

Chapter 19

Medical Management of Acute Rhinosinusitis in Children and Adults

Nathan Richards, Shannon Doyle Tiedeken, and Christopher C. Chang

Introduction

Rhinosinusitis is one of the most commonly seen health problems worldwide and is responsible for the use of vast healthcare resources. According to the US National Health Interview Survey, rhinosinusitis affects approximately 1 in 7 adults yearly [1]. In children, upper respiratory infections are contracted on an average of 6–8 per year with 0.5–5 % of these subsequently developing acute rhinosinusitis [2]. Twenty million doctor visits annually in the United States contribute to the high healthcare utilization of people with rhinosinusitis [3]. Nearly 3 billion dollars per year in the United States are used for the treatment of rhinosinusitis, with the costs derived from medications, testing, procedures, and outpatient and emergency room visits [4, 5].

Rhinosinusitis is the fifth most common diagnosis for which antibiotics are prescribed [4, 5]. Primary care physicians tend to make the diagnosis of acute bacterial rhinosinusitis clinically with little supportive objective criteria, and it is common to prescribe antibiotics as a first-line therapy in most cases. It has been estimated that antibiotics are initiated in up to 85–98 % of presumed rhinosinusitis cases [6, 7]. This contrasts with the fact that the majority of rhinosinusitis episodes are of viral origin and unrelated to a bacterial infection acutely. Nearly all cases of viral rhinosinusitis in an otherwise normal host will commonly resolve without antibiotic treatment provided the sinuses adequately drain once the virally induced inflammation resolves. If the disease has a nonbacterial inflammatory mechanism as the source of symptoms rather than a bacterial one, the addition of antibiotics will not be of benefit. In fact, the overuse of antibiotics will promote further bacterial resistance as well as increase the risk of the patient of the consequences of any adverse drug reaction. A major issue for healthcare providers in treating acute rhinosinusitis is when the initiation of antibiotic treatment will provide cost-effective clinical benefit.

Clinical Presentation

The clinical presentation of acute rhinosinusitis can differ between adults and children. In children, the ethmoid and the maxillary sinuses form in utero [8], and the sphenoid sinuses are generally pneumatized by 5 years of age [8]. On the other hand, the frontal sinuses frequently do not appear till about 7–8 years of age and typically do not completely develop until late adolescence [8] (see Chap. 2 for a more detailed discussion of the ontogeny of the sinuses). Pediatric guidelines describe acute bacterial rhinosinusitis as an infection of the paranasal sinuses lasting less than 30 days that presents with either persistent or severe symptoms of nasal or postnasal drainage, daytime cough, headache, facial pain, or some combination of

N. Richards, MD

Department of Allergy and Immunology, Thomas Jefferson University, 1600 Rockland Rd, Wilmington, DE 19803, USA
e-mail: nrichards11@gmail.com

S.D. Tiedeken, MD

Department of Pediatrics, Alfred I. duPont Hospital for Children, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: shannon.tiedeken@gmail.com

C.C. Chang, MD, PhD, MBA, FAAAAI, FAAAAI (✉)

Division of Allergy and Immunology, Department of Pediatrics, Thomas Jefferson University, 1600 Rockland Road, Wilmington, DE 19803, USA
e-mail: cchang@nemours.org

Table 19.1 Comparison of diagnostic criteria for acute bacterial rhinosinusitis

Guideline	Persistent symptoms	Severe symptoms	Worsening symptoms	Max duration symptoms	Radiographic studies
IDSA [9]	Yes, >10 days	Yes	Yes	None	Not required
RI [10]	Yes, >10 days	Yes	Yes	<28 days	Not required
EPOS [11]	Yes, >10 days	No	Yes	<12 weeks	Not required
CPG:AS [4]	Yes, >10 days	No	Yes	<4 weeks	Not required
BSACI [12]	Yes	No	No	<12 weeks	Required
JTFPP [13]	Yes, >10–14 days	Yes	No	<12 weeks	No required
Pediatrics [8]	Yes, >10–14 days	Yes	No	<30 days	Not required

these [8]. Persistent symptoms are those lasting longer than 10–14 days but less than 30 days [8]. Severe symptoms include a temperature of at least 39 °C and purulent nasal discharge which present concurrently for at least 3–4 consecutive days in an ill-appearing child [8].

For adults, multiple treatment guidelines have been set up to aid in differentiating bacterial from viral acute rhinosinusitis. These have been developed and presented by:

1. Infectious Diseases Society of America (IDSA) [9]
2. Rhinosinusitis Initiative (RI) [10]
3. Europeans Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EP³OS) [11]
4. Clinical Practice Guideline: Adult Sinusitis (CPG:AS) [4]
5. British Society for Allergy and Clinical Immunology (BASCI) [12]
6. Joint Task Force on Practice Parameters (JTFPP) [13]

Table 19.1 provides a comparison of the guidelines, with regard to severity and duration of symptoms, as well as radiographic findings. A more detailed description of each individual guideline is outlined below.

Definitions of Acute Rhinosinusitis

In the IDSA guideline, three clinical presentations are identified for which antimicrobial therapy should be initiated. The first clinical presentation is persistent symptoms or signs compatible with acute rhinosinusitis, lasting greater than or equal to 10 days without evidence of clinical improvement [9]. The second presentation is severe symptoms or signs of high fever (>39 °C) and purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days at the beginning of illness [9]. The final presentation is worsening symptoms or signs characterized by the onset of fever, headache, or an increase in nasal discharge following a typical viral upper respiratory infection that lasted 5–6 days which was initially improving [9]. These guidelines advise that anyone with one of these presentations should be started on empiric antimicrobial therapy [9].

The RI guidelines use a similar pattern of presentation of persistent, severe, or worsening symptoms. The criteria for diagnosis include pattern of symptoms, duration of symptoms with a minimum of 10 days and maximum of 28 days, presence of purulent nasal discharge for 3–4 days accompanied with fever or worsening disease, and symptoms that initially regress but proceed to worsen within 10 days of onset [10]. The criteria also include the following symptoms mandatory for diagnosis: anterior and/or posterior mucopurulent drainage in addition to nasal obstruction, facial pain, pressure, or fullness [10]. Finally, objective documentation of nasal airway examination for mucopurulent drainage beyond the vestibule by either anterior rhinoscopy or endoscopy for posterior pharyngeal drainage or radiographic evidence of acute rhinosinusitis is required [10].

The EPOS defines rhinosinusitis as inflammation of the nose and the paranasal sinuses characterized by 2 or more symptoms, including either nasal blockage, obstruction or congestion, or nasal discharge (anterior or posterior nasal drip) [11]. Facial pain or pressure and reduction of smell are also included as symptoms in rhinosinusitis [11]. Presumed bacterial rhinosinusitis is defined by an increase of symptoms after 5 days or persistent symptoms after 10 days with less than 12 weeks duration [11].

The CPG:AS criteria state that acute rhinosinusitis is diagnosed by up to 4 weeks of cardinal rhinosinusitis symptoms [4]. The cardinal symptoms include purulent nasal drainage accompanied by nasal obstruction, facial pain, pressure, or fullness [4]. The guidelines differentiate bacterial versus viral infection based upon duration and presentation of symptoms. Bacterial rhinosinusitis is presumed when symptoms or signs of acute rhinosinusitis are present 10 or more days beyond the onset of upper respiratory symptoms or symptoms worsen within 10 days after initial improvement [4].

