carr-Scarborough Microbiologicals, Stone Mountain, Ga.), transported immediately to the laboratory, and held at room temperature until they were set up for culture.

Processing for microbiological analysis. Most biopsy specimens were set up for culture within 1 to 4 h of collection, and all were set up within 18 h. Biopsy specimens (several millimeters in diameter) were ground in 1 ml of prereduced brain heart infusion broth in a sterile ground glass grinder. Use of this apparatus results in little aeration of the tissue. They were immediately inoculated, using 1 drop of fluid, onto aerobic plate media (sheep blood agar with a NADOX disk, MacConkey agar, chocolate agar, and phenylethyl alcohol agar [some specimens only]) incubated in 5% CO_2 at 35°C; onto Sabaruoud agar incubated aerobically at 28°C; onto anaerobic plate medium (prereduced brucella blood agar supplemented with vitamin K and hemin and colistin-nalidixic acid or phenylethyl alcohol agar) incubated anaerobically at 35°C; into prereduced brain heart infusion broth supplemented with vitamin K and hemin; and into Fildes broth incubated at 35°C. Anaerobic plates were placed into an anaerobic atmosphere immediately after plating and were examined at 48 h. Media were purchased from Prepared Media Laboratories, Richmond, British Columbia, Canada. One drop of fluid was also inoculated onto Microtrak slides (Syva Company, Palo Alto, Calif.) and Chlamydiazyme tubes (Abbott Laboratories, North Chicago, Ill.) for detection of *Chlamydia trachomatis*. Specimens were not cultured for *Mycoplasma* spp.

For the first 19 patients, all bacteriology plates and broths were held for 5 days. Since there was no increase in yield at 5 days, for the remainder of the specimens, the plates were held routinely for 2 days, and negative broths were held for 5 days. Organisms were isolated and identified by the standard methods described in the *Manual of Clinical Microbiology* (21). Growth of organisms was graded semiquantitatively from 1+ to 4+. The organisms identified were grouped as classical and nonclassical pathogens. Classical pathogens were defined as organisms that are highly pathogenic with a marked propensity to cause disease in healthy hosts. Nonclassical pathogens were defined as organisms with a lesser pathogenic potential which usually do not cause disease in healthy hosts and which tend to be part of the normal flora of the skin and respiratory mucous membranes.

Minimal essential medium was used for viral cell culture transport. It was controlled for quality at the Provincial Laboratory on a weekly basis and was stored at 4°C prior to use. Minimal essential medium contained penicillin, streptomycin, mycostatin, and 1% fetal calf serum. It was inoculated with 1 drop of the ground biopsy specimen, transported to the Provincial Laboratory within 24 h, and held at 4°C prior to further processing. Viral cultures were performed on the following cell lines. Rhesus monkey kidney cells were used for influenza virus, parainfluenza virus, and respiratory syncytial virus. Hemadsorption was done with guinea pig erythrocytes. MRC-5 (human fetal lung) cells were used for herpes simplex virus, adenovirus, cytomegalovirus, and respiratory syncytial virus. Vero cells were also used for herpes simplex virus. It is unlikely that respiratory syncytial virus would have survived the transport, but it should not have compromised the other viral cultures. Viral cultures were held for 10 days.

Nasal swabs were set up on sheep blood agar plates, and the plates were incubated in 5% CO_2 at 35°C for 2 days. Organisms were isolated and identified as described above.

Appropriate quality controls were performed on all media, reagents, incubators, and anaerobic chambers.

Data analysis. Data were recorded and analyzed on an IBM-compatible personal computer with Symphony software (Lotus Development Corporation, Cambridge, Mass.). The data were further analyzed on a mainframe computer by using SPX software. Statistical differences were analyzed by Fisher's exact probability two-tailed test (28).

RESULTS

During the period of study, 59 patients with chronic sinusitis were entered into the study. Microbiological data were available for all 59 patients, and clinical data were available for 34 of 59 patients. Left and right ethmoid sinuses were considered separate specimens.

