

Sinusitis in Children: a Pediatric Infectious Diseases Perspective

Itzhak Brook

Abstract

Sinusitis is a common illness in children. Most cases resolve spontaneously but a small proportion develops a secondary bacterial infection. Accurate diagnosis of sinusitis depends upon clinical assessment. Isolation of the causative agents must be considered in cases failing initial treatment. The most common bacterial isolates from children with community-acquired, acute purulent sinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, Group A beta-hemolytic streptococci, and *Staphylococcus aureus*. *S. aureus*, and anaerobic bacteria (*Prevotella* and *Porphyromonas*, *Fusobacterium* and *Peptostreptococcus* spp.) are the most common isolates in chronic infection. Aerobic Gram-negative rods including *Pseudomonas aeruginosa* are common in nosocomial sinusitis, the immunocompromised, those with human immunodeficiency virus infection and cystic fibrosis. Fungal and *P. aeruginosa* are common causes of sinusitis in neutropenic patients. The proper choice of antibiotic therapy depends on the likely infecting pathogens, bacterial antibiotic resistance and antibiotics' pharmacologic profiles. In addition to antibiotics, adjuvant therapies and surgery are utilized in the management of bacterial sinusitis. Accurate diagnosis and careful consideration when choosing therapy for sinusitis will optimize the chances of achieving an early recovery and avoiding complications.

Introduction

Sinusitis is one of the most common health problems in children and had increased in prevalence and incidence¹⁻³. Chronic sinusitis can induce significant physical symptoms that cause substantial functional and emotional impairment³.

Sinusitis is defined as an inflammation of the mucous membrane lining the paranasal sinuses and is classified chronologically into five categories⁴:

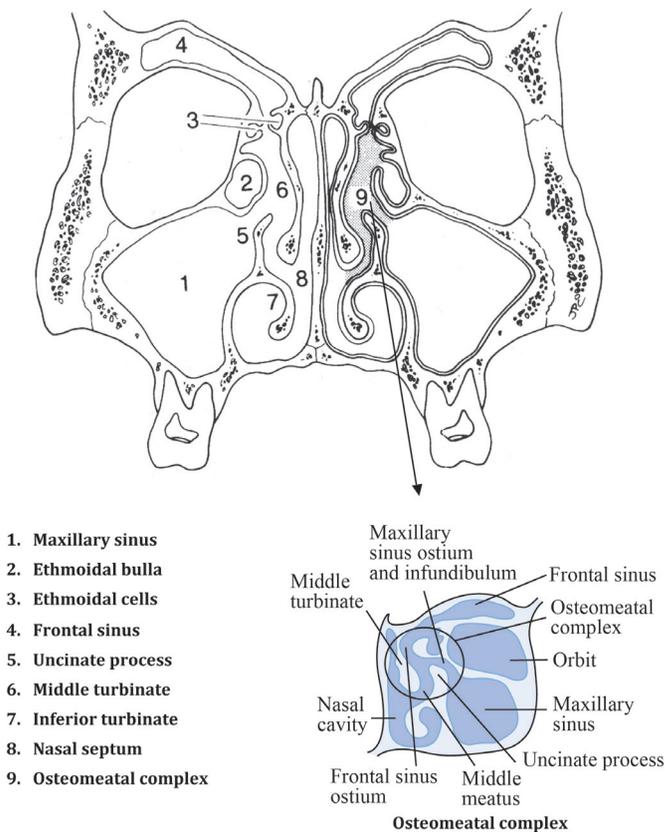
- acute sinusitis - a new infection that may last up to four weeks and can be subdivided symptomatically into severe and non-severe;
- recurrent acute sinusitis - four or more separate episodes of acute sinusitis that occur within one year;
- subacute sinusitis - an infection that lasts between four to 12 weeks, representing a transition between acute and chronic infection;
- chronic sinusitis - when signs and symptoms last for more than 12 weeks;
- acute exacerbation of chronic sinusitis - when the signs and symptoms of chronic sinusitis exacerbate, but return to baseline following treatment

Sinusitis can also be categorized according to the mode of transmission and underlying medical conditions. These are nosocomial sinusitis, sinusitis in the immunocompromised hosts, and sinusitis of odontogenic origin.

Anatomy and pathogenesis

The paranasal sinuses (maxillary, ethmoid, frontal, and sphenoid) include four symmetrical air-filled spaces lined by pseudostratified, ciliated, columnar epithelium. They are connected through the sinus ostia, which are small tubular openings, which drain into the nasal cavity (**Figure 1**). The frontal, anterior ethmoid, and maxillary sinuses drain into the middle meatus, while the posterior ethmoid and sphenoid ones open into the superior meatus. The osteomeatal complex (OMC) is the site where the drainage of the frontal, ethmoid and maxillary sinuses merge (**Figure 1**). Medially it is bordered by the middle turbinate, the basal lamella posteriorly and superiorly, and the lamina papyracea laterally. It opens for drainage anteriorly and inferiorly. Blockage or inflammation at the OMC is responsible for the development of viral and subsequently bacterial sinusitis, as it interferes with effective mucociliary clearance⁵.

Figure 1. Coronal view of the paranasal sinuses and the osteomeatal complex. (From Wald ER. Chronic sinusitis in children. *J Pediatr* 1995;127:339-347.)



Because the mucous membranes lining the nasal chambers and the sinuses are continuous with each other through the natural ostium, and are histologically similar, any upper respiratory infection commonly results in an inflammatory sinusitis. However, in most cases sinus infection does not persist after the nasal infection has subsided unless there is continued blockage at the OMC. At this stage, the blocked sinus does not drain freely and is susceptible to secondary bacterial infection.

