

# GENERAL GUIDELINES FOR THE EVALUATION OF NEW ANTI-INFECTIONAL DRUGS FOR THE TREATMENT OF RESPIRATORY TRACT INFECTIONS

## Evaluation of New Anti-Infective Drugs for the Treatment of Respiratory Tract Infections

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These guidelines deal with the evaluation of anti-infective drugs for the treatment of respiratory tract infections. Five clinical entities are described: streptococcal pharyngitis and tonsillitis, otitis media, sinusitis, bronchitis, and pneumonia. A wide variety of microorganisms are potentially pathogenetic in these diseases; these guidelines focus on the bacterial infections. Inclusion of a patient in a trial of a new drug is based on the clinical entity, with the requirement that a reasonable attempt will be made to establish a specific microbial etiology. Microbiologic evaluation of efficacy requires isolation of the pathogen and testing for in vitro susceptibility. Alternatively, surrogate markers may be used to identify the etiologic agent. The efficacy of new drugs is evaluated with reference to anticipated response rates. Establishment of the microbial etiology of respiratory tract infections is hampered by the presence of "normal flora" of the nose, mouth, and pharynx, which may include asymptomatic carriage of potential pathogens. This issue is addressed for each category of infection described. For example, it is suggested that for initial phase 2 trials of acute otitis media and acute sinusitis tympanocentesis or direct sinus puncture be used to collect exudate for culture. Acute exacerbations of chronic bronchitis also present difficulties in the establishment of microbial etiology. These guidelines suggest that clinical trials employ an active control drug but leave open the possibility of a placebo-controlled trial. For pneumonia, the guidelines suggest the identification and enrollment of patients by the clinical type of pneumonia, e.g., atypical pneumonia or acute bacterial pneumonia, rather than by etiologic organism or according to whether it was community or hospital acquired. For each respiratory infection, the clinical response is judged as cure, failure, or indeterminate. Clinical improvement is not acceptable unless quantitative response measures can be applied.

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## I. INTRODUCTION

This is one of a series of disease-specific guidelines that have been prepared to assist sponsors and investigators in the development, conduct, and analysis of studies of new anti-infective drugs. These guidelines deal with the conduct of phase 1 through phase 4 clinical trials and are subsets of the General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, which should be consulted for prerequisites to conducting studies in humans.

### A. Overview and Scope of Guidelines

These guidelines for the evaluation of drugs for the treatment of respiratory tract infections include acute streptococcal pharyngitis and tonsillitis, acute otitis media, acute and chronic sinusitis, acute exacerbations of chronic bronchitis, and acute infectious pneumonia (table 1). The focus is primarily on infections of bacterial etiology, especially those due to respiratory pathogens such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella (Branhamella) catarrhalis* and respiratory anaerobes (e.g., *Bacteroides* species, *Fusobacterium nucleatum*, and *Peptostreptococcus* species). Readers should consult the specific guidelines for the evaluation of new anti-infective drugs for mycobacterial and fungal infections. The guidelines for clinical microbiology provide important background information and should be used in concert with the current guidelines.

### B. General Principles of Care for Patients with Respiratory Tract Infections

The respiratory tract infections considered in these guidelines are among the most frequent disease entities encountered in both children and adults. They are associated with potentially serious morbidity if unattended or treated subop-

timally. They also are infections in which evaluation of specific anti-infective therapy may be difficult. The reasons for the difficulties include: (1) routine noninvasive collection of specimens and culture techniques are often inadequate, and specimens are regularly contaminated by the indigenous microflora of the oropharynx and the upper airways; (2) the microbial etiology is often complex and polymicrobial; and (3) newly recognized etiologic agents continue to emerge (e.g., *Legionella* species, *Chlamydia pneumoniae*, and *Coxiella burnetii*). Even with the use of sophisticated sampling and microbiologic techniques, the causative agents can be identified only for a small proportion (60%–80% at best) of patients. Furthermore, good clinical practice requires empiric initiation of anti-infective therapy for these conditions (with the possible exception of group A streptococcal pharyngitis) on the basis of a presumptive initial diagnosis before confirmatory microbiologic data are available. Frequently, the microbiologic response to therapy cannot be definitively evaluated, even when the etiologic agent has been identified. This is often the case in otitis media, sinusitis, and pneumonia, when the use of invasive procedures such as tympanocentesis, sinus puncture, or transtracheal aspiration to confirm microbial eradication in the patient who is improving clinically generally is considered unjustified. Thus, whereas microbiologic failure can be documented by repeat cultures, microbiologic eradication can only be assessed presumptively on the basis of clinical response.

The current standards of anti-infective therapy for the respiratory tract infections encompassed in these guidelines are summarized in table 1.

### C. Controversies and Future Trends

In addition to the changing trends in microbial etiology, several controversial areas exist: (1) the clinical significance of  $\beta$ -lactamase production among respiratory pathogens and

**Table 1.** General principles of anti-infective therapy for respiratory tract infections.

Infection	Currently recommended duration of treatment (d)	Anticipated response rates (%)
Streptococcal pharyngitis	10	80–90
Acute otitis media	10	80–90*
Acute sinusitis	10–14	70–80†
Chronic sinusitis	Unknown	30–40 (without concomitant surgery) 60–70 (with concomitant surgery)
Acute exacerbation of chronic bronchitis	7–10	50–70 cured
Pneumonia		
Acute pneumococcal pneumonia	7–10	50–90
Aspiration or respirator-associated pneumonia	4–21	Variable

\* 30% spontaneously.