Clinical findings. The clinical diagnosis of chronic sinusitis was confirmed for all 59 patients. Extensive data for 34 of 59 patients were available for clinical evaluation. The clinical data will be presented in detail in a future report. The average age of the patients was 49 years (range, 20 to 76 years). The male to female ratio was 3.3 to 1. The average duration of symptoms was 12 years and ranged from less then 1 year to more then 30 years. No cases were clinically of dental origin. Pus was present in the middle meatus in 21 of 43 specimens (49%), as determined by office endoscopy. Endoscopy in the operating room revealed pus in the middle meatus in 15 of 47 specimens (32%). The microbiology results for specimens from these 34 patients were not statistically different from the overall microbiology results for the 59 patients, as discussed below.

Microbiology results. Data were available for microbiological analysis for 94 biopsy specimens from 59 patients. Some specimens had multiple isolates. A total of 153 organisms were isolated. For convenience, we separated the organisms into those considered to be classical pathogens and those considered to be nonclassical pathogens.

Of the classical pathogens, *Staphylococcus aureus* was the most frequent isolate, being present in 30 of 94 speci-

TABLE 1. Classical pathogens found in this study in cultures of specimens[a]

Organism	No. of isolates
Staphylococcus aureus	31
Streptococci	
Group A	1
Group B	1
Group C	1
Group G	2
Streptococcus pneumoniae	2
Enterococcus spp.	1
Haemophilus influenzae	4
Escherichia coli	4
Proteus mirabilis	8
Enterobacter aerogenes	1
Enterobacter cloacae	2
Citrobacter freundii	1
Klebsiella ozaenae	2
Xanthomonas pseudomonas maltophilia	1
Pseudomonas aeruginosa	1
Acinetobacter spp.	1
Corynebacterium diptheriae	2
Chlamydia trachomatis	0
Anaerobes	0
Viruses	0
Fungi	1
Total	67

[a] Pathogens were cultured from 94 specimens.

mens (32%); there were a total of 31 *S. aureus* isolates (Table 1). For one patient, two *S. aureus* strains were isolated from the same side, with different antimicrobial susceptibility patterns. *Proteus* spp. were isolated in eight specimens, and a total of 18 members of the family *Enterobacteriaceae* were isolated. *Streptococcus pneumoniae* and *Haemophilus influenzae* were infrequent isolates. We isolated a nontoxigenic strain of *Corynebacterium diphtheriae* from both the right and left ethmoid sinuses of one patient. We did not culture any anaerobes, viruses, or *C. trachomatis*. The sole fungal species isolated was a *Paecilomyces* sp. For eight specimens, there was no growth on culture.

A total of 86 organisms considered to be nonclassical pathogens were isolated. Coagulase-negative staphylococci were the most frequent nonclassical pathogen, being present in 67 of 94 (71%) specimens, and were the most frequent overall isolate in our study. Other nonclassical pathogens isolated were eight viridans group streptococci, one *Haemophilus parainfluenzae*, nine *Corynebacterium* spp., and one *Neisseria* sp.

When the results from the left and right sides for all patients were combined, we obtained 109 isolates overall. *S. aureus* was found in 20 of 59 (34%) patients and coagulase-negative staphylococci were found in 43 of 59 (73%) patients. Eleven members of the family *Enterobacteriaceae*, three *H. influenzae*, and one *S. pneumoniae* were found. These results were not significantly different from those given above.

Cultures of nasal specimens were performed to determine the background nasal flora and to help assess the significance of organisms isolated from the ethmoid biopsy specimens. To analyze the nasal culture data, we separated them into two nonoverlapping groups. For the first group, we compared the qualitative growth on cultures of nasal and ethmoid specimens in which the same organism grew. We found that there was no significant difference between the amount of growth on cultures of the nasal swabs and that on cultures of the ethmoid biopsy specimens for any organism. In these cases, therefore, the nasal swab did not help to differentiate the primary source of these organisms, which could originate from an infection in the sinus or from colonization in the nose.

For the second group, we compared specimens in which an organism was present in either the nasal swab or the ethmoid culture, but not in both. In this analysis we found the following results: (i) ethmoid specimen culture positive and nasal swab culture negative, 10 *S. aureus*, 14 coagulase-negative staphylococci, 7 *Enterobacteriaceae*, versus (ii) ethmoid specimen culture negative and nasal swab culture positive, no *S. aureus*, six coagulase-negative staphylococci, and 1 *Enterobacteriaceae*. Compared with coagulase-negative staphylococci, *S. aureus* was more often present in the ethmoid sinus alone than it was on nasal swabs alone, but this trend was not significant ($P = 0.065$).

