Current Management of Acute Bacterial Rhinosinusitis and the Role of Moxifloxacin

Jack B. Anon

Department of Otolaryngology, University of Pittsburgh School of Medicine, Erie, Pennsylvania

Episodes of acute rhinosinusitis are common among adults and are associated with a significant amount of morbidity. The symptoms of rhinosinusitis are nasal drainage, congestion, and sinus pressure. A bacterial sinus infection is more likely if these symptoms worsen after 5–7 days or do not improve after 10–14 days. The majority of bacterial episodes have been associated with *Streptococcus pneumoniae* and *Haemophilus influenzae*. In the current era of increasing resistance to β-lactams and macrolides, treatment guidelines have been formulated worldwide to assist clinicians in the selection of antibacterials. According to one model, the following antibacterials are most likely to provide desired outcomes (90%–92% predicted clinical efficacy) for adults: respiratory fluoroquinolones (i.e., moxifloxacin, gatifloxacin, and levofloxacin), ceftriaxone, and high-dose amoxicillin-clavulanate (4 g of amoxicillin/day and 250 mg of clavulanate/day). Although the role of the fluoroquinolones in the treatment of this condition is evolving, fluoroquinolones are often recommended as second-line therapy or as first-line therapy for selected patients (e.g., those who received antibacterials in the previous 4–6 weeks or adults with moderate-to-severe disease).

Acute bacterial rhinosinusitis (ABRS) is a bacterial infection involving the paranasal sinuses and is usually preceded by a viral upper respiratory tract infection (URTI; i.e., the "common cold") or an acute exacerbation of an allergic disorder [1]. In 1996, the American Academy of Otolaryngology–Head and Neck Surgery Foundation developed working definitions of sinusitis in an attempt to standardize communication among health-care providers and researchers [2]. Because sinusitis is generally preceded by rhinitis and rarely occurs without concurrent rhinitis, the more appropriate term for this condition is "rhinosinusitis." Bacterial superinfection may occur at any time point after viral infection but is generally assumed to have occurred if symptoms have persisted for >10 days or have worsened after 5–7 days [2].

Because diagnosing ABRS can be difficult, the misuse and overuse of antibacterials for the treatment of URTIs has become a major problem throughout the world, as patients and clinicians incorrectly overdiagnose bacterial disease. The Centers for Disease Control and Prevention have reported that there are ~50 million unnecessary antibiotic prescriptions for the common cold and other viral infections—against which antibacterials are not effective—written in the United States [3]. Recently, the US Food and Drug Administration began requiring that the labeling for systemic antibacterials include statements about the unnecessary use of antibacterials and the association between such use and the increase in drug-resistant bacterial strains. By 1996 estimates, 9% of all antibiotic prescriptions in the United States are written for the treatment of ABRS [4].

The present article briefly reviews the pathophysiology, etiology, clinical presentation, and diagnosis of ABRS. Treatment options for ABRS in an era of antibiotic resistance are also presented, with a discussion of the role of fluoroquinolones, moxifloxacin in particular, in the treatment of this infection.

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF ABRS

A viral URTI usually precedes ABRS. Allergy, another inflammatory condition of the nose and paranasal si-

nuses, may also predispose individuals to develop ABRS. Viruses that cause infections of the upper airway include rhinovirus, coronavirus, influenza A and B viruses, parainfluenza virus, respiratory syncytial virus (RSV), and adenovirus. Most of these viral infections occur during the early fall to early spring, manifesting as a common cold, and the incidence of sinusitis is higher during this time [1]. Viral URTI stimulates increases in inflammation and in the local immune response of the nasopharynx and surrounding mucosa. Some viruses, such as influenza virus, produce significant mucosal damage. Others promote the local production of cytokines and other inflammatory mediators, leading to the signs and symptoms of the common cold (i.e., viral URTI) [5].

Numerous cytokines and proinflammatory mediators (e.g., IL-1β, IL-2, IL-6, IL-8, TNF-α, histamine, leukotriene C4, and prostaglandins) are up-regulated during ABRS episodes. Viruses have a suppressive effect on the function of neutrophils, macrophages, and lymphocytes [5], including diminished adherent, chemotactic, phagocytic, oxidative, secretory, and bactericidal functions of neutrophils. Viruses also decrease the function of macrophages and lymphocytes, resulting in patients with viral URTIs being generally more vulnerable to secondary overgrowth and subsequent bacterial infection by pathogens that colonize the nasopharynx, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Colonization with nontypeable *H. influenzae* is significantly affected by concurrent infection with RSV; however, the site of bacterial attachment is not known. The mechanism of attachment involves up-regulation of expression of epithelial cell–surface receptors, including CEACAM1 and intercellular adhesion molecule–1 [5]. Attachment sites for *S. pneumoniae* may also be exposed.

As for the role that allergy plays in ABRS, Blair et al. [6] instilled *S. pneumoniae* during ongoing nasal allergic inflammation in a mouse model and found that allergy augments the infection and the resultant inflammatory response. They also showed that allergy alone or allergen exposure did not enhance the sinus infection, which suggests that local inflammation is important. The scientific basis for the role that allergy plays in ABRS includes the following theories: release of mediators from mast cells during an allergic reaction causes greater transudation of fluid and increased proliferation of bacteria in the sinus cavities; inflammatory mediators released by eosinophils during an allergic reaction expose epithelial *S. pneumoniae* binding sites; and ciliary transport from the sinuses altered by allergic inflammation reduces clearance of bacteria.

The symptoms of rhinosinusitis are a consequence of the activation of inflammatory pathways and the parasympathetic nervous system. Fever, myalgia, and pharyngitis frequently associated with a viral URTI usually resolve by approximately day 5 [5]. Nasal congestion, postnasal drainage, and cough may persist into the second and third weeks. Notably, a change in the color of the nasal discharge does not suggest the presence of bacterial infection [5]. To determine the point in time if and when a secondary bacterial infection develops becomes a clinical and diagnostic dilemma, Lacroix et al. [7] studied 265 patients with URTIs and reported that there are no distinct signs or symptoms in patients with mild-to-moderate clinical presentations that predict the presence of pathogenic bacteria.

DIAGNOSIS OF ABRS

According to the ABRS treatment guidelines of the Sinus and Allergy Health Partnership (SAHP), a clinical diagnosis of ABRS may be made when URTI symptoms (e.g., nasal congestion, facial pressure and/orpain [especially unilateral], and postnasal drip) worsen after 5–7 days or do not improve after 10–14 days [5]. However, the identification of specific signs and symptoms at clinical examination does not appear to reliably predict bacterial infection [5].

Radiography provides only moderate sensitivity (76%) and moderate specificity (79%) for the diagnosis of ABRS [8]. A negative result of plain-film radiography has a better predictive value than does a positive results. Plain-film radiographs are valuable for visualizing the frontal and maxillary sinuses but are not useful if infection is ethmoid in origin; plain-film radiographs also do not reveal the extent of disease [5]. Furthermore, abnormal findings on plain-film radiographs do not differentiate viral from bacterial disease. In a group of patients with suspected bacterial ABRS and positive findings on radiographs, only ∼50% of sinus taps yielded pathogenic bacteria [9]. CT and MRI are not recommended for most patients with ABRS but may be valuable for patients with complicated episodes [5].