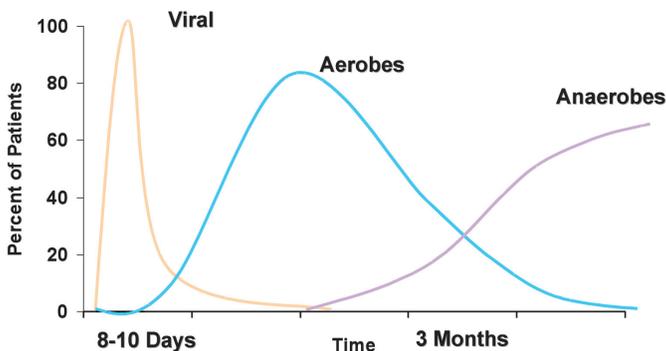
The sinuses develop gradually throughout childhood and reach adult size during adolescence. Since the infant is born only with the maxillary and ethmoid sinuses, the frontal sinuses are rarely infected prior the age six years. Blockage of the sinus ostium is the main predisposing factor causing suppurative infection, and often results from viral or other upper respiratory infection, which is common in early childhood. Other contributory factors are congenital and genetic factors ⁶, and acquired immune deficiencies ^{7,8}. Cyanotic congenital heart disease frequently is complicated by sinusitis. Mechanical obstruction resulting in sinusitis can be caused by septal dislocation owing to birth trauma, unilateral choanal atresia, foreign bodies placed in the nose, or fractures of the nose. Up to a third of cystic fibrosis patients develop polyps complicating the already abnormal sinus secretions that predispose them to sinusitis ⁹. Allergy, mostly asthma, is also an important predisposing factor in sinusitis ¹⁰. Dental infections can also be a source of sinusitis ¹¹.

The origin of the pathogens introduced into the sinuses that eventually cause sinusitis is mainly the nasal cavity. The normal flora at the nasal cavity contains certain bacterial species, and include *Staphylococcus aureus*, *Staphylococcus epidermidis*, alpha- and gamma-streptococci, *Propionibacterium acnes* and facultative diphtheroids ^{12,13}. Potential sinus pathogens are rarely found in the healthy nasal cavity.

Phases of sinusitis

The dynamics of sinusitis as well as otitis media progresses through several phases (**Figure 2**). The early one is generally viral (mostly rhinovirus, adenovirus, influenza and parainfluenza viruses) that generally lasts up to 10 days where complete recovery occurs in 99% of individuals ¹⁴.

Figure 2. The chronology of viral and bacterial causes of sinusitis.



In a small number of patients, a secondary acute bacterial infection may emerge, generally caused by aerobic bacteria (i.e., *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*). If resolution does not take place, anaerobic bacteria from the oropharyngeal flora become predominant over time¹⁵. The mechanism by which viruses predispose to bacterial sinusitis may involve viral-bacterial synergy, induction of local inflammation that blocks the sinus ostia, increase of bacterial attachment to the epithelial cells, and disruption of the local immune defense. Conditions which promote the growth of anaerobic bacteria include reduction in oxygen tension and an increase in acidity within the sinus. These are caused by the persistent edema and swelling, which decreases blood supply, and by the consumption of oxygen by the aerobic bacteria¹⁶. Another explanation for the slower appearance of anaerobes as pathogens is that expression of some of their virulence factors such as a capsule is slow¹⁷. Several anaerobic and aerobic bacteria that are part of the normal oropharyngeal flora can interfere with the growth of sinus pathogens. Interfering organisms were recovered in higher numbers in the nasopharynx of non-sinusitis-prone individuals, as compared to sinusitis prone ones¹⁸.

Microbiology

Acute Bacterial Sinusitis

The most common bacteria recovered from pediatric and adult patients with community-acquired, acute purulent sinusitis are *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, Group A beta-hemolytic streptococci, and *S. aureus*¹⁹⁻²⁵ (**Table 1**). The vaccination of children with the 7-valent pneumococcal vaccine introduced in 2000 in the USA, brought about the decline in the recovery rate of *S. pneumoniae* and an increase in *H. influenzae*²⁶. *S. aureus* is a common pathogen in sphenoid sinusitis²⁷, while the other organisms are found in other sinuses. Recent data illustrates a significant increase occurred in the rate of recovery of Methicillin resistant *S. aureus* (MRSA) in patients with upper respiratory tract infections including acute and chronic maxillary sinusitis²⁸.

The infection is polymicrobial in about a third of the patients. Enteric bacteria are rarely isolated, and anaerobes are isolated only from a few cases with acute sinusitis. However, proper methods for their recovery were rarely employed in most studies of acute sinusitis. Anaerobes account for about 8% of isolates and are often recovered from acute infection associated with an odontogenic origin, mainly as an extension of the infection from the roots of the premolar or molar teeth^{11, 29}.

Pseudomonas aeruginosa and other aerobic Gram-negative rods are mostly recovered from nosocomial sinusitis (mainly in those with nasal tubes or catheters), the immunocompromised, those with human immunodeficiency virus (HIV) infection and cystic fibrosis³⁰. However, anaerobes can also be isolated in these patients.

Chronic Bacterial Sinusitis

Bacteria are believed to play a major role in most cases, even though the etiology of inflammation associated with chronic sinusitis is uncertain^{31,32}. There are clear differences in the bacterial pathogens present in chronic as compared

with acute sinusitis. The main isolates in acute sinusitis (e.g., *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*) are present in lower frequency³¹ while *S. aureus*, *Staphylococcus epidermidis*, and anaerobic Gram-negative bacilli (AGNB) are common in chronic infection^{20-23, 33} (Table 1). The pathogenic role of *S. epidermidis*, a low virulence organisms that is a colonizer of the nasal cavity, is uncertain^{34,35}. Polymicrobial infection is common and can be synergistic¹⁷.

