

# IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

Anthony W. Chow,<sup>1</sup> Michael S. Benninger,<sup>2</sup> Itzhak Brook,<sup>3</sup> Jan L. Brozek,<sup>4,5</sup> Ellie J. C. Goldstein,<sup>6,7</sup> Lauri A. Hicks,<sup>8</sup> George A. Pankey,<sup>9</sup> Mitchel Seleznick,<sup>10</sup> Gregory Volturo,<sup>11</sup> Ellen R. Wald,<sup>12</sup> and Thomas M. File Jr<sup>13,14</sup>

<sup>1</sup>Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, Canada; <sup>2</sup>Otolaryngology, The Head and Neck Institute, Cleveland Clinic, Ohio; <sup>3</sup>Department of Pediatrics, Georgetown University School of Medicine, Washington, D.C.; <sup>4</sup>Department of Clinical Epidemiology and Biostatistics and <sup>5</sup>Department of Medicine, McMaster University, Hamilton, Ontario, Canada; <sup>6</sup>Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, CA; <sup>7</sup>R. M. Alden Research Laboratory, Santa Monica, California; <sup>8</sup>National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; <sup>9</sup>Department of Infectious Disease Research, Ochsner Clinic Foundation, New Orleans, Louisiana; <sup>10</sup>Division of General Internal Medicine, University of South Florida College of Medicine, Tampa; <sup>11</sup>Department of Emergency Medicine, University of Massachusetts, Worcester; <sup>12</sup>Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison; <sup>13</sup>Department of Infectious Diseases, Northeast Ohio Medical University, Rootstown; and <sup>14</sup>Summa Health System, Akron, Ohio

**Evidence-based guidelines for the diagnosis and initial management of suspected acute bacterial rhinosinusitis in adults and children were prepared by a multidisciplinary expert panel of the Infectious Diseases Society of America comprising clinicians and investigators representing internal medicine, pediatrics, emergency medicine, otolaryngology, public health, epidemiology, and adult and pediatric infectious disease specialties. Recommendations for diagnosis, laboratory investigation, and empiric antimicrobial and adjunctive therapy were developed.**

## EXECUTIVE SUMMARY

This guideline addresses several issues in the management of acute bacterial rhinosinusitis (ABRS), including (1) inability of existing clinical criteria to accurately differentiate bacterial from viral acute rhinosinusitis, leading to excessive and inappropriate antimicrobial therapy; (2) gaps in knowledge and quality evidence regarding empiric antimicrobial therapy for ABRS due to imprecise patient selection criteria; (3) changing prevalence and antimicrobial susceptibility profiles of bacterial isolates associated with ABRS; and (4) impact of the use of conjugated vaccines for *Streptococcus pneumoniae* on the emergence of nonvaccine serotypes associated with ABRS. An algorithm for subsequent

management based on risk assessment for antimicrobial resistance and evolution of clinical responses is offered (Figure 1). This guideline is intended for use by all primary care physicians involved in direct patient care, with particular applicability to patients managed in community or emergency department settings. Continued monitoring of the epidemiology and rigorous investigation of the efficacy and cost-benefit of empiric antimicrobial therapy for suspected ABRS are urgently needed in both children and adults.

Summarized below are the recommendations made in the new guideline for ABRS in children and adults. The panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines that includes a systematic weighting of the strength of recommendation (eg, “high, moderate, low, very low”) and quality of evidence (eg, “strong, weak”) using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [1–6] (Table 1). A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of this guideline.

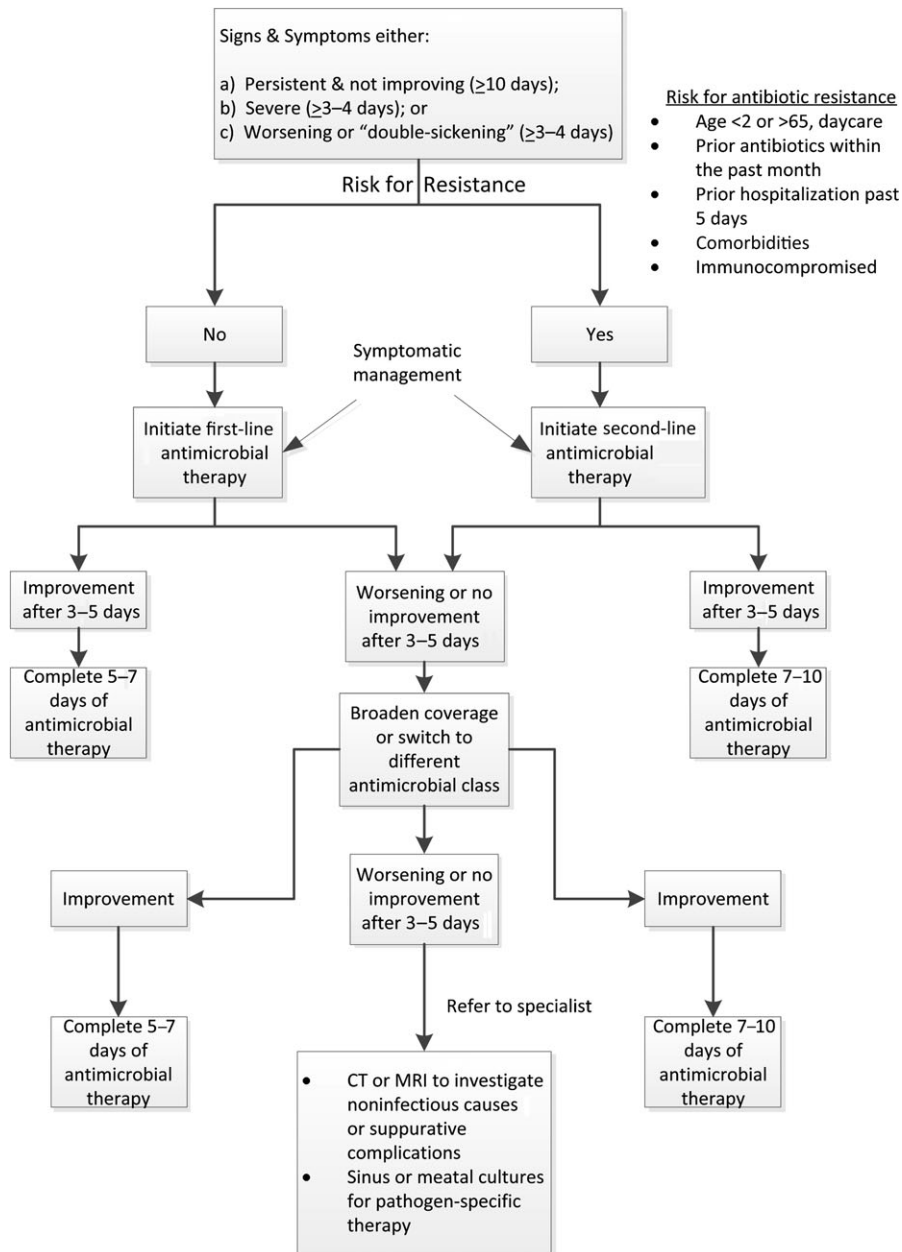
Received 15 December 2011; accepted 16 December 2011.

Correspondence: Anthony W. Chow, MD, Division of Infectious Diseases, Department of Medicine, University of British Columbia, 769 Burley Place, West Vancouver, BC V7T 2A2, Canada (tonychow@mail.ubc.ca).

### Clinical Infectious Diseases

© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cir1043



**Figure 1.** Algorithm for the management of acute bacterial rhinosinusitis. Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

## RECOMMENDATIONS

### INITIAL TREATMENT

#### *I. Which Clinical Presentations Best Identify Patients With Acute Bacterial Versus Viral Rhinosinusitis?*

**Recommendations.** 1. The following clinical presentations (any of 3) are recommended for identifying patients with acute bacterial vs viral rhinosinusitis:

i. Onset with *persistent* symptoms or signs compatible with acute rhinosinusitis, lasting for  $\geq 10$  days without

any evidence of clinical improvement (strong, low-moderate);

ii. Onset with *severe* symptoms or signs of high fever ( $\geq 39^{\circ}\text{C}$  [ $102^{\circ}\text{F}$ ]) and purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days at the beginning of illness (strong, low-moderate); or

iii. Onset with *worsening* symptoms or signs characterized by the new onset of fever, headache, or increase in nasal discharge following a typical viral upper respiratory infection (URI) that lasted 5–6 days and were initially improving (“double-sickening”) (strong, low-moderate).

## II. When Should Empiric Antimicrobial Therapy Be Initiated in Patients With Signs and Symptoms Suggestive of ABRS?

**Recommendation.** 2. It is recommended that empiric antimicrobial therapy be initiated as soon as the clinical diagnosis of ABRS is established as defined in recommendation 1 (strong, moderate).

## III. Should Amoxicillin Versus Amoxicillin-Clavulanate Be Used for Initial Empiric Antimicrobial Therapy of ABRS in Children?

**Recommendation.** 3. Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in children (strong, moderate).

## IV. Should Amoxicillin Versus Amoxicillin-Clavulanate Be Used for Initial Empiric Antimicrobial Therapy of ABRS in Adults?

**Recommendation.** 4. Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in adults (weak, low).

## V. When Is High-Dose Amoxicillin-Clavulanate Recommended During Initial Empiric Antimicrobial Therapy for ABRS in Children or Adults?

**Recommendation.** 5. “High-dose” (2 g orally twice daily or 90 mg/kg/day orally twice daily) amoxicillin-clavulanate is recommended for children and adults with ABRS from geographic regions with high endemic rates ( $\geq 10\%$ ) of invasive penicillin-nonsusceptible (PNS) *S. pneumoniae*, those with severe infection (eg, evidence of systemic toxicity with fever of 39°C [102°F] or higher, and threat of suppurative complications), attendance at daycare, age <2 or >65 years, recent hospitalization, antibiotic use within the past month, or who are immunocompromised (weak, moderate).

## VI. Should a Respiratory Fluoroquinolone Versus a $\beta$ -Lactam Agent Be Used as First-line Agents for the Initial Empiric Antimicrobial Therapy of ABRS?

**Recommendation.** 6. A  $\beta$ -lactam agent (amoxicillin-clavulanate) rather than a respiratory fluoroquinolone is recommended for initial empiric antimicrobial therapy of ABRS (weak, moderate).

## VII. Besides a Respiratory Fluoroquinolone, Should a Macrolide, Trimethoprim-Sulfamethoxazole, Doxycycline, or a Second- or Third-Generation Oral Cephalosporin Be Used as Second-line Therapy for ABRS in Children or Adults?

**Recommendations.** 7. Macrolides (clarithromycin and azithromycin) are not recommended for empiric therapy due to high rates of resistance among *S. pneumoniae* (~30%) (strong, moderate).

8. Trimethoprim-sulfamethoxazole (TMP/SMX) is not recommended for empiric therapy because of high rates of resistance among both *S. pneumoniae* and *Haemophilus influenzae* (~30%–40%) (strong, moderate).

9. Doxycycline may be used as an alternative regimen to amoxicillin-clavulanate for initial empiric antimicrobial therapy of ABRS in adults because it remains highly active against respiratory pathogens and has excellent pharmacokinetic/pharmacodynamic (PK/PD) properties (weak, low).

10. Second- and third-generation oral cephalosporins are no longer recommended for empiric monotherapy of ABRS due to variable rates of resistance among *S. pneumoniae*. Combination therapy with a third-generation oral cephalosporin (cefixime or cefpodoxime) plus clindamycin may be used as second-line therapy for children with non-type I penicillin allergy or from geographic regions with high endemic rates of PNS *S. pneumoniae* (weak, moderate).

## VIII. Which Antimicrobial Regimens Are Recommended for the Empiric Treatment of ABRS in Adults and Children With a History of Penicillin Allergy?

**Recommendations.** 11. Either doxycycline (not suitable for children) or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy in adults who are allergic to penicillin (strong, moderate).

12. Levofloxacin is recommended for children with a history of type I hypersensitivity to penicillin; combination therapy with clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxime) is recommended in children with a history of non-type I hypersensitivity to penicillin (weak, low).

## IX. Should Coverage for Staphylococcus aureus (Especially Methicillin-Resistant S. aureus) Be Provided Routinely During Initial Empiric Therapy of ABRS?

**Recommendation.** 13. Although *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]) is a potential pathogen in ABRS, on the basis of current data, routine antimicrobial coverage for *S. aureus* or MRSA during initial empiric therapy of ABRS is not recommended (strong, moderate).

## X. Should Empiric Antimicrobial Therapy for ABRS Be Administered for 5–7 Days Versus 10–14 Days?

**Recommendations.** 14. The recommended duration of therapy for uncomplicated ABRS in adults is 5–7 days (weak, low-moderate).

15. In children with ABRS, the longer treatment duration of 10–14 days is still recommended (weak, low-moderate).

## XI. Is Saline Irrigation of the Nasal Sinuses of Benefit as Adjunctive Therapy in Patients With ABRS?

**Recommendation.** 16. Intranasal saline irrigation with either physiologic or hypertonic saline is recommended as an adjunctive treatment in adults with ABRS (weak, low-moderate).

## ***XII. Are Intranasal Corticosteroids Recommended as an Adjunct to Antimicrobial Therapy in Patients With ABRS?***

**Recommendation.** 17. Intranasal corticosteroids (INCSs) are recommended as an adjunct to antibiotics in the empiric treatment of ABRS, primarily in patients with a history of allergic rhinitis (weak, moderate).

## ***XIII. Should Topical or Oral Decongestants or Antihistamines Be Used as Adjunctive Therapy in Patients With ABRS?***

**Recommendation.** 18. Neither topical nor oral decongestants and/or antihistamines are recommended as adjunctive treatment in patients with ABRS (strong, low-moderate).

## **NONRESPONSIVE PATIENT**

### ***XIV. How Long Should Initial Empiric Antimicrobial Therapy in the Absence of Clinical Improvement Be Continued Before Considering Alternative Management Strategies?***

**Recommendation.** 19. An alternative management strategy is recommended if symptoms worsen after 48–72 hours of initial empiric antimicrobial therapy or fail to improve despite 3–5 days of initial empiric antimicrobial therapy (strong, moderate).

### ***XV. What Is the Recommended Management Strategy in Patients Who Clinically Worsen Despite 72 Hours or Fail to Improve After 3–5 Days of Initial Empiric Antimicrobial Therapy With a First-line Regimen?***

**Recommendation.** 20. An algorithm for managing patients who fail to respond to initial empiric antimicrobial therapy is shown in Figure 1. Patients who clinically worsen despite 72 hours or fail to improve after 3–5 days of empiric antimicrobial therapy with a first-line agent should be evaluated for the possibility of resistant pathogens, a noninfectious etiology, structural abnormality, or other causes for treatment failure (strong, low).

### ***XVI. In Managing the Patient With ABRS Who Has Failed to Respond to Empiric Treatment With Both First-line and Second-line Agents, It Is Important to Obtain Cultures to Document Whether There Is Persistent Bacterial Infection and Whether Resistant Pathogens Are Present. In Such Patients, Should Cultures Be Obtained by Sinus Puncture or Endoscopy, or Are Cultures of Nasopharyngeal Swabs Sufficient?***

**Recommendations.** 21. It is recommended that cultures be obtained by direct sinus aspiration rather than by nasopharyngeal swab in patients with suspected sinus infection who have failed to respond to empiric antimicrobial therapy (strong, moderate).

22. Endoscopically guided cultures of the middle meatus may be considered as an alternative in adults, but their reliability in children has not been established (weak, moderate).

23. Nasopharyngeal cultures are unreliable and are not recommended for the microbiologic diagnosis of ABRS (strong, high).

## ***XVII. Which Imaging Technique Is Most Useful for Patients With Severe ABRS Who Are Suspected to Have Suppurative Complications Such as Orbital or Intracranial Extension of Infection?***

**Recommendation.** 24. In patients with ABRS suspected to have suppurative complications, axial and coronal views of contrast-enhanced computed tomography (CT) rather than magnetic resonance imaging (MRI) is recommended to localize the infection and to guide further treatment (weak, low).

## ***XVIII. When Is Referral to a Specialist Indicated in a Patient With Presumed ABRS?***

**Recommendation.** 25. Patients who are seriously ill and immunocompromised, continue to deteriorate clinically despite extended courses of antimicrobial therapy, or have recurrent bouts of acute rhinosinusitis with clearing between episodes should be referred to a specialist (such as an otolaryngologist, infectious disease specialist, or allergist) for consultation. As this is a “good clinical practice” statement rather than a recommendation, it is not further graded.

## **INTRODUCTION**

Throughout this guideline, the term *rhinosinusitis* is used interchangeably with *sinusitis*. Because the nasal mucosa is contiguous with that of the paranasal sinuses, any inflammation of the sinuses is almost always accompanied by inflammation of the nasal cavity [7, 8]. Rhinosinusitis is an extremely common condition. In a national health survey conducted during 2008, nearly 1 in 7 (13.4%) of all non-institutionalized adults aged  $\geq 18$  years were diagnosed with rhinosinusitis within the previous 12 months [9]. Incidence rates among adults are higher for women than men ( $\sim 1.9$ -fold), and adults between 45 and 74 years are most commonly affected [9].

Acute rhinosinusitis is defined as an inflammation of the mucosal lining of the nasal passage and paranasal sinuses lasting up to 4 weeks. It can be caused by various inciting factors including allergens, environmental irritants, and infection by viruses, bacteria, or fungi. A viral etiology associated with a URI or the common cold is the most frequent cause of acute rhinosinusitis. Prospective longitudinal studies performed in young children (6–35 months of age) revealed that viral URI occurs with an incidence of 6 episodes per patient-year [10]. In adults, the incidence is estimated to be 2–3 episodes per year [11]. Secondary bacterial infection of the paranasal sinuses following an antecedent viral URI is relatively uncommon, estimated to be 0.5%–2% of adult cases [12, 13] and approximately 5% in children [14]. The prevalence of a bacterial infection during acute rhinosinusitis is estimated to be 2%–10%, whereas viral causes account for 90%–98% [12]. Despite this, antibiotics are frequently

**Table 1. Strength of Recommendations and Quality of the Evidence<sup>a</sup>**

Strength of Recommendation and Quality of Evidence	Clarity of Balance Between Desirable and Undesirable Effects	Methodological Quality of Supporting Evidence (Examples)	Implications
Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research is unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Recommendation can apply to most patients in most circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-quality evidence	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from observational studies, RCTs with serious flaws or indirect evidence	Recommendation may change when higher-quality evidence becomes available. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Strong recommendation, very low-quality evidence (very rarely applicable)	Desirable effects clearly outweigh undesirable effects, or vice versa	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Recommendation may change when higher-quality evidence becomes available; any estimate of effect for at least 1 critical outcome is very uncertain.
Weak recommendation, high-quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies	The best action may differ depending on circumstances or patients or societal values. Further research is unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from unbiased observational studies	Alternative approaches likely to be better for some patients under some circumstances. Further research (if performed) is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low-quality evidence	Uncertainty in the estimates of Desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Weak recommendation, very low-quality evidence	Major uncertainty in the estimates of desirable effects, harms, and burden; desirable effects may or may not be balanced with undesirable effects	Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence	Other alternatives may be equally reasonable. Any estimate of effect, for at least 1 critical outcome, is very uncertain.

Abbreviation: RCT, randomized controlled trial.

<sup>a</sup> Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [1–6].

prescribed for patients presenting with symptoms of acute rhinosinusitis, being the fifth leading indication for antimicrobial prescriptions by physicians in office practice [15]. The total direct healthcare costs attributed to a primary medical diagnosis of sinusitis in 1996 were estimated to exceed \$3 billion per year [16]. A recent national survey of antibiotic prescriptions for URI in the outpatient setting showed that antibiotics were prescribed for 81% of adults with acute rhinosinusitis [17, 18], despite the fact that approximately 70% of patients improve spontaneously in

placebo-controlled randomized clinical trials [18]. Thus, overprescription of antibiotics is a major concern in the management of acute rhinosinusitis, largely due to the difficulty in differentiating ABRS from a viral URI. To address these issues, several practice guidelines for the treatment of ABRS have been published by various professional organizations in the United States and Canada within the past decade, including the American College of Physicians (2001) [19, 20], the American Academy of Pediatrics (2001) [21], the Rhinosinusitis Initiative (representing the American

Academy of Allergy, Asthma and Immunology; the American Academy of Otolaryngic Allergy; the American College of Allergy, Asthma and Immunology; the American Academy of Otolaryngology–Head and Neck Surgery [AAO-HNS]; and the American Rhinologic Society) (2004) [7], the Sinus and Allergy Health Partnership (2004) [22], the Joint Council of Allergy, Asthma and Immunology (2005) [23], the Agency for Health Care Research and Quality (2005) [24], and more recently by the AAO-HNS (2007) [25], the Institute for Clinical Systems Improvement (2008) [26], and the Canadian Society of Otolaryngology–Head and Neck Surgery (2011) [27]. These guidelines offer differing opinions regarding both clinical criteria for initiating antimicrobial therapy and choice of empiric antimicrobial regimens. The current guideline was developed by IDSA with a multidisciplinary panel to address some of the more controversial areas concerning initial empiric management of ABRS in both children and adults. A major area of emphasis includes identifying the clinical presentations that best distinguish bacterial from viral rhinosinusitis, and the selection of antimicrobial regimens based on evolving antibiotic susceptibility profiles of recent respiratory pathogens in the United States. The primary goal of this guideline is to improve the appropriate use of first-line antibiotics for patients with a presumptive diagnosis of ABRS. The secondary goals are to reduce excessive or inappropriate use of antimicrobial agents in patients with acute viral rhinosinusitis or self-limited bacterial infection, and to deter the emergence of antibiotic resistance among respiratory pathogens. The guideline is primarily intended for primary care physicians in community and the emergency department settings, including family practitioners, internists, pediatricians, and emergency physicians. The expanded audience includes infectious disease specialists, otolaryngologists, allergists, and head and neck surgeons. It is also among the first IDSA clinical practice guidelines to adopt the GRADE system to assess the quality of evidence and strength of recommendations [1–6] (Table 1).

The following 18 clinical questions are addressed in this guideline:

- I. Which clinical presentations best identify patients with acute bacterial vs viral rhinosinusitis?
- II. When should empiric antimicrobial therapy be initiated in patients with signs and symptoms suggestive of ABRS?
- III. Should amoxicillin vs amoxicillin-clavulanate be used for initial empiric antimicrobial therapy of ABRS in children?
- IV. Should amoxicillin vs amoxicillin-clavulanate be used for initial empiric antimicrobial therapy of ABRS in adults?
- V. When is “high-dose” amoxicillin-clavulanate recommended during initial empiric antimicrobial therapy for ABRS in children or adults?

VI. Should a respiratory fluoroquinolone vs a  $\beta$ -lactam agent be used as first-line initial empiric antimicrobial therapy of ABRS?

VII. Besides a  $\beta$ -lactam or a respiratory fluoroquinolone, should a macrolide, TMP/SMX, doxycycline, or a second- or third-generation oral cephalosporin be used as an alternative regimen for the initial empiric treatment of ABRS in children or adults?

VIII. Which antimicrobial regimens are recommended for the empiric treatment of ABRS in children and adults with a history of penicillin allergy?

IX. Should coverage for *S. aureus* (especially MRSA) be provided routinely during initial empiric therapy of ABRS?

X. Should empiric antimicrobial therapy for ABRS be administered for 5–7 days vs 10–14 days?

XI. Is saline irrigation of the nasal sinuses of benefit as adjunctive therapy in patients with ABRS?

XII. Are intranasal corticosteroids recommended as an adjunct to antimicrobial therapy in patients with ABRS?

XIII. Should topical or oral decongestants or antihistamines be used as adjunctive therapy in patients with ABRS?

XIV. How long should initial empiric antimicrobial therapy in the absence of clinical improvement be continued before considering alternative management strategies?

XV. What is the recommended management strategy in patients who clinically worsen despite 72 hours or fail to improve after 3–5 days of initial empiric antimicrobial therapy with a first-line regimen?

XVI. In managing the patient with ABRS who has failed to respond to empiric treatment with both first-line and second-line agents, it is important to obtain cultures to document whether there is persistent bacterial infection and whether resistant pathogens are present. In such patients, should cultures be obtained by sinus puncture or endoscopy, or will cultures from nasopharyngeal swabs suffice?

XVII. Which imaging technique is most useful for patients with severe ABRS who are suspected to have suppurative complications such as orbital or intracranial extension of infection?

XVIII. When should referral to a specialist be considered in the management of a patient with presumed ABRS?

### Overview of Therapeutic Dilemmas in ABRS

This guideline was prompted by a number of therapeutic dilemmas commonly encountered by physicians who provide primary care to children and adults with a presumptive diagnosis of ABRS.