Sinus puncture, with aspiration and culture, is the reference standard for identifying bacterial episodes, although it is basically a research tool. Some experts believe that positive results of bacteriological cultures of nasopharyngeal aspirates best identify those patients who may benefit from antibiotic treatment [7]. This idea was also proposed by Kaiser et al. [10]; of 288 patients with URTIs, 20% had nasopharyngeal cultures positive for *H. influenzae, Moraxella catarrhalis,* or *S. pneumoniae.* Among patients with proven bacterial infections, the rate of clinical cure among patients given amoxicillin-clavulanate therapy was 10 times higher, and the symptom scores on day 5 were significantly lower, compared with those for patients given placebo [10]. Additional studies are needed to validate this theory.

Talbot et al. [11] reported that, when cultures obtained by rigid nasal endoscopy were compared with those obtained by sinus puncture and aspiration, endoscopic cultures had a sensitivity of 85.7%, a specificity of 90.6%, a positive predictive value of 80%, a negative predictive value of 93.5%, and accuracy of 89.1%. Their study, which is the largest to date, demonstrated

that endoscopic sampling compares favorably with puncture and aspiration for identifying the major pathogens that cause ABRS.

In summary, a diagnosis of rhinosinusitis is typically made at clinical presentation, with bacterial episodes likely if symptoms persist for >1 week. Imaging techniques are not indicated for most cases seen in routine clinical practice, and microbiological sampling techniques are useful for clinical investigations, albeit with caveats about their sensitivity.

ETIOLOGY AND ISSUES OF RESISTANCE

The major pathogens responsible for ABRS in adults are *S. pneumoniae* and *H. influenzae.* Although the reported percentages of each vary, in a recent tap study [9], we identified 133 *S. pneumoniae* (33%) and 116 *H. influenzae* (29%) isolates (total, 399 isolates). The use of conjugate pneumococcal vaccine in the pediatric population may be responsible for an increase in the prevalence of *H. influenzae* in adults with rhinosinusitis.

Surveillance studies are used to monitor changes in resistance among the major pathogens. The Alexander Project is a surveillance network that examines the susceptibility of pathogens involved in community-acquired respiratory tract infections in adults [12]. In the most recent report, 8882 isolates of *S. pneumoniae,* 8523 isolates of *H. influenzae,* and 874 isolates of *M. catarrhalis* were collected during 1998–2000 from 26 countries. Among *S. pneumoniae* isolates, the worldwide prevalence of resistance to penicillin (MIC, $\geqslant 2$ mg/L) was 18.2%, and that of resistance to macrolides (erythromycin MIC, $\geqslant 1$ mg/L) was 24.6%. In the United States, 37% of 2432 *S. pneumoniae* isolates demonstrated resistance to penicillin. The worldwide prevalence of fluoroquinolone-resistant *S. pneumoniae* (ofloxacin MIC, $\geqslant 8$ mg/L) was low (1.1%) [12]. The prevalences of β-lactamase–producing *H. influenzae* and *M. catarrhalis* isolates are 16.9% and 92.1%, respectively. In this surveillance study, both *H. influenzae* and *M. catarrhalis* were highly susceptible to the tested fluoroquinolones (>99.8%).

Another surveillance network—the TRUST Study—examined global changes in resistance patterns among common sinus pathogens. Sahm et al. [13] reported that, for *S. pneumoniae,* increases in resistance to penicillin between 1999 and 2003 were detected only in China (from 2.3% to 25.0%) and Thailand (from 39.3% to 60.9%). Increases in resistance to azithromycin were detected in China (from 66.4% to 84.4%), Germany (from 13.4% to 28.8%), Hong Kong (from 44.6% to 75.5%), Thailand (from 47.6% to 65.2%), and the United Kingdom (from 9.8% to 29.4%). Multidrug resistance increased in China (from 2.3% to 21.9%); in other countries, the incidence remained similar to incidences reported for 2001–2002. For all countries combined, rates of resistance to levofloxacin remained low during the 3 study years: 0.6% (for 1999–2000), 0.7% (for 2001–2002), and 1.0% (for 2003). For *H. influenzae,* between 1999 and 2003, increases in production of β-lactamase were detected in France (from 33.7% to 37.2%), Germany (from 6.9% to 20.3%), South Africa (from 7.4% to 11.2%), and the United Kingdom (from 11.3% to 25.9%).

In the same study [13], *S. pneumoniae* sinus isolates collected during 3 consecutive respiratory tract infection seasons in the United States were tested against a panel of antimicrobials by use of NCCLS broth microdilution. Among 131 *S. pneumoniae* sinus isolates collected during 2000–2003, 52.6% of isolates were susceptible to penicillin, 59% were susceptible to azithromycin and erythromycin, 60.3% were susceptible to cefuroxime, 85.9% were susceptible to amoxicillin-clavulanate, and 99.4% were susceptible to levofloxacin. During 2003, levofloxacin, gatifloxacin, and moxifloxacin demonstrated equivalent susceptibilities (100%). From 2000 to 2003, only 3 levofloxacin-resistant isolates (0.6%) were identified. Multidrug-resistant phenotypes (i.e., those resistant to $\geqslant 3$ antimicrobial classes) accounted for 23.5% of isolates during 2000–2003. Resistance to penicillin, azithromycin, and trimethoprim-sulfamethoxazole (TMP-SMZ) was the most common multidrug-resistant phenotype, and >98% of strains with this phenotype were susceptible to levofloxacin.

ANTIMICROBIAL THERAPY AND TREATMENT GUIDELINES

Although it remains difficult to determine which patients should receive antimicrobial therapy, antibacterials are considered to be beneficial for treatment of known or suspected bacterial episodes of sinusitis [1, 5]. The landmark Agency for Health Care Policy and Research 1999 guidelines identified only 6 studies that met the criteria for a meta-analysis evaluating the benefits of antibacterials, versus no antibacterials, for the treatment of ABRS [8]. As shown in figure 1, antibacterials were significantly more effective, clinically curing one-third more cases and reducing treatment failures by one-half, compared with placebo [8]. According to French experts, antibiotic treatment has modified the treatment of acute purulent maxillary sinusitis, and indications for drainage and washing of the paranasal sinuses are now rare [20]. Historical data from the preantibiotic era also confirm that the treatment of acute disease with antibacterials has reduced the thrombophlebitic, CNS, and orbital complications of purulent sinusitis.

