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Review Article

Microbiology and antimicrobial management of sinusitis

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Abstract
Sinusitis generally develops as a complication of viral or allergic inflammation of the upper respiratory tract. The bacterial pathogens in acute sinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, while anaerobic bacteria and *Staphylococcus aureus* are predominant in chronic sinusitis. *Pseudomonas aeruginosa* has emerged as a potential pathogen in immunocompromised patients and in those who have nasal tubes or catheters, or are intubated. Many of these organisms recovered from sinusitis became resistant to penicillins either through the production of beta-lactamase (*H. influenzae, M. catarrhalis, S. aureus, Fusobacterium* spp., and *Prevotella* spp.) or through changes in the penicillin-binding protein *(S. pneumoniae)*. The pathogenicity of beta-lactamase-producing bacteria is expressed directly through their ability to cause infections, and indirectly through the production of beta-lactamase. The indirect pathogenicity is conveyed not only by surviving penicillin therapy, but also by 'shielding' penicillin-susceptible pathogens from the drug. The direct and indirect virulent characteristics of these bacteria require the administration of appropriate antimicrobial therapy directed against all pathogens in mixed infections. The antimicrobials that are the most effective in management of acute sinusitis are amoxycillin-clavulanate (given in a high dose), the newer quinolones (gatifloxacin, moxifloxacin) and the second generation cephalosporins (cefuroxime, cefpodoxime, cefprozil or cefdinir). The antimicrobials that are the most effective in management of chronic sinusitis are amoxycillin-clavulanate, clindamycin and the combination of metronidazole and a penicillin.

Key words: Sinusitis; Antibacterial Agents; Bacteria, Anaerobic; Beta-lactamase; *Streptococcus pneumoniae*

Introduction

The growing resistance to antimicrobial agents of all respiratory tract bacterial pathogens has made the management of sinusitis more difficult. The upper respiratory tract including the nasopharynx serves as the reservoir for pathogenic bacteria that can cause respiratory infections including sinusitis.[1] Potential pathogens can relocate during a viral respiratory infection, from the nasopharynx into the sinus cavity, causing sinusitis.[2] Establishment of the correct microbiology of all forms of sinusitis is of primary importance as it can serve as a guide for choosing adequate antimicrobial therapy. This review summarizes the current information regarding the microbiology of all forms of sinusitis and approaches to antimicrobial therapy.

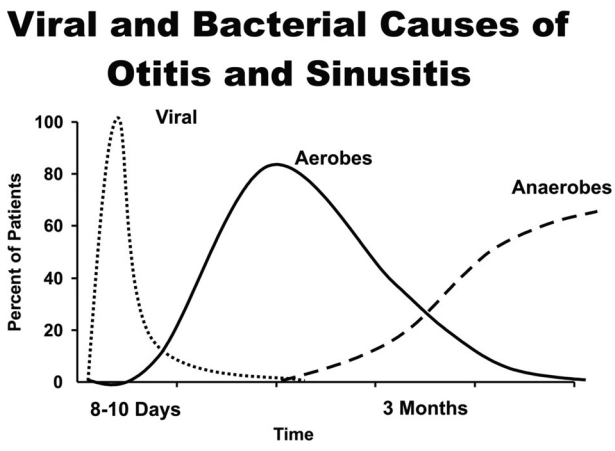

FIG. 1
The microbiological dynamics of sinusitis.

Microbiology

The pattern of many upper respiratory infections including sinusitis involves several phases (Figure 1).

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The early stage often is a viral infection that generally lasts up to 10 days and complete recovery occurs in most individuals.[3] However, in a small number of patients (estimated at 0.5 per cent) with viral sinusitis a secondary acute bacterial infection may develop. This is generally caused by facultative aerobic bacteria (i.e. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*). If resolution does not take place, anaerobic bacteria of oral flora origin become predominant over time. The dynamics of these bacterial changes were recently demonstrated by performing serial culture in patients with maxillary sinusitis.[22]

Viral illness is the most common predisposing factor for upper respiratory tract infections, including sinusitis.[3] Rhino, influenzae, adeno, and para-influenzae viruses are the most common causes of sinusitis.[4] It is not known for certain whether the viral infection precedes or is concurrent with the bacterial infection. The mechanism whereby viruses predispose to sinusitis may involve microbial synergy, induction of local inflammation that blocks the sinus ostia, increase of bacterial attachment to the epithelial cells, and disruption of the local immune defence.