Table 1. Microbiology of acute and chronic sinusitis (percent of patients)

	Maxillary		Ethmoid		Frontal		Sphenoid	
	Acute N=NS*	Chronic N=66	Acute N=26	Chronic N=17	Acute N=15	Chronic N=13	Acute N=16	Chronic N=7
Bacteria								
Aerobes								
<i>S. aureus</i>	4	14	15	24	-	15	56	14
<i>S. pyogenes</i>	2	8	8	6	3	-	6	-
<i>S. pneumoniae</i>	31	6	35	6	33	-	6	-
<i>H. influenzae</i>	21	5	27	6	40	15	12	14
<i>M. catarrhalis</i>	8	6	8	-	20	-	-	-
Enterobacteriaceae	7	6	-	47	-	8	-	28
<i>P. aeruginosa</i>	2	3	-	6	-	8	6	14
Anaerobes								
<i>Peptostreptococcus</i>	2	56	15	59	3	38	19	57
<i>P. acnes</i>	-	29	12	18	3	8	12	29
<i>Fusobacterium</i>	2	17	4	47	3	31	6	54
<i>Prevotella & Porphyromonas</i>	2	47	8	82	3	62	6	86
<i>B. fragilis</i>	-	6	-	-	-	15	-	-

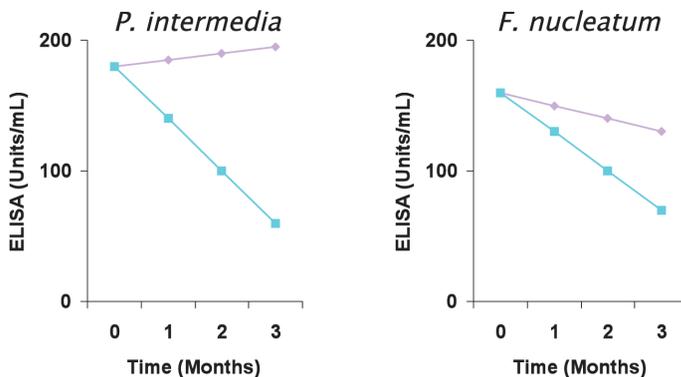
Data from Gwaltney et al²⁵ and from Brook^{19,24}. Since some patients had multiple isolates from the same specimen, the sum of percentages in each column exceeds 100%. * NS, not stated

Gram negative enteric rods (*P. aeruginosa*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter* spp. and *Escherichia coli*) can also be isolated^{36,37}. Their recovery could also be due to selection pressure caused by the administration of antimicrobial therapy. Gram-negative rods were more often from patients who had previous surgery or those who had sinus irrigation.³⁷ *P. aeruginosa* was also more common in those who had received systemic steroids. Other studies also noted higher recovery of Gram-negative rods in patients who have been treated extensively and repeatedly^{36,38}. The bacterial flora also included *Pseudomonas* spp., *Enterobacter* spp., MRSA, *H. influenzae*, and *M. catarrhalis*.

Most studies that examined the pathogens associated with chronic sinusitis did not use adequate methods for the isolation of anaerobic bacteria. That anaerobes can play a significant role in chronic sinusitis is supported by their ability to induce chronic sinusitis in a rabbit by intra-sinus inoculation of *Bacteroides fragilis*³⁹, and by the production of serum IgG antibodies against this anaerobe in the infected animals⁴⁰. Their pathogenic role is also supported by the detection of IgG antibodies in patients with chronic sinusitis to two anaerobic organisms that were recovered from their sinuses (*Fusobacterium nucleatum* and *Prevotella intermedia*)⁴¹. Antibody levels to these anaerobes decreased in patients who were cured, but did not decrease in those who failed therapy (**Figure 3**). The involvement of anaerobes in chronic sinusitis may be due to inadequate drainage and increased intranasal pressure that develops during inflammation. This can decrease the oxygen tension in the inflamed sinus by reducing the mucosal blood supply and depressing the mucociliary action⁴². The decrease in the oxygen content and pH of the sinus cavity supports the growth of anaerobes by providing an optimal oxidation-reduction potential^{16,42}.

Anaerobes are often isolated from infectious complications of chronic sinusitis, including periorbital cellulitis, brain abscess, subdural or epidural empyema⁴³⁻⁴⁵. This further supports their role in complicated sinus infections.

Figure 3. Serum IgG antibodies to *Fusobacterium nucleatum* and *Prevotella intermedia* in 23 patients with chronic sinusitis. (From Brook I, Yocum P. Immune responses to *Fusobacterium nucleatum* and *Prevotella intermedia* in patients with chronic maxillary sinusitis. *Ann Otol Rhinol Laryngol* 1999;108:293-295.)



Anaerobes were found in 13 studies in children and adults that included 1,758 patients (133 were children), the only ones that utilized methods adequate for their isolation (**Table 2**)^{19,20,46-57}. Anaerobes were isolated in 12% to 93% of the patients. The predominant isolates were pigmented *Prevotella*, *Fusobacterium* and *Peptostreptococcus* spp. The differences in recovery of anaerobes may due to differences in the methodologies used for transportation and cultivation of specimens, patient population, geography and previous antimicrobial therapy. Finegold et al⁴⁴ noted that among patients with chronic maxillary sinusitis, recurrence of signs and symptoms was twice as frequent when their sinus cultures had anaerobic bacterial counts were less than 10³ colony forming units per mL aspirate.

Table 2. Isolation of anaerobes from patients with chronic sinusitis

References	Country	No. patients	Presence of Anaerobes	
			Patients %	Organisms %
Frederick & Braude, 1974 [49]	USA	83	75	52
Van Cauwenberge et al, 1976 [50]	Belgium	66	39	39
Karma et al, 1979 [51]	Finland	40 (adult)	-	19
Brook, 1981 [19]	USA	40 (ped)	100	80
Berg et al, 1988 [52]	Sweden	54 (adult)	≥33	42
Tabaqchali, 1988 [54]	UK	35	79	39
Brook, 1989 [20]	USA	72 (adult)	88	71
Fiscella & Chow, 1991 [38]	USA	15 (adult)	38	48
Erkan et al, 1994 [46, 56]	Turkey	126 (adult)	88	71
		93 (ped)	93	74
Ito et al, 1995 [55]	Japan	10	60	82
Klossek et al, 1998 [57]	France	394	26	25
Finegold et al, 2002 [48]	USA	150 (adult)	56	48

Brook et al investigated the microbiology of chronic infection in 13 frontal²¹, seven sphenoid²², and 17 ethmoid sinuses²³. Anaerobes were isolated in over 66% of the patients and the predominant ones included *Prevotella*, *Peptostreptococcus*, and *Fusobacterium* spp. The most common aerobic isolates were Gram-negative bacilli (*H. influenzae*, *K. pneumoniae*, *E. coli*, and *P. aeruginosa*).