#### *Lack of Precision in Current Methods of Diagnosis*

The gold standard for the diagnosis of ABRS is the recovery of bacteria in high density ( $\geq 10^4$  colony-forming units per milliliter) from the cavity of a paranasal sinus [7, 12, 13]. Failure to adequately decontaminate the paranasal mucosa during

**Table 2. Conventional Criteria for the Diagnosis of Sinusitis Based on the Presence of at Least 2 Major or 1 Major and  $\geq 2$  Minor Symptoms**

Major Symptoms	Minor Symptoms
● Purulent anterior nasal discharge	● Headache
● Purulent or discolored posterior nasal discharge	● Ear pain, pressure, or fullness
● Nasal congestion or obstruction	● Halitosis
● Facial congestion or fullness	● Dental pain
● Facial pain or pressure	● Cough
● Hyposmia or anosmia	● Fever (for subacute or chronic sinusitis)
● Fever (for acute sinusitis only)	● Fatigue

Modified from Meltzer et al [7].

sinus aspiration or to quantify any bacterial isolates in the aspirate are the most common pitfalls that may lead to misinterpretation of results (ie, assuming the presence of infection when actually the bacteria recovered represent contaminants derived from the nose). Using this definition, several investigators [28–30] have confirmed the diagnosis of ABRS in both adults and children and validated the effect of appropriate antimicrobial therapy in eradicating bacterial pathogens from the paranasal sinuses [12]. Furthermore, treatment failure was associated with the recovery of antibiotic-resistant pathogens [29]. However, sinus aspiration is an invasive, time-consuming, and potentially painful procedure that does not have utility in the daily practice of primary care physicians. Although there has been interest in the use of endoscopically guided cultures of the middle meatus as a surrogate for sinus aspirates in patients with ABRS [31], performance of such cultures is beyond the scope of most primary care physicians, and its validity in children has not been established. Thus, the diagnosis of ABRS in most randomized controlled trials (RCTs) of antimicrobial therapy is based on the presence of compatible symptoms and signs of acute rhinosinusitis (Table 2) with radiographic confirmation of sinus involvement. Unfortunately, these diagnostic criteria do not adequately distinguish bacterial from viral infection. Consequently, a proportion of patients enrolled in such trials likely had a viral URI, which is self-limited and would not be expected to respond to antimicrobial therapy. This limitation results in an underestimation of the potential benefit of antimicrobial therapy [12].

#### **Imaging Studies of Presumed ABRS**

Imaging studies such as plain radiographs or CT are frequently used by clinicians for the diagnosis of ABRS. Unfortunately, these studies are nonspecific and do not distinguish bacterial from viral rhinosinusitis. Kovatch et al [32] found that more than half of children with both symptoms and signs of a viral

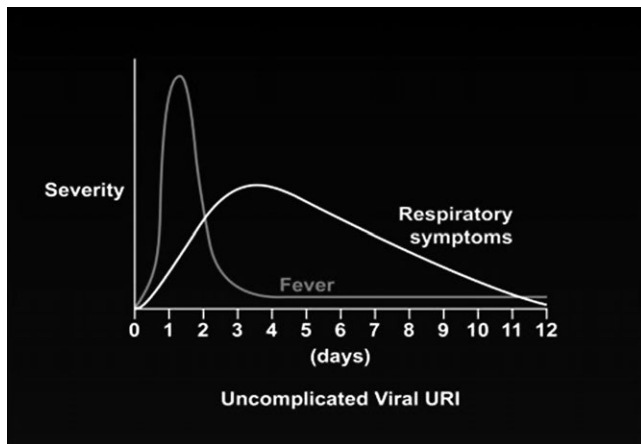
URI had abnormal maxillary sinus radiographs. Conversely, such radiographs are frequently abnormal in healthy children [32–34] and in children undergoing CT for a nonrespiratory complaint [35]. Gwaltney et al [36] deliberately obtained CTs from healthy young adults experiencing a new cold and found that 87% of the subjects had significant abnormalities of their maxillary sinuses. Finally, Kristo et al found that 68% of symptomatic children with acute respiratory infection [37] and 42% of healthy schoolchildren [38] had major abnormalities in their paranasal sinuses as evaluated by MRI.

Collectively, these studies indicate that during uncomplicated viral URI in children and adults, the majority will have significant abnormalities in imaging studies (either plain radiographs, CT, or MRI) that are indistinguishable from those associated with bacterial infection. Accordingly, while normal imaging studies can assure that a patient with respiratory symptoms almost certainly does not have ABRS, an abnormal radiographic study cannot confirm the diagnosis of ABRS, and such studies are unnecessary during the management of uncomplicated ABRS. Furthermore, studies in which the entry criteria included the presence of respiratory symptoms plus abnormal radiographs or other imaging studies (ie, most RCTs evaluating antimicrobial treatment of ABRS in the literature) cannot be accepted as credible or reliable for evaluating the natural history of ABRS or antimicrobial efficacy.

#### **Clinical Distinction of ABRS From Viral URI**

There are few studies in adults and children that have correlated the presence of respiratory signs and symptoms with the findings of sinus aspiration [12, 28, 30, 39]. The duration of symptoms beyond 7–10 days is often used as a surrogate criterion to distinguish bacterial from viral infection based on the natural history of rhinovirus infections [40] (Figure 2). However, the probability of confirming a bacterial infection by sinus aspiration is only about 60% among adult patients with symptoms lasting  $\geq 7$ –10 days [41]. To identify additional clinical features that may distinguish between bacterial and viral infection, the typical clinical course and natural history of rhinovirus infection (described by Gwaltney et al [40]) is further reviewed.

Viral URIs are characterized by the presence of nasal symptoms (discharge and congestion/obstruction) and/or cough. Patients may also complain of a scratchy throat. Usually the nasal discharge begins as clear and watery. Often, however, the quality of nasal discharge changes during the course of the illness. Most typically, the nasal discharge becomes thicker and more mucoid and may become purulent (thick, colored, and opaque) for several days. Then the situation reverses with the purulent discharge becoming mucoid and then clear again, or simply drying. The transition from clear to purulent to clear nasal discharge occurs in uncomplicated viral URIs without



**Figure 2.** Schematic characterization of the natural history and time course of fever and respiratory symptoms associated with an uncomplicated viral upper respiratory infection (URI) in children (courtesy of Dr Ellen Wald; adapted from Gwaltney et al [40] and Rosenfeld et al [13]).

the benefit of antimicrobial therapy. Most patients with uncomplicated viral URIs do not have fever. However, if fever is present, it tends to be present early in the illness, often in concert with other constitutional symptoms such as headache and myalgia. Typically, the fever and constitutional symptoms disappear in the first 24–48 hours and the respiratory symptoms become more prominent. The time course of illness is an important characteristic. In most cases of uncomplicated viral URI, respiratory symptoms last 5–10 days. Although the patient may not be free of symptoms on the 10th day, almost always the respiratory symptoms have peaked in severity by days 3–6 and have begun to improve.

With this clinical picture of an uncomplicated viral URI for comparison, several clinical features were proposed by the Rhinosinusitis Initiative to correlate with ABRS rather than viral URI [7]. In addition to the duration of signs and symptoms, the time course and pattern of disease progression were considered to be important in differentiating bacterial from viral rhinosinusitis. Three typical clinical presentations were emphasized: (1) onset with *persistent* symptoms that last >10 days and were not improving; (2) onset with *severe* symptoms, characterized by high fever of at least 39°C (102°F) and purulent nasal discharge for at least 3–4 consecutive days at the beginning of illness; and (3) onset with *worsening* symptoms, characterized by typical viral URI symptoms that appear to improve followed by the sudden onset of worsening symptoms after 5–6 days (“double-sickening”) [7, 42].

In patients with persistent symptoms, nasal discharge (of any quality) and daytime cough (which may be worse at night) are both common, whereas the presence of fever,

headache, or facial pain is more variable. These patients come to medical attention primarily because of respiratory symptoms that may be low grade but simply do not resolve. In the patient with severe symptoms, the onset of fever, headache, and facial pain is distinguished from an uncomplicated viral URI in 2 ways. In viral URI, fever is present early in the clinical illness and disappears in 24–48 hours, while purulent nasal discharge is not generally present until the fourth or fifth day of illness. In contrast, the high fever and purulent nasal discharge during ABRS occur for at least 3–4 consecutive days at the beginning of the illness. Although the triad of headache, facial pain, and fever is considered a classic presentation of ABRS in adults, it is uncommon. Onset with persistent symptoms is far more frequent. In children, the most common manifestations of bacterial sinusitis are cough (80%) followed by nasal discharge (76%) and fever (63%). Parents of preschoolers often report malodorous breath. Headache, facial pain, and swelling are rare. In the patient with worsening symptoms, there may be a new onset of fever, a relapse or an increase in nasal discharge or cough, or the onset of severe headache. This double-sickening is a classic presentation for any secondary bacterial complication of a viral URI similar to ABRS, such as acute otitis media (AOM) and pneumonia. The validity of these clinical features in predicting ABRS is discussed in the “Evidence Summary” of recommendation 1 in the guideline.

#### **Issues in RCTs of Antimicrobial Therapy for Presumed ABRS**

Five systematic reviews or meta-analyses of antimicrobial therapy vs placebo for presumed ABRS in adults have been published since 2005 [18, 24, 25, 43, 44]. Data from 17 studies in adult patients and 3 pediatric studies in which antibiotics have been compared with placebo are available for further analysis (Table 3). In evaluating the quality of these studies, the single most challenging issue besides methodological flaws in randomization, concealment, and blinding is to ensure that the patients in the study populations actually have bacterial rather than viral rhinosinusitis in the absence of confirmation by sinus cultures. Two common methodological flaws identified in these studies among adult patients are that (1) many patients only had 7 days of symptoms (without qualification of whether these symptoms had begun to improve or were worsening) and that (2) imaging studies were often used as a diagnostic entry criterion. Because these patient selection criteria lack sensitivity and specificity for ABRS, there is good reason to believe that many patients enrolled in these studies had uncomplicated viral URI rather than ABRS [12]. Nonetheless, most of these studies do show a modest benefit in the use of antimicrobials. Overall, 13 (95% confidence interval [CI], 9–22) adults would need to be treated with antibiotics before 1 additional patient would benefit (Table 3). The finding that approximately 65% of placebo-treated patients improved spontaneously in these studies



**Table 3. Meta-analyses of Antibiotic Treatment Versus Placebo in Patients With Acute Rhinosinusitis**

Patient Population	No. of Studies	No. Cured or Improved/No. Enrolled (%)		OR (95% CI)	No. Needed to Treat (95% CI) <sup>a</sup>
		Antibiotic	Placebo		
Adults [45, 46, 47–60]	17	1213/1665 (72.9)	989/1521 (65.0)	1.44 (1.24–1.68)	13 (9–22)
Children [61, 62, 63, 64] <sup>b</sup>	3	151/192 (78.5)	70/118 (59.7)	2.52 (1.52–4.18)	5 (4–15)

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup> Calculated by inverting the difference from proportions of success rates between treatment groups [18].

<sup>b</sup> Study by Kristo et al [63] was excluded due to inadequate inclusion criteria and antimicrobial dosing regimen.

may lead to an erroneous conclusion that some patients with ABRS do not require antimicrobial therapy, when in fact they may not have ABRS at all. One can only surmise that the benefit of antimicrobial therapy would have been substantially magnified if more of the study patients actually had ABRS. Studies of children showed results in which the number needed to treat (NNT) was reduced to 5 (95% CI, 4–15). It is probable that this apparent difference in response rates between children and adults is due to more stringent inclusion criteria for ABRS in the pediatric studies; alternatively, children with ABRS may respond better to antibiotics than adults.

#### **Selection of Empiric Antimicrobial Regimens for Presumed ABRS on the Basis of RCTs**

The practice of evidence-based medicine requires that clinical decisions regarding the selection of empiric antimicrobial therapy for ABRS be supported by RCTs if available. Unfortunately, most published RCTs comparing different antimicrobial regimens for ABRS are only powered to evaluate noninferior clinical outcomes without microbiological confirmation. This situation, coupled with the high rate of spontaneous recovery in patients with uncomplicated acute rhinosinusitis, allows agents with poor antimicrobial efficacy to appear more efficacious, and drugs with excellent antibacterial activity to appear less efficacious, than they really are, that is, the “Pollyanna effect” described by Marchant et al [65]. Thus, although a multitude of antimicrobial regimens have been found to be noninferior to amoxicillin in clinical efficacy, they are not truly equivalent to first-line agents for the treatment of ABRS.

#### **Clinical Relevance of Antibiotic Resistance**

The emergence of increasing antimicrobial resistance among respiratory pathogens initiates a self-perpetuating vicious cycle in which broad-spectrum antibiotics are encouraged and in turn drive selection pressure to promote more resistance [66, 67]. This dilemma is further exacerbated by the lack of appropriate microbiological studies to confirm an etiological diagnosis and assess microbiological outcome. Finally, although there are

clear exceptions, the laboratory designation of antimicrobial resistance may not necessarily correlate with poor patient outcome. Documentation of bacterial persistence in association with clinical failure in the absence of structural abnormalities or suboptimal PK/PD data is necessary to confirm the clinical relevance of antimicrobial resistance. As a case in point, the penicillin susceptibility breakpoints of *S. pneumoniae* for intravenous treatment of nonmeningeal infection were revised in 2008 by the Clinical and Laboratory Standards Institute (CLSI) (“intermediate” changed from  $\leq 1$   $\mu\text{g/mL}$  to 4  $\mu\text{g/mL}$ ; “resistant” changed from  $\geq 2$   $\mu\text{g/mL}$  to  $\geq 8$   $\mu\text{g/mL}$ ), because earlier breakpoints based on achievable cerebrospinal fluid concentrations of penicillin did not correlate with a suboptimal clinical outcome in patients with nonmeningeal invasive pneumococcal infections [68]. Because oral amoxicillin has better PK/PD properties than oral penicillin VK, it is the preferred oral  $\beta$ -lactam agent for the treatment of nonmeningeal pneumococcal infections. The revised breakpoints for oral amoxicillin are the same as for intravenous penicillin (intermediate, 4  $\mu\text{g/mL}$ ; resistant,  $\geq 8$   $\mu\text{g/mL}$ ). The clinical relevance of macrolide resistance among *H. influenzae* and *S. pneumoniae* has also been questioned. Nonetheless, recent studies provide clear-cut evidence that infection with macrolide-resistant and penicillin-resistant pneumococci is a notable risk factor for treatment failure with these agents in community-acquired respiratory tract infections [69–72]. Similar data exist when inappropriate antimicrobial therapy was administered to patients with ABRS caused by *H. influenzae* on the basis of posttreatment sinus puncture studies [12]. A related concern is that the emergence of antimicrobial resistance is a dynamic process and constantly evolving. Antimicrobial regimens found to be effective in RCTs performed prior to the emergence of antimicrobial resistance (eg,  $\beta$ -lactamase-producing *H. influenzae* in the 1970s) clearly cannot be relied upon for contemporary treatment without confirmation by susceptibility testing. This further diminishes the value of RCTs in the selection of contemporary empiric antimicrobial regimens for the treatment of ABRS.

For all the reasons stated above, antimicrobial recommendations for the management of ABRS need to be reevaluated. The current IDSA practice guideline aims to critically review the evidence and formulate recommendations that address some of these therapeutic dilemmas in ABRS using the GRADE system.

## METHODS

### Practice Guidelines

“Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate healthcare for specific clinical circumstances” [73]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [73].

### Panel Composition

A panel of multidisciplinary experts in the management of ABRS in children and adults was convened in April 2008. The panel consisted of internists and pediatricians as well as infectious disease and emergency physicians and an otolaryngologic specialist. Panel participants included representatives from the American College of Physicians, Society of Academic Emergency Medicine, Centers for Disease Control and Prevention, the GRADE Working Group, and the IDSA Standards and Practice Guidelines Committee.

### Process Overview and the GRADE Approach

The group convened a face-to-face meeting in December 2008 in which an outline of the guideline was discussed and the process of guideline development using the GRADE approach was briefly reviewed.

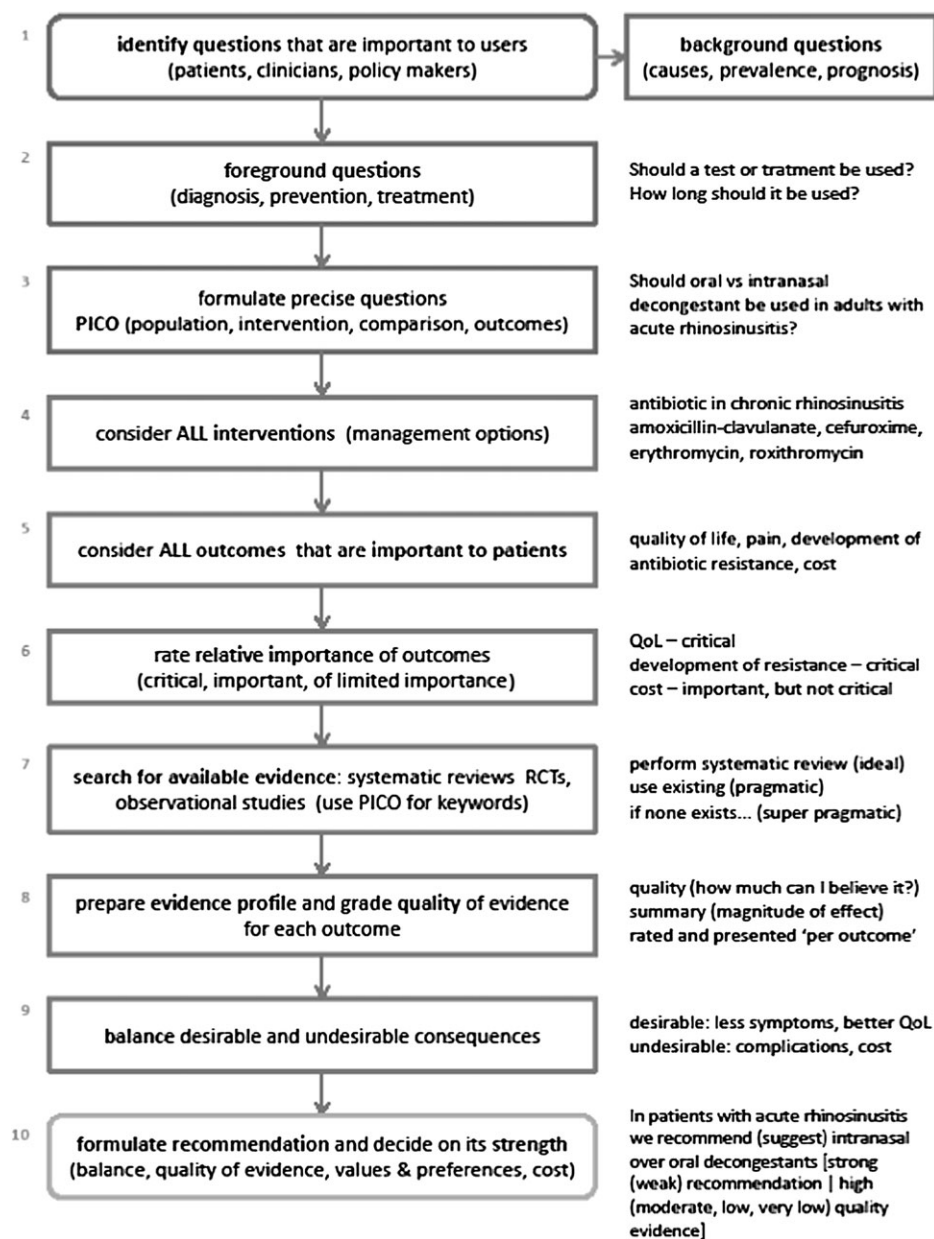
GRADE is a newly created system for evaluating the quality of evidence and strength of recommendations for healthcare. The essential steps for developing recommendations by the GRADE approach are summarized in Figure 3. The first task is to identify and formulate precise questions to be addressed by the guideline (steps 1–3). These should address clinically important outcomes and focus on specific patient populations and interventions that are relevant at the point of care (steps 4–6). The next task is to search for available evidence, prepare an evidence profile, and grade the quality of evidence for each important outcome (steps 7–8). The final task is to formulate recommendations based on the balance of desirable vs undesirable consequences for the intervention, and make a value judgment regarding the strength of the recommendation. Thus, the GRADE approach separates decisions regarding the quality of evidence from strength of recommendations. This is a fundamental difference from the previous IDSA–US Public Health Service grading system [74]. High-quality

evidence does not necessarily constitute strong recommendations, and conversely, strong recommendations can still arise from low-quality evidence if one can be confident that the desired benefits clearly outweigh the undesirable consequences. The main advantages of the GRADE approach are the detailed and explicit criteria for grading the quality of evidence and the transparent process for making recommendations.

The quality of evidence reflects the extent to which the confidence in estimates of the effects is adequate to support a particular recommendation. Hence, judgments about the quality of evidence are always made relative to the specific context in which this evidence is used. The GRADE system categorizes the quality of evidence as high, moderate, low, or very low (Table 1) [6]. *High-quality evidence* indicates that further research is very unlikely to change our confidence in the estimate of effects. *Moderate-quality evidence* indicates that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. *Low-quality evidence* suggests that further research is very likely to have an important impact on our confidence in the estimate of effect or change the estimate. *Very low-quality evidence* indicates that any estimate of effect is very uncertain. Expert opinion is not a category of evidence. Expert opinion represents an interpretation of evidence ranging from observations in an expert’s own practice (uncontrolled observations, case reports) to the interpretation of RCTs and meta-analyses known to the expert in the context of other experiences and knowledge.

The quality of evidence may be upgraded or downgraded by additional considerations. For example, high-quality evidence based on RCTs may be downgraded due to limitations in study design or implementation, imprecise estimates (eg, wide confidence intervals), unexplained variability in results, indirectness of the evidence, and publication bias. Conversely, low-quality evidence based on observational studies may warrant upgrading if the magnitude of the treatment effect is very large, if there is evidence of a dose–response relation, or if all plausible biases would decrease the magnitude of an apparent treatment effect. To facilitate this process, a software program (GRADEprofiler) was used to produce evidence tables including the assessment of quality of evidence and a summary of findings (the effect size in the intervention and comparison groups, and the magnitude of relative and absolute effects). Thus the evidence profile is a transparent summary of evidence on which those making recommendations can base their judgments.

The strength of recommendation is not solely linked to the quality of evidence. Rather, the key determinant of the strength of a recommendation is the balance between the desirable and undesirable outcomes (ie, risks vs benefits) for



**Figure 3.** Essential steps in formulating recommendations by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. QoL, quality of life; RCT, randomized controlled trial.

a clinically important question [1]. This implies a careful selection of the important clinical questions to be addressed and the key outcomes to be evaluated. Other factors that determine the strength of recommendation are the resource implications and variability in values and preferences for or against an alternative management strategy considered by the guideline panel. Only 2 grades are assigned for the strength of recommendation in GRADE: *strong* or *weak*. A strong recommendation reflects a high degree of confidence that the

desirable effects of an intervention outweigh the undesirable effects. A weak recommendation denotes that the desirable effects of adhering to a recommendation probably outweigh the undesirable effects, but the panel is less confident. The GRADE approach offers a structured, systematic, and transparent process to formulate recommendations based on explicit criteria that go beyond just the quality of available evidence (please visit the GRADE website at <http://www.gradeworkinggroup.org/> for more information).

A series of monthly teleconferences was conducted in which a list of clinical questions to be addressed by the guideline was generated, discussed, and prioritized. It was determined by the panel that because the entity of chronic rhinosinusitis is so fundamentally different from acute rhinosinusitis in patient populations, epidemiology, pathophysiology, and management strategies, the current guideline would only address issues related to the initial management of ABRS in both adults and children. Consensus among the panel members in grading the quality of evidence and strength of recommendations was developed using the GRADE “grid” technique and the Delphi method [3]. The draft recommendations were circulated to all panel members and each member was asked to provide an opinion regarding their assessment of the recommendations (either strongly agree, agree with reservation, or reject) along with the reasons for their judgment. After each round, an impartial facilitator provided an anonymous summary of the independent panel responses as well as their justification. Panelists were encouraged to revise their earlier answers in light of the replies from the other members of the panel. The process was repeated until consensus was developed for 80% of the responses for each clinical question. Because this was the first guideline to use the GRADE system, preparation of the evidence profile was assisted by a GRADE representative on the panel who provided expert advice on methodological issues throughout the guideline development.

The panel met on 2 additional occasions and held multiple teleconferences to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions, distribute writing assignments, and finalize recommendations. All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. The guideline was reviewed and approved by the IDSA Standards and Practice Guidelines Committee and the Board of Directors prior to dissemination.

#### **Statistical Analysis and Evidence Summary Profiles**

Statistical analysis including relative risk (RR), odds ratios (ORs), 95% CIs, positive and negative predictive values, and  $\chi^2$  statistics was performed using the Prism 4.0 software package (GraphPad, San Diego, California). Evidence summary profiles were generated using GRADEprofiler 3.2.2 software (GRADE Working Group).