Although data support the use of antibacterials, the development of resistance in several key respiratory pathogens has led to new paradigms for treating ABRS. Antibacterials once approved by the US Food and Drug Administration may no longer have a pharmacokinetic/pharmacodynamic profile needed to provide optimal bacterial killing. Treatment guidelines for the management of ABRS have been developed by several expert groups throughout the world. A brief review of their findings and recommendations is presented below.
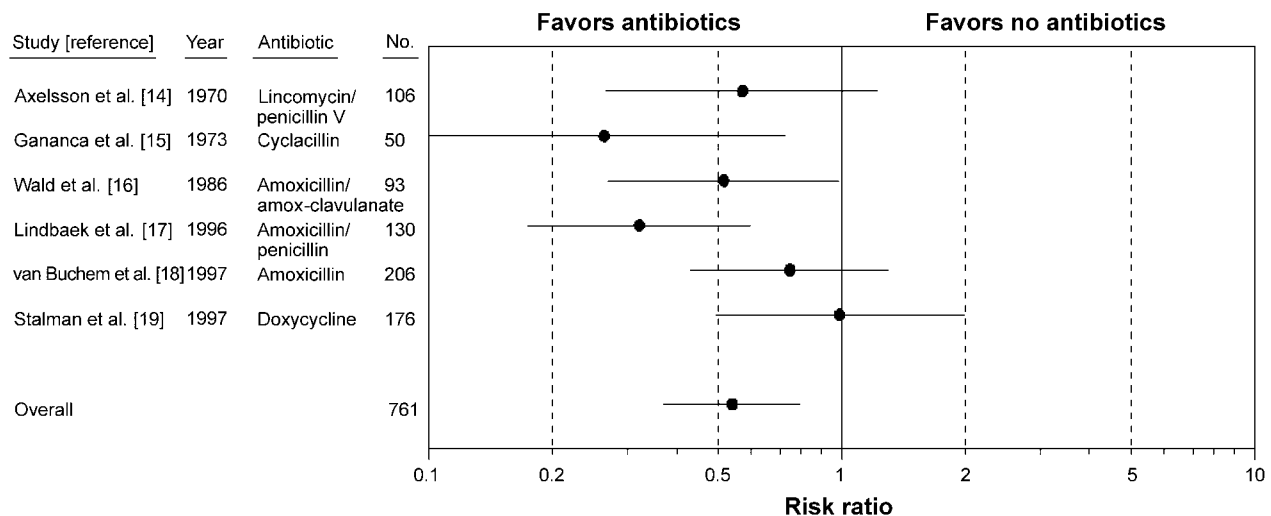
Figure 1. Meta-analysis of studies favoring vs. those not favoring the use of antibacterials to treat acute bacterial rhinosinusitis episodes [8]

US guidelines. In 2000, the SAHP published guidelines that thoroughly reviewed the various aspects of ABRS, with emphasis on appropriate antibiotic choices in an era of resistance [21]. Work on these guidelines began after the Centers for Disease Control and Prevention's Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group published an article on the treatment of acute otitis media in an era of resistant pneumococci [22]. The SAHP recently revised these guidelines in 2004, to consider further changes that had occurred in antibiotic resistance patterns [5].

The current SAHP treatment guidelines are based on a mathematical model of ABRS treatment that predicts the bacteriological and clinical efficacy of antibacterials according to pathogen distribution, rates of spontaneous resolution without treatment, and in vitro microbiological activity at pharmacokinetic/pharmacodynamic break points [23]. According to this model, after the best data are used, antibacterials can be placed into the following relative rank order according to their predicted clinical efficacy in adults: 90%–92%, the respiratory fluoroquinolones (i.e., moxifloxacin, gatifloxacin, and levofloxacin), ceftriaxone, and high-dose amoxicillin-clavulanate (4 g of amoxicillin/day and 250 mg of clavulanate/day); 83%–88%, high-dose amoxicillin (4 g/day), amoxicillin (1.5 g/day), cefpodoxime proxetil, cefixime (on the basis of *H. influenzae* and *M. catarrhalis* coverage), cefuroxime axetil, cefdinir, and TMP-SMZ; 77%–81%, doxycycline, clindamycin (on the basis of gram-positive coverage only), azithromycin, clarithromycin and erythromycin, and telithromycin; and 65%–66%, cefaclor and loracarbef (figure 2). The predicted rate of spontaneous resolution among patients with a clinical diagnosis of ABRS is 62%.

The 2004 SAHP guidelines divide patients with ABRS into 2 general categories: (1) those with mild disease who have not received antibacterials within the past 4–6 weeks or (2) those

with mild disease who have received antibacterials within the past 4–6 weeks and those with moderate disease, regardless of recent antibiotic exposure [5]. The terms "mild" and "moderate" are not further defined, leaving the definition of severity up to the clinical judgment of the health-care provider. Patients who have received recent antibiotic therapy or those with moderate disease are more likely to be infected with a resistant organism; for these patients, there is also more concern about the long-term consequences if treatment fails.

Current SAHP recommendations for initial therapy for adult patients with mild disease who have not received antibacterials in the previous 4–6 weeks include the following options: amoxicillin-clavulanate (1.75–4 g of amoxicillin/day and 250 mg of clavulanate/day), amoxicillin (1.5–4 g/day), cefpodoxime proxetil, cefuroxime axetil, or cefdinir [5]. TMP-SMZ, doxycycline, or macrolides-azalides-ketolides (i.e., azithromycin, clarithromycin, erythromycin, or telithromycin) may be considered for patients with allergies to β-lactams (table 1). If there is no improvement after 72 h, patients should have treatment switched to a respiratory fluoroquinolone, high-dose amoxicillin-clavulanate, ceftriaxone (1–2 g/day for 5 days), or combination therapy (e.g., high-dose amoxicillin or clindamycin plus cefixime or rifampin).

Adults with mild disease who have received antibacterials during the previous 4–6 weeks or adults with moderate disease may be treated with respiratory fluoroquinolones or high-dose amoxicillin-clavulanate. However, the SAHP warns that the widespread use of respiratory fluoroquinolones for patients with milder disease may promote resistance of a wide spectrum of organisms to this class of agents. Ceftriaxone or combination therapy with adequate coverage for gram-positive and -negative bacteria may also be considered (i.e., high-dose amoxicillin or clindamycin plus cefixime or rifampin).
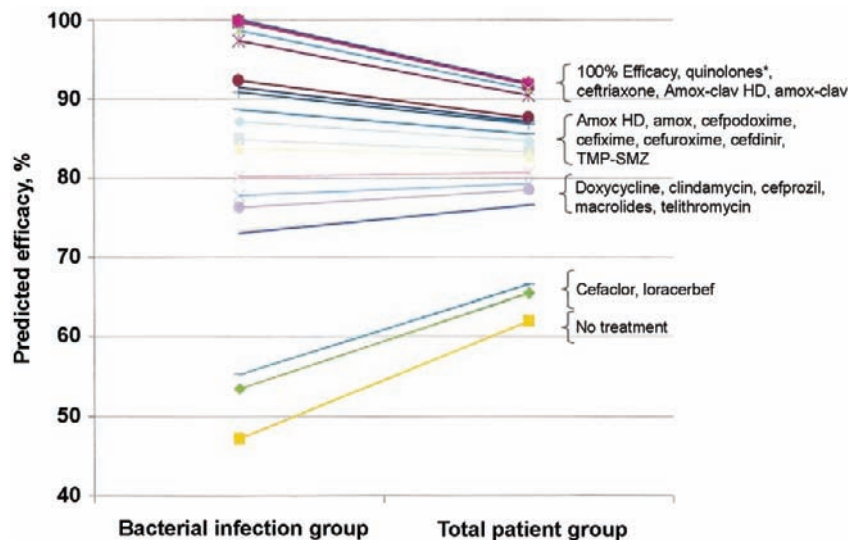
Figure 2. "Marchant" plot for antibacterials used to treat acute bacterial rhinosinusitis in adults. *Respiratory quinolone (i.e., gatifloxacin, levofloxacin, or moxifloxacin). Amox, amoxicillin; clav, clavulanate; HD, high dose; TMP-SMZ, trimethoprim-sulfamethoxazole. Reprinted with permission from the American Academy of Otolaryngology–Head and Neck Surgery Foundation [5].