In addition, Gram stain was positive for only 5 of 94 specimens. Two of these were *S. aureus*, and three were coagulase-negative staphylococci. The two specimens with *S. aureus* and two of three specimens with coagulase-negative staphylococci were associated with polymorphonuclear leukocytes.

DISCUSSION

To compare our microbiology results with those in the literature, we selected those studies which used modern aerobic and anaerobic techniques and we placed them into the following four study groups: (i) acute maxillary sinusitis, (ii) chronic maxillary sinusitis, (iii) chronic ethmoid sinusitis (this study), and (iv) mixed acute and chronic sinusitis of various sinuses (Table 2). Cultures for viruses were not done in most studies. Organisms were listed by the number of positive cultures. Organisms listed by group included all species within that group (for example, anaerobes).

Results from our study indicate that the frequencies of organism isolation were different from those in the other studies (Table 2). When we combined the results for specimens obtained from the right and left sides, our results or conclusions were not significantly affected. In particular, we found a predominance of *S. aureus* and members of the family *Enterobacteriaceae* compared with the predominance found in other studies of chronic sinus disease. In our study, results from Gram staining were supportive of a role for *S. aureus*, and the analysis of nasal and ethmoid cultures are supportive of a role for both *S. aureus* and the *Enterobacteriaceae* as pathogens in chronic ethmoid sinusitis. In view of the chronicity of disease in our patients, the isolation of *S. aureus*, which has a propensity for causing chronic infections, is not surprising. We isolated relatively few *S. pneumoniae* and *H. influenzae*, which are the pathogens most commonly isolated from cases of acute sinusitis and which were more common in studies of cases of chronic maxillary sinusitis than in our study (Table 2). *Paecilomyces* sp. is a

TABLE 2. Organisms isolated from patients with sinusitis

Organism isolated	No. (%) of organisms from patients with sinusitis			
	Acute maxillary[a]	Chronic maxillary[b]	Chronic ethmoid[c]	Mixed[d]
Streptococcus pneumoniae	140 (23)	14 (6)	2 (2)	20 (7)
Haemophilus influenzae	222 (37)	45 (19)	4 (4)	35 (12)
Branhamella catarrhalis	22 (4)	4 (2)	0 (0)	3 (1)
Staphylococcus aureus	5 (1)	14 (6)	31 (33)	30 (10)
Coagulase-negative staphylococci	30 (5)	27 (11)	67 (71)	27 (9)
β-Hemolytic streptococci	27 (4)	12 (5)	5 (5)	8 (3)
Enterobacteriaceae	3 (0.5)	4 (2)	18 (19)	13 (4)
Anaerobes	41 (7)	173 (72)	0 (0)	234 (80)
Viridans group streptococci	12 (2)	78 (32)	8 (9)	37 (13)
Neiserria spp.	7 (1)	18 (7)	1 (1)	10 (3)
Pseudomonas spp.	3 (0.5)	2 (1)	2 (2)	1 (0.3)
Corynebacterium spp.	3 (0.5)	19 (8)	9 (10)	4 (1)
Other	7 (1)	10 (4)	6 (6)	30 (10)
Virus	13 (2)	ND[e]	0 (0)	2 (1)
No growth	154 (26)	50 (21)	8 (9)	41 (14)
Total	602	241	94	291

[a] Data were obtained from previous reports (8, 15, 17, 35), but specimens were cultured for viruses only in references 15 and 35.
[b] Data were obtained from previous reports (1, 6, 18, 32).
[c] Data are from this study.
[d] Mixed indicates mixed acute, subacute, and/or chronic sinusitis, from frontal, ethmoid, sphenoid, and/or maxillary sinuses (5, 12, 13, 22, 34).
[e] ND, not done.