Acute exacerbation of chronic sinusitis

Acute exacerbation of chronic sinusitis (AECS) is defined as a sudden worsening of the baseline manifestation of chronic sinusitis with either worsening or appearance of new symptoms. Typically, the acute (not chronic) symptoms resolve completely between occurrences. Brook et al investigated the microbiology of maxillary AECS by obtaining repeated endoscopic aspirations in seven patients over a period of 125 to 242 days⁵⁸. Bacteria were isolated in all aspirates and the number of isolates per aspirate varied between two to four. The aerobes isolated were *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *S. aureus* and *K. pneumoniae*. The predominate anaerobes were pigmented *Prevotella* and *Porphyromonas*, *Peptostreptococcus*, and *Fusobacterium* spp., and *Propionibacterium acnes*. A change in the type of isolates was noted in all consecutive cultures obtained from the same individual, as different organisms emerged, and previously ones were no longer isolated. An increase in the antimicrobial resistance occurred in six instances. Brook et al⁵⁹ also compared the microbiology of maxillary AECS in 30 patients with chronic maxillary sinusitis. The study demonstrated the predominance of anaerobes and the polymicrobial nature of both infections (2.5-3 isolates/sinus). However, aerobes that are usually found in acute infections (e.g. *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*) emerged in some of the episodes of AECS. These observations highlight the importance of obtaining cultures from patients with AECS for guidance in selection of appropriate antimicrobial therapy.

Nosocomial Sinusitis

Nosocomial sinusitis often occurs in patients with extended periods of intensive care (postoperative patients, burn victims, patients with severe trauma) that involves prolonged endotracheal or nasogastric intubation. *P. aeruginosa* as well as other aerobic and facultative Gram-negative rods are common in sinusitis of nosocomial origin (especially in patients who have nasal tubes or catheters), the immunocompromised, those with human immune-deficiency viral infection, and patients who suffer from cystic fibrosis^{30,60}.

Patient with nasotracheal intubation are at a substantially higher risk for nosocomial sinusitis than orotracheal intubation. About a quarter of those requiring nasotracheal intubation for more than five days develop nosocomial sinusitis⁶¹. In contrast to community-acquired sinusitis, the common pathogens are Gram-negative enteric bacteria (i.e., *P. aeruginosa*, *K. pneumoniae*, *Enterobacter* spp., *Proteus mirabilis*, *Serratia marcescens*) and Gram-positive cocci (occasionally streptococci and staphylococci). Whether these bacteria are pathogenic is unclear as their recovery may represent only colonization of an environment with impaired mucociliary transport and presence of foreign body in the nasal cavity.

A study of the bacteriology of nosocomial sinusitis in nine children with neurological impairment revealed anaerobic bacteria, always mixed with aerobic and facultative bacteria in six (67%) sinus aspirates, and aerobic bacteria only in three (33%) [62]. There were 24 bacterial isolates, 12 aerobic or facultative and 12 anaerobic. The predominant aerobes were *K. pneumoniae*, *E. coli*, *S. aureus*, *P. mirabilis*, *P. aeruginosa*, *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*. The predominant anaerobes were *Prevotella* spp., *Peptostreptococcus* spp,

F. nucleatum, and *B. fragilis*. Organisms similar to those recovered from the sinuses were also recovered from the tracheostomy site and gastrostomy wound aspirates in five of seven patients. This study highlights the uniqueness of the microbiologic features of sinusitis in neurologically impaired children, in which facultative and anaerobic Gram-negative organisms that colonize other body sites are predominant.

Sinusitis in the Immunocompromised Host

Sinusitis occurs in a wide range of immunocompromised hosts including neutropenics, diabetics, patients in critical care units, and patients infected with HIV. Fungal and *P. aeruginosa* are the most common form of sinusitis in neutropenic patients. *Aspergillus* spp. is commonly the causative organism, although mucus, rhizopus, alternaria, and other molds have been implicated⁶³. Fungi and *S. aureus*, streptococci and Gram-negative enteric bacteria are the most frequent isolates in patients with diabetes mellitus⁶⁴⁻⁶⁶. The causative pathogens in patients with HIV infection include *S. aureus*, *P. aeruginosa*, streptococci, anaerobes, and fungi (*Aspergillus*, *Cryptococcus*, and *Rhizopus*)⁶⁷. Refractory parasitic sinusitis caused by *Microsporidium*, *Cryptosporidium* and *Acanthamoeba* has also been described in patients with advanced immunosuppression. Other etiologic agents are cytomegalovirus, atypical Mycobacteria and *Mycobacterium kansasii*⁶⁰.

Sinusitis of Odontogenic Origin

Odontogenic sinusitis accounts for about 10% to 12% of cases of maxillary sinusitis. Brook et al¹¹ evaluated the microbiology of 20 patients with acute and 28 patients with chronic maxillary sinusitis associated with odontogenic infection. Polymicrobial infection was common with 3.4 isolates per specimen, and 90% of the isolates were anaerobes in both acute and chronic infections. The predominant anaerobes were AGNB, *Peptostreptococcus* and *Fusobacterium* spp. The predominant aerobes were a-hemolytic streptococci, microaerophilic streptococci, and *S. aureus*.

The microorganisms recovered from odontogenic infections generally reflect the indigenous oral microflora. An association between periapical abscesses and sinusitis was established in a study of purulent aspirates from five periapical abscesses of the upper jaw and their corresponding maxillary sinuses⁶⁸. Polymicrobial flora was present in all cases, where the number of isolates varied from two to five. Anaerobes were recovered from all specimens. The most common organisms were *Prevotella*, *Porphyromonas*, *Peptostreptococcus* spp. and *F. nucleatum*. Concordance in the microbiological findings between periapical abscess and the maxillary sinus flora was evident in all instances, suggesting contiguous spread of infection from the periapical abscess. The proximity of the maxillary molar teeth to the floor of the maxillary sinus enables such a spread.