French guidelines. French treatment guidelines recommend the following first-line agents for the treatment of adult patients with ABRS: amoxicillin-clavulanate, second-generation oral cephalosporins (cefuroxime axetil), some third-generation oral cephalosporins (cefpodoxime proxetil), and pristinamycin (a naturally occurring streptogramin not available in the United States) [20]. They also recommend that fluoroquinolones active against *S. pneumoniae* should be reserved for patients for whom first-line treatment fails. The French Agency for Sanitary Safety of Health Products also states that amoxicillin and macrolides are no longer recommended first-line treatments for ABRS. Per these guidelines, a 7–10-day antimicrobial treatment course is advised. These guidelines also suggest that short-course adjunctive corticosteroid therapy may be beneficial for some patients.

German guidelines. The German sinus treatment guidelines recommend amoxicillin as empirical first-line therapy [24]. Many alternatives are listed in those guidelines, including β-lactam/β-lactamase inhibitor combinations, second-generation oral cephalosporins, macrolides, ketolides, TMP-SMZ, doxycycline, and clindamycin. For patients with more-severe disease (risk factors) or for whom first-line therapy failed, amoxicillin-clavulanate, second-generation cephalosporins, or, alternatively, respiratory fluoroquinolones or third-generation cephalosporins are the recommended therapies.

Spanish guidelines. Treatment guidelines for ABRS have also been published by the Spanish Society of Chemotherapy and the Spanish Society of Otorhinolaryngology and Cervico-Facial Pathology [25]. These recommendations were based on the following susceptibility data for the geographic region: *S. pneumoniae* was highly susceptible to moxifloxacin (99.6%), levofloxacin (99.6%), telithromycin (98.92%), and high-dose amoxicillin

(94.9%). However, high resistance rates for cefaclor (41.6%), cefuroxime and cefpodoxime (each 31.4%), and the macrolides (35%) were observed. In Spain, *H. influenzae* was usually susceptible to moxifloxacin (100%), levofloxacin (100%), amoxicillin-clavulanate (99.5%), cefuroxime (99.3%), and cefixime (99.8%). Approximately 25% of *H. influenzae* strains were β-lactamase positive. For immunocompetent patients with mild maxillary disease and no comorbidity, either no treatment or amoxicillin is recommended. For patients with moderate infection, including patients who have underlying immunosuppression, comorbidities, or frontal/sphenoid disease, a respiratory fluoroquinolone is the first-line choice. Third-generation cephalosporins are advised for patients with severe complicated episodes.

FLUOROQUINOLONES IN ABRS

The respiratory fluoroquinolones have excellent activity against *H. influenzae* and *M. catarrhalis,* as well as potency against *S. pneumoniae*. Although there remain some questions about the proper role of fluoroquinolones in the treatment of ABRS, fluoroquinolones appear to be highly effective as second-line therapy or as first-line therapy for certain "sicker" patients. The SAHP's 2004 recommendations on fluoroquinolone use state that "fluoroquinolones should not be used indiscriminately, and the most pharmacodynamically potent fluoroquinolones should be used to treat the suspected pathogen. When the decision is made to use a fluoroquinolone, preference should be given to agents that are most likely to achieve optimal pharmacokinetic/pharmacodynamic parameters" [5, page 29].

S. pneumoniae *pharmacodynamics.* Because of increasing

Table 1. Treatment guidelines for adults with acute bacterial rhinosinusitis.

Patient's status, recommended treatment

Mild disease[a]
  No recent antimicrobial use (past 4–6 weeks)[b]
    Amoxicillin-clavulanate (1.75–4 g/250 mg/day)[c]
    Amoxicillin (1.5–4 g/day)
    Cefpodoxime proxetil
    Cefuroxime axetil
    Cefdinir
    Respiratory fluoroquinolone[d]
    Amoxicillin-clavulanate (4 g/250 mg)[c]
    Ceftriaxone
    Combination therapy[e]
  History of β-lactam hypersensitivity
    TMP-SMZ
    Doxycycline
    Macrolide (i.e., azithromycin, clarithromycin, erythromycin)
    Respiratory fluoroquinolone[d]
    Rifampin plus clindamycin
Mild or moderate disease[a]
  With recent antimicrobial use (past 4–6 weeks)[b]
    Respiratory fluoroquinolone[d]
    Amoxicillin-clavulanate (4 g/250 mg)[c]
    Ceftriaxone
    Combination therapy[e]
    Reevaluate patient[f]
  History of β-lactam hypersensitivity
    Respiratory fluoroquinolone[d]
    Rifampin plus clindamycin
    Reevaluate patient[f]

NOTE. Adapted with permission from the American Academy of Otolaryngology–Head and Neck Surgery Foundation [5]. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] The difference in severity of disease does not imply the presence or absence of antimicrobial resistance but indicates the relative degree of acceptance of possible therapeutic failure and the likelihood of achieving spontaneous resolution of symptoms.

[b] Prior antibiotic therapy within 4–6 weeks is a risk factor for infection with resistant organisms.

[c] The total daily dose of amoxicillin and the amoxicillin component of amoxicillin-clavulanate can vary from 1.5 to 4 g/day. Lower daily doses (1.5 g/day) are more appropriate in patients with mild disease who have no risk factors for infection with a resistant pathogen (including recent antibiotic use). Higher daily doses (4 g/day) may be advantageous in areas with a high prevalence of penicillin-resistant *Streptococcus pneumoniae* or drug-resistant *S. pneumoniae,* for patients with moderate disease, for patients who may need better coverage for *Haemophilus influenzae,* or for patients with risk factors for infection with a resistant pathogen. There is a greater potential for treatment failure or resistant pathogens in these groups of patients.

[d] Respiratory fluoroquinolones include gatifloxacin, levofloxacin, and moxifloxacin.

[e] On the basis of the in vitro spectrum of activity; combination therapy using appropriate gram-positive and -negative coverage may be appropriate. Combination therapy regimens may include high-dose amoxicillin (4 g/day), clindamycin plus cefixime (which is not currently available in the United States), high-dose amoxicillin (4 g/day), or clindamycin plus rifampin.