TABLE 3. Comparison of anaerobes isolated from pus in the clinical specimen

Type of sinusitis	No. of specimens	% of specimens with:	
		Clinical pus	Anaerobes
Chronic ethmoid[a]	47	32	0
Acute maxillary[b]	497	56	7
Chronic maxillary[c]	125	77	24
Chronic mixed[d]	83	100	96

[a] Data are from this study.
[b] Data were obtained from previous reports (8, 17, 35).
[c] Data were obtained from previous reports (18, 32).
[d] Data were obtained from a previous report (13).

possible pathogen (16). The isolation of *C. diphtheriae* from one patient in our study illustrates the importance of maintaining skill in the isolation and identification of this potential pathogen.

We isolated no anaerobes in our study of patients with chronic ethmoid sinusitis, in contrast to other studies of patients with chronic and acute sinusitis, as shown in Table 2. We propose that the ethmoid sinus may have fewer anaerobes than the maxillary and frontal sinuses by virtue of the fact that it is less likely to be obstructed and is more likely to be exposed to inspired oxygen. With obstruction there is oxygen resorption, an increase in partial pressure of CO_2 (pCO_2), and transudation of fluid, which then becomes a growth medium for organisms trapped in the sinus, predisposing the patient to bacterial sinusitis (9, 10). With bacterial infection there is chemotaxis of polymorphonuclear leukocytes into the sinus, which further reduces the pO_2 and pH and increases the pCO_2 (7). Clinically, this creates a purulent exudate with a low pO_2 that is a good medium to support anaerobes, as is the case with abscesses (13). Therefore, we also propose that the ethmoid sinus is more likely to have anaerobes in the presence of a purulent exudate.

Frederick and Braude (13) studied chronically infected frontal, ethmoid, and maxillary sinuses and found anaerobes in pure culture in 23 of 83 specimens; they isolated 80 anaerobes in all. Relative to the total number of organisms isolated, Brook (4, 6) and Frederick and Braude (13) identified a much higher percentage of anaerobes than the other studies did (Table 2). In those studies (4, 6, 13), they did not determine that all of these organisms were pathogens. Rice (27) notes, and we agree, that it is impossible to design a bacteriologically pure study on sinusitis; this makes all studies subject to criticism, including our own.

It is possible that technical factors could have decreased the number of fastidious anaerobes isolated in our study. We note that most anaerobes isolated by Brook (4, 6) and Frederick and Braude (13) were not particulary fastidious. If the percentage of no growth is used to assess the sensitivity of our technique to detect organisms in significant numbers, then our results with the lowest percentage of no-growth specimens suggest that factors other than technical ones likely contributed to the absence of anaerobes (Table 2).

We believe that one important factor for the absence of anaerobes in our study was the conservative presurgical medical treatment which was used. Such treatment may increase the drainage of purulent material and may sufficiently oxygenate the ethmoid sinuses to eliminate the anaerobes. We found that fewer patients had pus on endoscopic examination of the middle meatus in the operating room than during the original endoscopic examination in the office.

To further support our theory that the ethmoid sinus is more likely to have anaerobes in the presence of pus, results of several studies in which modern anaerobic techniques were used are examined in Table 3. These results indicate that there is a strong correlation of anaerobes with purulence on clinical examination; but this correlation was not found for *S. aureus*, *S. pneumoniae*, or *H. influenzae*. We are conducting further studies to test our theories that these factors are important in the isolation of anaerobes.

Our study is also important in that we examined the sinuses for both *C. trachomatis* and respiratory viruses, but none were found.

In conclusion, in this prospective study we examined the microbiology of chronic ethmoid sinusitis. The ethmoid sinuses are believed to be the key to the etiology and management of chronic paranasal sinusitis. We found *S. aureus* and members of the family *Enterobacteriaceae* to be the most frequent classical pathogenic bacteria isolated. Results of our study indicated that, in this select group of patients, anaerobes do not play a prominent role. Our results do not imply that anaerobes cannot be involved in other patients with chronic ethmoid sinus disease. One must be careful in the interpretation of studies done with organisms from different anatomic locations or patients from different geographical locations or socioeconomic groups, different time frames, or different incidences of disease of dental origin. Our findings also suggest that if empiric antimicrobial therapy is used to treat chronic ethmoid sinusitis, it should have activity against *S. aureus* and members of the family *Enterobacteriaceae*. We have begun a study to determine the efficacy of long-term, broad-spectrum antibiotic therapy in patients with chronic ethmoid sinusitis.

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