BSACI guidelines define acute rhinosinusitis as symptoms lasting less than 12 weeks in duration [12]. The patient must have one of the following major symptoms: nasal congestion, nasal obstruction, posterior or anterior nasal discharge with or without facial pain, pressure, or olfactory disturbance [12]. The patient must also have either endoscopic signs of polyps, mucopurulent discharge from the middle meatus, edema or obstruction at the middle meatus, or CT signs of sinus disease [12]. The authors of the BSACI guidelines do not provide criteria for starting antimicrobial therapy.

Fig. 19.1 Bacterial pathogens in adult acute rhinosinusitis (Adapted from Sinus and Allergy Health Partnership [14]. With permission from Sage Publications)

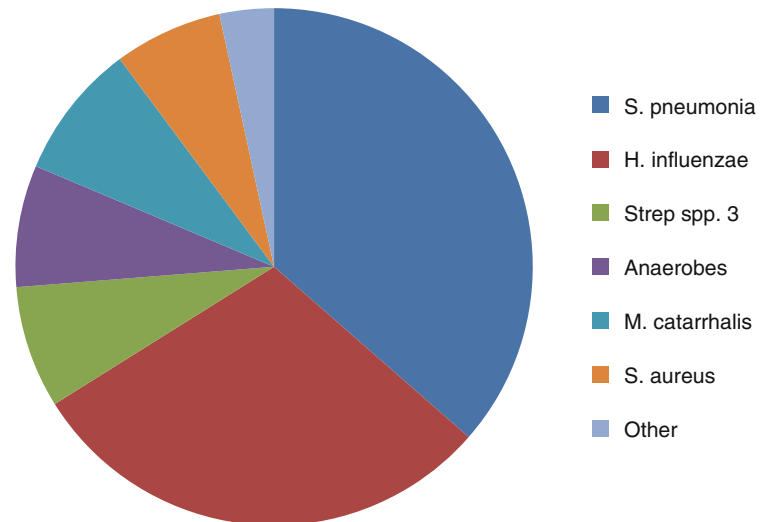
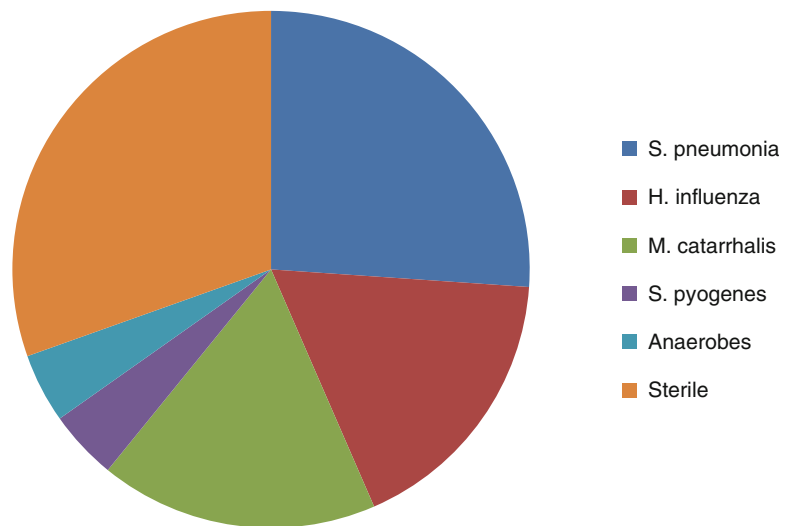


Fig. 19.2 Bacterial pathogens in childhood acute rhinosinusitis (Adapted from Sinus and Allergy Health Partnership [14]. With permission from Sage Publications)



The JTFPP state that the signs and symptoms of rhinosinusitis are nasal congestion, purulent rhinorrhea, facial or dental pain, postnasal drainage, headache, cough, sinus tenderness to palpation, and dark circles under the eyes [13]. The guidelines state that if symptoms last >10–14 days and are unusually severe or if there is a history of fever with purulent nasal discharge, facial pain or tenderness, or periorbital swelling, it should be considered a bacterial etiology [13].

Pathogens

Although there is some disagreement regarding what exactly constitutes bacterial rhinosinusitis, overall, the guidelines are fairly consistent among the recommended criteria from different agencies. In truth, only culture of the sinuses can ever definitively diagnose a role of a bacterial pathogen in a case of rhinosinusitis. This is a difficult hurdle in that nasal swabs do not commonly represent the predominant bacteria within an infected sinus. Moreover, inflammation is often confused with infection. Nevertheless, from the perspective of a practicing physician, any of these diagnostic guidelines can be used to establish the probable diagnosis of acute bacterial rhinosinusitis. Once the diagnosis is made, the appropriate antibiotic can be prescribed.

In order to initiate empiric therapy, it is important to know the typical bacterial causes of rhinosinusitis. Between adults and children, the pathogenic bacteria in acute rhinosinusitis are similar but not identical. The main difference is a higher prevalence of *Moraxella catarrhalis* infections in children than in adults. Figures 19.1 and 19.2 depict pie charts representing a breakdown of the typical bacterial pathogens in acute rhinosinusitis infections [14]. In children and adults, *Streptococcus*

pneumoniae is the main bacteria causing up to 1/3 of the cases of acute bacterial rhinosinusitis followed closely by *Haemophilus influenzae* and *Moraxella catarrhalis*. In children, one third of the cases of presumed bacterial rhinosinusitis have no causal agent with bacterial cultures being sterile.

Most cases of acute rhinosinusitis are caused by viral infections associated with the common cold [15]. The most commonly implicated virus is rhinovirus (30–80 %) [16]. Other viral entities implicated in causing acute rhinosinusitis are coronavirus (10–15 %), influenza virus (5–15 %), human parainfluenza virus, human respiratory syncytial virus (RSV), adenoviruses, enteroviruses, and metapneumovirus [16–18]. Frequently, more than one virus is present [19]. In total, over 200 different viral species are associated with colds [18].

Fungi are rarely implicated in acute rhinosinusitis and only seen in a secondary immune-compromised host. In contrast, fungi, when involved, can induce three variations of allergic inflammation: eosinophilic fungal rhinosinusitis, eosinophilic mucin rhinosinusitis, and allergic fungal rhinosinusitis. None of these represent acute infections. All refer to a rhinosinusitis state that is chronic (>12 weeks' duration) and accompanied by sinus opacification with allergic mucin [20] (see Chap. 8 for a detailed discussion of fungal rhinosinusitis). Allergic rhinitis flares can be complicated by a superimposed acute fungal rhinosinusitis. However, none of these involve fungal invasion below the mucosal surface. Rather, they are symptomatic rhinosinusitis events that result from various atopic sensitizations. Despite more than 100,000 molds recognized in the environment, few genera are associated with allergic disease [20]. *Aspergillus* species and the dematiaceous molds that include *Alternaria* and *Cladosporium* species are those most frequently implicated, although *Bipolaris* and *Curvularia* species have also been reported [20].