[f] Reevaluation is necessary because the antibacterials recommended for initial therapy provide excellent activity against the predominant acute bacterial rhinosinusitis pathogens, including *S. pneumoniae* and *H. influenzae.* Additional history, physical examination, cultures, and/or CT scan may be indicated, and the possibility of other less common pathogens considered.

demands to promote more-sensible antimicrobial use, the most potent antimicrobial therapy must be carefully selected to target the suspected pathogens and to minimize the emergence of resistant mutants. Among the pathogens most commonly associated with ABRS, *S. pneumoniae* is the key pathogen against which the respiratory fluoroquinolones have varying potency and pharmacodynamic properties. To optimize both clinical and bacteriological success in patients with pneumococcal sinusitis episodes and to prevent the selection of resistant mutants, examination of key pharmacodynamic measures (C_{max}: MIC or area under the plasma concentration time–curve [AUC]:MIC values), including concentrations to prevent the selection of resistant mutants, needs to be considered.

When commonly reported MIC_{90} values against *S. pneumoniae* and steady-state AUC values corrected for protein binding are used, the AUC:MIC values for the 3 respiratory fluoroquinolones are as follows: 200 for moxifloxacin (400 mg/day), 166 for gatifloxacin (400 mg/day), 71 for levofloxacin (750 mg/day), and 34 for levofloxacin (500 mg/day) [26–29]. On the basis of the premise that the AUC:MIC must exceed 30–40 for *S. pneumoniae* to achieve desired patient success, only moxifloxacin, gatifloxacin, and high-dose levofloxacin consistently exceed the suggested minimum ratio.

The importance of pharmacodynamics is not limited to serum concentrations but should be evaluated for targeted tissue sites. Two studies have shown that moxifloxacin achieves high concentrations in sinus tissues [30]. Following the administration of single oral doses (400 mg) to 20 patients, Dinis et al. [30] found that moxifloxacin was distributed extensively throughout both inflamed and noninflamed sinus mucsoa, although concentrations were highest in the maxillary sinus. The tissue-to-blood ratios were >4:1 at most sites. In a second study, Gehanno et al. [31] measured moxifloxacin concentrations in sinus tissue after steady-state conditions (i.e., 400 mg/day for 5 days) had been reached in patients with chronic sinusitis. Concentrations of moxifloxacin in sinus mucosa were consistently higher than those in plasma: 4.56–5.73 mg/kg at 2–6 h after administration of a dose versus 1.25–2.81 mg/kg at 12–36 h after administration of a dose. The tissue:plasma ratio was 200%–328.9% (2–36 h after administration of a dose). Similar findings were found in other types of sinus tissue (e.g., maxillary sinus and anterior ethmoid sinus or nasal polyps). In both studies, sinus mucosal concentrations were well above MIC_{90} values of moxifloxacin against a wide range of bacteria. In a study that used pharmacodynamic end points to evaluate gatifloxacin for the treatment of acute maxillary sinusitis, the median 24-h AUC for sinus aspirates and plasma samples was 1.51 (range, 0.88–2.23) [32].

The emergence of resistance to fluoroquinolones in *S. pneumoniae* occurs after mutations in the genes encoding the target topoisomerase enzymes (i.e., *parC,* which encodes the A sub-

unit of DNA topoisomerase IV, and *gyrA,* which encodes the A subunit of DNA gyrase) [33]. Resistance to this pathogen occurs in 2 discrete steps, with spontaneous mutations occurring initially in *parC* and secondarily in *gyrA* [34–36]. Because there is increasing evidence that selection of resistant pneumococcal strains may vary among the respiratory fluoroquinolones, a new pharmacodynamic tool—the mutant prevention concentration (MPC) theory—has been developed. In brief, the MPC is the concentration required to inhibit the growth of the least susceptible wild-type mutants (i.e., single-step mutants), whereas the MIC is the lowest concentration needed to stop growth of wild-type bacteria [37]. Among a large number of clinical isolates of fluoroquinolone-susceptible *S. pneumoniae* ($n = 146$), moxifloxacin was found to be the fluoroquinolone least likely to select for resistant mutants, followed by gatifloxacin and levofloxacin [38, 39]. Additional preliminary in vitro data suggest that AUC:MICs >100 may protect against the selection of resistant *S. pneumoniae* mutants [40].

Moxifloxacin clinical trials. Burke et al. [41] reported the first findings of the efficacy of moxifloxacin for the treatment of 542 adult patients with community-acquired ABRS (i.e., radiographic evidence plus baseline signs and symptoms present for >7 days but <4 weeks). After a 10-day oral regimen of either moxifloxacin (400 mg/day) or cefuroxime axetil (250 mg b.i.d.), the percentage of patients with a clinical response at the end of therapy (7–14 days after therapy) was 90% and 89%, respectively. Clinical relapse rates were low for both treatment groups (3 patients receiving moxifloxacin and 5 patients receiving cefuroxime axetil).

Siegert et al. [42] conducted a multicenter trial in which 242 patients were randomized to receive 400 mg of moxifloxacin once daily for 7 days and were compared with 251 patients who received 250 mg of cefuroxime axetil twice daily for 10 days. The clinical success rate at the end of treatment was significantly higher in moxifloxacin-treated patients (96.7% [204/211]) than in the cefuroxime axetil–treated patients (90.7% [204/225]; 95% CI, 1.5%–10.6%). At baseline, a total of 224 isolates (45%; 109 from moxifloxacin-treated patients and 115 from cefuroxime axetil–treated patients) were obtained by use of middle meatal swabs or cannula and were evaluated for efficacy. The response rates of the major respiratory pathogens to treatment with moxifloxacin or cefuroxime axetil were as follows: for *S. pneumoniae,* 97.4% for moxifloxacin and 93.8% for cefuroxime axetil; for *H. influenzae,* 96.6% for moxifloxacin and 85.7% for cefuroxime axetil; and for *M. catarrhalis,* 100% for moxifloxacin and 88.9% for cefuroxime axetil.

Rakkar et al. [43] also established that moxifloxacin (400 mg/day) was at least as effective as amoxicillin-clavulanate (875 mg b.i.d.); clinical resolution at the test-of-cure visit (i.e., 14–21 days after therapy) was reported for 85% versus 82% of patients whose results could be evaluated for efficacy, respec-

tively. Gehanno et al. [44] enrolled 258 patients in a prospective study to evaluate the use of oral moxifloxacin (400 mg/day for 7 days) for treatment of acute maxillary sinusitis after first-line treatment failure, as well as in patients with a high risk of complications. Positive plain-film radiographs were used as part of the enrollment criteria. Ninety-two patients had 102 bacterial isolates identified via middle meatus cultures, of which 29% were *S. pneumoniae* and 27% were *H. influenzae.* The rate of resistance to penicillin for *S. pneumoniae* in this series was 65%, and 58% of *H. influenzae* isolates were β-lactamase positive. Of 216 efficacy-valid patients, the clinical and bacteriological success rates 7–10 days after treatment were 92.6% and 96%, respectively.