Microbiology of acute sinusitis

Bacteria can be isolated from two thirds of patients with maxillary sinusitis.[5] Using sinus aspiration, by puncture or surgery, the common respiratory pathogens *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and beta-haemolytic streptococci organisms are recovered from the paediatric and adult population with community-acquired acute, purulent maxillary, frontal, and ethmoid sinusitis (Table I).[5-9] *Staphylococcus aureus* and *H. influenzae* are common pathogens in sphenoid sinusitis.[9]

The bacteria that cause the infection in children are generally the same as those found in acute otitis media. *S. pneumoniae* was isolated in 28 per cent of 50 children with acute sinusitis, and *H. influenzae* and *M. catarrhalis* were both isolated in 19 per cent of the aspirates.[7] Beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis* were found in 20 per cent and 27 per cent of the cases, respectively. The infection is polymicrobial in about a third of the cases. Enteric bacteria are recovered less commonly. Anaerobic bacteria are isolated from acute sinusitis associated with dental disease, mostly as an extension of the infection from the roots of the premolar or molar teeth.[10,11]

Pseudomonas aeruginosa and other aerobic Gram negative rods are common in sinusitis of nosocomial origin (especially in patients who have nasal tubes or catheters), sinusitis in mechanically ventilated patients,[12] immunocompromised individuals, patients with human immunodeficiency virus (HIV) infection and patients who suffer from cystic fibrosis.[13] Fungal sinusitis is common in immunocompromised or diabetic individuals.[14]

The bacteriology of nosocomial sinusitis was assessed in 20 mechanically ventilated children.[12] A total of 58 isolates (2.9 / specimen), 30 aerobic or facultative (1.5 / specimen) and 28 anaerobic (1.4 / specimen), were recovered. Aerobes only were present in eight patients (40 per cent), anaerobes only in five (25 per cent), and mixed aerobic and anaerobic flora in seven (35 per cent). The predominant aerobes were *P. aeruginosa*, *S. aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*. The predominant anaerobes were *Peptostreptococcus*, *Prevotella*, and *Fusobacterium* spp. Thirty isolates similar to the sinus isolates were also recovered from the trachea, six from blood culture specimens, and six from other sites. Anaerobes were more commonly isolated from sinus aspirate samples obtained after 18 days of mechanical ventilation (21 *vs* 7, $p<0.05$). This study demonstrates the polymicrobial aerobic-anaerobic flora of nosocomial sinusitis in mechanically ventilated children.

Microbiology of chronic sinusitis

Anaerobes were identified in chronic maxillary sinusitis whenever techniques for their cultivation were employed.[15-18] The predominant isolates were pigmented *Prevotella*, *Fusobacterium* and *Peptostreptococcus* spp. (Table I). The predominant aerobic bacteria were *S. aureus*, *M. catarrhalis* and *Haemophilus* spp. Aerobic and anaerobic beta-

TABLE I

MICROBIOLOGY OF SINUSITIS (% OF PATIENTS)[6,8,9,20,39]

	Maxillary		Ethmoid		Frontal		Sphenoid	
Bacteria	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Aerobic								
S. aureus	4	14	15	24	–	15	56	14
S. pyogenes	2	8	8	6	3	–	6	–
S. pneumoniae	31	6	35	6	33	–	6	–
H. influenzae	21	5	27	6	40	15	12	14
M. catarrhalis	8	6	8	–	20	–	–	–
Enterobactiaceae	7	6	–	47	–	8	–	28
P. aeruginosa	2	3	–	6	–	8	6	14
Anaerobic								
Peptostreptococcus spp.	2	56	15	59	3	38	19	57
P. acnes	–	29	12	18	3	8	12	29
Fusobacterium spp.	2	17	4	47	3	31	6	54
Prevotella & Porphyromonas spp.	2	47	8	82	3	62	6	86
B. fragilis	–	6	–	–	–	15	–	–

