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DIAGNOSIS AND MANAGEMENT OF INFECTIOUS SINUSITIS

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Although sinusitis may be self-limiting, its toll on healthcare is vast. Sinusitis affects 16% of the U.S. adult population with an overall direct annual health care cost of $5.8 billion.[1] Sinusitis results in Americans spending $2 billion on over the counter medications, filling 15 million antibiotic prescriptions, and attending 17 million office visits annually.[2] One in five antibiotic prescriptions are for patients with sinusitis symptoms.[3] However, widespread use of conjugate pneumococcal vaccine has led to a modest decrease in the incidence of infectious acute sinusitis.[4]

There are numerous potential implications and collateral damage with over diagnosis of sinusitis and subsequent unnecessary treatment with antibiotics. Approximately 38% of adults presenting with symptoms of sinusitis actually have a bacterial infection.[5] Antibiotics are frequently prescribed for acute sinusitis, even though the causative agent may be viral in origin. Viral sinusitis typically resolves within three weeks without the need for antibiotics; although, viral upper repiratory tract infections (URTI) often precede acute sinusitis.[1] Injudicious use of antibiotics contributes to the current increase in drug resistance among respiratory pathogens.[5] In addition to the development of resistant microorganisms, other potential issues with antibiotics include, allergic reactions, destruction of beneficial bowel flora, immune suppression, overgrowth of *Candida albicans*, nutrient loss and resulting deficiency state due to diarrhea, and the cost of antibiotic therapy.[6]

Throughout this report, sinusitis and rhinosinusitis will be used interchangeably as inflammation of the paranasal sinuses is naturally accompanied by inflammation of the nasal mucosa. This article will provide useful information regarding the clinical diagnosis of infectious sinusitis as well as describe symptoms, common causative organisms, and predisposing factors. Finally, using primary literature, this article will underscore the management of infectious acute sinusitis including a clinical summary table.

PATHOPHYSIOLOGY

Classification of infectious sinusitis is based on duration of symptoms, the specific sinus involved, or both. Sinuses are air-filled cavities lined with both pseudostratified and ciliated columnar epithelium. Pathogens are eliminated by a natural defense system via a mucociliary clearance that relies on functional mucous and ciliary activity.[7] The 4 paranasal sinuses include the frontal sinus, the ethmoid sinuses, the maxillary sinus, and the sphenoid sinus. Sinusitis is characterized by inflammation of, most commonly, the maxillary and ethmoid sinuses.[5] Si-

INSIDE THIS ISSUE:

nusitis is characterized as acute with symptoms that last less than 4 weeks, as subacute with symptoms that last 4 - 8 weeks, or as chronic when symptoms last longer than 8 weeks. All types of sinusitis have similar symptoms and are often difficult to distinguish. Recurrent sinusitis is defined as having 3 or more acute episodes a year. In contrast to acute sinusitis, most chronic sinusitis may be thought of as an inflammatory disease.[7] Notable nonspecific symptoms of sinusitis include purulent rhinorrhea, facial-dental pain, postnasal drainage, and nasal congestion.[1] Malaise, headache, fever and possibly a cough may also accompany sinusitis.[8]

Symptoms of sinusitis are often vague and clinical diagnosis is frequently rooted in subjective findings. However, diagnosis can be confirmed with certain imaging techniques, in combination with a clinical history, physical examination, and/or laboratory tests. Computer tomography (CT) is the gold standard of imaging techniques because it can detect abnormalities in both the ostiomeatal complex and the paranasal sinus cavities.[1] The ostiomeatal complex (OMC) is a narrow drainage pathway positioned in the middle meatus, which allows ventilation of the anterior ethmoid, frontal, and maxillary sinuses.[7] Maxillary sinus aspiration is the best means to indentify the pathological organism causing the sinusitis.[7] Some predisposing factors for infectious sinusitis include viral infections, both allergic and nonallergic rhinitis, gastroesophageal reflux disease (GERD), immunodeficiency, cystic fibrosis, and cilliary dysfunction.[1]