Klossek et al. [45] compared the efficacy of oral moxifloxacin (400 mg/day for 7 days) with that of oral trovafloxacin (200 mg/day for 10 days) in 452 patients with radiologically proven ABRS. At the evaluation performed 7–10 days after therapy, moxifloxacin was found to be statistically equivalent to trovafloxacin (clinical success rates, 96.9% vs. 92.1%, respectively). Corresponding clinical success rates at the late follow-up visit were 94.9% and 97.6%, respectively. The most common causes of sinusitis were *S. pneumoniae, H. influenzae,* and *Staphylococcus aureus.* Bacteriological success rates at the posttherapy evaluation were similar for both treatment groups: 94.4% for patients given moxifloxacin and 90.1% for patients given trovafloxacin.

In a pooled analysis of 2 clinical open-label sinusitis trials, the efficacy of moxifloxacin against penicillin-susceptible and penicillin-resistant *S. pneumoniae* (PRSP) was examined [46]. All patients received oral moxifloxacin (400 mg/day) for 7–10 days. Of 806 patients enrolled in the 2 studies, 69 patients had ABRS caused by *S. pneumoniae,* including 15 confirmed cases of PRSP infection. Approximately one-third of episodes (26 [37.7%]) were considered to be severe, according to the investigator's evaluation. Clinical and bacteriological success at the test-of-cure visit (21–37 days after completion of therapy) occurred in 93.3% (14/15) of patients with PRSP infection, compared with 88.4% (61/69) of all patients infected with *S. pneumoniae,* regardless of penicillin susceptibility. Moxifloxacin had low MIC values (0.06–0.25 mg/L) against all 15 PRSP strains. The results for this small cohort of patients with ABRS caused by PRSP demonstrate the effectiveness of moxifloxacin.

Gatifloxacin clinical trials. In a large noncomparative study, the efficacy of gatifloxacin (400 mg/day for 10 days) was evaluated in >11,000 adult patients with ABRS [47]. The primary pretherapy pathogens isolated were *M. catarrhalis* (91% of which were β-lactamase producers), *H. influenzae* (28% of which were β-lactamase producers), *S. pneumoniae* (32% of which were penicillin resistant), and *S. aureus.* Among 10,353 patients who could be clinically evaluated, 91.6% experienced a cure, and >90% of major pathogens were eradicated.

A second study by Sher et al. [48] evaluated the efficacy of

a short-course, 5-day gatifloxacin regimen (400 mg/day), compared with standard 10-day regimens with either amoxicillin-clavulanate (875 mg b.i.d.) or gatifloxacin (400 mg/day) in 445 patients with acute, uncomplicated maxillary sinusitis. At the test-of-cure visit (7–14 days after therapy), clinical cure rates for patients who could be clinically evaluated were 74% for those given gatifloxacin for 5 days, 80% for those given gatifloxacin for 10 days, and 72% for those given amoxicillin-clavulanate for 10 days. This study suggests that, for select patients with maxillary sinusitis, short-course gatifloxacin therapy is effective.

Levofloxacin clinical trials. At least 2 comparative trials have established the effectiveness of levofloxacin for the treatment of adults with ABRS [49, 50]. In one trial, a total of 535 patients who could be clinically evaluated randomly received levofloxacin (500 mg/day) or amoxicillin-clavulanate (500 mg of amoxicillin t.i.d. and 125 mg of clavulanate t.i.d.) for 10–14 days [49]. Clinical cure/improvement rates, 2–5 days after therapy, were 88.4% for levofloxacin-treated patients, compared with 87.3% for amoxicillin-clavulanate–treated patients. In a second trial, 216 patients were randomized in double-blind fashion to receive therapy with either levofloxacin (500 mg/day) or clarithromycin (500 mg b.i.d.) for 2 weeks [50]. Among 190 patients who could be evaluated, clinical cure/improvement rates were 96.0% for levofloxacin, compared with 93.3% for clarithromycin. At the follow-up evaluation 1 month after therapy, 4.1% of patients receiving levofloxacin and 7.2% receiving clarithromycin experienced a relapse of symptoms. Although these studies demonstrate the effectiveness of levofloxacin for ABRS, both of these studies were conducted almost 10 years ago, prior to the emergence of multidrug resistance in *S. pneumoniae*. At the time of the writing of this article, there were no published studies evaluating the efficacy of high-dose levofloxacin for the treatment of ABRS.

DISCUSSION

The goal of antibiotic therapy is to eradicate bacterial pathogens at the site of infection. It has been touted that the failure of an antibiotic to achieve this goal increases the potential for clinical failure, incurs further costs, and may also select bacteria that are resistant [51].

Failures are often due to infection with resistant pathogens or suboptimal pharmacokinetics/pharmacodynamics of the antimicrobial agent. Gwaltney et al. [52] recently examined a number of studies of ABRS and made the following recommendations: (1) for patients with a community-acquired bacterial sinusitis episode, antimicrobial treatment should be administered for 7–10 days, and (2) selected empirical agents should be effective against the most common antimicrobial-resistant pathogens, including *S. pneumoniae, H. influenzae,* and *M. catarrhalis.*

Numerous treatment guidelines have been crafted worldwide to assist practitioners in treating patients with ABRS. Collectively, treatment guidelines from North America and some countries in Europe reveal that amoxicillin and amoxicillin-clavulanate are the most commonly recommended agents for the treatment of ABRS [5, 20]. Macrolides are the second most commonly used class globally, but national guidelines from the United States, France, and Spain recommend either no role or a limited role for macrolides, because of concerns about resistance in *S. pneumoniae* and because of their intrinsically poor activity against *H. influenzae* [5, 20]. The respiratory fluoroquinolones are positioned for use in patients with moderate or severe disease and those who have a history of recent antimicrobial use, when there is a failure to improve on the results of initial therapy after 72 h, and if there is an environment of antimicrobial resistance [5].

The increase in rates of antimicrobial resistance in *S. pneumoniae* and *H. influenzae* during the past decade has made the selection of empirical antimicrobial therapy for many respiratory tract infections, including ABRS, very challenging [53]. The role of many available oral β-lactams and macrolides in the treatment of respiratory tract pathogens is at a critical juncntion and requires close susceptibility monitoring, because failure rates often are as high as 25% [23]. Accordingly, the search for new agents to fill the gap continues.

When the best data currently available are used, the Poole therapeutic outcomes model predicts that only the respiratory fluoroquinolone or high-dose amoxicillin-clavulanate has the optimal intrinsic properties to lead to clinical success [23]. Because high-dose amoxicillin-clavulanate continues to provide high success rates (>90%) for many mild episodes of ABRS, it is recommended most often as first-line therapy in many treatment guidelines, including those from the United States [5]. Fluoroquinolones are only recommended as first-line therapy for patients who have a recent history of failure associated with another antimicrobial, in the presence of moderate/severe disease, or if patients have received recent nonquinolone antimicrobial therapy in the prior 4–6 weeks [5].