#### **Literature Review and Analysis**

We identified up-to-date valid systematic reviews from the MEDLINE database and the Cochrane Library, and also, in selected cases, reference lists of the most recent narrative reviews or studies on the topic. Unless specified otherwise, the search period was 1980–2011 and the search was restricted to the English literature. Articles were also retrieved

by searches for clinical diagnosis, symptoms and signs, microbiology, antimicrobial resistance, CT scan, MRI, intranasal steroids, saline irrigations, and complications. The panel members contributed reference lists in these areas. The quality of evidence was evaluated after the literature review. We based our judgments on these systematic reviews and, if applicable, on additional studies published after the reviews were done. When no systematic review was available, we evaluated the original studies to inform judgments about the quality of the underlying evidence from a crude examination of these studies. Primary key search terms were as follows:

- Amoxicillin-clavulanic acid
- Antimicrobial resistance
- Appropriate antimicrobial
- $\beta$ -lactams
- Decongestants
- Fluoroquinolones
- *H. influenzae*
- Hypertonic and isotonic saline
- *M. catarrhalis*
- Pathogens
- Rhinosinusitis (children and adults)
- Sinusitis
- Sinus aspiration
- *S. pneumoniae*
- Stewardship
- Steroids
- Upper respiratory

#### **Guideline and Conflict of Interest**

All members of the expert panel complied with the IDSA policy regarding conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the expert panel completed a conflicts of interest disclosure statement from the IDSA. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The panel made decisions on a case-by-case basis as to whether an individual’s role should be limited as a result of a perceived conflict. No limiting conflicts were identified.

#### **Revision Dates**

At annual intervals, the panel chair, the liaison advisor, and the chair of the Standards and Practice Guidelines Committee will determine the need to update the guideline based on an examination of the current literature. If necessary, the entire panel will reconvene to discuss potential changes. When appropriate, the panel will recommend full revision of the guideline to the IDSA Standards and Practice Guidelines Committee and the IDSA Board for review and approval.

## RECOMMENDATIONS CONCERNING INITIAL TREATMENT

### I. Which Clinical Presentations Best Identify Patients With Acute Bacterial Versus Viral Rhinosinusitis?

#### Recommendations

1. The following clinical presentations (any of 3) are recommended for identifying patients with acute bacterial vs viral rhinosinusitis:

- i. Onset with *persistent* symptoms or signs compatible with acute rhinosinusitis, lasting for  $\geq 10$  days without any evidence of clinical improvement (strong, low-moderate);
- ii. Onset with *severe* symptoms or signs of high fever ( $\geq 39^{\circ}\text{C}$  [ $102^{\circ}\text{F}$ ]) and purulent nasal discharge or facial pain lasting for at least 3–4 consecutive days at the beginning of illness (strong, low-moderate); or
- iii. Onset with *worsening* symptoms or signs characterized by the new onset of fever, headache, or increase in nasal discharge following a typical viral URI that lasted 5–6 days and were initially improving (“double-sickening”) (strong, low-moderate).

#### Evidence Summary

The clinical diagnosis of ABRS requires a 2-step process: (1) evidence of sinusitis based on compatible symptoms and signs and (2) evidence suggestive of bacterial rather than viral infection based on typical onset and temporal progression of the clinical course. Earlier studies that evaluated the utility of clinical symptoms and signs for the diagnosis of acute rhinosinusitis were based on sinus radiographs or CT imaging, which do not differentiate bacterial from viral rhinosinusitis [75, 76]. These studies identified several major and minor symptoms that are useful to identify patients with acute rhinosinusitis (ie, presence of at least 2 major symptoms, or 1 major plus  $\geq 2$  minor symptoms as summarized in Table 2) [7]. However, to increase the likelihood of a bacterial rather than viral infection, additional clinical criteria are required. Two studies performed in adult patients attempted to determine the predictive value of symptoms and signs for maxillary sinusitis compared with sinus puncture [77–79]. Unfortunately, these comparisons were based on the quality and appearance of the sinus aspirate (ie, purulent vs mucopurulent or nonpurulent) rather than culture results, and therefore are of very limited value (Table 4). A subsequent analysis evaluated the predictive value of these same clinical parameters for culture-proven maxillary sinusitis in a Danish general practice adult population [78]. Only maxillary toothache (OR, 2.9 [95% CI, 1.3–6.3]) and temperature  $>38^{\circ}\text{C}$  ( $>100.4^{\circ}\text{F}$ ) (OR, 4.6 [95% CI, 1.9–11.2]) were significantly associated with positive sinus culture for *S. pneumoniae* or *H. influenzae* (Table 5). However, maxillary toothache is an uncommon manifestation of ABRS except in odontogenic sinusitis, and  $>50\%$  of sinus

aspirates in this study yielded no growth. Thus, there are no validated studies that examined the predictive value of specific clinical symptoms or signs for the diagnosis of ABRS based on bacterial cultures of sinus aspirates.

The current guideline recommends the adoption of characteristic patterns of clinical presentations for the clinical diagnosis of ABRS, taking into account not only the duration of respiratory symptoms but also the severity of illness, temporal progression, and classic double-sickening in the clinical course to differentiate bacterial from acute viral rhinosinusitis. These recommendations are intended to improve the likelihood of separating acute bacterial from viral rhinosinusitis solely based on the duration of symptoms  $\geq 7$ –10 days. These inclusion criteria were first proposed in 2003 by a multidisciplinary consensus panel jointly established by 5 national societies of otolaryngology–head and neck surgery, allergy, asthma, immunology, and otolaryngic allergy and rhinology [42] (See “Overview” section). A similar definition for ABRS (ie, persistent symptoms after 10 days with  $<12$  weeks’ duration or worsening of symptoms after 5 days) has been adopted by the European Position Paper on Rhinosinusitis and Nasal Polyps 2007 [80]. The validity of these inclusion criteria has been primarily verified in pediatric patients. Wald et al [30] performed sinus puncture in pediatric patients who presented with either persistent symptoms or severe disease and recovered significant pathogens in high density in 77% of the children. In contrast, the probability of confirming bacterial infection by sinus aspiration among adult patients with respiratory symptoms  $\geq 7$ –10 days without qualifying additional characteristics in clinical presentation is only approximately 60% [41]. Similarly, in a more recent placebo-controlled RCT of antimicrobial therapy for ABRS in adults with respiratory symptoms  $\geq 7$  days, only 64% of enrolled patients had positive bacterial cultures by sinus puncture [45]. This suggests that the current practice of basing the diagnosis of ABRS solely on the presence of 7–10 days of compatible respiratory symptoms without qualifying additional characteristics in clinical presentation is inadequate in differentiating bacterial from viral acute rhinosinusitis. However, the utility of such clinical criteria for initiating empiric antimicrobial therapy in adults remains to be validated.

Further evidence in support of adopting more stringent clinical criteria for ABRS is suggested by the different response rates among children and adults enrolled in placebo-controlled RCTs of antimicrobial therapy. In 3 RCTs performed in children in which more stringent criteria of persistent, severe, or worsening presentations were used as patient selection criteria [61, 62, 81], significantly higher cure rates were demonstrated with antibiotics compared with placebo (mean, 78% vs 60%, respectively; OR, 2.52 [95% CI, 1.52–4.18], and NNT of 5)

**Table 4. Predictive Value of Various Clinical Findings in the Diagnosis of Presumed Acute Bacterial Maxillary Rhinosinusitis Compared With Aspiration of Pus From the Sinus Cavity**

Outcomes	Illustrative Comparative Risks <sup>a</sup> (95% CI)		Relative Effect, OR (95% CI)	No. of Participants (No. of Studies)	Quality of the Evidence (GRADE)	Reference
	Assumed Risk	Corresponding Risk				
Maxillary toothache	Study population (medium risk) 512 per 1000	Documenting Pus in Sinus Cavity 663 per 1000 (515–784)	1.87 (1.01–3.45)	174 (1 study)	⊕ ⊕ ⊕ ⊕ very low <sup>b</sup>	Hansen et al [79]
Unilateral facial pain	Study population (medium risk) 378 per 1000	Documenting Pus in Sinus Cavity 510 per 1000 (361–656)	1.71 (.93–3.14)	174 (1 study)	⊕ ⊕ ⊕ ⊕ low <sup>c</sup>	Hansen et al [79]
Unilateral maxillary tenderness	Study population (medium risk) 317 per 1000	Documenting Pus in Sinus Cavity 489 per 1000 (340–640)	2.06 (1.11–3.83)	174 (1 study)	⊕ ⊕ ⊕ ⊕ low	Hansen et al [79]
Previous history of sinusitis	Study population (medium risk) 805 per 1000	Documenting Pus in Sinus Cavity 617 per 1000 (450–764)	0.39 (.198–.786)	174 (1 study)	⊕ ⊕ ⊕ ⊕ very low <sup>b</sup>	Hansen et al [79]
Absence of classical combination of findings <sup>c,d,e,f</sup>	Study population (medium risk) 494 per 1000	Documenting Pus in Sinus Cavity 14 per 1000 (2–101)	0.015 (.002–.115)	155 (1 study)	⊕ ⊕ ⊕ ⊕ very low <sup>g</sup>	Berg and Carenfelt [77]
Presence of 3 of 4 clinical criteria	Study population (medium risk) 80 per 1000	Documenting Pus in Sinus Cavity 574 per 1000 (351–770)	15.37 (6.18–38.18)	155 (1 study)	⊕ ⊕ ⊕ ⊕ very low <sup>g</sup>	Berg and Carenfelt [77]

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio.

<sup>a</sup> The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>b</sup> Self-reported history may not be reliable.

<sup>c</sup> Purulent rhinorrhea with unilateral predominance (symptom).

<sup>d</sup> Facial pain with unilateral predominance (symptom).

<sup>e</sup> Bilateral purulent rhinorrhea (sign).

<sup>f</sup> Presence of pus in nasal cavity (sign).

<sup>g</sup> Pus as surrogate for positive bacterial cultures.

(Table 3). A fourth RCT [63] was not included in this analysis as patients were treated with inadequate dosing of antimicrobials. In contrast, among placebo-controlled RCTs in adults in which duration of symptoms  $\geq 7$ –10 days was the primary inclusion criteria, the beneficial effect of antimicrobial therapy was less prominent (73% vs 65%; OR, 1.44 [95% CI, 1.24–1.68], and NNT of 13).

The criteria of persistent symptoms  $\geq 10$  days duration and worsening symptoms or signs within 5–10 days after initial improvement (double-sickening) were based on earlier studies of the natural history of rhinovirus infections [40] (Figure 2). Although 25% of patients with rhinovirus infection prospectively studied by Gwaltney et al [40] had symptoms longer than 14 days, their clinical course was improving before the 10-day mark.

The criterion of severe symptoms or signs of high fever ( $\geq 39^\circ\text{C}$  [102°F]) and purulent nasal discharge or facial pain lasting for 3–4 days at the beginning of illness identifies a subpopulation with severe disease in whom antimicrobial therapy is clearly warranted before the 10-day “waiting” period. This

criterion was not included in the AAO-HNS guideline for adult rhinosinusitis [13], but was included in the consensus recommendations by Meltzer et al [42].

**Benefits.** More stringent criteria of patient selection based on duration as well as characteristic progression of the clinical course should improve the differentiation of ABRS from viral rhinosinusitis and identify the patient population most likely to benefit from empiric antimicrobial therapy.

**Harms.** Adoption of more stringent clinical criteria for the diagnosis of ABRS may result in delay of appropriate antimicrobial therapy in some patients. However, more accurate distinction will be made between bacterial vs viral rhinosinusitis, and the overuse of antibiotics will be minimized. Reserving antimicrobial therapy for patients with severe or prolonged manifestation of ABRS fails to address quality of life or productivity issues in patients with mild or moderate symptoms of ABRS.

**Other Considerations.** Radiographic confirmation of sinus disease for patients with uncomplicated ABRS is not necessary and is not advised.

**Table 5. Predictive Value of Various Clinical Findings in the Diagnosis of Acute Bacterial Rhinosinusitis Compared With Positive Culture by Sinus Puncture**

Outcomes	Illustrative Comparative Risks <sup>a</sup> (95% CI)		Relative Effect, OR (95% CI)	No. of Participants (No. of Studies)	Quality of the Evidence (GRADE)	Reference
	Assumed Risk	Corresponding Risk				
Self-reported history of previous sinusitis	Study population (medium-risk) 805 per 1000	Positive Culture From Sinus Puncture 623 per 1000 (426–788)	0.40 (.18–.90)	127 (1 study)	⊕⊕⊕⊕ moderate <sup>b</sup>	Hansen et al [78]
History of maxillary toothache	Study population (medium-risk) 512 per 1000	Positive Culture From Sinus Puncture 750 per 1000 (571–871)	2.86 (1.27–6.41)	127 (1 study)	⊕⊕⊕⊖ low	Hansen et al [78]
Temperature >38°C	Study population (medium-risk) 110 per 1000	Positive Culture From Sinus Puncture 364 per 1000 (184–591)	4.63 (1.83–11.70)	127 (1 study)	⊕⊕⊕⊖ low	Hansen et al [78]

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio.

<sup>a</sup> The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>b</sup> Self-reported history may not be reliable.

**Conclusions and Research Needs.** The clinical differentiation of bacterial from viral acute rhinosinusitis remains problematic without direct sinus aspiration and culture. Additional RCTs of antibiotic vs placebo in adult patients meeting stringent clinical criteria as outlined above are urgently needed. Such studies should incorporate both pre- and posttherapy sinus cultures to provide critical information regarding the natural history of sinus infection and efficacy of antimicrobial therapy. The use of endoscopic middle meatus cultures in lieu of sinus aspiration should be further evaluated for this purpose.

## II. When Should Empiric Antimicrobial Therapy Be Initiated in Patients With Signs and Symptoms Suggestive of ABRS? Recommendation

2. It is recommended that empiric antimicrobial therapy be initiated as soon as the clinical diagnosis of ABRS is established as defined in recommendation 1 (strong, moderate).

### Evidence Summary

Because adoption of more stringent clinical criteria based on characteristic onset and clinical presentations is more likely to identify patients with bacterial rather than acute viral rhinosinusitis, withholding or delaying empiric antimicrobial therapy is not recommended. Prompt initiation of antimicrobial therapy as soon as the clinical diagnosis of ABRS is established as defined in recommendation 1 should shorten the duration of illness, provide earlier symptomatic relief, restore quality of life, and prevent recurrence or suppurative complications. This recommendation contravenes a popular management strategy of “watchful waiting” in which antibiotic therapy is withheld unless patients fail to respond to symptomatic management [13, 82]. The proponents of this approach cite the

findings of RCTs in which approximately 70% of patients in the placebo arm improved spontaneously by 7–12 days [25], and that a strategy of delaying antimicrobial prescriptions for patients with mild upper respiratory tract infections is an effective means of reducing antibiotic usage [83]. However, as discussed earlier in this review, the high spontaneous resolution rate in these placebo-controlled RCTs is most certainly due to less stringent patient selection and the inclusion of patients who had viral rather than true ABRS. In contrast, when more stringent inclusion criteria such as those outlined in recommendation 1 were employed, Wald et al [61] reported a considerably lower spontaneous improvement rate of only 32% at 14 days in children receiving placebo, compared with 64% in those treated with amoxicillin-clavulanate, giving an NNT of 3 (95% CI, 1.7–16.7;  $P < .05$ ). This RCT is notable not only for its stringent inclusion/exclusion criteria for initiating antimicrobial therapy, but also for its adoption of a clinical severity score for monitoring patient progress. Thus, a watchful waiting strategy is only reasonable if one is uncertain about the diagnosis of ABRS owing to mild symptoms but cannot be recommended when more stringent clinical criteria for the diagnosis of ABRS are applied.

**Benefits.** Prompt antimicrobial therapy for patients more likely to have acute bacterial rather than viral rhinosinusitis should shorten the duration of illness, provide earlier symptom relief, restore quality of life, and prevent recurrent infection or suppurative complications.

**Harms.** Prompt antimicrobial therapy may result in overuse of antibiotics, enhanced cost, and risk of adverse effects in those patients who do have true bacterial infection but mild disease. However, the patient selection criteria specified in recommendation 1 make this possibility less likely.

**Table 6. Prevalence (Mean Percentage of Positive Specimens) of Various Respiratory Pathogens From Sinus Aspirates in Patients With Acute Bacterial Rhinosinusitis**

Microbial Agent	Publications Before 2000		Publications in 2010	
	Adults <sup>a</sup> (%)	Children <sup>b</sup> (%)	Adults <sup>c</sup> (%)	Children <sup>d</sup> (%)
<i>Streptococcus pneumoniae</i>	30–43	44	38	21–33
<i>Haemophilus influenzae</i>	31–35	30	36	31–32
<i>Moraxella catarrhalis</i>	2–10	30	16	8–11
<i>Streptococcus pyogenes</i>	2–7	2	4	...
<i>Staphylococcus aureus</i>	2–3	...	13	1
Gram-negative bacilli (includes <i>Enterobacteriaceae</i> spp)	0–24	2	...	...
Anaerobes ( <i>Bacteroides</i> , <i>Fusobacterium</i> , <i>Peptostreptococcus</i> ) <sup>e</sup>	0–12	2	...	...
Respiratory viruses	3–15	...	...	...
No growth	40–50	30	36	29

<sup>a</sup> Data compiled from [87–89].

<sup>b</sup> Data compiled from [81, 90].

<sup>c</sup> Data from [45].

<sup>d</sup> Data extrapolated from middle ear fluid of children with acute otitis media [86, 91].

<sup>e</sup> Primarily in odontogenic infections [92].

**Other Considerations.** Some patients with mild but persistent symptoms may be observed without antibiotic treatment for 3 days (because 84% of clinical failures occurred within 72 hours in children receiving placebo) [61]. Such patients require close observation; antimicrobial therapy should be initiated promptly after 3 days if there is still no improvement.

**Conclusions and Research Needs.** More placebo-controlled RCTs that incorporate both pre- and posttherapy sinus cultures and a clinical severity scoring system are urgently needed to provide critical information regarding the natural history of ABRS as well as the timeliness and efficacy of antimicrobial therapy.

### III. Should Amoxicillin Versus Amoxicillin-Clavulanate Be Used for Initial Empiric Antimicrobial Therapy of ABRS in Children?

#### Recommendation

3. Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in children (strong, moderate).

#### Evidence Summary

The recommendation that amoxicillin-clavulanate rather than amoxicillin alone be considered as first-line therapy for ABRS is based on 2 observations: (1) the increasing prevalence of *H. influenzae* among other upper respiratory tract infections of children, particularly AOM, since the introduction of

conjugated pneumococcal vaccines [84]; and (2) the high prevalence of  $\beta$ -lactamase-producing respiratory pathogens in ABRS (particularly *H. influenzae* and *Moraxella catarrhalis*) among recent respiratory tract isolates [85]. Although earlier studies that compared amoxicillin to amoxicillin-clavulanate did not find a superior outcome with amoxicillin-clavulanate [62, 64], these studies were performed in an era when both the prevalence of *H. influenzae* (33%) and the proportion of  $\beta$ -lactamase-producing *H. influenzae* (18%) were relatively low [30]. In contrast, both the prevalence of *H. influenzae* (40%–45%) and proportion of  $\beta$ -lactamase-producing *H. influenzae* (37%–50%) (extrapolated from middle ear fluid cultures of children with AOM) have markedly increased among other upper respiratory tract infections since the widespread use of conjugated pneumococcal vaccines [86].

The microbiology of acute sinusitis in children obtained by sinus puncture is summarized in Table 6. The data were analyzed according to reports published prior to 2000 and more recently in 2010. The microbiology of ABRS in children was last studied in detail in 1984 [81], and no current data are available. Thus, more recent data were extrapolated from middle ear fluid cultures of children with acute AOM in the post-pneumococcal vaccine era [84, 86, 91]. Whereas *S. pneumoniae* was more common than *H. influenzae* prior to 2000, the prevalence of *H. influenzae* has clearly increased while that of *S. pneumoniae* has decreased in the post-pneumococcal vaccine era, such that currently they are approximately equal [86]. Ampicillin resistance among *H. influenzae* due to  $\beta$ -lactamase production is highly prevalent worldwide [85]. In the United States during 2005–2007, 27%–43% of *H. influenzae* clinical isolates were resistant to amoxicillin but susceptible to amoxicillin-clavulanate [93–95] (Table 7). Furthermore, treatment failure from amoxicillin associated with the isolation of  $\beta$ -lactamase-producing *H. influenzae* has been well documented in children with ABRS [81, 96]. Accordingly, the addition of clavulanate would improve the coverage of many  $\beta$ -lactamase-producing respiratory pathogens in children with ABRS, estimated to be approximately 25% of all patients with ABRS, including approximately 25%–35% of *H. influenzae* and 90% of *M. catarrhalis* infections [94].

**Benefits.** The addition of clavulanate to amoxicillin substantially improves the coverage for both ampicillin-resistant *H. influenzae* and *M. catarrhalis* in ABRS.

**Harms.** The combination of clavulanate with amoxicillin for empiric therapy of ABRS adds to the cost, increased likelihood of adverse effects due to diarrhea, and rare instances of hypersensitivity reaction due to clavulanate.

**Other Considerations.** In children with vomiting that precludes administration of oral antibiotics, a single dose of ceftriaxone (50 mg/kg/day) may be given intravenously or intramuscularly. Therapy with an oral antibiotic may be initiated 24 hours later, provided the vomiting has resolved.



**Table 7. Antimicrobial Susceptibility of Invasive Community-Acquired Respiratory Pathogens in the United States**

Antimicrobial	Susceptible Breakpoint (µg/mL)		Harrison et al (2005–2007) [94]			Critchley et al (2005–2006) [93]		Sahm et al (2005) [95]	
	CLSI	PK/PD	MIC <sub>90</sub> (µg/mL)	CLSI (% Susceptible)	PK/PD (% Susceptible)	MIC <sub>90</sub> (µg/mL)	CLSI (% Susceptible)	MIC <sub>90</sub> (µg/mL)	CLSI (% Susceptible)
<i>Haemophilus influenzae</i>			n = 143 (42% BLP)			n = 987 (27% BLP)		n = 907 (28% BLP)	
Amox, standard	≤2	≤0.5	16	58	55				
Amox, high	≤4	≤4	16	58	58				
Amox-clav, standard	≤2/1	≤0.5/0.25	1	100	92	1	100	2	100
Amox-clav, high	≤4/2	≤4/2	1	100	100				
Cefaclor	≤8	≤0.5	16	83	4				
Cefprozil	≤8	≤1	16	83	29				
Cefuroxime axetil	≤4	≤1	2	99	88	2	98	2	100
Cefdinir	≤1	≤0.25	0.5	100	84	1	95		
Cefixime	NA	≤1	0.06	100	100				
Ceftriaxone	≤2	≤2	0.06	100	100				
Azithromycin	≤4	≤0.12	8	87	0	2	99	2	100
Levofloxacin	≤2	≤2	NA	NA	NA	≤0.06	100	0.03	100
TMP/SMX	≤0.5	≤0.5	8	73	73	8	65	>4	74
<i>Streptococcus pneumoniae</i>			n = 208 (41% PS, 29% PI, 30% PR)			n = 1543 (62% PS, 22% PI, 16% PR)		n = 4958 (65% PS, 17% PI, 17% PR)	
Amox, standard	NA	≤0.5	2	NA	74	2	92	2	92
Amox, high	≤2	≤2	2	89	89	NA	NA	NA	NA
Cefaclor	≤1	≤0.5	16	47	29	NA	NA	NA	NA
Cefprozil	≤2	≤1	16	71	67	NA	NA	NA	NA
Cefuroxime axetil	≤1	≤1	8	69	69	8	78	4	80
Cefdinir	≤0.5	≤0.25	16	59	59	8	77	NA	NA
Cefixime	NA	≤1	16	NA	58	NA	NA	NA	NA
Ceftriaxone	≤1	≤2	2	89	95	NA	NA	1	97
Azithromycin	≤0.5	≤0.12	16	63	57	8	66	>256	71
Levofloxacin	≤2	≤2	NA	NA	NA	1	99	1	99
TMP/SMX	≤0.5	≤0.5	16	51	51	8	69	4	73
Doxycycline	≤2	≤2	NA	NA	NA	NA	NA	>8	85
Clindamycin	≤0.25	≤0.25	16	85	85	NA	NA	0.06	88
<i>Moraxella catarrhalis</i>			n = 62 (95% BLP)			n = 486 (92% BLP)		n = 782 (94% BLP) <sup>a</sup>	
Amox, standard	NA	≤0.5	≥16	5	5	NA	NA	NA	NA
Amox, high	NA	≤2	≥16	5	11	NA	NA	NA	NA
Amox-clav, standard	NA	≤0.5/0.25	1	NA	89	0.25	NA	0.25	100
Amox-clav, high	≤4/2	≤2/1	1	NA	100	NA	NA	NA	NA

Table 7 continued.