Defining the bacterial pathogens, if any, in cases of chronic rhinosinusitis is difficult and discussed in more detail in Chaps. 5 and 6. It should be remembered that chronic rhinosinusitis (CRS) is a group of inflammatory diseases of the nasal cavities that may or may not include polyp formation with no unifying theory based on scientific evidence that will explain the pathophysiology of chronic airway disease in all cases. In contrast, the etiology appears to be multifactorial. Research has focused on alterations involving inflammatory cell and T-cell stimulation, the role of TGF- β on remodeling, generation of inflammatory mediators such as leukotrienes and prostaglandins, the role of IgE and microorganisms, and also the role of the epithelium as an immunologic barrier to infection or insult. While much of the more recent literature appears to focus primarily on CRS as an inflammatory disease, that is not to say that bacteria and microorganisms are not involved in some cases and that antibiotics will not be helpful in alleviating some symptoms [21]. Bacteria have been shown to play a role in some patients with CRS either directly by infection or by stimulation of infection [22]. The main bacteria implicated in causing infection or triggering inflammation in patients with CRS, especially those with nasal polyps and asthma, is *Staphylococcus aureus* (*S. aureus*) [22]. In a recent study, swabs from the middle meatus of controls and patients with CRS were taken during endoscopic surgery and analyzed by quantitative polymerase chain reaction (PCR). There was no statistically significant difference in the total bacteria seen between CRS patients and the controls, but the abundance of *S. aureus* was increased in CRS patients with allergic rhinitis, nasal polyps, and asthma [22]. Nevertheless, the antibiotic approach to a CRS patient experiencing an acute flare of rhinosinusitis should include a drug choice directed against the same organisms defined above. Although there is no consensus on when or how long to treat flares of acute disease in CRS patients, the majority of medical providers would tend to use antibiotics earlier and sometimes longer than traditional guidelines suggest.

Medical Management

Antibiotics

The role of antibiotics in acute rhinosinusitis is controversial. As stated earlier, in a majority of cases, sinusitis is triggered by a viral upper respiratory infection and not responsive to antibiotic therapy. In general, only 1–2 of every 100 otherwise healthy patients with sinus symptoms have a concomitant bacterial infection [23]. It is often difficult to distinguish between those who will recover spontaneously and those who will require antibiotic therapy. In many cases, there is no evidence of any infectious etiology (viral, bacterial, or fungal), and indeed the disease may be a manifestation of an inflammatory process rather than infection. Antibiotics would only have minimal to no benefit to these patients. It is therefore imperative to at least attempt to determine which patients will benefit from antibiotic therapy, so as to avoid unnecessary antibiotic use and potentiating the development of bacterial resistance.

With growing concerns about antibiotic resistance among community-acquired pathogens, choosing the appropriate empiric antibiotic can be challenging. In adults, the empiric therapy should cover *Streptococcus pneumoniae* and *Haemophilus influenzae*. In children, the antibiotic of choice should also cover *Moraxella catarrhalis*. In the latest Cochrane Review, the studies that compared different classes of antibiotics demonstrated a similar efficacy among them [23]. However, the risk of clinical failure on amoxicillin-clavulanate compared to that for cephalosporins at 7–15 days was statistically significant, but the risk of failure disappeared at longer follow-up [23]. Based on their review, it was concluded that none of the antibiotic preparations in this study were significantly inferior in terms of efficacy [23].

Another randomized, open-labeled, double-blind study of acute rhinosinusitis patients was performed comparing the efficacy and safety of amoxicillin-clavulanate and a third-generation cephalosporin. A group of 50 patients received 2 weeks of treatment with either amoxicillin-clavulanate or a third-generation cephalosporin and afterward received paranasal sinus X-rays and nasal endoscopies to evaluate their progress and symptom relief. After 2 weeks, the improvement rate was 95–96 % for both groups. The only noted benefit of the third-generation cephalosporin over amoxicillin-clavulanate was that there were fewer adverse effects, primarily less gastrointestinal complications [24].

While beta-lactamase-resistant antibiotics are the current first-line recommendation for treatment of acute bacterial rhinosinusitis, cefdinir, a third-generation cephalosporin, also offers a convenient treatment option in patients with mild disease and no other recent antibiotic use. Cefdinir is an oral third-generation cephalosporin which has rapid oral absorption and efficient respiratory tissue penetration. It can be prescribed daily and has bactericidal activity against the most common bacterial pathogens including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Cefdinir is well tolerated and does not significantly suppress the normal gut flora causing less gastrointestinal adverse effects. Children have also been seen to favor cefdinir due to its taste and smell [25].

A recent study evaluated the treatment of acute rhinosinusitis with amoxicillin. The study included 166 adults with RI diagnostic criteria for acute bacterial rhinosinusitis. It was found that after 3 days of treatment with amoxicillin versus placebo, there was no difference in symptoms between the two groups [26]. While amoxicillin is a typical starting point for the treatment of acute rhinosinusitis, this study demonstrated the ineffectiveness of amoxicillin on either antibiotic-resistant pathogens or nonbacterial causes of acute rhinosinusitis.

Most traditional courses of antibiotic treatment for acute bacterial rhinosinusitis are 10 days in duration. Newer studies have looked at an abbreviated course of treatment with azithromycin [27]. A 3–5-day course of treatment with azithromycin has proven equally effective, and the shorter course increases the likelihood of patient compliance. Other advantages include lower rates of bacterial resistance and fewer adverse effects to the medication [27]. The efficacy of azithromycin was evaluated for its clinical efficacy and tolerability in treating children with acute respiratory infections. A study of 135 children treated with a single 10 mg/kg dose of azithromycin for 3 consecutive days showed 100 % resolution of symptoms in those with acute rhinosinusitis after 10 days and no recurrences were observed. Benefits of treating with the shorter course again included increased tolerance and improved compliance to the medication [28].

Due to the increasing resistance of causal bacteria to beta lactams and macrolides, new treatment guidelines have been instituted to aide physicians in choosing an appropriate antibiotic. Fluoroquinolones including moxifloxacin, gatifloxacin, and levofloxacin are often recommended as second-line therapy, or even first line for patients who have recently received other antibiotic therapy [29]. The Respiratory Surveillance Program (RESP) sampled 16,213 nasal swabs taken by primary care physicians in an outpatient setting on patients believed to have bacterial rhinosinusitis over a 10-month period. Pathogens were isolated from 34 % of samples with four accountable for most cases: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. High rates of resistance were seen against penicillins and macrolides. The four major causal bacteria had a 95–100 % susceptibility rate to fluoroquinolones. This study provided physicians with information about susceptibilities of pathogens within different communities and aided them in choosing appropriate antibiotic therapy. It also supported the use of fluoroquinolones in treating patients with previous antibiotic exposure [30].

One of the main adverse effects of fluoroquinolones in children is arthropathy. A systemic literature search was done to investigate the safety of using ciprofloxacin in pediatric populations. The search identified 105 articles that met inclusion criteria. Of the 16,184 pediatric patients included across all studies, 1,065 reported adverse reactions with the most common being musculoskeletal. Of all the musculoskeletal adverse effects, arthralgia accounted for 50 %. The age of occurrence ranged from 7 months to 17 years with the mean age of 10 years old. However, all cases of arthropathy resolved with appropriate management. From this study, it was estimated that the risk of a pediatric patient developing arthropathy from a fluoroquinolone is 1.57 %. Arthropathy is an adverse effect but can be reversed with appropriate treatment. At the present time, fluoroquinolones will require further controlled studies before they can be routinely recommended for treatment in children [31].

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated in some cases of acute and chronic rhinosinusitis. A literature search was performed to study cases of acute or chronic rhinosinusitis that were culture positive for MRSA and treated for MRSA. Twelve different studies discussed patients with acute and chronic rhinosinusitis with positive cultures for MRSA. Subjects received different treatment regimens. It was found that no one therapy was superior to the others [32]. *Staphylococcus aureus* can also cause sinusitis in children. In a recent study by Texas Children's Hospital, 56 patients were identified to have *S. aureus* sinus infections based on positive cultures from sinus surgery. Twelve of the 56 patients had MRSA. None of the MRSA cases were susceptible to macrolides and co-pathogens. The most commonly seen co-pathogen was *Haemophilus influenzae*, which was isolated in 77 % of the cases. Children with MRSA had higher recurrence of disease but were not found to be at greater risk than children with MSSA sinusitis to develop complications including cellulitis, abscess, meningitis, subdural empyema, or orbital cellulitis [33].