Gwaitney, 2000
Brook *et al*., 1989,2002,2003

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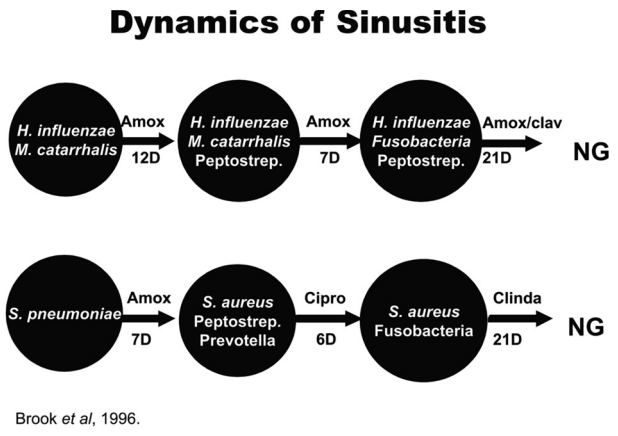

FIG. 2
Demonstration of the microbiological dynamics of sinusitis in two patients.[22]

lactamase-producing bacteria (BLPB) were isolated from over one third of these patients.[15-19] These BLPB were *S. aureus*, *Haemophilus*, *Prevotella* and *Fusobacterium* spp. Nord[18] summarized 12 studies of chronic sinusitis, including 1090 patients (40 children). Anaerobes were recovered in 11 of these studies in 12–80 per cent of the patients.

The unique microbiological features of chronic maxillary sinusitis that persist after sinus surgery was recently demonstrated.[20] Aspirates of 108 chronically inflamed maxillary sinuses were processed for aerobic and anaerobic bacteria. *P. aeruginosa* and Gram negative aerobic bacilli were more often isolated in the 33 patients who had surgery than in patients who did not have surgery. Anaerobes were isolated more often in patients who did not have surgery than in those who had previous surgery.

The authors recently evaluated the microbiology of 13 chronically infected frontal sinuses,[8] seven chronically infected sphenoid sinuses[9] and 17 chronically infected ethmoid sinuses[20] (Table I). Anaerobic bacteria were recovered in over two thirds of the patients. The predominant anaerobes included *Prevotella*, *Peptostreptococcus*, and *Fusobacterium* spp., the main aerobic organisms were Gram negative bacilli (*H. influenzae*, *K. pneumoniae*, *E. coli*, and *P. aeruginosa*).

That anaerobes play a role in chronic sinusitis is supported by the detection of antibodies (IgG) to two anaerobic organisms commonly recovered from sinus aspirates (*Fusobacterium nucleatum* and *Prevotella intermedia*).[21] Antibody levels to these organisms declined in the patients who responded to therapy and were cured, but did not decrease in those who failed therapy.

A recent study illustrated the transition from acute to chronic sinusitis by repeated aspirations of sinus secretions by endoscopy in five patients who presented with acute maxillary sinusitis that did not respond to antimicrobial therapy (Figure 2).[22] Most bacteria isolated from the first culture were aerobic or facultative bacteria, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. Failure to respond to therapy was associated with the emergence of resistant aerobic and anaerobic bacteria in subsequent aspirates. These organisms included *F. nucleatum*, pigmented *Prevotella*, *Porphyromonas* and *Peptostreptococcus* spp. Eradication of the infection was finally achieved following administration of effective antimicrobial agents and in three cases also by surgical drainage.

As chronicity develops, the aerobic and facultative species are gradually replaced by anaerobes. This may result from the selective pressure of antimicrobial agents that enable resistant organisms to survive, and from the development of conditions appropriate for anaerobic growth, which include the reduction in oxygen tension and an increase in acidity within the sinus. These are caused by persistent oedema and swelling, which reduces blood supply, and by the consumption of oxygen by the aerobic bacteria.[23] Other factors are the emergence over time, or selection, of anaerobes that possess virulence factors such as a capsule.[24]

Polymicrobial infection is common in chronic sinusitis, which is synergistic[25] and may be more difficult to eradicate with narrow-spectrum antimicrobial agents.

Antimicrobial resistance

The management of bacterial sinusitis is often a challenging endeavour in which selection of the most appropriate antimicrobial agents remains a key decision. This has become more difficult in recent years as all the predominant bacterial pathogens have gradually developed resistance to the commonly used antibiotics. Three major mechanisms of resistance to penicillin occur:

(1) porin channel blockage (e.g. used by *Pseudomonas* spp. to resist carbapenems);
(2) production of the enzyme beta-lactamase (e.g. utilized by *H. influenzae* and *M. catarrhalis*);
(3) alterations in the penicillin-binding protein (e.g. used by *S. pneumoniae*).