Antimicrobial	Susceptible Breakpoint (µg/mL)			Harrison et al (2005–2007) [94]			Critchley et al (2005–2006) [93]			Sahm et al (2005) [95]		
	CLSI	PK/PD	MIC <sub>90</sub> (µg/mL)	CLSI (% Susceptible)	PK/PD (% Susceptible)	MIC <sub>90</sub> (µg/mL)	CLSI (% Susceptible)	MIC <sub>90</sub> (µg/mL)	CLSI (% Susceptible)	MIC <sub>90</sub> (µg/mL)	CLSI (% Susceptible)	
Cefaclor	≤8	≤0.5	8	95	7	NA	NA	NA	NA	NA	NA	
Cefprozil	NA	≤1	4	NA	37	NA	NA	NA	NA	NA	NA	
Cefuroxime axetil	≤4	≤1	4	98	37	2	NA	2	NA	2	99	
Cefdinir	NA	≤0.25	2	NA	81	0.5	NA	NA	NA	NA	NA	
Cefixime	NA	≤1	0.25	NA	100	NA	NA	NA	NA	NA	NA	
Ceftriaxone	≤2	≤2	2	97	97	NA	NA	NA	NA	NA	NA	
Azithromycin	≤2	≤0.12	0.06	100	98	≤0.12	NA	≤0.12	NA	0.03	100	
Levofloxacin	≤2	≤2	NA	NA	NA	≤0.06	NA	≤0.06	NA	0.06	100	
TMP/SMX	≤0.5	≤0.5	NA	NA	NA	0.5	NA	0.5	NA	0.25	99	

Abbreviations: Amox, amoxicillin; amox-clav, amoxicillin-clavulanate; BLP, β-lactamase positive; CLSI, Clinical Laboratory Standards Institute; MIC<sub>90</sub>, minimum inhibitory concentration for 90% of isolates; N, no. of isolates tested; NA, not available; PD/PK, pharmacodynamic/pharmacokinetic; PI, penicillin-intermediate; PR, penicillin-resistant; PS, penicillin-susceptible; TMP/SMX, trimethoprim-sulfamethoxazole.

<sup>a</sup> Data for 2004 were shown because data for 2005 were unavailable.

**Conclusions and Research Needs.** Continued surveillance of antimicrobial susceptibility profiles of all respiratory pathogens (both regional and national) should be performed at regular intervals to guide initial empiric antimicrobial therapy.

#### IV. Should Amoxicillin Versus Amoxicillin-Clavulanate Be Used for Initial Empiric Antimicrobial Therapy of ABRS in Adults?

##### Recommendation

4. Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in adults (weak, low).

##### Evidence Summary

National surveillance data in the United States indicate that during 2005–2007, the prevalence rate of β-lactamase-producing *H. influenzae* was 27%–43% [93–95] (Table 7). The rate of amoxicillin resistance varied from region to region, ranging from 35% in the Southeast to 25% in the Southwest, but there was little or no regional difference in the susceptibility to amoxicillin-clavulanate. As with children, posttreatment sinus cultures are rarely performed in adults in North America, and there are no reports of positive sinus cultures for β-lactamase-producing *H. influenzae* following amoxicillin therapy in adults with ABRS. However, in one Scandinavian study, a high percentage (49%) of patients with antimicrobial treatment failure had positive cultures for β-lactamase-producing *H. influenzae* by sinus puncture [77]. Most of these patients (66%) had received phenoxymethyl penicillin and none had received either amoxicillin or ampicillin. Thus, the recommendation of choosing amoxicillin-clavulanate over amoxicillin as first-line therapy for ABRS in adults is relatively weak. Furthermore, although *M. catarrhalis* is almost uniformly resistant to amoxicillin but susceptible to amoxicillin-clavulanate, it is a less frequent cause of ABRS in adults compared with children. Nevertheless, in a recent study in adults that examined the microbiology of ABRS by sinus puncture [45], *H. influenzae* was isolated in 36% of patients with positive bacterial cultures consistent with ABRS, compared with 38% for *S. pneumoniae* and 16% for *M. catarrhalis* (Table 6). Unfortunately, the rate of β-lactamase-producing *H. influenzae* was not reported in this study. Interestingly, similar to the case with AOM in children, the introduction of conjugated pneumococcal vaccines also had a significant impact on the frequency of recovery of both *H. influenzae* and *S. pneumoniae* in adults with maxillary sinusitis. Brook et al [97] obtained middle meatus cultures from 156 adults with ABRS between 1997 and 2000 (prevaccination) and 229 patients between 2001 and 2005 (postvaccination). The recovery of *S. pneumoniae* was significantly reduced (46% prevaccination vs 35% postvaccination;  $P < .05$ ), whereas that of *H. influenzae* was significantly increased (36% prevaccination vs 43% postvaccination;  $P < .05$ ). In the same study,

the proportion of  $\beta$ -lactamase-producing *H. influenzae* also increased slightly (from 33% to 39%), although this difference was not statistically significant.

Thus, the recommendation of amoxicillin-clavulanate in adult patients with ABRS is primarily based on in vitro susceptibility data and the current prevalence rates of  $\beta$ -lactamase production among *H. influenzae*.

**Benefits.** The addition of clavulanate to amoxicillin will improve the coverage of both ampicillin-resistant *H. influenzae* and *M. catarrhalis* in adults with ABRS.

**Harms.** The addition of clavulanate to amoxicillin adds to the cost of antibiotics, a potential increased risk of diarrhea, and rare instances of hypersensitivity reaction due to clavulanate.

**Other Considerations.** None.

**Conclusions and Research Needs.** Standard-dose amoxicillin-clavulanate is recommended as first-line therapy for ABRS in both children and adults. However, this regimen is inadequate for PNS *S. pneumoniae*, in which the mechanism for ampicillin resistance is due to a mutation in penicillin binding protein 3 (PBP3) that cannot be overcome by the addition of a  $\beta$ -lactamase inhibitor. In addition, there are increasing reports of  $\beta$ -lactamase-positive, amoxicillin-clavulanate-resistant strains of *H. influenzae* isolated from various parts of the world [85, 98]. The prevalence of these isolates in the United States is currently unknown. Continued surveillance of antimicrobial susceptibility profiles of all respiratory pathogens should be performed both nationally and regionally.

## V. When Is High-Dose Amoxicillin-Clavulanate Recommended During Initial Empiric Antimicrobial Therapy for ABRS in Children or Adults?

### Recommendation

5. High-dose (2 g orally twice daily or 90 mg/kg/day orally twice daily) amoxicillin-clavulanate is recommended for children and adults with ABRS from geographic regions with high endemic rates ( $\geq 10\%$ ) of invasive PNS *S. pneumoniae*, those with severe infection (eg, evidence of systemic toxicity with fever of 39°C [102°F] or higher, and threat of suppurative complications), attendance at daycare, age <2 or >65 years, recent hospitalization, antibiotic use within the past month, or who are immunocompromised (weak, moderate).

### Evidence Summary

High-dose amoxicillin is preferred over standard-dose amoxicillin primarily to cover PNS *S. pneumoniae* and the less common occurrence of ampicillin-resistant non- $\beta$ -lactamase-producing *H. influenzae* [94]. Increased resistance among PNS *S. pneumoniae* is due to alterations in PBP3 and not  $\beta$ -lactamase production. The frequency of PNS *S. pneumoniae* is highly variable depending on the geographic region, being highest in the Southeast (~25%) and lowest in the Northwest

(~9%) [93]. Using pre-2008 CLSI breakpoints for oral treatment of penicillin-intermediate (minimum inhibitory concentration [MIC]  $\leq 1$   $\mu\text{g/mL}$ ; treatable with high-dose amoxicillin) and penicillin-resistant *S. pneumoniae* (MIC  $\geq 2$   $\mu\text{g/mL}$ ; untreatable with high-dose amoxicillin), the Centers for Disease Control and Prevention showed in a 10-state surveillance study in 2006–2007 that 15% and 10% of all invasive *S. pneumoniae* isolates were penicillin-intermediate and penicillin-resistant, respectively, whereas 75% were susceptible [68]. Higher susceptibility profiles for *S. pneumoniae* were reported by Harrison et al (89% susceptible) [94], Critchley et al (92% susceptible) [93], and Sahm et al (92% susceptible) [95] (Table 7). In addition, introduction of the 13-valent pneumococcal conjugated vaccine (PCV13) in 2010 may further decrease the prevalence of invasive pneumococcal infections including those caused by some PNS *S. pneumoniae* isolates [99]. This would suggest that unless the endemic rate of PNS *S. pneumoniae* is unusually high ( $\geq 10\%$ ), standard-dose amoxicillin-clavulanate should suffice as first-line therapy for nonmeningeal pneumococcal infections including ABRS.

There are no clinical data in the literature that compared the efficacy of high-dose vs standard-dose amoxicillin, either with or without clavulanate, in the treatment of children or adults with ABRS. However, there is indirect evidence to support high-dose amoxicillin-clavulanate as initial empiric therapy of ABRS among patients with increased risk factors for PNS *S. pneumoniae* (such as those with prior hospitalization or recent antimicrobial use, attendance at daycare, age <2 or >65 years), and those who are severely ill and may have a poor outcome from treatment failure [100, 101].

There are also theoretical advantages of high-dose amoxicillin in the empiric treatment of ABRS. Fallon et al [102] utilized Monte Carlo simulations to predict steady-state bactericidal time-concentration profiles of various oral  $\beta$ -lactam regimens to achieve pharmacodynamic exposure against various pathogens causing AOM and ABRS. Against *S. pneumoniae*, high-dose amoxicillin (90 mg/kg/day) achieved the greatest cumulative fraction of response, followed by standard-dose amoxicillin-clavulanate and amoxicillin regimens. Amoxicillin-clavulanate also achieved the highest cumulative fraction of response against *H. influenzae* isolates. Apart from PNS *S. pneumoniae*, the emergence of  $\beta$ -lactamase-negative ampicillin-resistant *H. influenzae* (due to PBP3 mutation) may also favor the use of high-dose amoxicillin during initial empiric treatment of ABRS [85]. Clinicians should be alert to the possibility of such isolates, although reports in the United States are limited.

The main disadvantages of high-dose amoxicillin-clavulanate are the added cost and potential for more adverse effects. Thus, despite the theoretical advantages of high-dose vs standard-dose

**Table 8. Efficacy of Fluoroquinolones Compared to a  $\beta$ -Lactam for the Treatment of Acute Bacterial Rhinosinusitis**

Outcomes	Illustrative Comparative Risks <sup>a</sup> (95% CI)		Relative Effect, OR (95% CI)	No of Participants (No. of Studies)	Quality of the Evidence (GRADE)	Reference
	Assumed Risk	Corresponding Risk				
Clinical response follow-up: 10–31 days	$\beta$ -Lactam	FQ	1.09 (.85–1.39)	2133 (5 studies)	$\oplus \oplus \oplus \ominus$ moderate <sup>b,c,d,e</sup>	Karageorgopoulos et al [115]
	861 per 1000	871 per 1000 (840–896)				

Patient or population: patients with acute sinusitis. Settings: initial therapy. Intervention: FQ. Comparison:  $\beta$ -lactam.

Abbreviations: CI, confidence interval; FQ, fluoroquinolone, GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio.

<sup>a</sup> The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>b</sup> Only 5 of 11 studies included; only those comparing respiratory fluoroquinolones are included.

<sup>c</sup> Most enrolled on clinical diagnosis and may have included viral etiology.

<sup>d</sup> Three of 5 randomized, but not blinded.

<sup>e</sup> Difference in timing of endpoints (10–31 days).

amoxicillin-clavulanate, until clear evidence of high failure rates ( $\geq 10\%$ ) from standard-dose amoxicillin-clavulanate emerges, the panel consensus is to reserve high-dose amoxicillin-clavulanate for patients from geographic regions with high endemic rates of PNS *S. pneumoniae* ( $\geq 10\%$ , using 2008 CLSI revised breakpoints), those seriously ill with evidence of systemic toxicity (eg, fever of 39°C [102°F] or higher) and threat of suppurative complications, those who are immunocompromised, and those with risk factors for acquiring PNS *S. pneumoniae* as outlined above.

**Benefits.** Until a clear need for high-dose amoxicillin-clavulanate is demonstrated by unacceptably high failure rates from standard-dose amoxicillin-clavulanate, delaying the use of high-dose amoxicillin-clavulanate as empiric therapy for all patients with presumed ABRS may be more cost-effective and result in fewer adverse effects and less antibiotic selection pressure for resistance.

**Harms.** Standard-dose amoxicillin-clavulanate is inadequate for the treatment of ABRS caused by PNS *S. pneumoniae* and the rare occurrence of ampicillin-resistant  $\beta$ -lactamase–negative *H. influenzae*.

**Other Considerations.** It should be noted that the prevalence of resistant or intermediate *S. pneumoniae* in a given community may vary not only geographically but also temporally. This is evidenced by the shift in *S. pneumoniae* susceptibility profiles in some communities following the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7), which resulted in the subsequent emergence of highly virulent and resistant nonvaccine serotypes of *S. pneumoniae* such as serotypes 14 and 19A [86, 103]. In 2010, PCV13 replaced the PCV7 for all children [104]. PCV13 contains 6 additional pneumococcal serotype antigens including

serotype 19A and is expected to dramatically reduce PNS *S. pneumoniae* disease. Protection against serotype 19A disease has been documented in a PCV13 vaccine effectiveness study [99]. Thus, decisions regarding appropriate dosing regimens should be guided by antimicrobial susceptibility profiles of prevalent pathogens through diligent surveillance by local or national reporting agencies.

**Conclusions and Research Needs.** More studies are needed to directly compare the cost-effectiveness of high-dose vs standard-dose amoxicillin-clavulanate as initial empiric antimicrobial therapy of presumed ABRS in both adults and children.

## VI. Should a Respiratory Fluoroquinolone vs a $\beta$ -Lactam Agent Be Used as First-line Agents for the Initial Empiric Antimicrobial Therapy of ABRS?

### Recommendation

6. A  $\beta$ -lactam agent (amoxicillin-clavulanate) rather than a respiratory fluoroquinolone is recommended for initial empiric antimicrobial therapy of ABRS (weak, moderate).

### Evidence Summary

The respiratory fluoroquinolones (both levofloxacin and moxifloxacin) have remained highly active against all common respiratory pathogens, including PNS *S. pneumoniae* and  $\beta$ -lactamase–producing *H. influenzae* or *M. catarrhalis* [105, 106]. Nevertheless, respiratory fluoroquinolones were not superior to  $\beta$ -lactam antibiotics in 8 RCTs of the treatment of ABRS [107–114]. A meta-analysis of these trials confirmed that initial treatment with the newer fluoroquinolones conferred no benefit over  $\beta$ -lactam antibiotics [115]. The comparator agents in these trials were amoxicillin-clavulanate in 5, cefuroxime in 2, and cefdinir in 1. Specifically, in

a subset analysis of 5 studies that evaluated the efficacy of the respiratory fluoroquinolones (moxifloxacin, levofloxacin, or gatifloxacin) there was no difference in clinical outcomes compared with amoxicillin-clavulanate or cefuroxime. Clinical success was observed in 87% (924 of 1062) of patients treated with the fluoroquinolones compared with 86% (922 of 1071) treated with a  $\beta$ -lactam (Table 8). Adverse events occurred more frequently with the fluoroquinolones than with  $\beta$ -lactam antibiotics in 2 double-blind RCTs.

A limitation of these RCTs is that none evaluated high-dose amoxicillin-clavulanate as a comparator; accordingly, it is not possible to directly assess any difference between a respiratory fluoroquinolone and the currently recommended first-line agents for patients with severe infection or those at risk for PNS *S. pneumoniae* infection. It is also possible that high-dose amoxicillin-clavulanate may result in more adverse effects compared with a fluoroquinolone. The one RCT in which the microbiological data were most complete (all patients had cultures by maxillary sinus puncture or endoscopy of the middle meatus within 24 hours before the initiation of treatment) found that only 51% (292 of 576) had a pathogen identified [107]. In this study, the combined clinical and microbiological outcomes at 14–21 days of therapy were 86% (83 of 96) and 88% (85 of 97) for moxifloxacin and amoxicillin-clavulanate, respectively. It is likely that each of the study arms included patients with a viral rather than bacterial infection. However, even among patients with positive cultures by sinus puncture, a recent placebo-controlled RCT reported that the clinical response rate to moxifloxacin was not significantly different from placebo (78% vs 67%) [45]. Thus, the role of respiratory fluoroquinolones for the empiric treatment of moderate to severe infection in ABRS remains to be determined. At present, respiratory fluoroquinolones should be reserved for those who have failed to respond to first-line agents, those with a history of penicillin allergy, and as second-line therapy for patients at risk for PNS *S. pneumoniae* infection. This recommendation places a relatively high value on limiting the development of antibiotic resistance and resource use.

**Benefits.** Therapy with a  $\beta$ -lactam provided comparable efficacy in the clinical resolution of symptoms compared with fluoroquinolones without added cost or adverse effects.

**Harms.** Fluoroquinolones are associated with a variety of adverse effects including central nervous system events (seizures, headaches, dizziness, sleep disorders), peripheral neuropathy, photosensitivity with skin rash, disorders of glucose homeostasis (hypoglycemia and hyperglycemia), prolongation of QT interval, hepatic dysfunction, and skeletal muscular complaints. Risk of Achilles tendon rupture

is particularly high in the adult population (estimated prevalence rate, 15–20 per 100 000), particularly among those with advancing age and antecedent steroid therapy.

**Other Considerations.** Limiting the overuse of fluoroquinolones may slow the development of resistance against this class of antimicrobial agents.

**Conclusions and Research Needs.** The role of the respiratory fluoroquinolones in the initial empiric treatment of ABRS in an era of increasing antimicrobial resistance remains uncertain. Appropriately powered RCTs that directly compare the efficacy, adverse effects, and cost-benefit of the respiratory fluoroquinolones vs high-dose amoxicillin-clavulanate are warranted.

## VII. Besides a Respiratory Fluoroquinolone, Should a Macrolide, TMP/SMX, Doxycycline, or a Second- or Third-Generation Oral Cephalosporin Be Used as Second-line Therapy for ABRS in Children or Adults?

### Recommendations

7. Macrolides (clarithromycin and azithromycin) are not recommended for empiric therapy due to high rates of resistance among *S. pneumoniae* (~30%) (strong, moderate).

8. TMP/SMX is not recommended for empiric therapy due to high rates of resistance among both *S. pneumoniae* and *H. influenzae* (~30%–40%) (strong, moderate).

9. Doxycycline may be used as an alternative regimen to amoxicillin-clavulanate for initial empiric antimicrobial therapy of ABRS in adults because it remains highly active against respiratory pathogens and has excellent PK/PD properties (weak, low).

10. Second- and third-generation oral cephalosporins are no longer recommended for empiric monotherapy of ABRS owing to variable rates of resistance among *S. pneumoniae*. Combination therapy with a third-generation oral cephalosporin (cefixime or cefpodoxime) plus clindamycin may be used as second-line therapy for children with non-type I penicillin allergy or those from geographic regions with high endemic rates of PNS *S. pneumoniae* (weak, moderate).

### Evidence Summary

Because RCTs have not found significant differences in response rates to various antimicrobial regimens for ABRS [24, 44], selection of alternative antimicrobial agents is primarily based on known prevalence of respiratory pathogens in the community, antimicrobial spectrum (including PNS *S. pneumoniae* and  $\beta$ -lactamase-producing *H. influenzae* and *M. catarrhalis*), cost, dosing convenience and tolerance or adverse effects. TMP/SMX, doxycycline, macrolides, second- or third-generation cephalosporins, and fluoroquinolones have all been recommended as alternatives to amoxicillin or amoxicillin-clavulanate in the past [116]. However, surveillance of recent respiratory isolates in the United States indicates a variable

but significant increase in penicillin-intermediate and macrolide or TMP/SMX-resistant *S. pneumoniae* and  $\beta$ -lactamase-producing *H. influenzae* [93–95] (Table 7). Cross-resistant and multidrug-resistant *S. pneumoniae* is also increasing (regional prevalence rates, 9%–25% in the United States during 2005–2006) [93]. Accordingly, antimicrobial agents previously recommended as an alternative to amoxicillin or amoxicillin-clavulanate, such as macrolides, TMP-SMX, or second- or third-generation oral cephalosporins, can no longer be recommended because of increasing resistance among *S. pneumoniae* and/or *H. influenzae*.

**Macrolides.** The prevalence of macrolide-resistant *S. pneumoniae* in the United States has escalated dramatically since the 1990s [117]. Surveillance data from the TRUST (Tracking Resistance in the United States Today) and PROTEKT (Prospective Resistant Organism Tracking and Epidemiology of the Ketolide Telithromycin) studies reveal that whereas only 5% of *S. pneumoniae* clinical isolates in the United States were resistant to macrolides in 1993, >30% had become resistant by 2006 [117]. During 2005–2007, 43% of invasive *S. pneumoniae* isolates were macrolide-resistant (Table 7). Importantly, the more prevalent low-level resistant genotypes caused by efflux mutations (*mefA* or *mefE*) were being gradually replaced by highly resistant methylation mutations (*ermB*), such that by 2006, *ermB*-mediated resistance (including resistance due to *ermB* and *mefA* combinations) accounted for 42% of all macrolide-resistant *S. pneumoniae* [118]. Macrolide resistance among *S. pneumoniae* is strongly correlated to prior antibiotic use, particularly macrolides,  $\beta$ -lactams, and TMP-SMX, and multidrug resistance or cross-resistance to these antibiotics is common [117]. The prevalence of macrolide resistance is highest among isolates from children <2 years of age (>50% during 2000–2006) [118]. In contrast to low-level resistance mediated by *mefA*, high-level resistance mediated by *ermB* cannot be overcome during therapy with macrolides despite their excellent PK/PD properties. Although the association between in vitro resistance and adverse clinical outcome in acute rhinosinusitis remains generally unproven (owing to lack of microbiological documentation), treatment failure associated with *ermB*-mediated resistance in bacteremic pneumococcal disease has been well documented [119]. In light of these findings, macrolides are no longer recommended for empiric antimicrobial therapy of *S. pneumoniae* infections [82, 93]. Although telithromycin remains highly active against all respiratory isolates including penicillin-resistant *S. pneumoniae* [93], it is no longer approved for the treatment of ABRS due to rare but severe instances of hepatotoxicity [120].

**Trimethoprim/Sulfamethoxazole.** TMP/SMX is also no longer recommended for empiric treatment of ABRS due to high rates of resistance among both *S. pneumoniae* and

*H. influenzae*. Harrison et al [94] evaluated the susceptibility to common pediatric antibiotics among *S. pneumoniae*, nontypeable *H. influenzae*, and *M. catarrhalis* isolated from 2005 through 2007. TMP/SMX resistance rates according to CLSI breakpoints were 50% for *S. pneumoniae* (75% for serotype 19A), 27% for *H. influenzae*, and 2% for *M. catarrhalis* (73% according to PK/PD breakpoints). Resistance to TMP/SMX among *S. pneumoniae* isolates is due to mutations in the dihydrofolate reductase gene [121], and is strongly associated with prior exposure to TMP/SMX, macrolides, or penicillin [117]. Not surprisingly, TMP/SMX resistance rates are significantly higher (>80%) among macrolide- or penicillin-resistant *S. pneumoniae* [122]. Similarly, among *H. influenzae* isolates collected during 2001–2005 in the TRUST program, resistance rates to TMP/SMX was 25% [95]. Resistance is twice as common among  $\beta$ -lactamase-producing *H. influenzae* as among its non- $\beta$ -lactamase-producing counterparts (32% vs 16%, respectively) [123]. Additionally, TMP/SMX has been associated with rare but severe adverse reactions from toxic epidermal necrolysis [124].