Common causative organisms of infectious sinusitis include viruses and bacteria. The rhinovirus, influenza virus, and parainfluenza virus are the most common viral pathogens.[1] This suggests that an annual flu vaccine could prevent some cases of infectious sinusitis. Also, widespread use of conjugate pneumococcal vaccine has led to decreasing incidence of acute bacterial rhinosinusitis.[4] If culture results are unavailable, the antibiotic should target the most common bacterial pathogen which include *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*. Other possible bacterial pathogens include anaerobic bacteria, *Staphylococcus aureus*, and gram-negative bacteria.[1] Antibiotics are primary therapy for bacterial sinusitis accounting for 21% of antibiotics prescribed for adults.[9] Antibiotic selection should take into account geographical prevalence of resistance patterns, predicted efficacy, cost, side effects and bacterial cultures to streamline therapy. However, an exact diagnosis would require a sample of the pathogen from the paranasal sinuses, which may not be feasible.[10]

CLINICAL TRIALS

Eight of the ten trials, all with a double-blind design, included a total of 2466 participants evaluating antibiotic treatment compared to placebo for infectious acute sinusitis (Lindbaek 1996; Hansen 2000; Kaiser 2001; De Sutter 2002; Bucher 2003; Varonen 2003; Meltzer 2005; Merenstein 2005).[11-18] Upchurch 2006 compared the efficacy and safety of faropenem medoxomil for 7 or 10 days, with cefuroxime axetil for 10 days.[19] Poole 2006 compared two dosage strengths of levofloxacin. Six of the ten trials compared amoxicillin to placebo.[20] Kaiser et al. used a predefined subgroup of patients with *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*, resolution of symptoms by day 7 occurred in 73% of those treated with azithromycin compared with 47% of those who received placebo ($p = 0.007$).[13] Also, the median time before symptom resolution in the azithromycin group was five days compared to seven days in the placebo group ($p = 0.032$)[13] [see Table 1].

There is no definitive answer for the question of whether antibiotic treatment for infectious acute sinusitis has any clinical benefit. Four of the eight placebo controlled trials demonstrated advantageous results when treating with antibiotics.[11-18] The use of a topical nasal steroid for the treatment of infectious acute sinusitis is also controversial. Intranasal steroids have both an anti-inflammatory and potential decongestant action by inhibiting the transcription of proinflammatory mediators and stabilizing phospholipid membranes.[21] Meltzer et al. found that mometasone furoate nasal spray (MFNS) 200 mcg twice daily was significantly superior to placebo ($p<0.001$) and amoxicillin ($p=0.002$) at improving symptoms.[17] However, Williamson et al. reported that neither an antibiotic nor a topical steroid alone or in combination was effective for acute sinusitis in the primary setting.[21]

TREATMENT OPTIONS

Guidelines concerning the diagnosis and management of infectious sinusitis, provided by the American Academy of Allergy, Asthma and Immunology, have been endorsed by the Centers for Dis-

Table 1. Descriptive characteristics of controlled trials for the use of antibiotics in acute sinusitis

Author	Country	N	Comparator	Antibiotic	Dose/ Frequency	Duration of Therapy (days)	Median Illness Duration, (days)	F/U (days)	Authors Conclusion
Lindbaek (1996)	Norway	130	pcb/pcn/ amox	pcn, amox	1320 mg TID, 500 mg TID	10	pcn-11, amox-9, placebo-17	30	pcn (p = 0.008) and amox (p < 0.001) are significantly more effective than pcb
Hansen (2000)	Denmark	133	pcb/pcn	pcn	1333 mg BID	7	6	NA	pcn is more effective than pcb (p < 0.05) in the treatment of acute maxillary sinusitis
Kaiser (2001)	Switzerland	269	pcb/azith	azith	500 mg QD	3	4	8	azith treatment is of clinical benefit (p = 0.007) compared to pcb
De Sutter (2002)	Belgium	416	pcb/amox	amox	500 mg TID	10	7.4	NA	amox provides no clinically important benefits (p = 0.08)
Bucher (2003)	Switzerland	252	pcb/amox/ clav	amox/clav	875mg/125mg BID	6	4.5	NA	amox/clav has no advantage over placebo (95% CI: 0.68,1.45)
Varonen (2003)	Finland	150	pcb/amox/ doxy/pcn	amox, doxy, pcn	750mg BID, 100mg BID, 1500mg BID	7	>5 for 73%	14	abxs hasten symptom relief in AMS (p = 0.068)
Meltzer (2005)	14 countries	981	pcb/MFNS/ amox	amox	500 mg TID	10	7 to 28	28	MFSN 200 microgram BID monotherapy was significantly more effective than amox (p = 0.002) or placebo (p < 0.001)
Merenstein (2005)	USA	135	pcb/amox	amox	NA	10	11.2	NA	for most patients there was no improvement seen with abxs over placebo (p = NS)
Upchurch (2006)	USA/ Canada	1080	faro/cef	faro,cef	300 mg QD, 250 mg BID	7 or 10, 10	NA	NA	7 day (95% CI: 0.1,13.6) and 10 day (95% CI: 0.1,13.6) faro were noninferior to a 10 day cef regimen
Poole (2006)	USA	780	lev 500/ lev 750	lev	750 mg QD, 500 mg QD	5, 10	NA	NA	lev 750 mg for 5 days is noninferior to lev 500 mg for 10 days (95% CI: -10.0,4.2)