Clinical features and diagnosis

Suspicion of bacterial sinusitis is based on clinical symptoms and signs when at least two major or one major and two minor criteria are present (Table 3)⁶⁹. The most common presentation is a persistent (and no improvement) nasal discharge or cough (or both) lasting more than 10 days⁷⁰. A 10-day period generally marks the limit of simple viral upper respiratory tract infection (URTI) and separates it from bacterial

sinusitis because most uncomplicated viral URTI last between five to seven days and by day 10 most patients have improved.

Table 3. Major and minor clinical criteria suggestive of bacterial sinusitis*

Major criteria	Minor criteria
Facial pain or pressure (requires a second major criterion to constitute a suggestive history)	Headache
Facial congestion or fullness	Fever (for subacute and chronic sinusitis)
Nasal congestion or obstruction	Halitosis
Nasal discharge, purulence or discoloured postnasal drainage	Fatigue
Hyposmia or anosmia	Dental pain
Fever (for acute sinusitis; requires a second major criterion to constitute a strong history)	Cough
Purulence on intranasal examination	Ear pain, pressure or fullness
* A strongly suggestive history requires the presence of two major criteria or one major and two or more minor criteria. A suggestive history requires the presence of one major criterion or two or more minor criteria.	

The symptoms and signs of acute bacterial infection can be divided into non-severe and severe (**Table 4**)⁴. The severe form carries a higher risk of complications and mandates earlier use of antimicrobial therapy. The combination of high fever and purulent nasal discharge that lasts for at least 3 to 4 days suggests a bacterial sinusitis.

Table 4. Severity of symptoms and signs in acute bacterial sinusitis

Non-severe	Severe
Rhinorrhea (of any quality)	Purulent (thick, colored, opaque) rhinorrhea
Nasal congestion	Nasal congestion
Cough	Facial pain or headache
Headache, facial pain, and irritability (variable)	Periorbital edema (variable)
Low-grade or no fever	High fever (temperature $\geq 39^{\circ}\text{C}$)

Individuals with acute bacterial sinusitis often have nasal mucous membranes edema, mucopurulent nasal discharge, persistent postnasal drip, fever, and malaise.

The quality of the nasal discharge varies, and can be thin or thick, clear mucoid, or purulent. Tenderness and pain of the involved sinus can be induced by percussion of the affected sinus. Cellulitis can also be present overlying the affected sinus. Other findings, especially in acute ethmoiditis, are periorbital cellulitis, edema, and proptosis. Failure to transilluminate the sinus and the presence of nasal voice can be present in many patients. Direct smear of nasal secretions usually shows the predominance of neutrophils, and the observation of numerous eosinophils suggests allergy.

The symptoms are generally protracted and vary considerably in subacute or chronic bacterial sinusitis. Fever can be of low grade or be absent. The patient may complain of malaise, easy fatigability, irregular nasal or postnasal discharge, frequent headaches, difficulty in mental concentration, anorexia, and pain or tenderness to palpation over the affected sinus. Cough and nasal congestion can persist, and a sore throat (because of mouth-breathing) is frequent. The location of the facial pain can point to the involved sinus. Maxillary sinusitis is commonly associated with pain in the cheeks, frontal with the forehead, ethmoid with medial canthus, and sphenoid with occipital pain. In patients with chronic infection, changes in motion or position can worsen or alleviate the sinus symptoms. Pathology in the upper molar teeth can be the source of maxillary sinusitis.

Further work-up and consideration for hospitalization may be required when there is suspicion of nosocomial sinusitis (recent intubation, feeding or suction device), the presence of an immuno compromised status, possible meningitis or other intracranial complications, or frontal or sphenoid sinusitis.

Plain film X rays are generally not helpful in documenting the presence of infection, and are less specific and sensitive than computed tomography (CT) for analysis of the degree of sinus abnormalities. As a result their use has decreased and they have been replaced by CT. CT is especially advantageous in children because their sinuses are often asymmetrical and smaller than those in adults⁷¹. Clouding, opacity, and thickening of the mucosal interface (> than 4mm) of the affected sinus usually are present. Fluid level can often be noted.

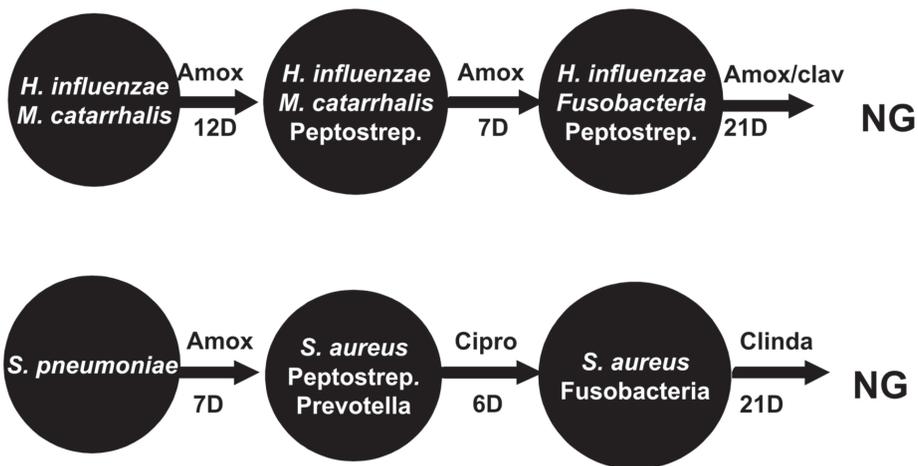
Treatment

Bacterial antimicrobial resistance against the antimicrobials used for the treatment of sinusitis has consistently increased over time. The production of the enzyme beta-lactamase is one of the important mechanisms of penicillin resistance. Beta-lactamase producing bacteria (BLPB) can protect penicillin-susceptible organisms from the activity of penicillin, thereby contributing to their persistence⁷². The ability of BLPB to shield penicillin-sensitive organisms has been demonstrated *in vitro* and *in vivo*⁷³. The actual activity of the enzyme beta-lactamase and the phenomenon of 'shielding' were demonstrated in acutely and chronically inflamed sinus fluids⁷⁴. BLPB were isolated in sinus aspirates from four of 10 patients with acute sinusitis, and 10 of 13 patients with chronic sinusitis. The predominate BLPB in acute sinusitis were *H. influenzae* and *M. catarrhalis*, and those isolated in chronic sinusitis were *Prevotella* and *Fusobacterium* spp. Up to half of *Prevotella* and *Fusobacterium* spp. are currently resistant to penicillins through the production of beta-lactamase⁷². These organisms are the predominant Gram-negative anaerobic bacilli in the oral flora, and are often recovered in

anaerobic infections in and around the oral cavity⁴⁴. The presence of BLPB in sinusitis⁷⁴ is not surprising, since over two-thirds of the patients with acute and all of the patients with chronic sinusitis received antimicrobial agents that might have selected for BLPB. It is therefore plausible that whenever BLPB are present, therapy need to be directed at their eradication.