**Doxycycline.** Doxycycline has remained active against all common respiratory pathogens, although there are few published reports for recent isolates in the United States [125, 126]. Data from national surveys in Canada reveal that doxycycline is highly active against all recent respiratory pathogens (93.2% of *S. pneumoniae*, 98.1% of *H. influenzae*, and 99.7% of *M. catarrhalis*) (G. G. Zhanel, University of Manitoba, Winnipeg; written communication, August 2010) [127, 128]. Similarly, in England, Wales, and Northern Ireland, recent invasive isolates of both *S. pneumoniae* and *H. influenzae* have remained highly susceptible to doxycycline (91% and 99%, respectively) [129]. However, the rate of cross-resistance to doxycycline among PNS *S. pneumoniae* in North America is unknown but is expected to be higher in these isolates compared with penicillin-susceptible strains. In one Swedish study, the rate of doxycycline resistance was 24% among PNS *S. pneumoniae* compared with 2% among penicillin-susceptible isolates collected during 2001–2004 [130]. The PK/PD properties of doxycycline are favorable and similar to those of the respiratory fluoroquinolones [125]. A recent prospective double-blind trial of doxycycline vs levofloxacin in the treatment of hospitalized patients with community-acquired pneumonia demonstrated similar clinical response rates and length of stay but at a significantly lower cost for doxycycline [126]. These data support the recommendation of doxycycline for the outpatient treatment of community-acquired pneumonia in the 2007 IDSA guideline [131]. There are only 5 RCTs of doxycycline for ABRS in the English literature since 1980, including 2 placebo-controlled trials [46, 132] and 3 comparative trials with brodimoprim, spiramycin, and loracarbef, respectively [133–135]. The clinical success rates were 80% for doxycycline and 67%

**Table 9. Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Children**

Indication	First-line (Daily Dose)	Second-line (Daily Dose)
Initial empirical therapy	● Amoxicillin-clavulanate (45 mg/kg/day PO bid)	● Amoxicillin-clavulanate (90 mg/kg/day PO bid)
β-lactam allergy		
Type I hypersensitivity		● Levofloxacin (10–20 mg/kg/day PO every 12–24 h)
Non-type I hypersensitivity		● Clindamycin <sup>a</sup> (30–40 mg/kg/day PO tid) plus cefixime (8 mg/kg/day PO bid) or cefpodoxime (10 mg/kg/day PO bid)
Risk for antibiotic resistance or failed initial therapy		● Amoxicillin-clavulanate (90 mg/kg/day PO bid)
		● Clindamycin <sup>a</sup> (30–40 mg/kg/day PO tid) plus cefixime (8 mg/kg/day PO bid) or cefpodoxime (10 mg/kg/day PO bid)
		● Levofloxacin (10–20 mg/kg/day PO every 12–24 h)
Severe infection requiring hospitalization		● Ampicillin/sulbactam (200–400 mg/kg/day IV every 6 h)
		● Ceftriaxone (50 mg/kg/day IV every 12 h)
		● Cefotaxime (100–200 mg/kg/day IV every 6 h)
		● Levofloxacin (10–20 mg/kg/day IV every 12–24 h)

Abbreviations: bid, twice daily; IV, intravenously; PO, orally; qd, daily; tid, 3 times a day.

<sup>a</sup> Resistance to clindamycin (~31%) is found frequently among *Streptococcus pneumoniae* serotype 19A isolates in different regions of the United States [94].

for placebo in one study [47], and 85% for both groups in the second study [46]. Of the 3 comparative trials, only the Scandinavian study enrolled sufficient patients [135]. In this double-blind, randomized study, 662 patients were enrolled and both pre- and posttreatment sinus punctures were performed. However, only 50% yielded positive pretreatment cultures and were evaluable for bacteriological eradication. In the intent-to-treat analysis, the clinical success rate was 91% in both groups (300 of 330 for doxycycline vs 303 of 332 for loracarbef). In the evaluable patients, the clinical success rate was 93% (153 of 164) in the doxycycline group vs 98% (165 of 168) in the loracarbef group ( $P = .05$  with Yates's correction) within 3 days posttreatment, and 92% for both groups at follow-up 1–2 weeks posttreatment (121 of 131 for doxycycline vs 129 of 140 for loracarbef). The microbiological eradication rate posttreatment was 81% (133 of 164) for doxycycline and 80% (135 of 168) for loracarbef. Microbiological failure due to presence of the same pathogen in the posttreatment cultures occurred in 27 (16%) of doxycycline-treated patients and 21 (13%) of loracarbef-treated patients. A different organism was isolated from posttreatment cultures in 4 (2.4%) of doxycycline vs 12 (7.1%) of loracarbef patients. The significance of these posttreatment cultures is difficult to interpret since they do not always correlate with the clinical response. Nevertheless, the available clinical as well as microbiological and PK/PD data do support the use of doxycycline as an alternative to amoxicillin-clavulanate for empiric antimicrobial therapy of ABRS in adults at low risk for acquisition of PNS *S. pneumoniae*.

**Oral Cephalosporins.** The in vitro activity of second- and third-generation oral cephalosporins (such as cefaclor, cefprozil, cefuroxime axetil, cefpodoxime, cefdinir, and cefixime) are highly variable particularly against penicillin-intermediate and resistant *S. pneumoniae*. Among these oral cephalosporins, cefpodoxime, cefuroxime axetil, and cefdinir are moderately active against penicillin-intermediate *S. pneumoniae* (<50% susceptible) followed by cefixime, whereas cefaclor and cefprozil are inactive [95, 136, 137]. Oral cephalosporins including cefpodoxime and cefdinir are inactive against penicillin-resistant *S. pneumoniae* [136, 138]. Intravenous ceftriaxone and cefotaxime remain active against nearly all *S. pneumoniae*, including penicillin-resistant strains, and are preferred as second-line empiric therapy (in place of high-dose amoxicillin-clavulanate) for hospitalized patients with severe infections. Cefpodoxime is the most active oral cephalosporin against both *H. influenzae* and *M. catarrhalis* (both β-lactamase positive and negative), followed by cefixime, cefuroxime, and cefdinir [138, 139]. Cefaclor and cefprozil are least active (Table 7). Based on these in vitro data, it is clear that considerable variability exists in the activity of second- and third-generation oral cephalosporins, particularly against *S. pneumoniae* and *H. influenzae*. For this reason, these agents are no longer recommended as monotherapy for the initial empiric treatment of ABRS in children or adults. If an oral cephalosporin is to be used, a third-generation cephalosporin (eg, cefixime or cefpodoxime) in combination with clindamycin is recommended for patients with ABRS from geographic regions with high endemic rates of PNS *S. pneumoniae* ( $\geq 10\%$  using 2008 CLSI revised breakpoints). However, clindamycin resistance is reported

**Table 10. Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Adults**

Indication	First-line (Daily Dose)	Second-line (Daily Dose)
Initial empirical therapy	● Amoxicillin-clavulanate (500 mg/125 mg PO tid, or 875 mg/125 mg PO bid)	● Amoxicillin-clavulanate (2000 mg/125 mg PO bid)
β-lactam allergy		● Doxycycline (100 mg PO bid or 200 mg PO qd)
		● Doxycycline (100 mg PO bid or 200 mg PO qd)
		● Levofloxacin (500 mg PO qd)
		● Moxifloxacin (400 mg PO qd)
Risk for antibiotic resistance or failed initial therapy		● Amoxicillin-clavulanate (2000 mg/125 mg PO bid)
		● Levofloxacin (500 mg PO qd)
		● Moxifloxacin (400 mg PO qd)
Severe infection requiring hospitalization		● Ampicillin-sulbactam (1.5–3 g IV every 6 h)
		● Levofloxacin (500 mg PO or IV qd)
		● Moxifloxacin (400 mg PO or IV qd)
		● Ceftriaxone (1–2 g IV every 12–24 h)
		● Cefotaxime (2 g IV every 4–6 h)

Abbreviations: bid, twice daily; IV, intravenously; PO, orally; qd, daily; tid, 3 times a day.

frequently among *S. pneumoniae* serotype 19A isolates (~31%) [94]. In such instances, a fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative. The recommended first-line and second-line regimens for empiric antimicrobial therapy of ABRS in children and adults are summarized in Tables 9 and 10, respectively.

**Benefits.** The respiratory fluoroquinolones are active against both β-lactamase-positive and -negative respiratory pathogens common in ABRS and can be administered with once- or twice-daily dosing regimens and improved compliance. Doxycycline appears more cost-effective than the respiratory fluoroquinolones. Third-generation oral cephalosporins (eg, cefixime or cefpodoxime) are well tolerated with minimal adverse effects. However, their coverage for *S. pneumoniae* is variable.

**Harms.** The respiratory fluoroquinolones are more costly than doxycycline, and escalating resistance with increased usage is a concern. Similar to other fluoroquinolones, moxifloxacin has been associated with severe hepatotoxicity [140, 141]. Doxycycline is not recommended for children ≤8 years of age due to staining of teeth. Oral third-generation cephalosporins are relatively costly and may cause diarrhea or hypersensitivity reactions. Clindamycin is an important cause of *Clostridium difficile*-associated enterocolitis, and clindamycin resistance is common among *S. pneumoniae* serotype 19A isolates (~31%).

**Other Considerations.** The introduction and large-scale implementation of PCV7 has led to the emergence of more virulent and resistant nonvaccine serotypes such as serotype

19A [86, 103]. The introduction of PCV13, which contains 6 additional serotype antigens including serotype 19A, is anticipated to decrease both overall and resistant invasive pneumococcal disease [99]. However, ongoing surveillance is required to detect the possibility of other emerging non-vaccine serotypes of PNS *S. pneumoniae*.

**Conclusions and Research Needs.** Doxycycline should be included in national and regional surveillance studies of respiratory pathogens, and more RCTs with this antimicrobial agent in the empiric treatment of adults with ABRS are warranted. Among the third-generation oral cephalosporins, cefditoren appears to have the best intrinsic activity against all common respiratory pathogens including PNS *S. pneumoniae* [137, 142]. More RCTs with this agent for the treatment of ABRS are warranted in both adults and children.

#### VIII. Which Antimicrobial Regimens Are Recommended for the Empiric Treatment of ABRS in Adults and Children With a History of Penicillin Allergy?

##### Recommendations

11. Either doxycycline (not suitable for children) or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy in adults who are allergic to penicillin (strong, moderate).

12. Levofloxacin is recommended for children with a history of type I hypersensitivity to penicillin; combination therapy with clindamycin plus a third-generation oral cephalosporin (cefixime or cefpodoxime) is recommended in children with a history of non-type I hypersensitivity to penicillin (weak, low).



### Evidence Summary

In patients with a questionable history of penicillin allergy, skin testing is strongly recommended to confirm or exclude an immediate hypersensitivity response. If an immunoglobulin E–mediated immediate-type hypersensitivity response is documented, a respiratory fluoroquinolone (levofloxacin, moxifloxacin) or doxycycline is recommended for adults. Macrolides and TMP/SMX, previously preferred for empiric treatment of ABRS in patients allergic to penicillin, can no longer be recommended because of increasing resistance among both *S. pneumoniae* and *H. influenzae*. The respiratory fluoroquinolones remain highly active against all common pathogens in ABRS and their ability to rapidly eradicate bacteria from the maxillary sinuses is well established [143, 144]. Doxycycline is also highly active against all common pathogens in ABRS and its PK/PD properties are similar to the respiratory fluoroquinolones.

For children with a history of immediate-type hypersensitivity response, levofloxacin is recommended as an alternative to amoxicillin-clavulanate, because experience with moxifloxacin in children is relatively scant and doxycycline is not recommended due to staining of teeth. Although use of levofloxacin in children is currently approved by the US Food and Drug Administration (FDA) only for patients following inhalational exposure to anthrax [145], its safety profile in children has been studied extensively [146–149]. The safety and tolerability of levofloxacin in children was assessed prospectively among 2523 children who participated in several randomized but nonblinded efficacy trials in the Pediatric Levaquin Program [149]. Levofloxacin was well tolerated during and for 12 months following therapy as evidenced by a similar incidence and character of adverse events in children receiving levofloxacin compared with those who received nonfluoroquinolone antibiotics. However, the incidence of musculoskeletal events (tendonopathy, arthritis, or arthralgia) involving weight-bearing joints was greater in levofloxacin-treated children at 2 months (1.9% vs 0.79%;  $P = .025$ ) and at 12 months (2.9% vs 1.6%;  $P = .047$ ) [150]. Similarly, the safety profile of ciprofloxacin in children was assessed prospectively among 684 children enrolled in several randomized double-blind efficacy trials. Although the difference was not statistically significant, the rate of arthropathy at 6 weeks among 335 children who received ciprofloxacin was higher than among 349 children who received a non-fluoroquinolone comparator both at 6 weeks (9.3% vs 6.0%, respectively [95% CI,  $-.8$  to 7.2]) and 1 year of follow-up (13.7% vs 9.5%, respectively [95% CI,  $-.6$  to 9.1]) [150]. Achilles tendon rupture, a known complication associated with the use of fluoroquinolone antibiotics in adults, is extremely rare in the pediatric population. The American Association of Pediatrics recently issued a policy statement

concerning the use of fluoroquinolones in several pediatric infections, including conjunctivitis, respiratory tract infections, and gastrointestinal and urinary tract infections [150]. It was concluded that use of a fluoroquinolone in a child or adolescent may be justified in situations where there is no safe and effective alternative. In light of these findings, the recommendation that levofloxacin be used as an alternative to amoxicillin-clavulanate in children with immediate-type hypersensitivity reactions to penicillin appears warranted.

For children with a history of non–type I hypersensitivity reaction to penicillin, a third-generation oral cephalosporin (eg, cefixime or cefpodoxime) in combination with clindamycin is recommended. The former is active against most strains of *H. influenzae* and *M. catarrhalis*, whereas clindamycin is active against most *S. pneumoniae* including some penicillin-intermediate and resistant strains (~85% susceptible to CLSI breakpoints) [94]. However, clindamycin resistance has been reported frequently among *S. pneumoniae* serotype 19A isolates (~31% resistant) [94]. In such instances, levofloxacin is recommended as an alternative. There is inadequate experience with cefditoren monotherapy for ABRS in children at this time. The recommended regimens for empiric antimicrobial therapy of ABRS in children and adults with a history of penicillin allergy are summarized in Tables 9 and 10, respectively.

**Benefits.** Doxycycline is a cost-effective alternative to the respiratory fluoroquinolones in adults who cannot tolerate amoxicillin-clavulanate.

**Harms.** The long-term safety of respiratory fluoroquinolones in children requires further evaluation.

**Other Considerations.** True type I hypersensitivity to  $\beta$ -lactam antibiotics is relatively uncommon. Every effort should be made to document such reactions with appropriate skin testing.

**Conclusions and Research Needs.** The increasing prevalence of PNS and cross-resistant *S. pneumoniae* among respiratory pathogens has complicated the management of penicillin-allergic patients and limited the choice of alternative agents particularly in children. Additional studies of the safety and efficacy of respiratory fluoroquinolones and monotherapy with cefditoren for ABRS in children are warranted.

### IX. Should Coverage for *S. aureus* (Especially MRSA) Be Provided Routinely During Initial Empiric Therapy of ABRS?

#### Recommendation

13. Although *S. aureus* (including MRSA) is a potential pathogen in ABRS, based on current data, routine antimicrobial coverage for *S. aureus* or MRSA during initial empiric therapy of ABRS is not recommended (strong, moderate).

## Evidence Summary

Payne et al [151] performed a meta-analysis on the recovery rates of *S. aureus* either by sinus puncture or middle meatus cultures in patients enrolled in prospective antimicrobial trials for ABRS. A total of 16 trials involving 4099 study patients reported in the English literature during 1990–2006 were included for analysis. The recovery rate was highly variable, ranging from 0% to 31% (mean, 8.8% [95% CI, 5.1–12.5]; median, 8.0%). Furthermore, these rates were somewhat inflated because they were based on the percentage of patients with positive sinus cultures. When the total numbers of enrolled patients are considered, the recovery rate of *S. aureus* is much lower, ranging from 0% to 21% (mean, 5.6% [95% CI, 3.1–8.1]; median, 4.6%). Brook et al [152] and Huang and Hung [153] also performed prospective studies by sinus puncture or culture of the middle meatus from 845 patients with ABRS during 2000–2006. Recovery rates of *S. aureus* were 8.5%–8.8% during 2000–2003 and 10.3% during 2004–2006. The corresponding recovery rates for MRSA were 2.5%–2.7% during 2000–2003 and 7.1% during 2004–2006. Previous antimicrobial therapy, recent hospitalization and a history of nasal surgery were the most important risk factors for recovery of MRSA from sinus cultures [153]. However, because the nose is a well-known reservoir for *S. aureus*, there remains a concern that at least in some instances the recovery of *S. aureus* could be due to contamination by the nasal flora during sinus aspiration or acquisition of cultures of the middle meatus. The concordance of results from sinus tap and middle meatus cultures does not eliminate this possibility as inadvertent contamination may occur by either specimen collection technique. In support of this notion, 7 of the 16 patients with MRSA reported by Huang and Hung were also positive for other well-established respiratory pathogens, and all patients recovered despite the fact that 6 of them received inadequate antimicrobial therapy for MRSA. Because both *S. aureus* (13%–20%) and *Staphylococcus epidermidis* (36%–50%) may be isolated from endoscopically guided middle meatus cultures in normal subjects [154, 155], only heavy growth (3 + or  $>10^4$  colony-forming units/mL) should be considered potential pathogens rather than commensal flora [156]. In the meta-analysis cited above [151], it is unclear whether quantitative cultures were performed in the various studies included for analysis. Collectively, these data do not refute the contention that *S. aureus* may be an important causative agent in ABRS, but there is insufficient evidence at the present time to support coverage for this organism during initial empiric therapy of ABRS. However, in severely ill patients with clinical manifestations suggestive of orbital or intracranial extension of infection, and hospitalized patients with nosocomial sinusitis associated with prolonged nasal

intubation, empiric coverage for MRSA while awaiting confirmation from positive cultures of the sinus or middle meatus would appear reasonable.

**Benefits.** More stringent criteria for establishing a causative role of *S. aureus* in ABRS will minimize overutilization of antistaphylococcal therapy.

**Harms.** Obtaining cultures of the middle meatus or sinus aspirates may not be well tolerated in children.

**Other Considerations.** None.

**Conclusions and Research Needs.** MRSA is an important pathogen both in the community and the healthcare setting. Accurate diagnosis of MRSA rhinosinusitis with microbiological confirmation is critical for appropriate antimicrobial therapy. More studies are needed to document the utility of endoscopically guided cultures of the middle meatus for distinguishing true infection from contamination by commensal flora.

## X. Should Empiric Antimicrobial Therapy for ABRS Be Administered for 5–7 Days Versus 10–14 Days?

### Recommendations

14. The recommended duration of therapy for uncomplicated ABRS in adults is 5–7 days (weak, low-moderate).

15. In children with ABRS, the longer treatment duration of 10–14 days is still recommended (weak, low-moderate).

### Evidence Summary

Existing clinical guidelines for ABRS generally recommend a course of antimicrobial therapy for 10–14 days, primarily on the basis of the duration of therapy in various RCTs [25]. Some investigators have recommended that antimicrobial therapy be continued for 7 days beyond the resolution of symptoms [157]. Kutluhan and colleagues [158] prospectively evaluated the duration of antimicrobial therapy and its effect on the nasal smears obtained from 4 patient groups with acute maxillary sinusitis who received antibiotics for 7, 14, 21, or 28 days. In all patients, the microbiology of maxillary sinusitis was confirmed by sinus puncture, and antibiotics were selected based on in vitro susceptibility. These authors concluded that the most appropriate duration of antimicrobial therapy for acute maxillary sinusitis was at least 2 weeks, because a significant difference in the neutrophil counts of nasal smears was observed in the study groups between 7 and 21 days of antimicrobial therapy. However, neutrophil count in nasal smears is a poor criterion of responsiveness to antimicrobial therapy. In other clinical trials, no significant difference in clinical resolution rates was observed among patients receiving 6–10 days vs 3–5 days of various antimicrobial regimens [159–163]. A recent meta-analysis by Falagas et al [164] examined the efficacy and safety of short vs longer courses of antimicrobial therapy for adults with ABRS enrolled in 12 RCTs. No statistical difference in efficacy was noted between short-course

**Table 11. Long Versus Short Courses of Antimicrobial Therapy for Acute Bacterial Rhinosinusitis [164]**

Outcomes	Illustrative Comparative Risks <sup>a</sup> (95% CI)		Relative Effect, OR (95% CI)	No. of Participants (No. of Studies)	Quality of the Evidence (GRADE)
	Assumed Risk	Corresponding Risk			
	Long Course (10–14 Days) Antibiotic Therapy	Short Course (5–7 Days) Antibiotic Therapy			
Clinical success with test-of-cure visit	Study population (medium-risk)		0.95 (.81–1.12)	4430 (12 studies)	⊕⊕⊕⊕ low <sup>b,c</sup>
Follow-up: 10–36 days	841 per 1000	834 per 1000 (811–856)			
Any adverse events	Study population (medium-risk)		0.88 (.71–1.09)	4172 (10 studies)	⊕⊕⊕⊕ low <sup>b,c,d</sup>
Follow-up: 10–36 days	258 per 1000	234 per 1000 (198–275)			
Any adverse effects	Study population (medium-risk)		0.79 (.63–.98)	2151 (5 studies)	⊕⊕⊕⊕ moderate <sup>d</sup>
(Only studies comparing 5 days vs 10 days of treatment were included)	232 per 1000	193 per 1000 (160–228)			
Follow-up: 10–36 days					

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio.

<sup>a</sup> The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>b</sup> Only included the per-protocol patients.

<sup>c</sup> Only 3 studies with a microbiological endpoint, variation in use of concomitant therapy.

<sup>d</sup> Adjunctive therapy was variable throughout studies.

(3–7 days) vs long-course (6–10 days) antibiotic therapy (OR, 0.95 [95% CI, .81–1.12]). In addition, no differences in microbiological efficacy (OR, 1.30 [95% CI, .62–2.74]), relapse rates (OR, 0.95 [CI .63–1.37]) or adverse effects (OR, 0.88 [CI, .71–1.09]) were found. However, if only the studies that compared 5 days (short-course) vs 10 days (long-course) were included (5 RCTs), adverse effects were significantly fewer in the short-course treatment groups (OR, 0.79 [95% CI, .63–.98]). This meta-analysis has a number of limitations. The study population was heterogeneous with respect to the entry criterion of symptom duration (any patient with symptoms <30 days with positive radiologic findings). There was overlap in the duration of short-course (3–7 days) vs long-course (6–10 days) treatment groups. Last, the concomitant administration of adjunctive medications may have minimized any real differences between the treatment groups in the various trials (Table 11). A major concern raised from earlier published RCTs is that the favorable outcome of shorter duration of treatment might be attributed to inclusion of patients without microbiological confirmation of ABRS. However, a recent study suggested that even among patients with confirmation of ABRS by sinus puncture, the clinical cure rate of treatment with 5 days of moxifloxacin was not significantly better than placebo (78% vs 67%, respectively) [45].

The duration of treatment for 5–7 days is chosen somewhat arbitrarily and is intermediate in the range of

literature recommendations, which varies from 3–5 days, to 5–7 days, to 6–10 days [164]. This recommendation is considered reasonable since in most patients with confirmation of ABRS by sinus puncture, both symptomatic improvement and bacteriological eradication from the maxillary sinus can be expected within 72 hours after initiation of appropriate antimicrobial therapy (see question XIV following). In any event, duration of antimicrobial therapy beyond 10 days in adult patients with uncomplicated ABRS is likely excessive. Data in pediatric patients, however, are inconclusive because the efficacy of shorter courses of therapy has not been specifically studied in a rigorous randomized fashion [165].

**Benefits.** Short courses of antimicrobial therapy may offer several advantages over longer courses of therapy including improved patient compliance, fewer adverse events, decreased bacterial antibiotic resistance, and lower cost [159, 160, 166–168].

**Harms.** Shorter courses of antimicrobial therapy may result in relapse or recurrent infection, particularly among the elderly and those with underlying disease or who are immunocompromised.

**Other Considerations.** None.

**Conclusions and Research Needs.** Most clinical trials of antimicrobial therapy in ABRS have excluded severely ill patients and have focused exclusively on acute maxillary sinusitis with little information on patients with involvement of

**Table 12. Nasal Saline Irrigation Compared to No Irrigation in Adults and Children With Acute Bacterial Rhinosinusitis or Rhinitis**

Outcomes	Illustrative Comparative Risks <sup>a</sup> (95% CI)		Relative Effect, OR (95% CI)	No. of Participants (No. of Studies)	Quality of the Evidence (GRADE)	Reference
	Assumed Risk	Corresponding Risk				
Mean nasal symptom score (0–4) at day 3		Mean nasal symptom score in the intervention groups was 0.07 standard deviations lower (0.45 lower to 0.31 higher)		108 (2 studies)	⊕⊕⊕⊕ low <sup>b,c,d,e</sup>	Adam et al, Bollag et al [170, 171]
Mean nasal secretion score (0–4) AT 3 weeks	2.06	Mean nasal secretion score in the intervention groups was 0.34 lower (0.49–0.19 lower)		490 (1 study)	⊕⊕⊕⊕ low <sup>c,d</sup>	Slapak et al [172]
Mean nasal patency score (0–4) at 3 weeks	1.58	Mean nasal patency at 2nd visit in the intervention groups was 0.33 lower (0.47–0.19 lower)		490 (1 study)	⊕⊕⊕⊕ low <sup>c,d</sup>	Slapak et al [172]
Antibiotic usage at 8 weeks	Study population (medium-risk) 89 per 1000    41 per 1000 (17–96)		0.44 (.18–1.09)	389 (1 study)	⊕⊕⊕⊕ moderate <sup>d</sup>	Slapak et al [172]
Time off work or school at 12 weeks	Study population (medium-risk) 248 per 1000    87 per 1000 (50–149)		0.29 (.16–.53)	389 (1 study)	⊕⊕⊕⊕ moderate <sup>d</sup>	Slapak et al [172]

Patient or population: patients with ABRS or common cold in adults and children. Intervention: nasal saline irrigation. Comparison: no irrigation.