amox = amoxicillin; azith = azithromycin; clav = clavulanate; doxy = doxycycline; pcn = penicillin V; faro = faropenem medoxomil; cef = cefuroxime axetil; lev = levofloxacin; MFNS = mometasone furoate nasal spray 200 mcg; abx = antibiotics; NA = not available; NS = not significant; AMS = acute maxillary sinusitis; pcb = placebo

ease Control and Prevention, the American College of Physicians-American Society of Internal Medicine, the American Academy of Family Practice, the American Academy of Pediatrics, and the Infectious Diseases Society of America. These guidelines conclude that antibiotics should be considered in those patients with severe signs and symptoms of sinusitis, regardless of duration of illness.[1] Amoxicillin is a prudent initial antibiotic choice for uncomplicated infectious acute sinusitis without a high prevalence of beta-lactamase producing bacterial strains. These resistant strains can be treated with amoxicillin-potassium clavulanate that is generally effective against most beta-lactamase-producing *H. influenzae*, *M. catarrhalis*, *S. aureus*, and anaerobic bacteria.[1]

The guidelines suggest that penicillin resistant *S pneumoniae* can be treated by increasing the prescribed amoxicillin dose to 90 mg/kg/day in two divided doses (maximum dose of amoxicillin is 1 gram every 12 hours).[1] Doxycycline provides broader antibiotic coverage, including activity against beta-lactamase-producing strains of *H. influenzae* and *M. catarrhalis*.[7] Cephalosporins are routinely prescribed for both acute and chronic sinusitis and cefuroxime axetil and cefprozil, second-generation cephalosporins have the advantage of twice-daily dosing and enhanced activity against beta -lactamase-producing *H influenzae*, *M catarrhalis*, and *S aureus*. Third generation cephalosporins, such as cefpodoxime axetil and cefdinir are appropriate choices.[1] Because azithromycin and clarithromycin are weakly effective against penicilln-resistant *H influenzae* and *S pneumoniae*, the use of these antibiotics may lead to increasing resistance to macrolides.[1] Varonen et al. recommend macrolides only as second -line drugs for acute maxillary sinusitis.[16] Even though fluoroquinolones offer broad spectrum antimicrobial coverage and are indicated for acute sinusitis, Karageorgopoulos et al. demonstrated that when treating acute infectious sinusitis, newer fluoroquinolones confer no benefit over beta-lactam antibiotics.[22] An overview of available antibiotics and their recommended doses can be found in Table 2.

The role of antibiotics in the management of acute sinusitis is controversial.[21] Also, the appropriate duration of therapy is not well defined. Poole et al. suggest that a shorter 5 day course of levofloxacin 750 mg is noninferior to a 10 day course of levofloxacin 500 mg.[20]

As adjuvant therapy, it is reasonable to consider using nasal corticosteroids to decrease the inflammatory response in sinusitis.[1] Nasal decongestants may provide temporary relief of nasal congestion by constricting the sinusoids, both regulated by $alpha_1$ and $alpha_2$ adrenoreceptors in the nasal mucosa. The nasal mucosal blood flow is not significantly affected by the $alpha_1$ agonists, but studies