Table 19.2 Oral antibiotics used in the treatment of acute bacterial rhinosinusitis

Antibiotic	Dosage/frequency	Calculated clinical efficacy (%)	Cost (in 2004)
Amoxicillin-clavulanate Potassium salt (Augmentin)	500 mg q8 h; 875 mg q12 h	91	\$83.96–112.08
High-dose Augmentin XR	2 g q12 h	–	\$112.08
Amoxicillin (Amoxil)	500 mg q8 h; 875 mg q12 h	88	\$7.35–8.77
High-dose amoxicillin	1 g q8 h	–	\$14.70–17.54
Cefpodoxime (Vantin)	200 mg q12 h	87	\$118.48
Cefuroxime (Ceftin)	250 mg or 500 mg q12 h	85	\$108.53–197.75
Cefdinir (Omnicef)	300 mg q24 h	83	\$44.66
Ceftriaxone (Rocephin)	1 g IM q24 h	91	\$255.80
TMP-SMX DS (Bactrim DS)	160–800 mg q12 h	83	\$6.64–27.76
Doxycycline (Vibramycin)	100 mg q12 h	81	\$5.00–27.36
Azithromycin (Zithromax)	500 mg day 1 and 250 mg day 2–5	77	\$47.44
Clarithromycin (Biaxin)	250 mg or 500 mg q12 h	77	\$90.22
Gatifloxacin (Tequin)	400 mg q24 h	92	\$95.68
Levofloxacin (Levaquin)	500 mg q24 h	92	\$101.47
Moxifloxacin (Avelox)	400 mg q24 h	92	\$101.92

Based on data from Ref. [34]

Table 19.3 Susceptibilities of most common isolates to antibiotics commonly prescribed for sinusitis

	<i>S. pneumoniae</i> % S/I/R (N=618)	<i>H. influenzae</i> % S/I/R (N=1,189)	<i>M. catarrhalis</i> % S/I/R (N=1,588)	<i>S. aureus</i> % S/I/R (N=983)
Penicillin	64/20/16 (2)	Not done	8.5/0/91.5 (1)	10.8/0/89.2 (6)
Gatifloxacin	99.8/0.2/0 (2)	100/0/0 (3)	100/0/0 (7)	97/1.1/2.0 (6)
Erythromycin	68/0.3/32 (2)	Not done	85/13/2 (7)	39/32/29 (7)
Azithromycin	64.7/0.6/34.7 (264)	99.4/0/0.6 (3)	100/0/0 (324)	31.2/18.7/50.1 (448)
Clarithromycin	65/0/35 (264)	64/31/5 (3)	100/0/0 (324)	68.8/2.1/29.2 (448)
Levofloxacin	99.8/0/0.2 (2)	100/0/0 (3)	100/0/0 (7)	95.1/1.6/3.3 (6)

Reprinted from Poole and Portugal [35]. With permission Elsevier

Values in parentheses indicate number not tested

S susceptible, I intermediate, R resistant

When choosing which antibiotic should be the drug of choice used to treat a patient with either acute rhinosinusitis or an acute flare of chronic rhinosinusitis, each individual case should be evaluated on its own merit. Many antibiotics have similar efficacy, so the primary factors to take into consideration include the differences in the adverse effects, costs of medication, history of drug sensitivity, and risk of promoting bacterial resistance [23]. Table 19.2 reviews antibiotics dosage, calculated clinical efficacy, and cost [34]. In general, the most effective antibiotic choice will be one that is beta lactamase resistant. Table 19.3 reviews susceptibilities of common community-acquired pathogens to frequently prescribed antibiotics [35]. In more severe and complicated cases, intravenous antibiotics may be warranted but that discussion is beyond the scope of this chapter [36].

Adjunctive Therapies

Mild symptoms, including minimal pain, low-grade temperature elevation, and non-purulent rhinorrhea, lasting less than 10 days may be managed by supportive care only [4]. Supportive therapies that have been investigated for treatment of acute rhinosinusitis include antihistamines, intranasal corticosteroids, oral corticosteroids, analgesics, decongestants, mucolytics, antileukotrienes, saline nasal irrigation, and herbal preparations. Table 19.4 lists all adjunctive therapies for treatment of acute rhinosinusitis.

Table 19.4 Adjunctive therapies for treatment of acute rhinosinusitis

Analgesics
Antihistamines
Antileukotrienes
Decongestants
Herbal preparations
Mucolytics
Nasal corticosteroids
Nasal irrigation
Oral corticosteroids

Antihistamines

The association of acute rhinosinusitis and allergy and atopy has not been clearly defined [37]. (See Chap. 11 for more details on this subject.) However, first-generation antihistamines have been used in acute rhinosinusitis to combat nasal drainage. This is primarily due to the anticholinergic effect of these drugs, an activity that is mostly absent in second-generation drugs (loratadine, fexofenadine, cetirizine) that are also now available over the counter. First-generation antihistamines may cause overdrying of the nasal mucosa and thus lead to further discomfort limiting their usefulness [15]. On the other hand, antihistamines can be effective in atopic patients due to their antihistamine activity. Antihistamines block the H1 histamine receptor and have been demonstrated to be effective in patients with documented aeroallergen allergies. Basophils and mast cells are stimulated to release histamine by the binding of cell-bound IgE antibodies to the offending aeroallergen protein. Therefore, antihistamines only help the acute sinusitis patient when rhinorrhea, sneezing, nasal congestion, and nasal pruritus are associated with basophil and mast cell release of histamine. A recent Cochrane Review noted that there is no evidence supporting the routine use of antihistamines in the treatment of acute rhinosinusitis in children. For most patients, antihistamines will not significantly alleviate nasal congestion, rhinorrhea, or sneezing in patients with an upper respiratory infection [38]. Therefore, antihistamines should not be used in acute rhinosinusitis unless the patient has documented allergies to aeroallergens that are present during the time of the infection. Further research needs to be conducted [39].

Though commonly utilized, the evidence above suggests that antihistamines should not be used as first-line treatment of acute rhinosinusitis. Not only has no study showed efficacy, but there are also potential side effects. First-generation H1 antihistamines cross the blood-brain barrier and are known to cause sedation. Other side effects of antihistamines include dizziness, dry mouth, a feeling of nervousness, excitability, irritability, blurry vision, and decreased appetite. Table 19.5 provides information on the different generations of antihistamines and some of their common adverse effects. Antihistamines, in general, are not an effective adjunctive therapy for acute rhinosinusitis unless the patient is experiencing concomitant allergy disease. In this circumstance, second-generation (e.g., loratadine, fexofenadine, cetirizine, levocetirizine) or topical antihistamines (e.g., azelastine, olopatadine) should be first considered.