Abbreviations: ABRS, acute bacterial rhinosinusitis; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio.

<sup>a</sup> The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>b</sup> Both studies were designed to look at other endpoints, such as nasal saline vs hypertonic saline or medicated nose drops. Nasal saline vs no nasal saline comparison was obtained by comparing the saline intervention to the control group in each study.

<sup>c</sup> Symptom score was very subjective, simply using a 1–4 scale.

<sup>d</sup> Blinding is difficult with irrigation vs no irrigation.

<sup>e</sup> It is not clear how many patients had ABRS; many if not most appear to have had simply a upper respiratory infection.

other sinuses. Further research is needed regarding the optimal duration of antimicrobial treatment in children and adults in whom the likelihood of a viral URI has been minimized by adhering to stringent clinical inclusion criteria.

### XI. Is Saline Irrigation of the Nasal Sinuses of Benefit as Adjunctive Therapy in Patients With ABRS?

#### Recommendation

16. Intranasal saline irrigations with either physiologic or hypertonic saline are recommended as an adjunctive treatment in adults with ABRS (weak, low-moderate).

#### Evidence Summary

There is limited evidence in support of physiologic or hypertonic saline irrigations as adjunctive therapy for patients with ABRS. A recent Cochrane review evaluated the efficacy of saline nasal irrigations in treating acute URIs including acute rhinosinusitis [169]. Three RCTs (total of 618 participants) were included for analysis and various nasal symptom scores were assessed. Although significant improvements were

observed in some symptom scores (nasal secretion, nasal patency, and overall health status), these changes were relatively minor (Table 12). The authors concluded that the trials were too small and had too high a risk of trial bias to be confident that the benefits were meaningful. Nevertheless, there was a trend toward reduced antibiotic use in one study as well as a significant reduction in time lost from work [172].

The value of intranasal saline irrigation in young children is less certain. In a small clinical trial, 69 children with acute sinusitis (mean age, 6 years [range, 3–12]) were randomized to receive either saline irrigation or no irrigation [173]. The Total Nasal Symptom Scores as well as the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire were significantly improved in the saline group. More important, the nasal peak expiratory flow rate was significantly improved in the saline irrigation group compared with no irrigation. However, it is unclear how well the saline irrigation procedure was tolerated particularly among the younger children. Minor discomfort is common during saline irrigation, and installation of nasal drops

is less well tolerated by babies, often making them cry and undoing any potential benefit of symptom relief.

Several other studies evaluated the role of hypertonic vs physiologic saline on nasal airway patency and mucociliary clearance in patients with symptomatic rhinosinusitis [174, 175]. Both saline preparations significantly improved mucociliary clearance compared with pretreatment values; however, only physiologic saline significantly improved nasal airway patency [174]. In other studies, hypertonic saline was found to significantly improve nasal symptoms as well as global quality of life [176, 177]. Finally, hypertonic saline caused increased nasal burning or irritation.

The mechanism by which physiologic or hypertonic saline irrigation improves sinus-specific symptoms is unclear. It has been postulated that saline irrigation improves nasal symptoms by enhancing mucociliary function, decreasing mucosal edema, mechanically clearing inspissated mucus, and decreasing inflammatory mediators [176].

**Benefits.** Intranasal saline irrigation may relieve symptoms in both children and adults, and improve disease-specific quality of life. The recommendation in favor of saline irrigation places a relatively high value on potential benefits of increased comfort and safety of the saline irrigations, and relatively low value on local adverse effects such as irritation and a burning sensation.

**Harms.** Nasal burning, irritation, and nausea were the most frequently reported adverse effects from intranasal saline irrigation (7%–32% in various studies). In addition, saline irrigants should be prepared from sterile or bottled water in light of recent reports of primary amebic encephalitis from contaminated tapwater used for saline nasal irrigation [178, 179]. Nasal saline irrigation is less well tolerated in babies and young children and may make them cry, undoing any potential benefit.

**Conclusions and Research Needs.** Given the small but consistent effect on symptoms and quality of life and relatively mild adverse effects, there is a net clinical benefit of intranasal physiologic or hypertonic saline irrigation as an adjunct to antimicrobial therapy in both adults and children with ABRS. The optimal concentration, volume, frequency, and most appropriate technique for nasal saline irrigation remain to be determined.

## **XII. Are Intranasal Corticosteroids Recommended as an Adjunct to Antimicrobial Therapy in Patients With ABRS?**

### **Recommendation**

17. INCSs are recommended as an adjunct to antibiotics in the empiric treatment of ABRS, primarily in patients with a history of allergic rhinitis (weak, moderate).

### **Evidence Summary**

INCSs offer modest symptomatic improvement and minimal adverse events with short-term use. Five trials [48, 180–183]

and a Cochrane review [184] have documented modest symptomatic improvement with INCSs compared with a placebo, although the relative risk of improvement was only marginal statistically (Table 13). Combining all study patients, 73% of treated patients improved clinically vs 66% in the placebo group (RR, 1.11 [95% CI, 1.04–1.18]), yielding an NNT of 15. No difference was noted in complications or relapse rate in the 2 studies that recorded these secondary outcomes. This suggests that the beneficial effect of INCSs, although consistently demonstrated in several studies, was relatively small. However, the quality of the evidence in these studies is high, and a dose-response effect was also demonstrated between mometasone 400 µg/day vs 200 µg/day (RR, 1.10 [95% CI, 1.02–1.18] vs RR, 1.04 [95% CI, .98–1.11], respectively). The beneficial effect of INCSs could be attributed to their anti-inflammatory properties, which may reduce mucosal swelling and promote drainage.

In another study, Williamson et al [48] randomized 207 adult patients with ABRS to receive either intranasal budesonide (200 µg/nostril) or placebo once daily for 10 days. No significant difference in clinical response rates was observed between the treatment groups (OR, 0.93 [95% CI, .54–1.62]). However, the duration of symptoms in these patients was relatively short prior to enrollment (median, 7 days [range, 4–14 days]), raising the possibility that at least some of the patients did not have bacterial infection. This is supported by the finding that 69% of the patients receiving placebo completely recovered by 10 days (Table 13).

The recommendation supporting the use of INCSs as adjunctive therapy places a relatively high value on a small additional relief of symptoms, and a relatively low value on avoiding increased resource expenditure.

**Benefits.** INCSs provide symptomatic relief and anti-inflammatory effects in the nasal mucosa, which theoretically decrease mucosal inflammation of the osteomeatal complex and allow the sinuses to drain.

**Harms.** Short-term risks of INCSs are minimal but may include susceptibility to oral candidiasis. Routine administration of INCSs will clearly increase the cost of treating ABRS. Use of any intranasal medications in children may not be well tolerated.

**Other Considerations.** The recommendation to prescribe INCSs for ABRS is relatively weak and considered optional since the benefits are only marginal with an NNT of 15. However, in patients with concurrent allergic rhinitis, INCS should be routinely administered.

**Conclusions and Research Needs.** Clinical trials have documented the relative safety and efficacy of INCSs in providing modest symptom relief in patients with ABRS.

**Table 13. Intranasal Corticosteroids Versus Placebo for Adults and Children With Acute Bacterial Rhinosinusitis**

Outcomes	Illustrative Comparative Risks <sup>a</sup> (95% CI)		Relative Effect (95% CI)	No. of Participants (No. of Studies)	Quality of the Evidence (GRADE)	Reference
	Assumed Risk	Corresponding Risk				
Symptom resolution or improvement (MFNS 400 µg/day)	Study population (medium-risk)		RR, 01.10 (1.02–1.18)	1130 (2 studies)	⊕⊕⊕⊕ high <sup>b,c</sup>	Meltzer et al, Nayak et al [182, 183]
Follow-up: 3 weeks	667 per 1000	734 per 1000 (680–787)				
Symptom resolution or improvement (MFNS 200 µg/day)	Study population (medium-risk)		RR, 1.04 (.98–1.11)	590 (2 studies)	⊕⊕⊕⊕ moderate <sup>b,c</sup>	Dolor et al, Meltzer et al [181, 182]
Follow-up: 3 weeks	850 per 1000	884 per 1000 (833–944)				
Relapse rate (MFNS 200, 400 & 800 µg/day)	Study population (medium-risk)		RR, 0.71 (.44–1.15)	825 (2 studies)	⊕⊕⊕⊕ moderate	Dolor et al, Meltzer et al [181, 182]
Follow-up: 3 weeks	100 per 1000	71 per 1000 (44–115)				
Symptoms persisting >10 days (BDSN 200 µg/day)	Study population (medium-risk)		OR, 0.93 (.54–1.62)	207 (1 study)	⊕⊕⊕⊖ moderate <sup>d</sup>	Williamson et al [48]
Follow-up: 14 days	314 per 1000	299 per 1000 (198–426)				

Patient or population: patients with adults and children with ABRS. Setting: outpatient clinic. Intervention: intranasal corticosteroids. Comparison: placebo.

Abbreviations: ABRS, acute bacterial rhinosinusitis; BDSN, budesonide nasal spray; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MFNS, mometasone furoate nasal spray; OR, odds ratio; RR, relative risk.

<sup>a</sup> The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

<sup>b</sup> Mometazone 400 µg/day vs 200 µg/day for 21 days.

<sup>c</sup> A 400-µg dose was superior to 200-µg dose.

<sup>d</sup> Symptom duration was relatively short at enrollment (median, 7 days [range, 4–14 days]).

Further studies in larger populations with these agents are clearly needed.

### XIII. Should Topical or Oral Decongestants or Antihistamines Be Used as Adjunctive Therapy in Patients With ABRS?

#### Recommendation

18. Neither topical nor oral decongestants and/or antihistamines are recommended as adjunctive treatment in patients with ABRS (strong, low-moderate).

#### Evidence Summary

Although decongestants and antihistamines are frequently prescribed in patients with ABRS, there is scant evidence to support that they hasten recovery. Although patients may subjectively feel improvement in nasal airway patency,

objective rhinometric findings do not support this impression [185]. There have been several RCTs that assessed the possibility of an additive effect of topical or oral decongestants or antihistamines to antimicrobial therapy in adults with ABRS [175, 186, 187]. Inanli et al [175] prospectively evaluated the effect of topical decongestants (oxymetazoline) vs hypertonic (3%) or isotonic (0.9%) saline or no topical treatment on mucociliary clearance in patients with ABRS. All patients received 625 mg amoxicillin-clavulanate 3 times daily for 3 weeks. At 20 minutes after application, statistically significant improvements in mucociliary clearance compared with basal levels were only observed in the oxymetazoline and 3% saline treatment groups. At 3 weeks, significant improvement from basal levels was observed in all treatment groups as well as

the group that received no topical treatment; and there was no significant difference in improvement among these groups, Wiklund et al [186] used plain sinus radiography to evaluate the effect of topical oxymetazoline vs placebo, each in combination with oral penicillin in patients with acute maxillary sinusitis. Neither subjective symptom scores nor radiographic findings were significantly different in the treatment groups. On the contrary, topical treatment with decongestants may itself induce inflammation in the nasal cavity. Bende et al [188] confirmed this experimentally in rabbits with acute bacterial sinusitis. Topical oxymetazoline was instilled in one nasal cavity and placebo in the other. After 48 hours, histological sections of the maxillary sinus mucosa revealed significantly more inflammatory changes in the oxymetazoline-treated side than in the placebo-treated side.

McCormick et al [187] evaluated the efficacy of oral antihistamines (brompheniramine and phenylpropanolamine in syrup) in combination with nasal oxymetazoline vs placebo (oral syrup and nasal saline) in the treatment of ABRS in children. All patients received 14 days of oral amoxicillin. Patients were assessed by clinical symptoms and Waters' view plain radiographs for the degree of sinus involvement. The addition of decongestant-antihistamine did not provide added benefit compared with amoxicillin alone in this study. The antihistamine H1 antagonist loratadine does not possess any anticholinergic effects and is non-sedative. Its adjunctive effect to standard treatment with antibiotics and oral steroids was examined in a double-blind, placebo-controlled RCT in 139 adults with acute rhinosinusitis associated with a strong history of allergy [189]. All patients received amoxicillin-clavulanate (2 g daily) for 14 days and oral prednisone. Loratadine (10 mg daily) or placebo was administered for 28 days. Nasal symptom scores based on self-reporting as well as a rhinologic examination at baseline and 4 weeks were significantly improved in the loratadine compared with the placebo group at the end of 2 and 4 weeks. In particular, the degree of improvement was significantly greater for certain symptoms including sneezing and nasal obstruction. However, this patient population is unique in that all had acute exacerbation of allergic rhinosinusitis, and these findings do not apply to the typical patient with ABRS. Furthermore, it is unclear whether INCSs rather than oral steroids would have been more efficacious and thus minimizes the adjunctive effect of loratadine.

The recommendation against the use of decongestants or antihistamines as adjunctive therapy in ABRS places a relatively high value on avoiding adverse effects from these agents and a relatively low value on the incremental improvement of symptoms. These agents may still provide symptom relief in some patients with acute viral rhinosinusitis when antimicrobial therapy is not indicated.

**Benefits.** Topical and oral decongestants may provide a subjective impression of improving nasal airway patency.

**Harms.** Topical decongestants may induce rebound congestion and inflammation, and oral antihistamines may induce drowsiness, xerostomia, and other adverse effects. The FDA has recommended that these drugs in over-the-counter products not be used for infants and children <2 years of age because serious and potentially life-threatening side effects can occur [190]. Caution is advised in children aged  $\geq 2$  years particularly if such over-the-counter medications have multiple active ingredients.

**Other Considerations.** None.

**Conclusions and Research Needs.** Topical and oral decongestants and antihistamines should be avoided in patients with ABRS. Instead, symptomatic management should focus on hydration, analgesics, antipyretics, saline irrigation, and INCSs.

## RECOMMENDATIONS FOR THE NONRESPONSIVE PATIENT

### XIV. How Long Should Initial Empiric Antimicrobial Therapy in the Absence of Clinical Improvement Be Continued Before Considering Alternative Management Strategies?

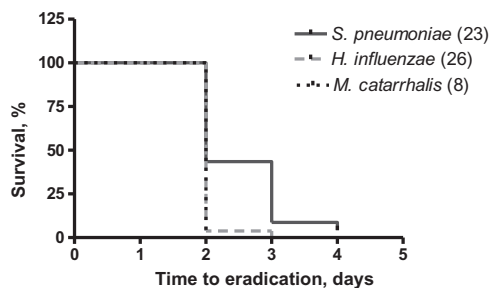
#### *Recommendation*

19. An alternative management strategy is recommended if symptoms worsen after 48–72 hours of initial empiric antimicrobial therapy, or fail to improve despite 3–5 days of initial empiric antimicrobial therapy (strong, moderate).

#### *Evidence Summary*

In general, patients with ABRS should begin to respond clinically by 3–5 days following initiation of effective antimicrobial therapy [61]. For example, in the placebo-controlled prospective study of empiric antimicrobial therapy for ABRS by Wald et al [64], 45% of patients on antibiotics vs 11% of children on placebo were cured on the third day of treatment (complete resolution of respiratory symptoms) and many others were improved by 3 days. Conversely, in Wald et al's recent prospective study that compared high-dose amoxicillin-clavulanate to placebo, 19 of 23 children who failed therapy (including 19 in the placebo group and 4 in the antibiotic group) either worsened or failed to improve clinically within 72 hours [61]. Bacteriological eradication studies also indicate that most causative organisms are eliminated from the maxillary sinuses by 3 days following appropriate antimicrobial therapy. Ambrose and his colleagues [144, 191, 192] devised an innovative technique to determine the time course for bacteriological eradication and pharmacodynamic endpoints in the antimicrobial treatment of ABRS, by inserting an indwelling catheter into the maxillary sinus. This allowed serial sinus aspirate sampling

for Gram stain, culture, and drug level measurements. Patients were treated with either gatifloxacin or levofloxacin. Among 8 patients with positive cultures (5 with *S. pneumoniae*, 2 with *H. influenzae*, and 1 with both *H. influenzae* and *M. catarrhalis*), 7 (87.5%) were sterile by 3 days following initiation of therapy. Similarly, Ariza et al [143] obtained cultures of the middle meatus by endoscopy from 42 patients who were receiving treatment with moxifloxacin for microbiologically documented ABRS. After 3 days, 97% of patients had eradication of all baseline bacteria. Figure 4 shows a Kaplan-Meier plot of the proportion of patients with positive cultures for *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis* at each day following initiation of antimicrobial therapy with a respiratory fluoroquinolone (either moxifloxacin, levofloxacin, or gatifloxacin). As can be seen, 96% of patients had negative cultures by day 3. Interestingly, the time to bacterial eradication was longest for *S. pneumoniae*, followed by *H. influenzae* and *M. catarrhalis*. In the studies by Ambrose et al [192], excellent correlation between time to bacterial eradication and time to clinical resolution was observed. At 3 days following the initiation of therapy, 81% of all signs and symptoms had improved by at least 50%. The median time to clinical resolution of individual signs and symptoms was 1–3 days, and 88% of all signs and symptoms were completely resolved by 5 days. Thus, a bacteriologic as well as clinical response may be expected within 3–5 days in most patients receiving appropriate antimicrobial therapy. If symptoms and signs worsen despite 72 hours of initial empiric antimicrobial therapy, the possible reasons for treatment failure must be considered, including resistant pathogens, structural abnormalities, or a nonbacterial cause. Similarly, if there is no clinical improvement within 3–5 days despite empiric antimicrobial therapy, an alternate management strategy should be considered even though there is no clinical worsening. It should be noted that elderly



**Figure 4.** Time to bacterial eradication from the maxillary sinus in patients with acute bacterial rhinosinusitis (ABRS) following initiation of therapy with respiratory fluoroquinolones (N = 50; multiple pathogens were isolated from some patients) [22, 143, 192].

patients and those with comorbid diseases may require longer time for clinical improvement. Lindbaek [193] conducted a prospective evaluation of factors present at the onset of acute sinusitis that might predict the total duration of illness among adults receiving antimicrobial therapy. As might be expected, age of the patient and the clinical severity of sinusitis at the onset of treatment were independent predictors of illness duration. However, even among elderly and severely ill patients, some improvement should be clinically evident after 3–5 days of appropriate antimicrobial therapy.

**Benefits.** Careful clinical evaluation of the patient at 3–5 days is critical to assess the response to empiric antimicrobial therapy and to consider alternative management options if treatment failure is suspected.

**Harms.** Premature discontinuation of first-line antimicrobial therapy in favor of second-line agents with broader antimicrobial coverage may promote overuse of antibiotics and increase costs as well as adverse effects.

**Other Considerations.** Little information is currently available on bacterial eradication rates in ABRS by antimicrobial classes other than the respiratory fluoroquinolones.

**Conclusions and Research Needs.** Treatment failure should be considered in all patients who fail to improve at 3–5 days after initiation of antimicrobial therapy. In the final analysis, clinical judgment and close monitoring of the patient are critical in determining whether there is treatment failure or simply a slow clinical response. More studies are needed to examine the bacterial eradication rates associated with different antimicrobial classes by sequential cultures of the middle meatus and correlate them with the clinical response.

## XV. What Is the Recommended Management Strategy in Patients Who Clinically Worsen Despite 72 Hours or Fail to Improve After 3–5 Days of Initial Empiric Antimicrobial Therapy With a First-line Regimen?

### Recommendation

20. An algorithm for managing patients who fail to respond to initial empiric antimicrobial therapy is shown in Figure 1. Patients who clinically worsen despite 72 hours or fail to improve after 3–5 days of empiric antimicrobial therapy with a first-line agent should be evaluated for the possibility of resistant pathogens, a noninfectious etiology, structural abnormality, or other causes for treatment failure (strong, low).

### Evidence Summary

Patients with presumed ABRS who fail to respond to initial empiric antimicrobial treatment should be investigated for possible causes of failure, including infection with resistant pathogens, inadequate dosing, and noninfectious causes including allergy and structural abnormalities.



There are few RCTs in which the microbiological diagnosis of ABRS is confirmed by sinus puncture at the time of clinical failure or follow-up. A review of available placebo-controlled trials (almost all involving patients with a clinical diagnosis) found only 1 study that provided data on the effect of a specific antimicrobial agent to treat clinical failures [61]. In this study, 4 children randomized to high-dose amoxicillin-clavulanate and 19 randomized to placebo who experienced treatment failure were provided cefpodoxime. All experienced successful outcomes following treatment with cefpodoxime for 10 days, although the reason for treatment failure with the study antibiotics was unclear, as sinus puncture was not performed in these patients. Brook et al [96] performed consecutive cultures from maxillary sinus aspirates of 20 children with ABRS who failed initial empiric antimicrobial therapy. Enhanced levels of resistance as demonstrated by an MIC at least 2-fold higher than for the pretreatment isolate was observed in 49% of patients. Thus, both inadequate dosing and bacterial resistance should be considered in all patients who fail to respond to initial empiric antimicrobial therapy. PK/PD principles should be followed to ensure adequate dosing for respiratory tract infections [194]. In choosing a second-line regimen in a patient who has failed initial antimicrobial therapy, an agent with broader spectrum of activity and in a different antimicrobial class should be considered [82, 195]. Antimicrobials selected should be active against PNS *S. pneumoniae* and ampicillin-resistant *H. influenzae* as well as other  $\beta$ -lactamase-producing respiratory pathogens. The recommended list of second-line antimicrobial agents suitable for children and for adults who experience treatment failure to first-line agents is shown in Tables 9 and 10, respectively. An algorithm for managing patients who fail to respond to initial empiric antimicrobial therapy is shown in Figure 1. If symptoms persist or worsen despite 72 hours of treatment with a second-line regimen, referral to an otolaryngologist, allergist, or infectious disease specialist should be considered. Additional investigations (such as sinus puncture or acquisition of cultures of the middle meatus, and CT or MRI studies) should be initiated.

**Benefits.** Provide a systematic and algorithm-based approach to antimicrobial therapy of patients failing initial therapy.

**Harms.** The potential for adding more selection pressure for resistance due to “antimicrobial surfing” and adding adverse effects without antimicrobial benefit.

**Other Considerations.** None.

**Conclusions and Research Needs.** RCTs are needed to evaluate and optimize clinical approaches to the management of patients who fail to respond to initial empiric antimicrobial therapy, and to systematically assess all causes of clinical treatment failure.

## XVI. In Managing the Patient With ABRS Who Has Failed to Respond to Empiric Treatment With Both First-line and Second-line Agents, It Is Important to Obtain Cultures to Document Whether There Is Persistent Bacterial Infection and Whether Resistant Pathogens Are Present. In Such Patients, Should Cultures Be Obtained by Sinus Puncture or Endoscopy, or Are Cultures of Nasopharyngeal Swabs Sufficient?

### Recommendations

21. It is recommended that cultures be obtained by direct sinus aspiration rather than by nasopharyngeal swabs in patients with suspected sinus infection who have failed to respond to empiric antimicrobial therapy (strong, moderate).

22. Endoscopically guided cultures of the middle meatus may be considered as an alternative in adults but their reliability in children has not been established (weak, moderate).

23. Nasopharyngeal cultures are unreliable and are not recommended for the microbiologic diagnosis of ABRS (strong, high).

### Evidence Summary

Benninger et al [31] reviewed the data from 5 studies correlating the microbiology obtained from nasopharyngeal swabs with cultures of sinus aspirates both in healthy adults and patients with acute maxillary sinusitis. In 4 of 5 studies, correlation was poor (42%–65%) [28, 39, 196, 197]. However, in one study by Jousimies-Somer et al [198], presumed respiratory pathogens were rarely isolated from nasopharyngeal swabs obtained from healthy adults compared with patients with acute maxillary sinusitis (0%–4% vs 6%–61%). When the maxillary sinus aspirate culture yielded a presumed sinus pathogen (ie, *S. pneumoniae*, *H. influenzae*, or *M. catarrhalis*), the same bacteria was found in 91% of nasopharyngeal swabs (positive predictive values, 20%–93%; negative predictive values, 84%–100%, depending on the bacterial species). Overall, nasopharyngeal cultures were considered unreliable for establishing the microbiologic diagnosis of ABRS.

In contrast to nasopharyngeal swabs, endoscopically directed cultures of the middle meatus correlated better with cultures from direct sinus puncture. Benninger et al [199] performed a meta-analysis involving 126 adult patients from 3 published studies and additional unpublished data. Endoscopically directed cultures of the middle meatus had a sensitivity of 81%, specificity of 91%, positive predictive value of 83%, negative predictive value of 89%, and overall accuracy of 87% (95% CI, 81.3%–92.8%).