The observed increase in bacterial resistance to antibiotics is related to their frequent use. Previous therapy can increase the prevalence of BLPB. In a study of 26 children who had received seven days of therapy with penicillin, 12 per cent harboured BLPB in their oropharyngeal flora prior to therapy.[26] This increased to 46 per cent at the conclusion of therapy, and the incidence was 27 per cent after three months. The incidence of BLPB was high in siblings and parents of patients treated with penicillin, who probably acquired these organisms from the patient.[27] A greater prevalence of recovery of BLPB in the oropharynx of children occurs in the winter and a lower one in the summer.[28] These changes correlated with the intake of beta-lactam antibiotics. Monitoring the local seasonal variations in the rate of recovery of BLPB in the community may help the empirical choice of antimicrobial agents, the proper and judicious use of which may help to control the increase of BLPB.

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Beta-lactamase production

Bacterial resistance to the antibiotics used for the treatment of sinusitis has consistently increased in recent years. Production of the enzyme beta-lactamase is one of the most important mechanisms of penicillin resistance. Several BLPB occur in sinusitis.

BLPB have been recovered from over a third of patients with sinusitis.[6,15] *H. influenzae* and *M. catarrhalis* are the predominant BLPB in acute sinusitis, and *S. aureus*, pigmented *Prevotella*, *Porphyromonas* and *Fusobacterium* spp. predominate in chronic sinusitis (Table I). BLPB may not only survive penicillin therapy but in a polymicrobial infection they also may 'shield' other penicillin-susceptible bacteria from penicillin by releasing the free enzyme into their environment. The actual activity of the enzyme beta-lactamase and the phenomenon of 'shielding' were demonstrated recently in acutely and chronically inflamed sinus fluids.[29] BLPB were isolated in four of 10 acute sinusitis aspirates and in 10 of 13 chronic sinusitis aspirates (Table II). The predominant BLPB isolated in acute sinusitis were *H. influenzae* and *M. catarrhalis*, and those found in chronic sinusitis were *Prevotella* and *Fusobacterium* spp.[29] Free beta-lactamase was detected in 86 per cent of these aspirates, and was associated with persistence of penicillin-susceptible pathogens.

S. pneumoniae *resistance*

S. pneumoniae utilizes a different mechanism of resistance to penicillin, through changes in penicillin-binding proteins. About half of the penicillin-resistant strains are currently intermediately resistant (minimal inhibitory concentration [MIC] of 0.1–1.0 mg/ml) and the rest are highly resistant (MIC>2.0 mg/ml). A larger problem is multidrug-resistant pneumococci. Penicillin-resistant strains can also show resistance to other antimicrobial agents – including oral third-generation cephalosporins, trimethoprim-sulphamethoxazole (TMP/SMX) and macrolides – but they are susceptible to vancomycin. Intermediately resistant *S. pneumoniae* are still susceptible *in vitro* to high concentrations of penicillin or amoxycillin.[30] Clindamycin and the oral second-generation cephalosporins, especially cefuroxime axetil and cefprozil, are also effective *in vitro* against over 95 per cent of intermediately penicillin-resistant strains.[31]

TABLE II

MICROBIOLOGY AND BETA-LACTAMASE DETECTION IN FOUR INDIVIDUALS WITH CHRONIC MAXILLARY SINUSITIS[29]

Beta-Lactamase Detected in Chronic Sinusitis Aspirates				
	Patient No.			
Organism	1	2	3	4
Staphylococcus aureus (BL +)		+		+
Streptococcus pneumoniae	+			
Peptostreptococcus spp	+			+
Propionibacterium acnes	+			
Fusobacterium spp (BL +)		+		+
Fusobacterium spp (BL -)		+		+
Prevotella spp (BL +)			+	
Prevotella spp (BL -)	+	+	+	
Bacteroides fragilis group (BL +)	+			+

Risk factors for the development of resistance to antimicrobial agents include prior antibiotic exposure, day-care attendance, <2 years of age, recent hospitalization and recurrent infection (especially at extreme ages).[32]

The variety of organisms involved in sinusitis, increasing levels of resistance to antibiotic agents and the phenomenon of beta-lactamase 'shielding' from antibiotic agents all contribute to the therapeutic challenges associated with the management of acute and chronic sinusitis.