Appropriate antibiotic therapy is essential for the prevention of complications⁷⁵. Culture obtained through direct aspiration or endoscopy can direct the selection of antimicrobials in the treatment of patients who fail to respond¹⁵. This was demonstrated when serial cultures of sinus aspirates were obtained from patients who failed to respond to antimicrobials. Most of the bacteria isolated from the first culture were aerobic or facultative bacteria: *S. pneumoniae*, *H. influenzae* non-type-b and *M. catarrhalis*. Subsequent sinus cultures of those who failed therapy generally yielded organisms that were resistant to the antimicrobial agents prescribed for treatment. Failure to improve was associated with the emergence of resistant aerobic and anaerobic bacteria in subsequent sinus aspirates (**Figure 4**). The infection was eradication in all individuals after the administration of antimicrobials effective against these bacteria, and in several instances by surgical drainage.

Figure 4. Changes in the bacterial flora in two patients with acute bacterial maxillary sinusitis that failed to respond to various antimicrobial regimens. (Amox), amoxicillin; (Amox\clav), amoxicillin\clavulanic-acid; (Clinda), clindamycin; (Cipro), ciprofloxacin; NG, no growth. (From Brook I, Frazier EH, Foote PA. Microbiology of the transition from acute to chronic maxillary sinusitis. J Med Microbiol 1996;45:372-375.)



Antimicrobials for Acute Bacterial Sinusitis

Amoxicillin can be adequate for the initial treatment of acute uncomplicated mild sinusitis (**Table 5**). However, antimicrobials with broader-spectrum may be indicated as initial therapy for those with more severe infection, co-morbidity, risk factors for bacterial resistance, and those who had failed amoxicillin therapy. These antimicrobials include: amoxicillin/clavulanate, the “newer” quinolones (e.g. levofloxacin, moxifloxacin) (in children > 16 years), and some second and third generation cephalosporins (cefdinir, cefuroxime-axetil, and cefpodoxime proxetil). Patients allergic to penicillin may be treated with a macrolide, trimethoprim-sulphamethoxazole (TMP-SMX), tetracyclines, or clindamycin ⁷⁵.

Table 5. Empirical antimicrobial therapy in acute bacterial sinusitis

Suitable for Amoxicillin Therapy (High-dose)
<ul style="list-style-type: none"> • Mild illness • No history of recurrent acute sinusitis • During summer months • When no recent antimicrobial therapy has been used • When patient has had no recent contact with patient(s) on antimicrobial therapy • When community experience shows high success rate of amoxicillin
Risk factors prompting a need for more effective antimicrobials*
<p>a) Bacterial resistance is likely</p> <ul style="list-style-type: none"> • Antibiotic use in the past month, or close contact with a treated individual(s) • Resistance common in community • Failure of previous antimicrobial therapy • Infection in spite of prophylactic treatment • Child in daycare facility • Winter season • Smoker or smoker in family
<p>b) Presence of moderate to severe infection</p> <ul style="list-style-type: none"> • Presentation with protracted (> 30 days) or moderate to severe symptoms • Complicated ethmoidal sinusitis • Frontal or sphenoidal sinusitis • Patient history of recurrent acute sinusitis
<p>c) Presence of co-morbidity and extremes of life</p> <ul style="list-style-type: none"> • Co-morbidity (i.e. chronic cardiac, hepatic or renal disease, diabetes) • Immunocompromised patient • Younger than 2 years of age or older than 55 years
<p>d) Allergy to penicillin</p> <ul style="list-style-type: none"> • Allergy to penicillin or amoxicillin, amoxicillin and clavulanic acid, 2nd and 3rd generation cephalosporins, and the “respiratory” quinolones (in those > 18 years old) .

The increase recovery of MRSA in acute and chronic sinusitis requires consideration of the need for coverage against these organisms. A comparison of the rate of recovery of MRSA between 2001-2003 to 2004-2006 in acute and chronic maxillary sinusitis illustrated a significant increase in the rate of recovery of this organism in patients with acute (from 3% of all isolates to 9%, $p < .01$) and chronic (from 4% of all isolates to 14%, $p < .01$ $p < .05$) maxillary sinusitis⁷⁶. This finding suggests the use of greater index suspicion for the presence of MRSA in sinusitis and greater use of sinus cultures especially in patients who do not improve or fail antimicrobial after 48 hours of therapy to guide the proper selection of antimicrobials agents.

Treatment of sinus infection associated with the recovery of MRSA is challenging. It is important to provide coverage against these organisms as well as other potential aerobic and anaerobic pathogens. Although vancomycin is considered the gold standard for therapy of MRSA infections, reports of increasing in vitro resistance to vancomycin⁷⁷ combined with reports of clinical failures (with this and other antistaphylococcal agents), underscore the need for alternative therapies. Older agents with favorable in vitro activity available in both oral and intravenous dose forms include TMP-SMX and clindamycin. Minimal clinical data exist to support their routine use as initial therapy in the treatment of MRSA infections. Newer treatment options of therapies for MRSA include linezolid, quinupristin-dalfopristin, daptomycin, and tigecycline.