The respiratory fluoroquinolones have enhanced activity against penicillin-susceptible and -resistant strains of *S. pneumoniae* and are highly active against most strains of *H. influenzae* and *M. catarrhalis,* including those that produce β-lactamase. Gatifloxacin is twice as active against *S. pneumoniae* as is levofloxacin, but moxifloxacin is even more potent, with 8 times more activity than levofloxacin [54]. Moxifloxacin specifically has been shown to be effective for the treatment of ABRS due to PRSP strains [46]. All 3 respiratory fluoroquinolones have been shown to be effective for the treatment of patients with ABRS, in clinical trials conducted during the past decade. Although fluoroquinolones are gaining a larger role in the treatment of ABRS, clinicians must use fluoroquinolones

judiciously and appropriately to maintain the activity of the class [55].

Although it is not evident from the outcomes of clinical trials, there are some subtle and important pharmacodynamic differences among the 3 widely used respiratory fluoroquinolones. The most evident difference is the pharmacodynamic activity in *S. pneumoniae,* wherein gatifloxacin and moxifloxacin have a predictably higher serum AUC:MIC (>135) than does levofloxacin, which may discourage the selection of resistant mutants [40]. In addition to having 24-h free drug AUC:MIC values, it appears that, if concentrations in sinus tissues exceed the MPC, selection of resistance strains should be minimal [35, 36, 38, 39, 55].

At present, respiratory fluoroquinolones are recommended as second-line therapy for the management of mild episodes of ABRS in patients who have no history of recent antimicrobial use and as first-line therapy for patients who recently have received antibiotics or who have moderate disease and are allergic to β-lactams [5]. Efforts to minimize inappropriate prescribing of fluoroquinolone therapy for ABRS are important to maintain the integrity of t his class of compounds. Selection of the most potent fluoroquinolone (i.e., one that demonstrates optimal microbiological and pharmacodynamic properties) is of utmost importance to increase the likelihood of clinical success while discouraging the emergence of resistance.

Acknowledgments

References

1. Gwaltney JM Jr. Acute community-acquired sinusitis. Clin Infect Dis **1996**; 23:1209–23.
2. Report of the Rhinosinusitis Task Force Committee Meeting. Alexandria, Virginia, August 17, 1996. Otolaryngol Head Neck Surg **1997**; 117(3 Pt. 2):S1–68.
3. Flynn R. Common cold and the flu: antibiotics are no quick fix. Washington, DC: National Research Center for Women and Families. Available at: http://www.center4policy.org/womenhlth9.html. Accessed 28 June 2004.
4. Ray NF, Baraniuk JN, Thamer M, et al. Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol **1999**; 103:408–14.
5. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg **2004**; 130:1–45.
6. Blair C, Nelson M, Thompson K, et al. Allergic inflammation enhances bacterial sinusitis in mice. J Allergy Clin Immunol **2001**; 108:424–9.
7. Lacroix JS, Ricchetti A, Lew D, et al. Symptoms and clinical and radiological signs predicting the presence of pathogenic bacteria in acute rhinosinusitis. Acta Otolaryngol **2002**; 122:192–6.
8. Lau J, Zucker D, Engels EA, et al. Diagnosis and treatment of acute bacterial rhinosinusitis. Evidence report/technology assessment no. 9 (contract 290–97–0019 to the New England Medical Center). Rockville, MD: Agency for Health Care Policy and Research, **1999**. Available at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.13219. Accessed 24 June 2004.
9. Anon J, Fergurson B. Pharmacokinetically enhanced amoxicillin/clavulanate 2000/125 mg twice daily in the treatment of acute bacterial sinusitis (ABS) in adults [abstract 300]. In: Program and abstracts of the 41st annual meeting of the Infectious Diseases Society of America (San Diego). Alexandria, VA: Infectious Diseases Society of America, **2003**.
10. Kaiser L, Lew D, Hirschel B, et al. Effects of antibiotic treatment in the subset of common-cold patients who have bacteria in nasopharyngeal secretions. Lancet **1996**; 347:1507–10.
11. Talbot GH, Kennedy DW, Scheld WM, Granito K. Rigid nasal endoscopy versus sinus puncture and aspiration for microbiologic documentation of acute bacterial maxillary sinusitis. Clin Infect Dis **2001**; 33: 1668–75.
12. Jacobs MR, Felmingham D, Appelbaum PC, Gruneberg RN. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J Antimicrob Chemother **2003**; 52:229–46.
13. Sahm DF, Weaver MK, Flamm RK, Jones ME, Evangelista AT, Thornsberry C. Antimicrobial susceptibility in *Streptococcus pneumoniae* recovered from sinus specimens: results from 2000–2003 TRUST Surveillance Studies [abstract C2-924]. In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: American Society for Microbiology, **2003**.
14. Axelsson A, Chidekel N, Grebelius N, Jensen C. Treatment of acute maxillary sinusitis: a comparison of four different methods. Acta Otolaryngol **1970**; 70:71–6.
15. Gananca M, Trabulsi LR. The therapeutic effects of cyclacillin in acute sinusitis: in vitro and in vivo correlations in a placebo-controlled study. Curr Med Res Opin **1973**; 1:362–8.
16. Wald ER, Chiponis D, Ledesma-Medina J. Comparative effectiveness of amoxicillin and amoxicillin-clavulanate potassium in acute paranasal sinus infections in children: a double-blind, placebo-controlled trial. Pediatrics **1986**; 77:795–800.
17. Lindbaek M, Hjortdahl P, Johnsen UL. Randomised, double blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults. BMJ **1996**; 313:325–9.
18. van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, Peeters MF. Primary-care-based randomized placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet **1997**; 349:683–7.
19. Stalman W, van Essen GA, van der Graaf Y, de Melker RA. The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? A placebo-controlled, double-blind doxycycline trial. Br J Gen Pract **1997**; 47:794–9.
20. French Agency for Sanitary Safety of Health Products. General antibiotherapy in current practice: acute sinusitis of the adult. Paris: French Agency for Sanitary Safety of Health Products, **2001**. Available at http://agmed.sante.gouv.fr. Accessed 10 July 2004.
21. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Sinus and Allergy Health Partnership. Otolaryngol Head Neck Surg **2000**; 123(1 Pt. 2):5–31.
22. Dowell SF, Butler JC, Giebink GS, et al. Acute otitis media: management and surveillance in an era of pneumococcal resistance—a report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Pediatr Infect Dis J **1999**; 18:1–9.
23. Poole MD. A mathematical therapeutic outcomes model for sinusitis. Otolaryngol Head Neck Surg **2004**; 130:46–50.
24. Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie. Leitlinie Antibiotikatherapie der Infektionen an Kopf und Hals. AWMF online Nr. 017/066. Düsseldorf, Germany: Association of the Scientific Medical Societies in Germany. Available at: http://www.uni-duesseldorf.de/WWW/AWMF/. Accessed January 2003.