Antimicrobial management

Antimicrobial agents

The antimicrobial agents most commonly used to treat acute sinusitis include amoxycillin (with and without clavulanic acid), oral and parenteral cephalosporins, macrolides and TMP/SMX. Amoxycillin is often used for sinusitis therapy and is safe and inexpensive, and when given in a high dose it is still the drug of choice for intermediately penicillin-susceptible *S. pneumoniae*. However, the growing resistance of *H. influenzae* and *M. catarrhalis* to amoxycillin increases the risk that it will fail to clear the infection. However, the addition of clavulanic acid (a beta-lactamase inhibitor) to amoxycillin or the use of antimicrobial agents resistant to beta-lactamase activity is effective against resistant organisms.

The increase in resistance of *S. pneumoniae* to penicillin mandates an increase in the amount of amoxycillin given to patients (up to 90 mg/kg/day in children and 4 grams/day in adults). This requires the addition of an equal amount of amoxycillin to amoxycillin-clavulanic acid or the use of the newer formulation of this drug (given twice daily) that contains higher proportions of amoxycillin to the beta-lactamase inhibitor.

First-generation cephalosporins lack sufficient efficacy against *H. influenzae* and many *S. pneumoniae* strains. The newer second-generation cephalosporins (cefuroxime axetil, cefdinir, cefprozil and cefpodoxime) are more effective because of their activity against penicillin-resistant *Haemophilus* and *Moraxella* spp. and intermediately penicillin-resistant *S. pneumoniae*.[31,32]

Oral third-generation cephalosporins (cefixime and ceftibuten) are most effective against penicillin-resistant *Haemophilus* and *Moraxella* spp., but they are less effective against *S. pneumoniae* resistant to penicillin. Parenteral third-generation cephalosporins (cefotaxime or ceftriaxone) are effective against *H. influenzae* and *M. catarrhalis* that produce beta-lactamase, as well as over 95 per cent of intermediately resistant *S. pneumoniae*.

TMP/SMX and erythromycin-sulphisoxazole acetyl have lost efficacy against all major pathogens, including Group A beta-haemolytic streptococci (GABHS). The sulpha component can cause hypersensitivity reactions.

Erythromycin is inactive against *H. influenzae* and some GABHS. Resistance of GABHS to erythromycin and other macrolides occurs in

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countries where these agents were overused (e.g. Japan, Finland, Spain, Taiwan and Turkey).[33] Cross-resistance of *S. pneumoniae* is common among all macrolides. Azithromycin has improved efficacy against aerobic Gram negative organisms (*H. influenzae* and *M. catarrhalis*), while clarithromycin is more efficient than erythromycin against aerobic gram-positive organisms.[34] Recent studies show, however, increased resistance of *S. pneumoniae* to all macrolides, and survival of azithromycin-susceptible *H. influenzae* in the middle ear and sinuses.[35] The persistence of the organism is believed to result from accumulation of azithromycin within the middle-ear white cells only, and not in the middle-ear fluid. Clindamycin has good efficacy against aerobic Gram positive organisms, including penicillin-resistant *S. pneumoniae*; however, it is not effective against aerobic Gram negative pathogens.[32] Vancomycin (a glycopeptide) is effective against penicillin-resistant S. pneumoniae and methicillin-resistant S. aureus. However, it has no efficacy against *H. influenzae* or *M. catarrhalis*.

The 'older' quinolones (i.e. ciprofloxacin, ofloxacin) are effective against *H. influenzae* and *M. catarrhalis*, but have minimal activity against *S. pneumoniae*. The 'newer' quinolones (e.g. levofloxacin, gatifloxacin, and moxifloxacin) have improved activity against *S. pneumoniae*.[34] However, these agents are currently not recommended for use in children because of the potential adverse effects on the cartilage.