A bacteriological cure over of 80-90% is expected for a 10-day course of therapy. However, it has been estimated that spontaneous cure can occur in about half of the patients^{75,78}. Wald et al⁷⁹ illustrated the effectiveness of antibiotic therapy in managing acute bacterial sinusitis in children. They evaluated the effectiveness of high-dose amoxicillin/clavulanate in the treatment of children in a randomized, double-blind, placebo-controlled study. Of the 28 children who received the antibiotic, 14 (50%) were cured, 4 (14%) were improved, 4 (14%) experienced treatment failure, and 6 (21%) withdrew. Of the 28 children who received placebo, 4 (14%) were cured, 5 (18%) improved, and 19 (68%) experienced treatment failure. Children receiving the antibiotic were more likely to be cured (50% vs 14%) and less likely to have treatment failure (14% vs 68%) than children receiving the placebo. The authors concluded that amoxicillin/clavulanate results in significantly more cures and fewer failures than placebo.

The recommended length of therapy for acute bacterial sinusitis is at least 14 days, or seven days beyond the resolution of symptoms, whichever is longer. However, no controlled studies of the optimal duration of therapy are available.

Antimicrobial for Chronic Bacterial Sinusitis

Many of the pathogens of chronically inflamed sinuses are resistant to penicillins because they produce beta-lactamase¹⁹⁻²⁴. Several studies showed the superiority of treatment effective against both aerobic and anaerobic BLPB in chronic sinusitis^{80,81}. These agents include the combination of a penicillin (e.g. amoxicillin) and a beta-lactamase inhibitor (e.g. clavulanic acid), clindamycin, the combination of metronidazole and a macrolide, and the 'newer' quinolones (e.g. levofloxacin, moxifloxacin) (in those > 18 years old). All of the above

agents (or similar ones) are available in oral and parenteral forms. When aerobic Gram-negative organisms, such as *P. aeruginosa*, are involved, an aminoglycoside, fourth-generation cephalosporins (cefepime or ceftazidime), or a fluoroquinolone (only in postpubertal patients) is added. Parenteral antimicrobials such as carbapenems (i.e., imipenem, meropenem, doripenem, ertapenem) are more expensive, but offers coverage for most potential anaerobes and aerobes pathogens. Coverage for MRSA should be considered (previously addressed). Therapy is administered for at least 21 days, and may be extended up to 10 weeks. Fungal sinusitis can be treated by surgical debridement and antifungal agents ⁸².

Adjuvant Therapies

In addition to antibiotics, other therapies have been utilized in the management of bacterial sinusitis. These therapies include topical and systemic decongestants, corticosteroids, anti-inflammatory agents, mucolytic agents, humidification, antihistamines, nasal lavage or saline nasal spray, spicy food, and hot dry air ⁸³. These agents induce rapid vasoconstriction, improve ostial patency, reduce swelling and congestion of the turbinates, and decrease inflammation at the OMC, thus facilitating sinus drainage.

The use of decongestants improves access into the congested nasal cavity for other therapeutic agents, such as corticosteroids, used in allergic sinusitis. The extended use of topical decongestants for >5 days can cause rebound vasodilatation and congestion (also called rhinitis medicamentosa). However, oral decongestants (eg, pseudoephedrine hydrochloride) can be used when the congestion lasts longer. In chronic sinusitis when therapy is required for a period >5 days, systemic decongestants are used.

Reduction in the viscosity and improvement in the quality of mucus can assist in resolution of the infection. Several methods achieve this goal, including nasal saline spray or irrigation, air humidification, adequate hydration, and mucolytic agents.

Nasal saline irrigation or spray is a simple and effective method, available in the form of a nasal spray of sterile saline solution. It can also be made by dissolving half a teaspoonful of salt (about 3 g) in warm water (260 ml), with or without baking soda (about 0.5 g). The solution can be placed in a spray bottle or a syringe for nasal lavage. Sprays of saline (2 to 4 puffs at a time) are inhaled three times a day, and when necessary, the nasal secretions can be washed out with syringe rinsing and aspiration. Its use is recommended in both acute and chronic bacterial sinusitis.

Inspired cool or hot humidified air and intake of adequate amounts of fluid are helpful in preventing and clearing thick secretions. Many mucolytic and mucoregulatory agents, as well as expectorants, are used to treat sinusitis. The most common is guaifenesin, which liquefies thick secretions effectively. It is available in liquid or tablet form, alone or in combination with oral decongestants.

Antihistamines are generally not used to treat bacterial sinusitis, because they can thicken and dry the secretions, which leads to crusting and further blocks the OMC. They can be useful, however, if the underlying cause is allergic.

Two classes of antihistamines are available: The first generation (ie, diphenhydramine, hydroxyzine, promethazine, meclizine, chlorpheniramine, and

tripelennamine). The newer second generation, which cause less dryness and are non-sedating (ie, cetirizine, fexofenadine, and loratadine).

Topical nasal corticosteroids are rarely used in acute bacterial sinusitis. They are, however, useful in the treatment of recurrent acute or chronic bacterial sinusitis and allergic rhinitis. Their use is based on the corticosteroid's powerful anti-inflammatory activity, and on its inhibition of cellular influx and all the phases of allergic reaction. Steroids have a delayed onset of action, and clinical improvement may take seven to 10 days. Corticosteroids are always used in conjunction with antimicrobial therapy.

The topical agents include fluticasone, budesonide, flunisolide, and triamcinolone acetonide, and can be administered for prolonged periods (in contrast to the limitations with topical decongestants). Topical agents can be delivered as an aerosol or aqueous solution. With prolonged use, topical side effects may occur (more so with the aerosol form than the aqueous form), and include irritation, sneezing, drying, burning sensation, crusting, bleeding, and (rarely) septal perforation⁸³. Systemic corticosteroids are rarely necessary in the treatment of allergic rhinitis, because of the generally good efficacy of topical corticosteroids or which immunotherapy may be effective⁸⁴.

Cromolyn sodium is available as a topical spray and helps to prevent perennial as well as seasonal allergic rhinitis⁸³. It works best when administered prior to exposure to an allergen and is given with a spray pump, in doses of one spray in each nostril every 4 hours during waking time. Relief is achieved between 4 and 7 days, whereupon the dose is reduced to an individual maintenance level. Side effects are infrequent, but include irritation and sneezing. Cromolyn sodium is effective in the treatment of allergic rhinitis, but does not help prevent the development of post viral sinus symptoms⁸⁴ and nonallergic bacterial sinusitis. It is not recommended for use in sinusitis, except to alleviate a concomitant allergic rhinitis.