Table 2. Antibiotics commonly prescribed for sinusitis

Antibiotic	Recommended Adult Dosage for ABS
Amoxicillin (Amoxil®)	500 mg bid
Amoxicillin/potassium clavulanate (Augmentin®)	500 mg – 875 mg bid
Azithromycin (Zithromax®)	500 mg qd on day 1, then 250 mg qd on days 2-5
Cefdinir (Omnicef®)	300 mg bid
Cefpdoxime (Vantin®)	200 mg bid
Cefprozil (Cefzil®)	250 mg – 500 mg bid
Cefuroxime (Ceftin®)	250 mg bid
Clarithromycin (Biaxin®)	500 mg bid
Clindamycin (Cleocin®)	150 mg – 450 mg qid
Doxycycline (Adoxa®)	100 mg – 200 mg qd
Gatifloxacin (Tequin®)	400 mg qd
Levofloxacin (Levaquin®)	500 mg qd

Table 3. Topical Vasoconstrictors for Decongestion of the Nasal Mucosa

Vasoconstrictors	Adrenoceptor Activity	Onset (minutes)	Duration of action (hours)	Dosage
Sympathomimetic amines Phenylephrine (Neo-Synephrine®)	$Alpha_1$	1 to 3	1 to 4	2 to 3 sprays in each nostril q3-4 hours
Imidasoline derivatives Naphazoline (Naphcon Forte®)	$Alpha_2$	1 to 3	2 to 6	1 to 2 sprays in each nostril no more than q6 hours
Oxymetazoline (Afrin 12-Hour®)	$Alpha_2$	1 to 3	5 to 12	2 to 3 sprays bid
Xylometazoline (Otrivin®)	$Alpha_2$	1 to 3	6 to 12	2 to 3 drops or 2 to 3 sprays q8-10 hours

Adapted from Fagnan L.J.[24]

suggest that oxymetazoline, a selective $alpha_2$ adrenoreceptor agonist, interferes with the healing of maxillary sinusitis by decreasing nasal mucosal blood flow.[23] As a result, $alpha_1$ agonists, such as phenylephrine, are the preferred topical mucosal decongestants. Because of the risk of rebound congestion (rhinitis medicamentosa), the use of topical nasal decongestants should be restricted to no more than three or four days of continuous use. In addition to alpha-adrenergic decongestants for symptomatic relief, other therapies include antihistamines, glucocorticosteroids and adjunctive therapies such as saline, mucolytics, and expectorants.[1] An overview of non-antibiotic treatment options can be found in Table 3.

SUMMARY

Although the role of antimicrobials in the management of infectious sinusitis is controversial, antibiotics are the primary therapy for infectious sinusitis. Treatment suggestions for acute infectious sinusitis are divided and vary from only treating patients with severe or persistent symptoms with narrow spectrum antibiotics to treating all patients with broad spectrum antibiotics. The purpose of antibiotics is to decrease symptoms and restore the sinuses to their normal function. Unnecessary antibiotic prescriptions should be avoided and clinicians need to evaluate the moderate benefits of antibiotic treatment against the potential adverse effects. The most common bacterial pathogens include *S pneumoniae*, *H* influenzae, and *M catarrhalis*. Acute bacterial sinusitis usually occurs following an upper respiratory infection that results in obstruction of the osteomeatal complex, impaired mucociliary clearance and overproduction of secretions. In summary, antibiotic treatment for infectious sinusitis may be effective. The guidelines recommend that antibiotics should be prescribed for 10 to 14 days, or 7 days after the patient is symptom free. If symptoms fail to improve in two to three days, it is rational to switch to a second line antibiotic.

REFERENCES

1. Slavin RG, Spector SL, Bernstein IL, et al. The diagnosis and management of sinusitis: A practice parameter update. American Academy of Allergy, Asthma, and Immunology 2005;116:S13-47.
2. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, et al. Antibiotics for acute maxillary sinusitis (Review). 2008 The Cochrane Collaboration.
3. Pearlman AN, Conley DB. Review of current guidelines related to the diagnosis and treatment of rhinosinusitis. Current Opinion in Otolaryngology & Head and Neck Surgery 2008;16:226-30.
4. Benninger MS. Acute bacterial rhinosinusitis and otitis media: Changes in pathogenicity following widespread use of pneumococcal conjugate vaccine. Otolaryngology-Head and Neck Surgery 2008;138:274-8.
5. Small CB, Bachert C, Lund VJ, et al. Judicious Antibiotic Use and Intranasal Corticosteroids in Acute Rhinosinusitis. The American Journal of Medicine 2007;120:289-294.
6. Wilson L. Beyond Antibiotics. http://