Principles of therapy

In the empirical choice of antimicrobial therapy for sinuses, several balances between narrow-spectrum and wide-spectrum antimicrobial agents must be made. If the patient fails to show significant improvement or shows signs of deterioration despite treatment, it is important to obtain a culture preferably through sinus puncture, as this may reveal the presence of resistant bacteria. Obtaining a culture through endoscopy is an alternative approach.[36] However, the specimen may be contaminated with nasal flora. Surgical drainage may be extremely important at that time. Culture of nasal pus or of sinus exudate obtained by rinsing through the sinus ostium can give unreliable information because of contamination by the resident bacterial nasal flora. Further antimicrobial treatment is based, whenever possible, on results of the culture. Selection of the appropriate agent(s) is generally made on an empirical basis, and the agents should be effective against any potential organisms that may cause the infection.[22]

The goal of antimicrobial therapy is to eradicate susceptible organisms in the sinus cavity. Although standard parameters of antimicrobial activity such as MIC and minimal bactericidal concentration are helpful, they do not provide information about the time course or rate of kill relative to concentration or whether post-antibiotic effects contribute to activity.[37] Antibiotics can be divided into two major groups: those that exhibit concentration-dependent killing and prolonged persistent effects and those that exhibit time-dependent killing and minimal-to-moderate persistent effects. With drugs that fall into the former group the area under the concentration-time curve (AUC) (i.e., quinolones) and peak levels (aminoglycosides) are the major parameters that correlate with efficacy. The ratio of peak concentration to MIC is a measure of potency that also indicates the efficacy of the drug in these agents. With drugs that exhibit time-dependent killing and minimal-to-moderate persistent effects, time above MIC is the major parameter determining efficacy. Beta-lactam and macrolide antibiotics belong to this second group. Studies in otitis media show that there appears to be a relationship between the time above MIC in serum and in middle-ear fluid (MEF) for beta-lactam antibiotics. It is predicted that to achieve at least 80–85 per cent bacteriological cure in otitis media, serum concentrations should exceed the MIC of pathogens for at least 40 per cent of the dosing interval. For the same cure rate, the peak MEF to MIC ratio should be in the range of 3–6. If the MICs for pathogens are known, it will be possible to predict those agents for which adequate concentrations can be achieved.

Factors within the sinus cavity that may enable organisms to survive antimicrobial therapy are inadequate penetration of antimicrobial agents, a high protein concentration (can bind antimicrobial agents), a high content of enzymes that inactivate antimicrobial agents (i.e. beta-lactamase), decreased multiplication rate of organisms that interfere with the activity of bacteriostatic agents and reduction in pH and oxygen partial pressure, which reduces the efficacy of some antimicrobial agents (e.g. aminoglycosides and quinolones).[38]

Failure to improve on completion of appropriate antibiotic therapy should prompt consideration of bacterial resistance, noncompliance, or complicated sinusitis. Antimicrobial agents that achieve good intrasinus concentrations can, however, fail to eradicate the pathogen(s) if there is impairment of local defences (e.g. phagocytosis, ciliary motility) or the sinus environment.

Acute sinusitis

A number of antimicrobial agents have been studied in the therapy of acute sinusitis over the past 25 years, with the use of pre-and post-treatment aspirate cultures. Those studied were ampicillin, amoxycillin, bacampicillin, cyclacillin, cefuroxime axetil, amoxycillin-clavulanic acid, loracarbef, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin.[39] For a 10-day course of therapy, the success rate was a bacteriological cure over of 80–90 per cent. Appropriate antibiotic therapy is of paramount importance, even though it is estimated that spontaneous recovery occurs in 48 per cent of patients.[39,40]

Antimicrobial therapy is beneficial and effective in the prevention of septic complications.[41] The recommended length of therapy for acute sinusitis is at least 14 days, or seven days beyond the resolution of symptoms, whichever is longer. However, no controlled studies have proved the length of therapy

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sufficient to resolve the infection.

Six panels of experts recently presented thorough reviews and rendered their recommendations on how to diagnose and manage sinusitis.[42-47] The recommendations of three of these guidelines are presented here.

The Sinus and Allergy Partnership published guidelines[43] are based on predicted bacterial efficacy rates from mathematic modelling of acute sinusitis. These are based on pathogen distribution, resolution rates without treatment, and *in vitro* microbiological efficacy. Antibiotics were placed into categories of expected clinical efficacy in adults and children with acute sinusitis.