Intranasal Corticosteroids

Intranasal corticosteroids are anti-inflammatory agents that reduce inflammation and edema. They have been shown to reduce inflammation of the nasal mucosa, nasal turbinates, and sinus ostia. Intranasal corticosteroids generally do not affect symptoms until after 2–4 days of usage. A recent study demonstrated the effectiveness of mometasone furoate nasal spray in the treatment of acute rhinosinusitis [40]. In this study, the authors evaluated minimal symptom days (defined by less than 4 days with symptom including rhinorrhea, postnasal drip, congestion, and sinus tenderness) while taking mometasone furoate nasal spray 200 µg once daily, versus twice daily, versus treatment with amoxicillin 500 mg three times a day, versus placebo [40]. The study concluded that mometasone furoate nasal spray twice daily significantly decreased symptom days as compared to amoxicillin or placebo in patients with acute rhinosinusitis and can improve outcomes with decreased unnecessary antibiotic use [40]. A previous study found that antibiotics and intranasal corticosteroids, either alone or in combination, were ineffective [41]. However, other studies have suggested that intranasal corticosteroids provide additional benefit in symptoms when used with antibiotics [42–48].

Table 19.5 Antihistamines by generation

Generic name	Trade name	Half-life (±5 h)	Skin test suppression mean (max) days	Adverse effects
<i>First generation (H1)</i>				<i>Cross the blood-brain barrier</i>
Brompheniramine	Dimetapp	24.9	>2 (4)	<i>More common:</i> sedation, dizziness, tinnitus, blurred vision, euphoria, uncoordination, anxiety, increased appetite leading to weight gain, insomnia, tremor, nausea and vomiting, constipation, diarrhea, dry mouth, and dry cough
Chlorpheniramine	Chlor-Trimeton	27.9	3 (6)	
Clemastine	Tavist	21.3	5 (10)	<i>Infrequent:</i> urinary retention, palpitations, hypotension, headache, hallucination, and psychosis
Cyproheptadine	Periactin	16	9 (11)	
Diphenhydramine	Benadryl	9.2	2 (5)	
Hydroxyzine	Atarax	20	5 (8)	
Promethazine	Phenergan	9–16	3 (5)	
Triprolidine	Actifed	3.2	3 (7)	
<i>Second/third generation</i>				<i>More selective for peripheral histamine receptors</i>
Acrivastine	Semprex-D	1.4	3	<i>Most common:</i> drowsiness, fatigue, headache, nausea, and dry mouth
Azelastine HCl	Astelin Nasal	22	2	
Cetirizine	Zyrtec	7	3	
Desloratadine	Clarinex	7.8	7	
Fexofenadine	Allegra	14.4	2	
Levocetirizine	Xyzal	7	Unknown	
Loratadine	Claritin	7.8	7	
Olopatadine HCl	Patanase Nasal	12	Unknown	

Table 19.6 Intranasal corticosteroids

Generic name	Trade name	Effects	Mechanism of action	Dose	Common adverse effects
Beclomethasone	Beconase AQ	First-line therapy to treat symptoms including nasal congestion	Decreases inflammation associated with allergies	1–2 sprays per nostril 1–2 times per day depending on agent use	Epistaxis
Budesonide	Rhinocort				Altered taste
Ciclesonide	Omnaris				Altered smell
Flunisolide	Nasarel, Nasalide				Nasal burning/stinging
Fluticasone	Flonase				Headache
Mometasone	Nasonex				Nasal septum perforation
Triamcinolone	Nasacort AQ				

A Cochrane Review published in 2009 evaluated four randomized controlled trials that included 1,943 patients in total [44–46, 48]. The review concluded that although the current evidence is limited, it does support the use of intranasal corticosteroids as monotherapy or as adjunctive therapy to antibiotics in acute rhinosinusitis [49]. Although the data for the use of intranasal corticosteroids is somewhat controversial, guidelines still recommended this class of drug as an option in treating acute rhinosinusitis [4, 8, 9, 11, 13]. Intranasal corticosteroids are effective for controlling symptoms including nasal congestion, nasal discharge, pruritus, sneezing, and postnasal drip. There are several intranasal corticosteroids that are available by prescription only (Table 19.6). In comparing oral antihistamines and nasal corticosteroids, the intranasal corticosteroids have shown to provide better overall relief [50].

Adverse effects associated with intranasal corticosteroids include nasal burning, epistaxis, nasal pruritus, headache, and pharyngitis. Rare and questionable systemic adverse effects include insomnia, nervousness, increased appetite, indigestion, headache, hyperglycemia, and diaphoresis. Systemic adverse effects are only seen if the nasal steroids are used off label in high doses for prolonged periods of time [51]. Another adverse effect of intranasal corticosteroids is nasal septum perforation. Patients should be advised to point away from the septum and laterally toward the inner canthus of the eye when administering intranasal steroids. Intranasal corticosteroids are a relatively safe medication and should be considered as an option alone or adjunctive medication for treatment of acute rhinosinusitis. Table 19.6 lists common intranasal corticosteroids and their adverse effects.

When beginning the discussion of starting a child on an inhaled corticosteroid, one of the parents' main concerns is how the inhaled corticosteroid will affect their child's growth and development. The word "steroid" poses fear in the hearts of parents used to hearing the serious effects this class of drug has on athletes that abuse them. In a recent controlled prospective study, growth and pulmonary function in children was evaluated during long-term treatment with orally inhaled budesonide. The results were compared to children who were not treated with inhaled corticosteroids. The study showed that there were

Table 19.7 Systemic corticosteroids

Corticosteroid	Relative glucocorticoid potency	Plasma half-life (min)	Estimated biological half-life (h)
Hydrocortisone	1	90	8–12
Cortisone acetate	0.8	30	8–12
Dexamethasone	25	200	36–54
Fludrocortisone	10	Unknown	18–36
Prednisone	3.5	60	18–36
Prednisolone	4	200	18–36
Methylprednisolone	5	180	12–36

no statistically significant changes in growth velocity, weight gain, or lung development in those treated with inhaled budesonide as compared to those who were not [52]. One study on intranasal steroids showed that there is no growth suppression with 100 mg intranasal mometasone furoate once daily in children. Overall, there is much less data regarding the effects of intranasal corticosteroids on growth. However, since there is less systemic exposure with intranasal corticosteroids than orally inhaled corticosteroids used for asthma due to lower total dosing, the risk should be even smaller.

Oral Corticosteroids

Some guidelines recommend oral corticosteroids as an option in treating acute rhinosinusitis [12]. Oral corticosteroids are used either alone, or in addition to intranasal corticosteroids for severe nasal obstruction and for short-term rescue treatment for uncontrolled respiratory symptoms despite conventional pharmacotherapy [12]. The recommended daily dosing of oral corticosteroids is 0.5 mg/kg orally for 5–10 days [12]. In a double-blind, randomized controlled study, patients over the age of 18 years with acute rhinosinusitis were treated with either antibiotic therapy in addition to a 3-day course of oral corticosteroids or antibiotic therapy alone [53]. The results showed that after the first 3 days of treatment, patients who received oral corticosteroids had fewer symptoms including pain and nasal obstruction. However, at the end of treatment protocol, both the antibiotic alone and the antibiotic plus steroid treatment groups were symptom free [53]. This study showed the positive impact oral corticosteroids have in the initial recovery phase while not significantly affected the ultimate outcome.