www.drlwilson.com/Articles/antibiotics.htm. Revised Dec 2007. Accessed July 16, 2008.
7. Leung RS, Katial R. The Diagnosis and Management of Acute and Chronic Sinusitis. Prim Care Clin Office Pract 2008;35:11-24.
8. Masood A, Moumoulidis L, Panesar J. Acute rhinosinusitis in adults: an update on current management. Postgrad Med. J. 2007;83:402-8.
9. Rosenfeld RM, Singer M, Jones S. Systematic review of antimicrobial therapy in patients with acute rhinosinusitis. American Academy of Otolaryngology-Head and Neck Surgery Foundation 2007;137:S32-S45.
10. Varonen H, Rautakorpi U, Nyberg S, et al. Implementing guidelines on acute maxillary sinusitis in general practice-a randomized controlled trial. Fam. Pract 2007;24:201-6.
11. Lindbaek M, Hjortdahl P, Johnsen UL. Randomised, double blind, placebo controlled trial of penicillin V and amoxicillin in treatment of acute sinus infections in adults. BMJ 1996;313:325–9.
12. Hansen JG, Schmidt H, Grinsted P. Randomised, double-blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. Scand J Prim Health Care 2000;18:44 –7.
13. Kaiser L, Morabia A, Stalder H, et al. Role of nasopharyngeal culture in antibiotic prescription for patients with common cold or acute sinusitis. Eur J Clin Microbiol Infect Dis 2001;20:445–51.
14. De Sutter AI, de Meyere MJ, Christiaens TC, et al. Does amoxicillin improve outcomes in patients with purulent rhinorrhea? A pragmatic, randomized double-blind controlled trial in family practice. J Fam Pract 2002;51:317– 23.
15. Bucher HC, Tschudi P, Young J, et al. Effect of amoxicillin/clavulanate in clinically diagnosed acute rhinosinusitis: a placebo-controlled, double-blind, randomized trial in general practice. Arch Intern Med 2003;163:1793– 8.
16. Varonen H, Kunnamo I, Savolainen S, et al. Treatment of acute rhinosinusitis diagnosed by clinical criteria or ultrasound in primary care. A placebo-controlled randomized trial. Scand J Prim Health Care 2003;21:121– 6.
17. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing the efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. J Allergy Clin Immunol 2005;116:1289 –95.
18. Merenstein D, Whittaker C, Chadwell T, et al. Are antibiotics beneficial for patients with sinusitis complaints? A randomized doubleblind clinical trial. J Fam Pract 2005;54:144 –51.
19. Upchurch J, Rosemore M, Tosiello R, et al. Randomized double-blind study comparing 7- and 10-day regimens of faropenem medoxomil with a 10-day cefuroxime axetil regimen for treatment of acute bacterial sinusitis. Otolaryngology-Head and Neck Surgery 2006;135:511-517.
20. Poole M, Anon J, Pagila M, et al. A Trial of High-Dose, Short-Course Levofloxacin for the Treatment of Acute Bacterial Sinusitis. Otolaryngology-Head and Neck Surgery 2006;134:10-17.
21. Williamson I, Rumsby K, Benge S, et al. Antibiotics and Topical Nasal Steroid for Treatment of Acute Maxillary Sinusitis. JAMA 2007;298(21):2487-96.
22. Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, et al. Fluoroquinolones compared with beta-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials. Canadian Medical Association 2008;178 (7):845-54.
23. Wiklund L, Stierna P, Berglund R, Westrin KM, Tonnesson M. The efficacy of oxymetazoline administered with a nasal bellows container and combined with oral phenoxymethyl-penicillin in the treatment of acute maxillary sinusitis. Acta Otolaryngol Suppl 1994;515:57-64.
24. Fagnan LJ. Acute Sinusitis: A Cost-Effective Approach to Diagnosis and Treatment. Family Physicians 1998;58:8-16.

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