For adults with mild disease or with moderate disease, bacterial efficacy rates are >90 per cent (gatifloxacin, levofloxacin, moxifloxacin, and amoxycillin/clavulanate), 80 to 90 per cent (high-dose amoxycillin, cefpodoxime proxetil, cefixime (based on *H. influenzae* and *M. catarrhalis* coverage only), cefuroxime axetil and TMP/SMX, 70 to 80 per cent (clindamycin [based on Gram positive coverage only], doxycycline, cefprozil, azithromycin, clarithromycin, and erythromycin), and 50 to 60 per cent (cefaclor and loracarbef). The predicted spontaneous resolution rate in adults with acute sinusitis is 46.6 per cent. Antibiotics were placed into a similar rank order of predicted efficacy in children except for the quinolones. Gatifloxacin, levofloxacin, and moxifloxacin are indicated for adults who are beta-lactam allergic or intolerant. Azithromycin, clarithromycin, erythromycin, or TMP/SMX are recommended if the patient has a history of hypersensitivity reaction to beta-lactams. Recommendations for initial therapy for those who have received antibiotics in the previous four to six weeks include amoxycillin/clavulanate, gatifloxacin, levofloxacin, moxifloxacin (in adults only), or combination therapy (amoxycillin or clindamycin [Gram positive coverage] plus cefpodoxime proxetil or cefixime [Gram negative coverage]).

In 2004, the Sinus and Allergy Health Partnership published antimicrobial treatment guidelines for acute bacterial rhinosinusitis[47] that updated the original that was published in 2000.[43] The more recent guidelines are similar to those of the original publication; the areas of significant update included diagnostic modalities, contemporary antibacterial susceptibility profiles, addition of newer antimicrobial agents as recommended therapy, and expansion of the various pharmacodynamic/-pharmacokinetic principles and therapeutic outcomes model used to predict potential success of the individual antimicrobials.

The agents recommended for use to treat paediatric and adult patients with mildly symptomatic sinusitis who had not been exposed to an antibiotic in the preceding four-to-six weeks were amoxycillin, amoxycillin-clavulanate, cefpodoxime, cefuroxime, and cefdinir. Treatment options for those adult patients with mild sinusitis who had been exposed to an antibiotic in the previous four-to-six weeks and those adult patients with moderately symptomatic sinusitis were gatifloxacin, levofloxacin, moxifloxacin, amoxycillin-clavulanate, ceftriaxone, or a combination of either amoxycillin or clindamycin and either cefixime or rifampin.

Treatment options for those paediatric patients with mild sinusitis, who had been exposed to an antibiotic in the previous four-to-six weeks, and those paediatric patients with moderately symptomatic sinusitis were amoxycillin-clavulanate, cefpodoxime, cefuroxime, cefdinir, ceftriaxone, or a combination of either amoxycillin or clindamycin and either cefixime or rifampin.

The Clinical Advisory Committee on Paediatric and Adult Sinusitis has developed guidelines, based primarily on expert opinion.[45] They recommended beginning treatment of bacterial sinusitis with an inexpensive first-line agent (e.g., amoxycillin). Because of the growing resistance to *S. pneumoniae* the amoxycillin dose should be doubled (up to 90 mg/kg/day in children; maximum of 4 g/day in adults).

TABLE III

EFFICACY OF ANTIBIOTICS IN THE THERAPY OF SINUSITIS

	Acute sinusitis			Chronic sinusitis		
Oral Antimicrobial	*S. pneumoniae*	*Haemophilus* spp.	*Moraxella catarrhalis*	*S. aureus*	Anaerobes	Enterics
Penicillin/ amoxycillin	+	0	0	0	0	0
Cephalosporins						
first-	+/-	0	0	+	0	0
second-	+	+	+	+	0	+/-
third generation	+/-	+	+	+/-	0	+
Amoxycillin/ Clavulanate	+	+	+	+	+	+
Macrolides	+/-	+/-	+/-	+	0	0
Clindamycin	+	0	0	+	+	0
Imipenem*/ Meropenem*	+	+	+	+	+	+
Trimethoprim/ sulphamethoxazole	-	+	+	+/-	0	+
Quinolones (older) or aminoglycosides*	+/-	+	+	+/-	-	+
Quinolones (newer)	+	+	+	+	+/-	+

0 = no activity; +/- = some activity; + = good activity.
* Available in parenteral form only.

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Second-line agents should be used in those who do not improve within three to five days and should also be considered for initial use when resistant pathogens are suspected.