There is a continued debate between allergist/immunologists and otolaryngologists regarding the use of oral corticosteroids for the treatment of acute rhinosinusitis. Otolaryngologists tend to favor the use of oral corticosteroids to treat the severe nasal congestion and inflammation that is commonly associated with acute rhinosinusitis. Allergist/immunologists generally defer the use of oral corticosteroids to only the most severe circumstances because of potential side effects. They point out that side effects from even a short course can include aseptic necrosis of the hip, glaucoma, lower extremity edema, hypertension, mood swings, and weight gain. When oral steroids are used more chronically, the list expands to include cataracts, hyperglycemia, osteoporosis, adrenal suppression, thinning of the skin, an increased risk of infection, and, in children, reduction in growth velocity. Further clinical trials are needed to assess the risks/benefit relationship of treating acute rhinosinusitis with oral corticosteroids before this debate can be settled. In general, considering the side effect profile, the oral method of steroid administration should not be considered a first-line treatment of acute rhinosinusitis. Table 19.7 outlines the different classes of oral corticosteroids [54].

When looking at growth velocity in children taking oral as compared to inhaled corticosteroids, there is a notable difference and deserves special mention. A meta-analysis of the effect of oral and inhaled corticosteroids on growth was performed which compared attained heights with expected heights in children treated with either oral or inhaled corticosteroids [55]. The study revealed that there was a weak association with growth impairment in children being treated with prednisone and other oral corticosteroids. In comparison, treatment with inhaled corticosteroids was associated with attaining normal stature. It is important to review these adverse effects with parents when considering treating children with oral corticosteroids under all circumstances.

Analgesics

Over-the-counter analgesics are typically used for mild to moderate pain associated with acute rhinosinusitis, including facial tenderness or sinus headaches. Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used analgesics. Symptomatically treating pain may allow the patient to carry on with daily activities more easily while sick. No studies have been done to evaluate if analgesics alone or in combination with antibiotics quicken resolution of acute

rhinosinusitis symptoms. There is no clear role for any stronger analgesics such as narcotics in the symptomatic relief of acute rhinosinusitis. Some patients with acute rhinosinusitis may develop migraine headaches. These are most commonly treated with oral NSAIDs along with triptans if this class of drug has already been established as effective for the individual patient in question. When presenting to a primary care physician, approximately 56 % of patients are recommended to take analgesics to help improve their symptoms and decrease inflammation [56]. This suggestion seems reasonable except in the case of a CRS patient with nasal polyps who demonstrate a high incidence of NSAID hypersensitivity (see Chap. 12). In general, more studies are needed to evaluate different classes of analgesics and their role in providing sinus symptom relief.

Decongestants

Intranasal decongestants, i.e., ephedrine, an α_1 -agonist, and xylometazoline, an α_2 -agonist, are sympathomimetics that increase nasal vasoconstriction. When combined with an intranasal corticosteroid, it has been demonstrated to have short-term benefits in acute exacerbations of chronic rhinosinusitis with nasal blockage [57]. In a Cochrane Review, seven studies were evaluated, and topical nasal decongestants were found to be modestly effective for short-term relief of congestion in adults with the common cold [38]. Oral decongestants such as pseudoephedrine are commonly suggested but there is little data to support their efficacy or an improvement in long-term outcome [58].

The abbreviated use of topical decongestants for less than 4 days is advised in order to avoid a rebound effect that sometimes occur from this class of medication (rhinitis medicamentosa) [12]. Rhinitis medicamentosa is a type of non-allergic rhinitis. Very little information is known about this phenomenon and there is no literature devoted solely to it. While there are no current treatment recommendations for rhinitis medicamentosa other than avoiding the inciting agent, an intranasal corticosteroid can be used to alleviate symptoms. If the intranasal corticosteroid alone is not providing sufficient relief in rhinitis medicamentosa, an intranasal antihistamine can also be added [59]. Ultimately, this problem generally self resolves once the topical decongestant has been discontinued.

Mucolytics

Mucolytics are not routinely recommended in the guidelines for treatment of rhinosinusitis. In a randomized placebo-controlled study, mucolytics as an adjunctive therapy were studied in the treatment of children with acute rhinosinusitis. Erdosteine, a mucolytic, was administered to 49 children while 43 received placebo [60]. Both groups also received an antibiotic throughout the course of treatment. After 2 weeks of treatment with either antibiotic and mucolytic or antibiotic alone, there was no significant difference between the two groups [60]. This study concluded that the use of erdosteine as a mucolytic agent in children with acute rhinosinusitis does not improve or hasten resolution of symptoms. Mucolytics are not routinely given for treatment of acute rhinosinusitis. To date, there is little evidence supporting them as a beneficial adjunctive therapy.

Antileukotrienes

While antileukotrienes have been proven to be modestly effective in treating allergic rhinitis, there are no randomized, controlled trials on the use of antileukotrienes in the treatment of acute rhinosinusitis. Antileukotrienes have also demonstrated efficacy in the treatment of nasal polyposis [61]. The exact anti-inflammatory role of montelukast on inflammatory cells in the nasal passages and sinuses has not been firmly defined. In 2012, a pilot study was initiated to evaluate the role of montelukast in preventing early and late inflammatory cells response to specific allergens causing persistent rhinitis. Patients were randomized into montelukast versus placebo groups for 4 weeks after both received a 4 week nasal wash out. There were fewer inflammatory cells noted, specifically macrophages and neutrophils, in the treatment group after receiving montelukast as compared to the control group, but the results were not statistically significant [62].

In general, there is no place for antileukotrienes as adjuvant therapy for acute rhinosinusitis unless the drug is being used regularly for concurrent allergic rhinitis, asthma, and/or nasal polyposis.

Saline Nasal Irrigation

Saline nasal irrigation or nasal douching is a safe, inexpensive treatment for acute rhinosinusitis. It is commonly used in continental Europe. It may be used to soften viscous secretions and improve mucociliary clearance. Evidence exists that saline nasal irrigation reduces the symptoms of chronic rhinosinusitis [63–67]. No clinical trials exist for the treatment of

acute rhinosinusitis, but irrigation with nasal saline appears safe. Minor adverse effects can be avoided with modification of administration technique and adjustment of the saline concentration, and there have been no reports of serious adverse events. Nasal saline irrigation can be recommended as a supportive mode of treatment in acute rhinosinusitis.

Herbal Preparations

Nasodren (Sinuforte) is a nasal spray obtained from the juice and natural aqueous extract of fresh tubers of the plant *Cyclamen europaeum*. In two studies from Russia, Nasodren has been reported to be effective in the treatment of acute rhinosinusitis [68, 69]. The first study evaluated 50 patients with acute suppurative bacterial rhinosinusitis [68]. Half were treated with Nasodren, amoxicillin, and xylometazoline with the other half treated with only amoxicillin and xylometazoline for 8 days [68]. A higher proportion of patients receiving the Nasodren described their overall treatment as excellent. The treatment group also had a statistically significant increase in mucociliary transport time [68]. Another study evaluated 30 patients with acute rhinosinusitis treated with Nasodren alone [69]. All 30 patients received Nasodren monotherapy [69]. The study showed that for these patients with moderately severe acute rhinosinusitis, Nasodren alone ensured recovery in 73 % of cases by day 7 [69]. Based on these studies, Nasodren proved to be beneficial in relieving symptoms due to acute rhinosinusitis both as an adjunctive therapy and on its own. Sinupret® is an herbal medicinal product made from gentian root, primula flower, elder flower, sorrel herb, and verbena herb. It is frequently used as a complementary and alternative medicine (CAM) in the treatment of acute and chronic rhinosinusitis and URIs. Sinupret® was shown to have significant antiviral activity against many viruses including adenovirus C subtype 5, human rhinovirus B subtype 14, and RSV [70].