25. Diagnosis and antimicrobial treatment of sinusitis [in Spanish]. Rev Esp Quimioter **2003**; 16:239–51.

26. Doern GV. Antimicrobial use and the emergence of antimicrobial resistance with *Streptococcus pneumoniae* in the United States. Clin Infect Dis **2001**; 33(Suppl 3):S187–92.

27. Tequin (Gatifloxacin) tablets. Tequin (Gatifloxacin) injection [package insert]. Princeton, NJ: Bristol-Myers Squibb, **2002**.

28. Levaquin tablets/injection (levofloxacin tablets/injection) [package insert]. Raritan, NJ: Ortho-McNeil, **2001**.

29. Avelox PO/IV (moxifloxacin HCL) [package insert]. West Haven, CT: Bayer Pharmaceuticals, **2002**.

30. Dinis PB, Monteiro MC, Martins ML, Silva N, Morais JG. Sinus tissue concentration of moxifloxacin after a single oral dose. Ann Otol Rhinol Laryngol **2004**; 113:142–6.

31. Gehanno P, Darantiere S, Dubreuil C, et al. A prospective, multicentre study of moxifloxacin concentrations in the sinus mucosa tissue of patients undergoing elective surgery of the sinus. J Antimicrob Chemother **2002**; 49:821–6.

32. Ambrose PG, Anon JB, Owen JS, et al. Use of pharmacodynamic end points in the evaluation of gatifloxacin for the treatment of acute maxillary sinusitis. Clin Infect Dis **2004**; 38:1513–20.

33. Pan XS, Ambler J, Mehtar S, Fisher LM. Involvement of topoisomerase IV and DNA gyrase as ciprofloxacin targets in *Streptococcus pneumoniae*. Antimicrob Agents Chemother **1996**; 40:2321–6.

34. Pestova E, Millichap JJ, Noskin GA, Peterson LR. Intracellular targets of moxifloxacin: a comparison with other fluoroquinolones. J Antimicrob Chemother **2000**; 45:583–90.

35. Boswell FJ, Andrews JM, Jevons G, Wise R. Comparison of the in vitro activities of several new fluoroquinolones against respiratory pathogens and their abilities to select fluoroquinolone resistance. J Antimicrob Chemother **2002**; 50:495–502.

36. Li X, Zhao X, Drlica K. Selection of *Streptococcus pneumoniae* mutants having reduced susceptibility to moxifloxacin and levofloxacin. Antimicrob Agents Chemother **2002**; 46:522–4.

37. Drlica K. The mutant selection window and antimicrobial resistance. J Antimicrob Chemother **2003**; 52:11–7.

38. Blondeau JM, Zhao X, Hansen G, Drlica K. Mutant prevention concentrations of fluoroquinolones for clinical isolates of *Streptococcus pneumoniae*. Antimicrob Agents Chemother **2001**; 45:433–8.

39. Hansen GT, Metzler K, Drlica K, Blondeau JM. Mutant prevention concentration of gemifloxacin for clinical isolates of *Streptococcus pneumoniae*. Antimicrob Agents Chemother **2003**; 47:440–1.

40. Zinner SH, Lubenko IY, Gilbert D, et al. Emergence of resistant *Streptococcus pneumoniae* in an in vitro dynamic model that simulates moxifloxacin concentrations inside and outside the mutant selection window: related changes in susceptibility, resistance frequency and bacterial killing. J Antimicrob Chemother **2003**; 52:616–22.

41. Burke T, Villanueva C, Mariano H Jr, et al. Comparison of moxifloxacin and cefuroxime axetil in the treatment of acute maxillary sinusitis. Sinusitis Infection Study Group. Clin Ther **1999**; 21:1664–77.

42. Siegert R, Gehanno P, Nikolaidis P, et al. A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults. The Sinusitis Study Group. Respir Med **2000**; 94:337–44.

43. Rakkar S, Roberts K, Towe BF, Flores SM, Heyd A, Warner J. Moxifloxacin versus amoxicillin clavulanate in the treatment of acute maxillary sinusitis: a primary care experience. Int J Clin Pract **2001**; 55:309–15.

44. Gehanno P, Berche P, Perrin A. Moxifloxacin in the treatment of acute maxillary sinusitis after first-line treatment failure and acute sinusitis with high risk of complications. J Int Med Res **2003**; 31:434–47.

45. Klossek JM, Siegert R, Nikolaidis P, Arvis P, Leberre MA. Comparison of the efficacy and safety of moxifloxacin and trovafloxacin for the treatment of acute, bacterial maxillary sinusitis in adults. J Laryngol Otol **2003**; 117:43–51.

46. Johnson P, Cihon C, Herrington J, Choudhri S. Efficacy and tolerability of moxifloxacin in the treatment of acute bacterial sinusitis caused by penicillin-resistant *Streptococcus pneumoniae:* a pooled analysis. Clin Ther **2004**; 26:224–31.

47. Sher LD, Poole MD, Von Seggern K, Wikler MA, Nicholson SC, Pankey GA. Community-based treatment of acute uncomplicated bacterial rhinosinusitis with gatifloxacin. Otolaryngol Head Neck Surg **2002**; 127:182–9.

48. Sher LD, McAdoo MA, Bettis RB, Turner MA, Li NF, Pierce PF. A multicenter, randomized, investigator-blinded study of 5- and 10-day gatifloxacin versus 10-day amoxicillin/clavulanate in patients with acute bacterial sinusitis. Clin Ther **2002**; 24:269–81.

49. Lasko B, Lau CY, Saint-Pierre C, Reddington JL, Martel A, Anstey RJ. Efficacy and safety of oral levofloxacin compared with clarithromycin in the treatment of acute sinusitis in adults: a multicentre, double-blind, randomized study. The Canadian Sinusitis Study Group. J Int Med Res **1998**; 26:281–91.

50. Adelglass J, DeAbate CA, McElvaine P, Fowler CL, LoCocco J, Campbell T. Comparison of the effectiveness of levofloxacin and amoxicillin-clavulanate for the treatment of acute sinusitis in adults. Otolaryngol Head Neck Surg **1999**; 120:320–7.

51. Garau J. Why do we need to eradicate pathogens in respiratory tract infections? Int J Infect Dis **2003**; 7(Suppl 1):S5–12.

52. Gwaltney JM Jr, Wiesinger BA, Patrie JT. Acute community-acquired bacterial sinusitis: the value of antimicrobial treatment and the natural history. Clin Infect Dis **2004**; 38:227–33.

53. Jones ME, Karlowsky JA, Blosser-Middleton R, et al. Longitudinal assessment of antipneumococcal susceptibility in the United States. Antimicrob Agents Chemother **2002**; 46:2651–5.

54. Saravolatz LD, Leggett J. Gatifloxacin, gemifloxacin, and moxifloxacin: the role of 3 newer fluoroquinolones. Clin Infect Dis **2003**; 37:1210–5.

55. Scheld WM. Maintaining fluoroquinolone class efficacy: review of influencing factors. Emerg Infect Dis **2003**; 9:1–9.