The correlation between endoscopically directed cultures of the middle meatus and sinus puncture in pediatric patients with ABRS has not been established. However, even in children without respiratory symptoms, cultures of the middle meatus often show *S. pneumoniae* and *H. influenzae* [200].

**Benefits.** Sinus culture provides the most accurate information compared with nasopharyngeal swabs or cultures of the middle meatus obtained endoscopically; however, cultures of the middle meatus are easier to obtain and less invasive and hence better tolerated by patients.

**Harms.** Sinus culture is invasive, time consuming, and not well tolerated by patients.

**Other Considerations.** Middle meatus cultures may not correlate with an infection of the sphenoidal sinuses but still would be expected to correlate with infection of the ethmoid or frontal sinuses because the latter primarily drain through the middle meatus. In contrast, a maxillary sinus tap would not be expected to identify pathogens from the ethmoid, frontal, or sphenoidal sinuses.

**Conclusions and Research Needs.** More data are needed to validate the use of cultures of the middle meatus for assessing microbiological eradication rates and efficacy of antimicrobial therapy.

## **VII. Which Imaging Technique Is Most Useful for Patients With Severe ABRS Who Are Suspected to Have Suppurative Complications Such as Orbital or Intracranial Extension of Infection?**

### **Recommendation**

24. In patients with ABRS suspected to have suppurative complications, obtaining axial and coronal views of contrast-enhanced CT rather than MRI is recommended for localization of infection and to guide further treatment (weak, low).

### **Evidence Summary**

Most cases of ABRS do not require radiographic evaluation because findings on plain radiographs or CT are nonspecific and do not distinguish bacterial from viral infection. The usefulness of imaging is in determining disease location and the extent of involvement beyond the original source. Occasionally, imaging studies may be useful to support the diagnosis or provide evidence of the degree of mucosal involvement, potentially guiding a more aggressive approach to therapy [23]. In general, more advanced imaging modalities such as CT or MRI should be reserved for recurrent or complicated cases or when suppurative complications are suspected. Suppurative complications of ABRS are rare, estimated to be 3.7%–11% among hospitalized pediatric patients with sinusitis, and are primarily related to orbital cellulitis and intracranial extension of infection [201]. Only approximately 1 of 95 000 hospital admissions in the United States is due to sinusitis-associated brain abscess [202]. Overall, the evidence supporting a superiority of CT vs MRI for the diagnosis of suppurative complications of ABRS is very poor, consisting primarily of case reports and small retrospective observational studies. In general, CT is considered the gold standard for assessing bony and anatomical

changes associated with acute or chronic sinusitis, whereas MRI is useful to further delineate the extent of soft tissue abnormalities and inflammation [203–205]. CT is also necessary for surgical planning and for intraoperative image-guided surgical navigation. Younis et al [206] evaluated the diagnostic accuracy of clinical assessment vs CT or MRI in the diagnosis of orbital and intracranial complications arising from sinusitis and confirmed by intraoperative findings. A total of 82 adults and children were studied retrospectively from a single medical center during 1985–1999. Among 43 patients with orbital infections (most had unilateral ethmoid sinusitis complicated by periorbital cellulitis), the diagnostic accuracy was 82% by clinical assessment and 91% by CT imaging. Among 39 patients with intracranial infections (most had sphenoidal sinusitis complicated by meningitis), the diagnostic accuracy was 82% by clinical assessment, 87% by CT, and 97% by MRI. Thus, MRI appears more sensitive than CT for detecting soft tissue involvement in patients with suspected intracranial complications and is not associated with ionizing radiation [207, 208]. In a retrospective descriptive study of 12 children with sinogenic intracranial empyema (SIE), Adame et al [209] reported that the diagnosis was missed in 4 patients who underwent nonenhanced CT. Axial imaging alone was unable to demonstrate SIE in 1 child with sphenoidal and ethmoid sinusitis, and coronal images were needed to demonstrate its presence and extent. Using contrast-enhanced CT or MRI, SIE was diagnosed in all 12 children. The American College of Radiology has recently developed appropriateness criteria for imaging examinations for acute rhinosinusitis in both adults [210] and children [211], and stated that MRI and CT are complementary studies for the investigation of suspected orbital and/or intracranial complications of sinusitis. Thus, the recommendation of the IDSA panel in favor of contrast-enhanced CT over MRI places greater value on relative availability and speed of diagnosis by CT, and a lack of need for sedation, which is frequently required for MRI studies in infants and children.

**Benefits.** The availability of CT and MRI has greatly improved the management and outcome of patients with suspected orbital or intracranial complication of ABRS.

**Harms.** There are definite risks associated with these procedures. CT scanning results in low levels of radiation exposure, which may lead to radiation-induced illnesses if multiple scans are obtained [212]. With either CT or MRI, there is a potential risk of allergic reactions to the contrast material, and appropriate precaution should be undertaken in patients with renal impairment.

**Other Considerations.** None.

**Conclusions and Research Needs.** Because most of our knowledge in this area is based on retrospective case series or

**Table 14. Indications for Referral to a Specialist**

- Severe infection (high persistent fever with temperature >39°C [ $>102^{\circ}\text{F}$ ]; orbital edema; severe headache, visual disturbance, altered mental status, meningeal signs)
- Recalcitrant infection with failure to respond to extended courses of antimicrobial therapy
- Immunocompromised host
- Multiple medical problems that might compromise response to treatment (eg, hepatic or renal impairment, hypersensitivity to antimicrobial agents, organ transplant)
- Unusual or resistant pathogens
- Fungal sinusitis or granulomatous disease
- Nosocomial infection
- Anatomic defects causing obstruction and requiring surgical intervention
- Multiple recurrent episodes of acute bacterial rhinosinusitis (ABRS) (3–4 episodes per year) suggesting chronic sinusitis
- Chronic rhinosinusitis (with or without polyps or asthma) with recurrent ABRS exacerbations
- Evaluation of immunotherapy for allergic rhinitis

reports, the overall quality of evidence is weak. As technology continues to evolve, more studies are needed to clarify the indications of these imaging techniques in the management of ABRS.

### **XVIII. When Is Referral to a Specialist Indicated in a Patient With Presumed ABRS?**

#### **Recommendation**

25. Patients who are seriously ill, immunocompromised, continue to deteriorate clinically despite extended courses of antimicrobial therapy, or have recurrent bouts of acute rhinosinusitis with clearing between episodes should be referred to a specialist (such as an otolaryngologist, infectious disease specialist, or allergist) for consultation. As this is a “good clinical practice” statement rather than a recommendation, it is not further graded.

#### **Evidence Summary**

Most patients with ABRS will respond to empiric antimicrobial therapy, usually within 3–5 days after initiation of treatment. However, when such patients fail to respond despite a change in antimicrobial therapy to broaden coverage for presumed bacterial resistance, prompt referral to a specialist such as an otolaryngologist, allergist, or infectious disease specialist should be considered. The choice of the specialist should be based on the indication for referral (see Table 14), and whether the suspected cause of treatment failure is primarily surgical, medical, or of an immunologic/allergic nature. A confirmation of diagnosis is probably best determined by an otolaryngologist, who may assist in obtaining cultures by sinus puncture or middle meatus endoscopy. Severe infection, particularly in the immunocompromised host, or patients with multiple medical problems that may

complicate appropriate dosing or predispose to unusual microorganisms, should be referred to an infectious disease specialist. Patients with recurrent infection or suspected to have an underlying hypersensitivity or immunologic disorder should be referred to an allergist. Patients with rapid deterioration and manifestations suggestive of orbital or intracranial suppurative complications require urgent consultation and a multidisciplinary approach.

**Benefits.** Prompt and appropriate referral should hasten the recovery in patients with complicated ABRS.

**Harms.** Delay in appropriate referral to specialists may prolong illness, result in chronic disease, and occasionally lead to catastrophic consequences if life-threatening complications are not recognized. Unnecessary referral adds to the burden of healthcare costs.

**Other Considerations.** None.

**Conclusions and Research Needs.** Timely referral is indicated if chronic or recurrent symptoms severely affect the patient’s productivity or quality of life. Early access to critical diagnostic facilities (such as imaging studies, endoscopy, surgical biopsies, and immunologic testing) is needed to improve healthcare and prevent the development of chronic sequelae.

#### **Performance Measures**

The American Medical Association–Physician Consortium for Performance Improvement (AMA-PCPI) has developed performance measures for sinusitis. The measure set, specifications, patient selection criteria, and other information can be found on the AMA-PCPI website (<http://www.ama-assn.org/apps/listserv/x-check/qmeasure.cgi?submit=PCPI>). Examples of suitable performance measures include:

1. Percentage of patients treated for sinusitis who met the criteria for therapy (based on question I.)
2. Percentage of patients treated for sinusitis for which the appropriate antimicrobial is used as listed in Tables 9 and 10.
3. Percentage of patients treated for recommended duration of therapy (based on question X.)
4. Percentage of patients who fail initial therapy and have an appropriate culture obtained (based on question XVI.)

#### **Notes**

**Acknowledgments.** The panel thanks Drs Jim Hadley, Ralph Gonzales, and Gregory Moran for their thoughtful reviews of the guideline; Holger J. Schünemann for his continued interest and advice in the development of this guideline; Brad Marple for his early involvement with the guideline; Tamar F. Barlam as liaison of the IDSA Standards and Practice Guidelines Committee; Jennifer Padberg for overall guidance and coordination; and Vita Washington and Genet Demisashi for their capable assistance in all aspects of the development of this guideline.

**Disclaimer.** Guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to this guideline to

be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances.

**Financial support.** This work was supported by the Infectious Diseases Society of America.

**Potential conflicts of interest.** A. W. C. has served as a consultant to Inimex, Migenix, Bayer, Merck, and Wyeth, has provided expert testimony for MEDACorp Clinical Advisors, has received honoraria from Inimex and MEDACorp, has received stocks/bonds from Inimex and Migenix, and has received consulting fees or honoraria from Pfizer, Merck-Frosst Canada, and Core Health. T. M. F. has served as a consultant to Bayer, GlaxoSmithKline, Forest, Nabriva Pharm, Merck, Daichi, Sankyo, Tetrphase, Pfizer, Cubist, and Astellas/Theravance; and has received research grants from Cemptra, Pfizer, Boehringer Ingelheim, Gilead, Tibotec, and the Medicines Co. E. J. C. G. has served as a consultant to Theravance, Bayer, Merck, and Optimer; has received honoraria from Bayer, Merck, and Optimer; has served on advisory boards for Merck, Optimer, Bayer, Bio-K+, and Kindred; has served on the speakers' bureaus of Bayer, Merck, Sanofi Pasteur, and Forest Labs; has received research grants from Merck, Schering-Plough Pharm, Optimer Pharm, Theravance, Cubist, Pfizer, Astellas, Cerexa, Impex, Novoxel, Novartis, Clinical Microbiology Institute, Genzyme, Nanopacific Holdings, Romark Laboratories GL, Viroxix Corp., Warner Chilcott, Avidbiotics Corp, GLSynthesis, Immunome, and Toltec Pharma LLC; and has received other remuneration from Schering-Plough, Pfizer, Astella/Theravance, Cubist, and Salix. G. A. P. has served as a consultant to Optimer. G. V. has served as a consultant to the National Heart, Lung, and Blood Institute (NHLBI) and Pfizer and has received honoraria from Boston Scientific and the NHLBI. M. S. has served as a consultant to Eli Lilly and Pfizer and has received honoraria from Boston Scientific and the NHLBI. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *BMJ* **2008**; 336:1049–51.
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **2008**; 336:924–6.
3. Jaeschke R, Guyatt GH, Dellinger P, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ* **2008**; 337:a744.
4. Guyatt GH, Oxman AD, Kunz R, et al. Incorporating considerations of resources use into grading recommendations. *BMJ* **2008**; 336:1170–3.
5. Schunemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* **2008**; 336:1106–10.
6. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is “quality of evidence” and why is it important to clinicians? *BMJ* **2008**; 336:995–8.
7. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *J Allergy Clin Immunol* **2004**; 114:155–212.
8. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* **2003**; 129:S1–32.
9. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. *Vital Health Stat* **2009**; 1–157.
10. Revai K, Dobbs LA, Nair S, Patel JA, Grady JJ, Chonmaitree T. Incidence of acute otitis media and sinusitis complicating upper respiratory tract infection: the effect of age. *Pediatrics* **2007**; 119:e1408–12.
11. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* **2007**; 1–136.
12. 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.
13. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis. *Otolaryngol Head Neck Surg* **2007**; 137:S1–31.
14. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: duration of and frequency of complications. *Pediatrics* **1991**; 87:129–33.
15. Anand VK. Epidemiology and economic impact of rhinosinusitis. *Ann Otol Rhinol Laryngol Suppl* **2004**; 193:3–5.
16. 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.
17. Gill JM, Fleischut P, Haas S, Pellini B, Crawford A, Nash DB. Use of antibiotics for adult upper respiratory infections in outpatient settings: a national ambulatory network study. *Fam Med* **2006**; 38:349–54.
18. Young J, De Sutter A, Merenstein D, et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. *Lancet* **2008**; 371:908–14.
19. Snow V, Mottur-Pilson C, Gonzales R. Principles of appropriate antibiotic use for treatment of nonspecific upper respiratory tract infections in adults. *Ann Intern Med* **2001**; 134:487–9.
20. Hickner JM, Bartlett JG, Besser RE, Gonzales R, Hoffman JR, Sande MA. Principles of appropriate antibiotic use for acute rhinosinusitis in adults: background. *Ann Intern Med* **2001**; 134:498–505.
21. American Academy of Pediatrics Subcommittee on Management of Sinusitis and Committee on Quality Improvement. Clinical practice guideline: management of sinusitis. *Pediatrics* **2001**; 108:798–808.
22. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* **2004**; 130:1–45.
23. Slavin RG, Spector SL, Bernstein IL, et al. The diagnosis and management of sinusitis: a practice parameter update. *J Allergy Clin Immunol* **2005**; 116:S13–47.
24. Ip S, Fu L, Balk E, Chew P, Devine D, Lau J. Update on acute bacterial rhinosinusitis. *Evid Rep Technol Assess (Summ)* **2005**; 1–3.
25. Rosenfeld RM, Singer M, Jones S. Systematic review of antimicrobial therapy in patients with acute rhinosinusitis. *Otolaryngol Head Neck Surg* **2007**; 137:S32–45.
26. Institute for Clinical Systems Improvement. ICSI healthcare guidelines: diagnosis and treatment of respiratory illness in children and adults. 2nd ed. Bloomington, MN: Institute for Clinical Systems Improvement, **2008**: 1–72.
27. Desrosiers M, Evans GA, Keith PK, et al. Canadian clinical practice guidelines for acute and chronic rhinosinusitis. *Allergy Asthma Clin Immunol* **2011**; 7:2.
28. Evans FO Jr, Sydnor JB, Moore WE, et al. Sinusitis of the maxillary antrum. *N Engl J Med* **1975**; 293:735–9.
29. Hamory BH, Sande MA, Sydnor A Jr, Seale DL, Gwaltney JM Jr. Etiology and antimicrobial therapy of acute maxillary sinusitis. *J Infect Dis* **1979**; 139:197–202.
30. Wald ER, Milmoie GJ, Bowen A, Ledesma-Medina J, Salamon N, Bluestone CD. Acute maxillary sinusitis in children. *N Engl J Med* **1981**; 304:749–54.
31. Benninger MS, Appelbaum PC, Denny JC, Osguthorpe DJ, Stankiewicz JA. Maxillary sinus puncture and culture in the diagnosis of acute rhinosinusitis: the case for pursuing alternative culture methods. *Otolaryngol Head Neck Surg* **2002**; 127:7–12.
32. Kovatch AL, Wald ER, Ledesma-Medina J, Chiponis DM, Bedingfield B. Maxillary sinus radiographs in children with nonrespiratory complaints. *Pediatrics* **1984**; 73:306–8.
33. Shopfner CE, Rossi JO. Roentgen evaluation of the paranasal sinuses in children. *Am J Roentgenol Radium Ther Nucl Med* **1973**; 118:176–86.

34. Maresh M, Washburn A. Paranasal sinuses from birth to late adolescence. Clinical and roentgenographic evidence in infection. *Am J Dis Child* **1940**; 60:841–61.
35. Diamant MJ, Senac MO Jr, Gilsanz V, Baker S, Gillespie T, Larsson S. Prevalence of incidental paranasal sinuses opacification in pediatric patients: a CT study. *J Comput Assist Tomogr* **1987**; 11:426–31.
36. Gwaltney JM Jr, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. *N Engl J Med* **1994**; 330:25–30.
37. Kristo A, Uhari M, Luotonen J, et al. Paranasal sinus findings in children during respiratory infection evaluated with magnetic resonance imaging. *Pediatrics* **2003**; 111:e586–9.
38. Kristo A, Alho OP, Luotonen J, Koivunen P, Tervonen O, Uhari M. Cross-sectional survey of paranasal sinus magnetic resonance imaging findings in schoolchildren. *Acta Paediatr* **2003**; 92:34–6.
39. Gwaltney JM Jr, Sydnor A Jr, Sande MA. Etiology and antimicrobial treatment of acute sinusitis. *Ann Otol Rhinol Laryngol Suppl* **1981**; 90:68–71.
40. Gwaltney JM Jr, Hendley JO, Simon G, Jordan WS Jr. Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. *JAMA* **1967**; 202:494–500.
41. Gwaltney JM Jr, Scheld WM, Sande MA, Sydnor A. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: a fifteen-year experience at the University of Virginia and review of other selected studies. *J Allergy Clin Immunol* **1992**; 90:457–61; discussion 62.
42. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: developing guidance for clinical trials. *Otolaryngol Head Neck Surg* **2006**; 135:S31–80.
43. Falagas ME, Giannopoulou KP, Vardakas KZ, Dimopoulos G, Karageorgopoulos DE. Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. *Lancet Infect Dis* **2008**; 8:543–52.
44. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev* **2008** (2):CD000243.
45. Hadley JA, Mosges R, Desrosiers M, Haverstock D, van Veenhuizen D, Herman-Gnjidic Z. Moxifloxacin five-day therapy versus placebo in acute bacterial rhinosinusitis. *Laryngoscope* **2010**; 120:1057–62.
46. 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 randomized doxycycline trial. *Br J Gen Pract* **1997**; 47:794–9.
47. Varonen H, Kunnamo I, Savolainen S, et al. Treatment of acute rhinosinusitis diagnosed by clinical criteria or ultrasound in primary care. A placebo-controlled randomised trial. *Scand J Prim Health Care* **2003**; 21:121–6.
48. 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**; 298:2487–96.
49. Bucher HC, Tschudi P, Young J, et al. Effect of amoxicillin-clavulanate in clinically diagnosed acute rhinosinusitis: a placebo-controlled, double-blind, randomized trial in general practice. *Arch Intern Med* **2003**; 163:1793–8.
50. Hansen JG, Schmidt H, Grinstead P. Randomised, double blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. *Scand J Prim Health Care* **2000**; 18:44–7.
51. Haye R, Lingaas E, Hoivik HO, Odegard T. Azithromycin versus placebo in acute infectious rhinitis with clinical symptoms but without radiological signs of maxillary sinusitis. *Eur J Clin Microbiol Infect Dis* **1998**; 17:309–12.
52. Lindbaek M, Hjortdahl P. Acute sinusitis and antibiotic treatment. *Br J Gen Pract* **1998**; 48:1341.
53. De Sutter AI, De Meyere MJ, Christiaens TC, Van Driel ML, Peersman W, De Maeseneer JM. Does amoxicillin improve outcomes in patients with purulent rhinorrhea? A pragmatic randomized double-blind controlled trial in family practice. *J Fam Pract* **2002**; 51:317–23.
54. 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.
55. Kaiser L, Morabia A, Stalder H, et al. Role of nasopharyngeal culture in antibiotic prescription for patients with common cold or acute sinusitis. *Eur J Clin Microbiol Infect Dis* **2001**; 20:445–51.
56. 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.
57. Merenstein D, Whittaker C, Chadwell T, Wegner B, D'Amico F. Are antibiotics beneficial for patients with sinusitis complaints? A randomized double-blind clinical trial. *J Fam Pract* **2005**; 54:144–51.
58. van Buchem FL, Knottnerus JA, Schrijnemaekers VJ, Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. *Lancet* **1997**; 349:683–7.
59. Norrelund N. [Treatment of sinusitis in general practice. A controlled investigation of pivampicillin (Pondocillin)]. *Ugeskr Laeger* **1978**; 140:2792–5.
60. 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.
61. Wald ER, Nash D, Eickhoff J. Effectiveness of amoxicillin/clavulanate potassium in the treatment of acute bacterial sinusitis in children. *Pediatrics* **2009**; 124:9–15.
62. Garbutt JM, Goldstein M, Gellman E, Shannon W, Littenberg B. A randomized, placebo-controlled trial of antimicrobial treatment for children with clinically diagnosed acute sinusitis. *Pediatrics* **2001**; 107:619–25.
63. Kristo A, Uhari M, Luotonen J, Ilkko E, Koivunen P, Alho OP. Cefuroxime axetil versus placebo for children with acute respiratory infection and imaging evidence of sinusitis: a randomized, controlled trial. *Acta Paediatr* **2005**; 94:1208–13.
64. 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.
65. Marchant CD, Carlin SA, Johnson CE, Shurin PA. Measuring the comparative efficacy of antibacterial agents for acute otitis media: the “Pollyanna phenomenon”. *J Pediatr* **1992**; 120:72–7.
66. Austin DJ, Kristinsson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc Natl Acad Sci U S A* **1999**; 96:1152–6.
67. Magee JT, Pritchard EL, Fitzgerald KA, Dunstan FD, Howard AJ. Antibiotic prescribing and antibiotic resistance in community practice: retrospective study, 1996–8. *BMJ* **1999**; 319:1239–40.
68. Centers for Disease Control and Prevention. Effects of new penicillin susceptibility breakpoints for *Streptococcus pneumoniae*—United States, 2006–2007. *MMWR Morb Mortal Wkly Rep* **2008**; 57:1353–5.
69. File TM Jr. Clinical implications and treatment of multiresistant *Streptococcus pneumoniae* pneumonia. *Clin Microbiol Infect* **2006**; 12(Suppl 3):31–41.
70. File TM Jr, Tan JS, Boex JR. The clinical relevance of penicillin-resistant *Streptococcus pneumoniae*: a new perspective. *Clin Infect Dis* **2006**; 42:798–800.
71. Klugman KP. Clinical impact of antibiotic resistance in respiratory tract infections. *Int J Antimicrob Agents* **2007**; 29(Suppl 1):S6–10.
72. Poole MD. Acute bacterial rhinosinusitis: clinical impact of resistance and susceptibility. *Am J Med* **2004**; 117(Suppl 3A):29S–38.
73. Field MJ, Kathelin N. Institute of Medicine committee to advise the Public Health Service on Clinical Practice guidelines (1990). *Clinical practice guidelines: directions for a new program*. Washington, DC: National Academies Press, **1990**: 52–77.
74. Kish MA. Guide to development of practice guidelines. *Clin Infect Dis* **2001**; 32:851–4.