Surgical Therapy

Surgical drainage may be needed in cases that fail medical therapy especially when complications occur. Surgical drainage is the mainstay of treatment for chronic sinusitis, especially in patients that have not responded to medical therapy. The goals of surgery are to prevent persistence, recurrence, progression and complications of chronic sinusitis. This is accomplished by removal of diseased tissue, preservation of normal tissue, promotion of drainage (or obliteration if this is not possible) and consideration of the cosmetic outcome. Functional endoscopic sinus surgery (FESS) has become the main surgical technique used. Radical procedures are reserved primarily for acute or chronic sinusitis complicated by orbital or intracranial involvement. Endoscopic surgery can achieve up to 80–90% success in both adults and children^{86,87}.

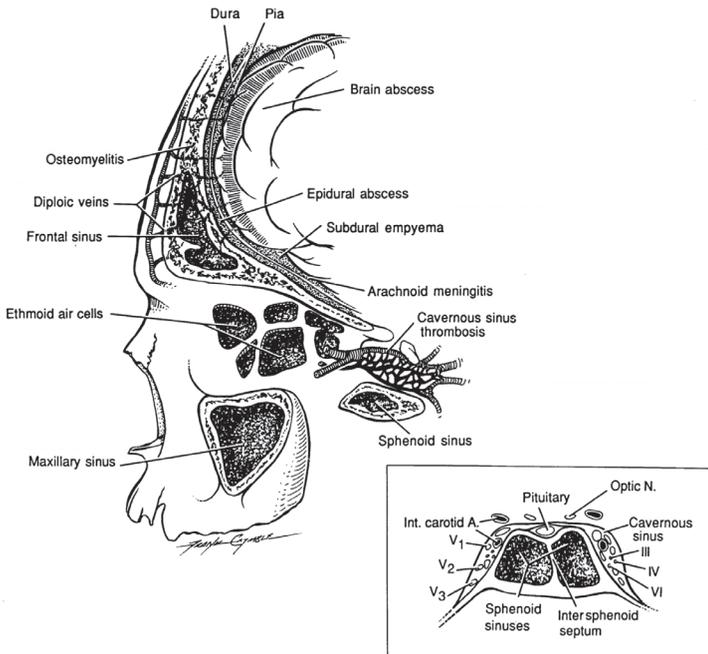
Complications

When not treated promptly and properly sinus infection can spread via anastomosing veins or by direct extension to nearby structures (**Figure 5**). Orbital complications were categorized by Chandler *et al.*⁸⁸ into five stages according to their severity. Contiguous spread to the orbital area can result in periorbital

cellulitis, subperiosteal abscess, orbital cellulitis, and abscess. Orbital cellulitis can complicate acute ethmoiditis if thrombophlebitis of the anterior and posterior ethmoidal veins spreads the infection to the lateral or orbital side of the ethmoid labyrinth. Sinusitis can extend also to the central nervous system, where it can cause cavernous sinus thrombosis, retrograde meningitis, and epidural, subdural, and brain abscesses⁸⁸⁻⁹¹. Orbital symptoms often precede intracranial extension of the infection^{43,90}. Other emerging complications include sinobronchitis, maxillary osteomyelitis, and osteomyelitis of the frontal bone⁹⁰⁻⁹⁷. Osteomyelitis of the frontal bone often originates from a spreading thrombo-phlebitis. A periostitis of the frontal sinus causes an osteitis and a periostitis of the outer membrane, which produces a tender, puffy swelling of the forehead.

Diagnosis is assisted by finding local tenderness and dull pain, and is confirmed by CT and nuclear isotope scanning. The most common causes are anaerobic bacteria and *S. aureus*. Management includes surgical drainage and antimicrobial therapy. Surgical debridement is rarely necessary after a properly extended course of parenteral antimicrobial therapy⁹⁸. Antibiotics should be administered for at least six weeks. Monitoring for possible intracranial complication is warranted⁹⁸.

Figure 5. Intracranial complications of sinusitis. The sagittal section shows the major routes for intracranial extension, either by contiguous spread or by the vascular supply. The coronal section demonstrates the structures adjoining the sphenoid sinus. (From Chow AW. Infections of the sinuses and parameningeal structures. In: Infectious Diseases, 3rd ed., Gorbach SL, Bartlett JG, Blacklow NR (eds.), Lippincott Williams & Wilkins, 2004, pp. 428-443.)



Conclusions

Sinusitis is one of the most common complaints resulting in physician visits in the United States. An antecedent viral infection of the upper respiratory tract is the most common presentation. Despite its prevalence, the vast majority of cases resolve spontaneously. Only a small proportion develops a secondary bacterial infection which will benefit from antimicrobial therapy. However, many individuals are treated with antimicrobials even though they do not suffer from bacterial sinusitis. What makes the decision to treat only symptomatically or to add also antimicrobials is often difficult and is generally done based only on clinical judgment. Because there are currently no good markers that define viral sinusitis from bacterial one many clinicians elect when in doubt to administer antimicrobials to their patients. This is often done because of non medical reasons such as wish to satisfy patients' requests and the assumption that the use of antimicrobials will facilitate recovery and has no adverse effects.

However, this common approach is one of the main contributors to the world wide increase of resistance to antimicrobial agents of all respiratory tract bacterial pathogens that has made the management of true bacterial sinusitis more difficult. It is hopeful that newer studies will explore the utility of adjuvant therapies as well as the correct timing of introduction of antimicrobials to treat bacterial sinusitis. These studies can lead to developed better guidelines that may lead to the judicious use of these therapies.

The recent introduction of new vaccinations against *S. pneumoniae* and the expected new vaccines against other potential sinus pathogens (i.e. non-type b *H. influenzae*) may change the bacterial etiology. The increase recovery of MRSA is an example of such a change. Continuous monitoring of the evolving bacterial etiology of bacterial sinusitis are therefore of great importance.

Additional informations about sinusitis in children can be found at the author's Web site: <http://sinusitisunderstood.blogspot.com/>

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