More people are using herbal preparations for treatment of a multitude of diseases. In fact, it has been shown that many individuals will seek out complementary and alternative medications to help them find a more natural approach to the treatment of their diseases. Many people are also wary of the side effects of the various commercially prepared “Western” medications, and with the rising costs of these medications, the herbal preparations appear to many patients to be a more attractive therapeutic option.

One should be careful in using complementary and alternative medicines. Most of these have not been adequately studied and may contain components that are harmful to health. Some even contain corticosteroids, and the chronic ingestion of these products may lead to severe long-term sequelae. Many of these products are under investigation using modern laboratory methods, but as of the present time, they are not under the regulation of a federal agency, in the same manner that drugs are regulated by the FDA.

Immunotherapy

The role of subcutaneous immunotherapy (SCIT) in the treatment of rhinosinusitis is unclear. If the rhinosinusitis is related to an underlying allergic disease, then immunotherapy may be of benefit. Immunotherapy has been effective in the treatment of allergic fungal rhinosinusitis. This is discussed in more detail in Chap. 8. The use of sublingual immunotherapy (SLIT) has not been adequately studied in the treatment of rhinosinusitis.

Conclusion

The diagnosis and medical treatment of acute rhinosinusitis remains controversial, but general guidelines to therapy have been defined. A majority of cases of rhinosinusitis are caused by viral infections. The difficulty is defining when a case of acute rhinosinusitis is complicated by bacterial infection. Many guidelines have been developed to aid in the diagnosis of acute bacterial rhinosinusitis and to differentiate it from other nonbacterial causes. Most of the guidelines state severe persistent symptoms as the main reason to treat a patient with oral antibiotics. However, recent evidence has shown that even if a bacterial cause for the acute rhinosinusitis is suspected, antibiotic treatment may not promote a more rapid clearance of the bacteria from the sinuses or resolution of symptoms. When choosing to use antibiotics, the best choice in the ambulatory care setting is a drug that is beta lactamase resistant such as amoxicillin-clavulanate or a second-generation cephalosporin. Nasal rinsing with isotonic or hypertonic tepid saline is commonly beneficial and has been shown to hasten recovery. There is some data to support the use of topical nasal steroids and even short-course systemic corticosteroids for symptom relief although the side effect profile of this format of therapy clearly favors the topical application. Other adjunctive therapies such as antihistamines, decongestants, and mucolytics may be beneficial for symptomatic relief in selected cases, but few studies clearly show additional efficacy when used alone or in conjunction with antibiotics.

References

1. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U. S. adults: National Health Interview Survey, 2008. National Center for Health Statistics. *Vital Health Stat.* 2009;10(242):1–157.
2. Ramadan HH. Pediatric sinusitis: update. *J Otolaryngol.* 2005;34 Suppl 1:S14–7.
3. Ahovuo-Saloranta A, Rautakorpi UM, Borisenko OV, Liira H, Williams Jr JW, Makela M. Antibiotics for acute maxillary sinusitis (Review). *Cochrane Rev.* 2011;(Issue 3):1.
4. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg.* 2007;137(3 Suppl):S1–31.
5. Anon JB, Jacobs MR, Poole MD, et al., Sinus and Allergy Health Partnership (SAHP). Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg.* 2004;130(1 Suppl):S1–45.
6. Gonzales R, Steiner JF, Lum A, Barret PH. Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. *JAMA.* 1999;273:214–9.
7. Dosh SA, Hickner JM, Mainous AG, Ebell MH. Predictors of antibiotic prescribing for non-specific upper respiratory infections, acute bronchitis, and acute sinusitis. An UPRNet study. Upper Peninsula Research Network. *J Fam Pract.* 2000;49:407–14.
8. Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics.* 2001;108:798–808.
9. Chow AW, Benninger MS, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. *Clin Infect Dis.* 2012;54(8):1041–5.
10. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis initiative. Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol.* 2004;118(5 Suppl):S17–61.
11. Thomas M, Yawn B, et al. EPOS primary care guidelines: European position paper on the primary care diagnosis and management of rhinosinusitis and nasal polyps 2007 – a summary. *Prim Care Respir J.* 2008;17(2):79–89.
12. Scadding GK, Durham SR, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy.* 2007;38:260–75.
13. Slavin RG, Spector SL, Bernstein IL, et al., AAAAI, the ACAAI, and the JCAAI. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol.* 2005;116(6 Suppl):S13–47.
14. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg.* 2004;130(1 Suppl):1–45.
15. Aring AM, Chan MM. Acute rhinosinusitis in adults. *Am Fam Physician.* 2011;83(9):1057–63.
16. Palmenberg AC, Spiro D, Kuzmickas R, Wang S, Djikeng A, Rathe JA, Fraser-Liggett CM, Liggett SB. Sequencing and analyses of all known human rhinovirus genomes reveals structure and evolution. *Science.* 2009;324(5923):55–9.
17. Eccles R. Understanding the symptoms of the common cold and influenza. *Lancet Infect Dis.* 2005;5(11):718–25.
18. Common Cold. National Institute of Allergy and Infectious Diseases. 2011. <http://www.niaid.nih.gov/topics/commoncold/Pages/default.aspx>. Retrieved 30 June 2012.
19. Stefanska I, Romanowska M, et al. Co-infections with influenza and other respiratory viruses. *Adv Exp Med Biol.* 2012;756:291–301.
20. Thompson GR, Patterson TF. Fungal disease of the nose and paranasal sinuses. *J Allergy Clin Immunol.* 2012;129:321–6.
21. Van Crmbruggen K, Zhang N, Gavaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. *J Allergy Clin Immunol.* 2011;128(4):728–32.
22. Ramakrishnan VR, Feazel LM, Abrass LJ, Frank DN. Prevalence and abundance of *Staphylococcus aureus* in the middle meatus of patients with chronic rhinosinusitis, nasal polyps, and asthma. *Int Forum Allergy Rhinol.* 2013;3(4):267–71.
23. Ahovuo-Saloranta A, Rautakorpi UM, et al. Antibiotics for acute maxillary sinusitis: Cochrane Review. *Cochrane Collaboration.* 2011;3:1–145.
24. Lee JE, Han DH, Won TB, Rhee CS. A randomized, double-blinded, open label study of the efficacy and safety of cefcapene pivoxil and amoxicillin•clavulanate in acute presumed bacterial rhinosinusitis. *Clin Exp Otorhinolaryngol.* 2011;4(2):83–7.
25. Hadley JA. The efficacy of cefdinir in acute bacterial rhinosinusitis. *Expert Opin Pharmacother.* 2006;7(8):1075–83.
26. Garbutt JM, Banister C, Spitznagel E, Piccirillo JF. Amoxicillin for acute rhinosinusitis: a randomized controlled trial. *JAMA.* 2012;307(7):685–92.
27. Hadley JA. Value of short-course antimicrobial therapy in acute bacterial rhinosinusitis. *Int J Antimicrob Agents.* 2005;26:S164–9.
28. Bottaro G, Rotolo N, Bonforte S, De Luca P, Ficarra G, Gulino A, Melillo P, Nicosia A, Prestifilippo F. Evaluation of the clinical efficacy of azithromycin in acute respiratory infections in children. *Clin Ter.* 1994;145(7):35–9.
29. Anon JB. Current management of acute bacterial rhinosinusitis and the role of moxifloxacin. *Clin Infect Dis.* 2005;41 Suppl 2:S167–76.
30. Sokol W. Epidemiology of sinusitis in the primary care setting: results from the 1999–2000 respiratory surveillance program. *Am J Med.* 2001;111(9):19–24.
31. Adefurin A, Sammons H, Jacqz-Aigrain E, Choonara I. Ciprofloxacin safety in paediatrics: a systematic review. *Arch Dis Child.* 2011;96(9):874–80.
32. McCoul ED, Jourdy DN, Schaberg MR, Anand VK. Methicillin-resistant *Staphylococcus aureus* sinusitis in nonhospitalized patients: a systematic review of prevalence and treatment outcomes. *Laryngoscope.* 2012;122:2125–31.
33. Whitby CR, Kaplan SL, Mason Jr EO, Carrillo-Marquez M, Lamberth LB, Hammerman WA, Hultén KG. *Staphylococcus aureus* sinus infections in children. *Int J Pediatr Otorhinolaryngol.* 2011;75(1):118–21.
34. Scheid DC, Hamm RM. Acute bacterial rhinosinusitis in adults: part II. Treatment. *Am Fam Physician.* 2004;70(9):1697–704, 1711–12.
35. Poole MD, Portugal LG. Treatment of rhinosinusitis in the outpatient setting. *Am J Med.* 2005;118(7A):45S–50S.
36. Schaberg MR, Anand VK, Singh A. Hyperostotic chronic sinusitis as an indication for outpatient intravenous antibiotics. *Laryngoscope.* 2010;120 Suppl 4:S245.