75. Lindbaek M, Hjortdahl P, Johnsen UL. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med* **1996**; 28:183–8.
76. Williams JW Jr, Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis. Making the diagnosis by history and physical examination. *Ann Intern Med* **1992**; 117:705–10.
77. Berg O, Carenfelt C. Analysis of symptoms and clinical signs in the maxillary sinus empyema. *Acta Otolaryngol* **1988**; 105:343–9.
78. Hansen JG, Højbjerg T, Rosborg J. Symptoms and signs in culture-proven acute maxillary sinusitis in a general practice population. *APMIS* **2009**; 117:724–9.
79. Hansen JG, Schmidt H, Rosborg J, Lund E. Predicting acute maxillary sinusitis in a general practice population. *BMJ* **1995**; 311: 233–6.
80. Thomas M, Yawn BP, Price D, Lund V, Mullol J, Fokkens W. 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**; 17:79–89.
81. Wald ER, Reilly JS, Casselbrant M, et al. Treatment of acute maxillary sinusitis in childhood: a comparative study of amoxicillin and cefaclor. *J Pediatr* **1984**; 104:297–302.
82. Anon JB. Upper respiratory infections. *Am J Med* **2010**; 123:S16–25.
83. Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review. *Br J Gen Pract* **2003**; 53:871–7.
84. Coker TR, Chan LS, Newberry SJ, et al. Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review. *JAMA* **2010**; 304:2161–9.
85. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial resistance in *Haemophilus influenzae*. *Clin Microbiol Rev* **2007**; 20:368–89.
86. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. *Pediatr Infect Dis J* **2010**; 29:304–9.
87. Chow AW. Acute sinusitis: current status of etiologies, diagnosis, and treatment. *Curr Clin Top Infect Dis* **2001**; 21:31–63.
88. Gwaltney JM Jr. Acute community-acquired sinusitis. *Clin Infect Dis* **1996**; 23:1209–23; quiz 24–5.
89. Noye K, Brodovsky D, Coyle S, Desrosiers M, Frenkiel S. Classification, diagnosis and treatment of sinusitis: evidence-based clinical practice guidelines. *Can J Infect Dis* **1998**; 9(Suppl B):3–24.
90. Wald ER. Microbiology of acute and chronic sinusitis in children. *J Allergy Clin Immunol* **1992**; 90:452–6.
91. Kaur R, Adlowitz DG, Casey JR, Zeng M, Pichichero ME. Simultaneous assay for four bacterial species including *Alloicoccus otitidis* using multiplex-PCR in children with culture negative acute otitis media. *Pediatr Infect Dis J* **2010**; 29:741–5.
92. Mehra P, Jeong D. Maxillary sinusitis of odontogenic origin. *Curr Infect Dis Rep* **2008**; 10:205–10.
93. Critchley IA, Brown SD, Traczewski MM, Tillotson GS, Janjic N. National and regional assessment of antimicrobial resistance among community-acquired respiratory tract pathogens identified in a 2005–2006 U.S. faropenem surveillance study. *Antimicrob Agents Chemother* **2007**; 51:4382–9.
94. Harrison CJ, Woods C, Stout G, Martin B, Selvarangan R. Susceptibilities of *Haemophilus influenzae*, *Streptococcus pneumoniae*, including serotype 19A, and *Moraxella catarrhalis* paediatric isolates from 2005 to 2007 to commonly used antibiotics. *J Antimicrob Chemother* **2009**; 63:511–19.
95. Sahn DF, Brown NP, Draghi DC, Evangelista AT, Yee YC, Thornsberry C. Tracking resistance among bacterial respiratory tract pathogens: summary of findings of the TRUST Surveillance Initiative, 2001–2005. *Postgrad Med* **2008**; 120:8–15.
96. Brook I, Gober AE. Resistance to antimicrobials used for therapy of otitis media and sinusitis: effect of previous antimicrobial therapy and smoking. *Ann Otol Rhinol Laryngol* **1999**; 108:645–7.
97. Brook I, Foote PA, Hausfeld JN. Frequency of recovery of pathogens causing acute maxillary sinusitis in adults before and after introduction of vaccination of children with the 7-valent pneumococcal vaccine. *J Med Microbiol* **2006**; 55:943–6.
98. Gotoh K, Qin L, Watanabe K, et al. Prevalence of *Haemophilus influenzae* with resistant genes isolated from young children with acute lower respiratory tract infections in Nha Trang, Vietnam. *J Infect Chemother* **2008**; 14:349–53.
99. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. *Vaccine* **2011**; 29:9127–31.
100. Jacobs MR. Antimicrobial-resistant *Streptococcus pneumoniae*: trends and management. *Expert Rev Anti Infect Ther* **2008**; 6:619–35.
101. Lynch JP 3rd, Zhanell GG. *Streptococcus pneumoniae*: epidemiology, risk factors, and strategies for prevention. *Semin Respir Crit Care Med* **2009**; 30:189–209.
102. Fallon RM, Kuti JL, Doern GV, Giroto JE, Nicolau DP. Pharmacodynamic target attainment of oral beta-lactams for the empiric treatment of acute otitis media in children. *Paediatr Drugs* **2008**; 10:329–35.
103. Dagan R. Impact of pneumococcal conjugate vaccine on infections caused by antibiotic-resistant *Streptococcus pneumoniae*. *Clin Microbiol Infect* **2009**; 15(Suppl 3):16–20.
104. Advisory Committee on Immunization Practices (ACIP). Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children. *MMWR Recomm Rep* **2010**; 59:258–61.
105. Anon JB. Current management of acute bacterial rhinosinusitis and the role of moxifloxacin. *Clin Infect Dis* **2005**; 41(Suppl 2):S167–76.
106. Patel SN, McGeer A, Melano R, et al. Susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. *Antimicrob Agents Chemother* **2011**; 55:3703–8.
107. Arrieta JR, Galgano AS, Sakano E, et al. Moxifloxacin vs amoxicillin/clavulanate in the treatment of acute sinusitis. *Am J Otolaryngol* **2007**; 28:78–82.
108. Henry DC, Kapral D, Busman TA, Paris MM. Cefdinir versus levofloxacin in patients with acute rhinosinusitis of presumed bacterial etiology: a multicenter, randomized, double-blind study. *Clin Ther* **2004**; 26:2026–33.
109. Jareoncharsri P, Bunnag C, Foonant S, et al. An open label, randomized comparative study of levofloxacin and amoxicillin/clavulanic acid in the treatment of purulent sinusitis in adult Thai patients. *Rhinology* **2004**; 42:23–9.
110. 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.
111. 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.
112. 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.
113. 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.
114. 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.
115. Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, Dimopoulos G, Falagas ME. Fluoroquinolones compared with beta-lactam antibiotics for the treatment of acute bacterial sinusitis:

- a meta-analysis of randomized controlled trials. *CMAJ* **2008**; 178: 845–54.
116. de Ferranti SD, Ioannidis JP, Lau J, Anninger WV, Barza M. Are amoxicillin and folate inhibitors as effective as other antibiotics for acute sinusitis? A meta-analysis. *BMJ* **1998**; 317:632–7.
  117. Lynch JP 3rd, Zhanel GG. *Streptococcus pneumoniae*: does antimicrobial resistance matter? *Semin Respir Crit Care Med* **2009**; 30:210–38.
  118. Jenkins SG, Farrell DJ. Increase in pneumococcus macrolide resistance, United States. *Emerg Infect Dis* **2009**; 15:1260–4.
  119. Daneman N, McGeer A, Green K, Low DE. Macrolide resistance in bacteremic pneumococcal disease: implications for patient management. *Clin Infect Dis* **2006**; 43:432–8.
  120. Brinker AD, Wassel RT, Lyndly J, et al. Telithromycin-associated hepatotoxicity: clinical spectrum and causality assessment of 42 cases. *Hepatology* **2009**; 49:250–7.
  121. Marimon JM, Perez-Trallero E, Ercibengoa M, Gonzalez A, Fenoll A. Molecular epidemiology and variants of the multidrug-resistant *Streptococcus pneumoniae* Spain14-5 international clone among Spanish clinical isolates. *J Antimicrob Chemother* **2006**; 57:654–60.
  122. Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis* **2005**; 40:1288–97.
  123. Hoban D, Felmingham D. The PROTEKT surveillance study: antimicrobial susceptibility of *Haemophilus influenzae* and *Moraxella catarrhalis* from community-acquired respiratory tract infections. *J Antimicrob Chemother* **2002**; 50(Suppl S1):49–59.
  124. See S, Mumford JM. Trimethoprim/sulfamethoxazole-induced toxic epidermal necrolysis. *Ann Pharmacother* **2001**; 35:694–7.
  125. Ludlam HA, Enoch DA. Doxycycline or moxifloxacin for the management of community-acquired pneumonia in the UK? *Int J Antimicrob Agents* **2008**; 32:101–5.
  126. Mokabberi R, Haftbaradaran A, Ravakhah K. Doxycycline vs. levofloxacin in the treatment of community-acquired pneumonia. *J Clin Pharm Ther* **2010**; 35:195–200.
  127. Zhanel GG, Palatnick L, Nichol KA, Low DE, Hoban DJ. Antimicrobial resistance in *Haemophilus influenzae* and *Moraxella catarrhalis* respiratory tract isolates: results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002. *Antimicrob Agents Chemother* **2003**; 47:1875–81.
  128. Zhanel GG, Palatnick L, Nichol KA, Bellyou T, Low DE, Hoban DJ. Antimicrobial resistance in respiratory tract *Streptococcus pneumoniae* isolates: results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002. *Antimicrob Agents Chemother* **2003**; 47:1867–74.
  129. Blackburn RM, Henderson KL, Lillie M, et al. Empirical treatment of influenza-associated pneumonia in primary care: a descriptive study of the antimicrobial susceptibility of lower respiratory tract bacteria (England, Wales and Northern Ireland, January 2007–March 2010). *Thorax* **2011**; 66:389–95.
  130. Wimmerstedt A, Kahlmeter G. Associated antimicrobial resistance in *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Clin Microbiol Infect* **2008**; 14:315–21.
  131. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* **2007**; 44(Suppl 2):S27–72.
  132. Varonen H, Rautakorpi UM, Huikko S, et al. Management of acute maxillary sinusitis in Finnish primary care. Results from the nationwide MIKSTRA study. *Scand J Prim Health Care* **2004**; 22:122–7.
  133. Arndt J, Riebenfeld D, Maier H, Weidauer H. Therapeutic efficacy and tolerability of brodimoprim in comparison with doxycycline in acute sinusitis in adults. *J Chemother* **1994**; 6:322–7.
  134. Boezeman AJ, Kayser AM, Siemelink RJ. Comparison of spiramycin and doxycycline in the empirical treatment of acute sinusitis: preliminary results. *J Antimicrob Chemother* **1988**; 22(Suppl B):165–70.
  135. Group SS. Loracarbef versus doxycycline in the treatment of acute bacterial maxillary sinusitis. Scandinavian Study Group. *J Antimicrob Chemother* **1993**; 31:949–61.
  136. Fenoll A, Gimenez MJ, Robledo O, et al. In vitro activity of oral cephalosporins against pediatric isolates of *Streptococcus pneumoniae* non-susceptible to penicillin, amoxicillin or erythromycin. *J Chemother* **2008**; 20:175–9.
  137. Fenoll A, Gimenez MJ, Robledo O, et al. Influence of penicillin/amoxicillin non-susceptibility on the activity of third-generation cephalosporins against *Streptococcus pneumoniae*. *Eur J Clin Microbiol Infect Dis* **2008**; 27:75–80.
  138. Sader HS, Jacobs MR, Fritsche TR. Review of the spectrum and potency of orally administered cephalosporins and amoxicillin/clavulanate. *Diagn Microbiol Infect Dis* **2007**; 57:5S–12S.
  139. Jansen WT, Verel A, Beitsma M, Verhoef J, Milatovic D. Surveillance study of the susceptibility of *Haemophilus influenzae* to various antibacterial agents in Europe and Canada. *Curr Med Res Opin* **2008**; 24:2853–61.
  140. Verma R, Dhamija R, Batts DH, Ross SC, Loehrke ME. Moxifloxacin induced fatal hepatotoxicity in a 72-year-old man: a case report. *Cases J* **2009**; 2:8063.
  141. Van Bambeke F, Tulkens PM. Safety profile of the respiratory fluoroquinolone moxifloxacin: comparison with other fluoroquinolones and other antibacterial classes. *Drug Saf* **2009**; 32:359–78.
  142. Poachanukoon O, Kitcharoensakkul M. Efficacy of cefditoren pivoxil and amoxicillin/clavulanate in the treatment of pediatric patients with acute bacterial rhinosinusitis in Thailand: a randomized, investigator-blinded, controlled trial. *Clin Ther* **2008**; 30:1870–9.
  143. Ariza H, Rojas R, Johnson P, et al. Eradication of common pathogens at days 2, 3 and 4 of moxifloxacin therapy in patients with acute bacterial sinusitis. *BMC Ear Nose Throat Disord* **2006**; 6:8.
  144. Ambrose PG, Anon JB, Bhavnani SM, et al. Use of pharmacodynamic endpoints for the evaluation of levofloxacin for the treatment of acute maxillary sinusitis. *Diagn Microbiol Infect Dis* **2008**; 61:13–20.
  145. Li F, Nandy P, Chien S, Noel GJ, Tornoe CW. Pharmacometrics-based dose selection of levofloxacin as a treatment for postexposure inhalational anthrax in children. *Antimicrob Agents Chemother* **2010**; 54:375–9.
  146. Arguedas A, Dagan R, Pichichero M, et al. An open-label, double tympanocentesis study of levofloxacin therapy in children with, or at high risk for, recurrent or persistent acute otitis media. *Pediatr Infect Dis J* **2006**; 25:1102–9.
  147. Bradley JS, Arguedas A, Blumer JL, Saez-Llorens X, Melkote R, Noel GJ. Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia. *Pediatr Infect Dis J* **2007**; 26:868–78.
  148. Noel GJ, Blumer JL, Pichichero ME, et al. A randomized comparative study of levofloxacin versus amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media. *Pediatr Infect Dis J* **2008**; 27:483–9.
  149. Noel GJ, Bradley JS, Kauffman RE, et al. Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders. *Pediatr Infect Dis J* **2007**; 26:879–91.
  150. Bradley JS, Jackson MA. The use of systemic and topical fluoroquinolones. *Pediatrics* **2011**; 128:e1034–45.
  151. Payne SC, Benninger MS. *Staphylococcus aureus* is a major pathogen in acute bacterial rhinosinusitis: a meta-analysis. *Clin Infect Dis* **2007**; 45:e121–7.
  152. Brook I, Foote PA, Hausfeld JN. Increase in the frequency of recovery of methicillin-resistant *Staphylococcus aureus* in acute and chronic maxillary sinusitis. *J Med Microbiol* **2008**; 57:1015–17.
  153. Huang WH, Hung PK. Methicillin-resistant *Staphylococcus aureus* infections in acute rhinosinusitis. *Laryngoscope* **2006**; 116:288–91.

154. Javer AR, Genoway K, Tsaparas Y. Comparison of swabs versus suction traps for endoscopically guided sinus cultures. *J Otolaryngol Head Neck Surg* **2008**; 37:185–91.
155. Klossek JM, Dubreuil L, Richet H, Richet B, Sedallian A, Beutter P. Bacteriology of the adult middle meatus. *J Laryngol Otol* **1996**; 110:847–9.
156. Nadel DM, Lanza DC, Kennedy DW. Endoscopically guided sinus cultures in normal subjects. *Am J Rhinol* **1999**; 13:87–90.
157. Wald ER. Sinusitis. *Pediatr Ann* **1998**; 27:811–18.
158. Kutluhan A, Akdeniz H, Kaya Z, Kiroglu F, Kiris M, Ugras S. The treatment duration of acute maxillary sinusitis: how long should it be? A nasal smear controlled study. *Rhinology* **2002**; 40:198–202.
159. Williams JW Jr, Holleman DR Jr, Samsa GP, Simel DL. Randomized controlled trial of 3 vs 10 days of trimethoprim/sulfamethoxazole for acute maxillary sinusitis. *JAMA* **1995**; 273:1015–21.
160. Henry DC, Riffer E, Sokol WN, Chaudry NI, Swanson RN. Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis. *Antimicrob Agents Chemother* **2003**; 47:2770–4.
161. Tellier G, Brunton SA, Nusrat R. Telithromycin for the treatment of acute bacterial maxillary sinusitis: a review of a new antibacterial agent. *South Med J* **2005**; 98:863–8.
162. Poole M, Anon J, Paglia M, Xiang J, Khashab M, Kahn J. A trial of high-dose, short-course levofloxacin for the treatment of acute bacterial sinusitis. *Otolaryngol Head Neck Surg* **2006**; 134:10–17.
163. Anderson VR, Perry CM. Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs* **2008**; 68:535–65.
164. Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaiou DK. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. *Br J Clin Pharmacol* **2009**; 67:161–71.
165. Pichichero ME. Short course antibiotic therapy for respiratory infections: a review of the evidence. *Pediatr Infect Dis J* **2000**; 19:929–37.
166. Hadley JA. Value of short-course antimicrobial therapy in acute bacterial rhinosinusitis. *Int J Antimicrob Agents* **2005**; 26(Suppl 3):S164–9.
167. Keating KN, Friedman HS, Perfetto EM. Moxifloxacin versus levofloxacin for treatment of acute rhinosinusitis: a retrospective database analysis of treatment duration, outcomes, and charges. *Curr Med Res Opin* **2006**; 22:327–33.
168. Ioannidis JP, Chew P, Lau J. Standardized retrieval of side effects data for meta-analysis of safety outcomes. A feasibility study in acute sinusitis. *J Clin Epidemiol* **2002**; 55:619–26.
169. Kassel JC, King D, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. *Cochrane Database Syst Rev* **2010** (3):CD006821.
170. Adam P, Stiffman M, Blake RL Jr. A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis. *Arch Fam Med* **1998**; 7:39–43.
171. Bollag U, Albrecht E, Wingert W. Medicated versus saline nose drops in the management of upper respiratory infection. *Helv Paediatr Acta* **1984**; 39:341–5.
172. Slapak I, Skoupa J, Strnad P, Hornik P. Efficacy of isotonic nasal wash (seawater) in the treatment and prevention of rhinitis in children. *Arch Otolaryngol Head Neck Surg* **2008**; 134:67–74.
173. Wang YH, Yang CP, Ku MS, Sun HL, Lue KH. Efficacy of nasal irrigation in the treatment of acute sinusitis in children. *Int J Pediatr Otorhinolaryngol* **2009**; 73:1696–701.
174. Hauptman G, Ryan MW. The effect of saline solutions on nasal patency and mucociliary clearance in rhinosinusitis patients. *Otolaryngol Head Neck Surg* **2007**; 137:815–21.
175. Inanli S, Ozturk O, Korkmaz M, Tutkun A, Batman C. The effects of topical agents of fluticasone propionate, oxymetazoline, and 3% and 0.9% sodium chloride solutions on mucociliary clearance in the therapy of acute bacterial rhinosinusitis in vivo. *Laryngoscope* **2002**; 112:320–5.
176. Tomooka LT, Murphy C, Davidson TM. Clinical study and literature review of nasal irrigation. *Laryngoscope* **2000**; 110:1189–93.
177. Rabago D, Zgierska A, Mundt M, Barrett B, Bobula J, Maberry R. Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial. *J Fam Pract* **2002**; 51:1049–55.
178. Louisiana Department of Health and Hospitals—Office of Public Health/Infectious Disease Epidemiology Section. Louisiana morbidity reports 2011. **2011**: 1–5. Available at: <http://new.dhh.louisiana.gov/index.cfm/newsroom/detail/2037>. Accessed 22 December 2011.
179. Louisiana Department of Health and Hospitals—Office of Public Health/Infectious Disease Epidemiology Section. North Louisiana woman dies from rare ameba infection: DHH warns residents about improper neti pot use. **2011**. Available at: <http://new.dhh.louisiana.gov/index.cfm/newsroom/detail/2332>. Accessed 22 December 2011.
180. Barlan IB, Erkan E, Bakir M, Berrak S, Basaran MM. Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann Allergy Asthma Immunol* **1997**; 78:598–601.
181. Dolor RJ, Witsell DL, Hellkamp AS, Williams JW Jr, Califf RM, Simel DL. Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. *JAMA* **2001**; 286:3097–105.
182. 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**; 116:1289–95.
183. Nayak AS, Settipane GA, Pedinoff A, et al. Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Ann Allergy Asthma Immunol* **2002**; 89:271–8.
184. Zalmanovici A, Yaphe J. Intranasal steroids for acute sinusitis. *Cochrane Database Syst Rev* **2009** (4):CD005149.
185. Sipila J, Suonpaa J, Silvonien P, Laippala P. Correlations between subjective sensation of nasal patency and rhinomanometry in both unilateral and total nasal assessment. *ORL J Otorhinolaryngol Relat Spec* **1995**; 57:260–3.
186. Wiklund L, Stiern P, Berglund R, Westrin KM, Tonnesson M. The efficacy of oxymetazoline administered with a nasal bellows container and combined with oral phenoxymethyl-penicillin in the treatment of acute maxillary sinusitis. *Acta Otolaryngol Suppl* **1994**; 515:57–64.
187. McCormick DP, John SD, Swischuk LE, Uchida T. A double-blind, placebo-controlled trial of decongestant-antihistamine for the treatment of sinusitis in children. *Clin Pediatr (Phila)* **1996**; 35:457–60.
188. Bende M, Fukami M, Arfors KE, Mark J, Stiern P, Intaglietta M. Effect of oxymetazoline nose drops on acute sinusitis in the rabbit. *Ann Otol Rhinol Laryngol* **1996**; 105:222–5.
189. Braun JJ, Alabert JP, Michel FB, et al. Adjunct effect of loratadine in the treatment of acute sinusitis in patients with allergic rhinitis. *Allergy* **1997**; 52:650–5.
190. US Food and Drug Administration. Public health advisory. Over-the-counter medicines for infants and children. Available at: <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforhealthcareprofessionals/publichealthadvisories/ucm051137.htm>. Accessed 1 December 2011.
191. Anon JB, Paglia M, Xiang J, Ambrose PG, Jones RN, Kahn JB. Serial sinus aspirate samples during high-dose, short-course levofloxacin treatment of acute maxillary sinusitis. *Diagn Microbiol Infect Dis* **2007**; 57:105–7.
192. Ambrose PG, Anon JB, Owen JS, et al. Use of pharmacodynamic endpoints in the evaluation of gatifloxacin for the treatment of acute maxillary sinusitis. *Clin Infect Dis* **2004**; 38:1513–20.



193. Lindbaek M, Hjørtedahl P. Predictors of duration of acute sinusitis episodes treated with antibiotics. *Scand J Prim Health Care* **1998**; 16:24–9.
194. Craig WA. The hidden impact of antibacterial resistance in respiratory tract infection. Re-evaluating current antibiotic therapy. *Respir Med* **2001**; 95(Suppl A):S12–19. discussion S26–7.
195. Scheid DC, Hamm RM. Acute bacterial rhinosinusitis in adults: part II. Treatment. *Am Fam Physician* **2004**; 70:1697–704.
196. Axelson A, Brorson JE. The correlation between bacteriological findings in the nose and maxillary sinus in acute maxillary sinusitis. *Laryngoscope* **1973**; 83:2003–11.
197. Catlin FI, Cluff LE, Reynolds RC. The bacteriology of acute and chronic sinusitis. *South Med J* **1965**; 58:1497–502.
198. Jousimies-Somer HR, Savolainen S, Ylikoski JS. Comparison of the nasal bacterial floras in two groups of healthy subjects and in patients with acute maxillary sinusitis. *J Clin Microbiol* **1989**; 27:2736–43.
199. Benninger MS, Payne SC, Ferguson BJ, Hadley JA, Ahmad N. Endoscopically directed middle meatal cultures versus maxillary sinus taps in acute bacterial maxillary rhinosinusitis: a meta-analysis. *Otolaryngol Head Neck Surg* **2006**; 134:3–9.
200. Gordts F, Abu Nasser I, Clement PA, Pierard D, Kaufman L. Bacteriology of the middle meatus in children. *Int J Pediatr Otorhinolaryngol* **1999**; 48:163–7.
201. Younis RT, Lazar RH, Anand VK. Intracranial complications of sinusitis: a 15-year review of 39 cases. *Ear Nose Throat J* **2002**; 81:636–8. 40–2, 44.
202. Lau J, Zucker D, Engels EA, et al. Diagnosis and treatment of acute bacterial rhinosinusitis. *Evid Rep Technol Assess (Summ)* **1999**: 1–5.
203. Sievers KW, Dietrich U, Zoller E, Dost P, Jahnke K. [Diagnostic aspects of isolated sphenoid sinusitis]. *HNO* **1992**; 40:464–7.
204. Hurley MC, Heran MK. Imaging studies for head and neck infections. *Infect Dis Clin North Am* **2007**; 21:305–53. v-vi.
205. Mafee MF, Tran BH, Chapa AR. Imaging of rhinosinusitis and its complications: plain film, CT, and MRI. *Clin Rev Allergy Immunol* **2006**; 30:165–86.
206. Younis RT, Anand VK, Davidson B. The role of computed tomography and magnetic resonance imaging in patients with sinusitis with complications. *Laryngoscope* **2002**; 112:224–9.
207. McIntosh D, Mahadevan M. Failure of contrast enhanced computed tomography scans to identify an orbital abscess. The benefit of magnetic resonance imaging. *J Laryngol Otol* **2008**; 122: 639–40.
208. Herrmann BW, Forsen JW Jr. Simultaneous intracranial and orbital complications of acute rhinosinusitis in children. *Int J Pediatr Otorhinolaryngol* **2004**; 68:619–25.
209. Adame N, Hedlund G, Byington CL. Sinogenic intracranial empyema in children. *Pediatrics* **2005**; 116:e461–7.
210. Cornelius R, Wippold FJ II, Brunberg JA, et al. ACR Appropriateness Criteria—sinonasal disease expert panel on neurologic imaging [online publication]. Reston, VA: American College of Radiology, **2009**: 1–5.
211. Karmazyn BK, Gunderman RB, Coley BD, et al. ACR Appropriateness Criteria on developmental dysplasia of the hip—child. *J Am Coll Radiol* **2009**; 6:551–7.
212. Berrington de Gonzalez A, Mahesh M, Kim KP, et al. Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med* **2009**; 169:2071–7.