The risk factors for increased resistance include: antibiotic use in the past month, resistance common in the community, failure of first-line agent, infection in spite of prophylactic treatment, smoker in family, child in day-care facility, younger than two years of age, patient history, allergy to penicillin or amoxycillin, frontal or sphenoidal sinusitis, complicated ethmoidal sinusitis, and presentation with protracted (>30 days) symptoms. The second-line agents include agents with proven efficacy based on clinical and *in vitro* data against potential resistant pathogens. These agents include amoxycillin-clavulanate (containing high amoxycillin dose) and the second-generation cephalosporins with adequate *S. pneumoniae* and *H. influenzae* coverage (ceprozil, cefuroxime-axetil, cefpedoxime). For penicillin-allergic individuals, macrolides may be considered. If that approach failed, a combination of clindamycin plus a third-generation oral cephalosporin, or ceftriaxone (injectable), is an option. Fluoroquinolones with adequate *S. pneumoniae* coverage (gatifloxacin, moxifloxacin) can be used in adults.

- **Resistance to anti-bacterial agents used to treat sinusitis is becoming more common**
- **Most sinusitis develops from an initial viral infection or allergy**
- **Agents most effective in acute sinusitis are amoxycillin-clavulanate, the newer quinolones and second generation cephalosporins**
- **In chronic sinusitis, where anaerobic infection is more common, amoxycillin-clavulanate, clindamycin and metronidazole / penicillin combination are more appropriate**

The American Academy of Paediatrics subcommittee on Management of Sinusitis recommended that when antibiotics are indicated these should be a high dose of amoxycillin or amoxycillin-clavulanate 90 mg/kg/day, cefuroxime, cefpodoxime, or cefdinir.[46] Azithromycin or clarithromycin are contra-indicated in penicillin-allergic individuals.

Treatment of chronic sinusitis

Many of the pathogens isolated from chronically inflamed sinuses, are resistant to penicillins through the production of beta-lactamase.[29,48,49] These include both aerobic (*S. aureus*, *H. influenzae* and *M. catarrhalis*) and anaerobic isolates (*Bacteroides fragilis* and over half of the *Prevotella* and *Fusobacterium* spp.). Retrospective studies illustrate the superiority of therapy effective against both aerobic and anaerobic BLPB in chronic sinusitis.[49,50] Antimicrobial agents used for chronic sinusitis therapy should be effective against both aerobic and anaerobic BLPB; these include the combination of a penicillin (e.g. amoxycillin) and a beta-lactamase inhibitor (e.g. clavulanic acid), clindamycin, chloramphenicol, the combination of metronidazole and a penicillin or a macrolide, and the 'newer' quinolones (e.g. trovafloxacin). All of these agents (or similar ones) are available in oral and parenteral forms. Other effective agents are available only in parenteral form (e.g. cefoxitin, cefotetan and cefmetazole). If aerobic Gram negative organisms, such as *P. aeruginosa*, are involved parenteral therapy with an aminoglycoside, a fourth-generation cephalosporin (cefepime or ceftazidime) or oral or parenteral treatment with a fluoroquinolone (only in postpubertal patients) is added. Parenteral therapy with a carbapenem (e.g. imipenem) is more expensive, but provides coverage for most potential pathogens, both anaerobes and aerobes.

The length of therapy is at least 21 days, and may be extended up to 10 weeks. Fungal sinusitis can be treated with surgical debridement of the affected sinuses and antifungal therapy. In contrast to acute sinusitis, which is generally treated vigorously with antibiotics, many physicians believe that surgical drainage is the mainstay of therapy in chronic sinusitis. When the patient does not respond to medical therapy, the physician should consider surgical drainage. Impaired drainage may be a major contribution to the development of chronic sinusitis, and correction of the obstruction helps to alleviate the infection and prevent recurrence. The use of antimicrobial therapy alone without surgical drainage of collected pus may not result in clearance of the infection. The chronically inflamed sinus membranes with diminished vascularity may be a poor means of carrying an adequate antibiotic level to the infected tissue, even though the blood level may be therapeutic. Furthermore, the reduction in the pH and oxygen tension within the inflamed sinus may interfere further with the activity of the antimicrobial agents, which can result in bacterial survival despite a high antibiotic concentration.[38]

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