37. Karlsson G, Homberg K. Does allergic rhinitis predispose to sinusitis? *Acta Otolaryngol Suppl.* 1994;515:26–8.
38. De Sutter AI, Lemiengre M, Campbell H. Antihistamines for the common cold. *Cochrane Database Syst Rev.* 2003;(3):CD001267.
39. Shaikh N, Wald ER, Pi M. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. *Cochrane Database Syst Rev.* 2012;(9):CD007909.
40. Meltzer EO, Gates D, Bachert C. Mometasone furoate nasal spray increases the number of minimal-symptom days in patients with acute rhinosinusitis. *Ann Allergy Asthma Immunol.* 2012;108(4):275–9.
41. Williamson IG, Rumsby K, Bengt S, et al. Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: a randomized controlled trial. *JAMA.* 2007;298(21):2487–96.
42. Meltzer EO, Orgel HA, Backhaus JW, et al. Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. *J Allergy Clin Immunol.* 1993;92(6):812–23.
43. Meltzer EO, Charous BL, Busse WW, et al. Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. The Nasonex Sinusitis Group. *J Allergy Clin Immunol.* 2000;106(4):630–7.
44. Dolor RJ, Witsell DL, Hellkamp AS, et al., Ceftin and Flonase for Sinusitis Investigators. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFF trial: a randomized controlled trial. *JAMA.* 2001;286(24):3097–105. Published correction appears in *JAMA.* 2004;292(14):1686.
45. Nayak AS, Settupane GA, Pedinoff A, et al., Nasonex Sinusitis Group. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Ann Allergy Asthma Immunol.* 2002;89(3):271–78.
46. Barlan IB, Erkan E, Bakir M, et al. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann Allergy Asthma Immunol.* 1997;78(6):598–601.
47. Yilmaz G, Varan B, Yilmaz T, et al. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Eur Arch Otorhinolaryngol.* 2000;257(5):256–9.
48. Meltzer EO, Bachert C, Staudinger H. Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J Allergy Clin Immunol.* 2005;116(6):1289–95.
49. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. *Cochrane Database Syst Rev.* 2009;(4):CD005149.
50. Allergy statistics. American Academy of Allergy, Asthma & Immunology. www.aaaai.org/media/resources/media_kit/allergy_statistics.stm. Accessed 11 Mar 2008.
51. DeShazo RD, Kemp SF. Management of allergic rhinitis. UpToDate. www.uptodateonline.com.proxy.uwlib.uwyo.edu. Accessed 7 Mar 2008.
52. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med.* 1994;88(5):373–81.
53. Klossek JM, Desmots-Gohler C, Deslandes B, Coriat F, Bordure P, Dubreuil C, Gehanno P, Gilain L, Jankowski R, Serrano E, Stoll D. Treatment of functional signs of acute rhinosinusitis in adults. Efficacy and tolerance of administration of oral prednisone for 3 days. *Presse Med.* 2004;33(5):303–9.
54. About pharmacology: approximate relative potency and half-lives of oral corticosteroids (Table 5.34). About pharmacology. N.p., 2 Nov 2011. Web. 16 Jan 2013.
55. Allen D, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol.* 1994;93(6):967–76.
56. Klossek JM, Mesbah K. Presentation and treatment of acute maxillary sinusitis in general practice: a french observational study. *Rhinology.* 2011;49(1):84–9.
57. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomized, controlled trial. *Laryngoscope.* 2004;114:923–30.
58. Sharp HJ, Denman D, Puumala S, Leopold DA. Treatment of acute and chronic rhinosinusitis in the United States, 1999–2002. *Arch Otolaryngol Head Neck Surg.* 2007;133(3):260–5.
59. Varghese M, Glaum MC, Lockey RF. Drug-induced rhinitis. *Clin Exp Allergy.* 2010;40(3):381–4.
60. Unuvar E, Tamay Z, Yildiz I, Toprak S, Kilic A, Guler N, Oguz F, Sidal M. Effectiveness of erdosteine, a second generation mucolytic agent, in children with acute rhinosinusitis: a randomized, placebo controlled, double-blinded Clinical Study. *Acta Paediatr.* 2010;99(4):585–9.
61. Ragab S, Parikh A, Darby YC, Scadding GK. An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. *Clin Exp Allergy.* 2001;31:1385–91.
62. Braido F, Riccio AM, Rogkakou A, Massacane P, Guerra L, Fumagalli F, Stagi E, Balestracci S, Porcu A, Canonica GW. Montelukast effects on inflammation in allergic rhinitis: a double blind placebo controlled pilot study. *Eur Ann Allergy Clin Immunol.* 2012;44(2):48–53.
63. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. *Laryngoscope.* 2000;110:1189–93.
64. Taccariello M, Parikh A, Darby Y, et al. Nasal douching as a valuable adjunct in the management of chronic rhinosinusitis. *Rhinology.* 1999;37:29–32.
65. Rabago D, Pasic T, Zgierska A, et al. The efficacy of hypertonic saline nasal irrigation for chronic sinonasal symptoms. *Otolaryngol Head Neck Surg.* 2005;133:3–8.
66. Heatley DG, McConnell KE, Kille TL, Levenson GE. Nasal irrigation for the alleviation of sinonasal symptoms. *Otolaryngol Head Neck Surg.* 2001;125:44–8.
67. Shoseyov D, Bibi H, Shai P, et al. Treatment with hypertonic saline versus normal saline nasal wash of pediatric chronic sinusitis. *J Allergy Clin Immunol.* 1998;101:602–5.
68. Ovchinnikov A, Dzhenzhera GE, Lopatin AS. Efficiency of sinuforte in combined therapy of acute suppurative rhinosinusitis. *Vestn Otorinolaringol.* 2009;5:59–62.
69. Semenov VF, Banashek-Meshcheriakova TV. The efficacy of sinuforte in the starting monotherapy of the patients presenting with acute rhinosinusitis. *Vestn Otorinolaringol.* 2011;3:68–70.
70. Glatthaar-Saalmuller B, Rauchhaus U, Rode S, et al. Antiviral activity in vitro of two preparations of the herbal medicinal product Sinupret® against viruses causing respiratory infections. *Phytomedicine.* 2011;19:1–7.