† 15% spontaneously.

the need for their routine screening in the laboratory; (2) the acceptability of non-culture techniques (e.g., antigen-detection assays, nucleic acid probes, polymerase chain reaction procedures, serologic responses) for the microbiologic evaluation of new anti-infective agents; and (3) the importance of concentrations of drug in respiratory secretions as predictors of efficacy of new anti-infective agents.

## II. GENERAL CONSIDERATIONS

### A. Disease Definition

The respiratory tract infections under study should be categorized according to the age of the patient, chronicity of the disease, and any underlying or concomitant disease(s) in the patient.

### B. Preclinical Studies

The investigational drug should have *in vitro* activity against the specific respiratory tract pathogen to be evaluated in a pathogen-specific study and activity against the vast majority of strains of the most likely encountered pathogens in a disease-specific study. Evaluation of the influence of combination therapy is desirable, as is assessment of the emergence of resistance *in vitro*.

Information obtained from studies in animals may be of assistance in identifying preliminary dosage schedules for humans. Evaluations of efficacy in standardized animal models of infection may be performed. Determination of drug levels in respiratory tract secretions (such as sinus, middle-ear, or endotracheal aspirates) or in tissue (such as pulmonary parenchyma) is not required because at present the clinical significance of these concentrations is uncertain.

### C. Clinical Studies (Phases 1, 2, 3, and 4)

See General Guidelines, section III.A.

### D. Qualifications of Investigators and Institutions

#### 1. Investigators

See General Guidelines, section VII.

#### 2. Institutions

Institutions should be capable of performing the following studies relevant to the management of respiratory tract infections when appropriate to a specific protocol: nucleic acid probe analysis for identification of selected respiratory pathogens, radiography and computerized tomography (CT) and/or magnetic resonance imaging of the head and neck, sinuses, and chest; arterial blood gas determinations; tympanocente-

sis; sinus puncture; thoracentesis; and bronchoscopy. These studies should be done in addition to routine diagnostic microbiologic testing. Alternatively, special studies may be performed at a reference laboratory skilled in these procedures and approved by the appropriate authorities.

### E. Study Design and Implementation

The preferred design is the random assignment of patients to the investigational-drug and active-control-drug groups. The randomization schedule should be maintained by a study monitor. Patients should be stratified according to age, severity of infection, presence of underlying disease, and concomitant non-antibacterial therapy. Blinding of both subjects and investigators to treatment group (double-blind design) is encouraged whenever feasible.

In all cases, the inclusion and exclusion criteria should be clearly identified prior to initiation of the study. All patients enrolled in the study should be assessed on the basis of "intention to treat." A uniform approach to clinical and microbiologic assessment during and after therapy should be implemented. End points for both clinical and microbiologic evaluation should be clearly stated, and whenever possible a quantitative scoring system should be devised. Patient compliance should be verified (e.g., by pill counts or by appropriate assays of drug concentrations in serum or other body fluids).

### F. Sample Size, Statistical Methods, and Final Evaluation

See General Guidelines, section XVI and appendix.

### G. Methods of Assessing Safety

See General Guidelines, section XIV and appendix.

### H. Methods of Presenting and Analyzing Data

See General Guidelines, section XVI.

### I. Clinical and Microbiologic Evaluations

Clinical and microbiologic evaluations occur during therapy, at the end of therapy, and at a specific follow-up evaluation. A summary of the timetable for evaluations is presented in table 2.

### J. Methods of Ensuring Compliance and Ethical Conduct

See General Guidelines, sections IV and XI.E.

**Table 2.** Proposed timetable for evaluation of anti-infective drugs for the treatment of respiratory tract infections.

Evaluation	Evaluation at indicated time after initiation of treatment (total, 7-14 d)		
	3-5 d (during)	12-16 d (end)	28-42 d (follow-up)
Clinical	Improvement*/failure	Cure/failure/indeterminate	
Microbiologic	Presumed eradication or persistence	Eradication/persistence/relapse	
Final	Cure/failure/indeterminate		

\* If objective measurements are available (see General Guidelines, section XIII, for examples).

**K. Informed Consent**

See General Guidelines, section IV.D.

**III. SPECIFIC GUIDELINES**

**A. Group A  $\beta$ -Hemolytic Streptococcal Pharyngitis and Tonsillitis**

**1. Background**

Group A  $\beta$ -hemolytic streptococcal pharyngitis remains one of the most frequent acute infections seen in ambulatory patients, especially school children between 5 and 8 years of age [1-6]. Antibiotic therapy for streptococcal pharyngitis is aimed not only at symptomatic improvement of the acute infection [7-12] and the prevention of suppurative complications but also, and most importantly, at the prevention of the subsequent occurrence of acute rheumatic fever [1, 13]. The incidence of acute rheumatic fever in the United States has declined dramatically over the past several decades, such that by the 1980s it was a rare sequela of streptococcal pharyngitis [1, 5, 6]. However, between 1984 and 1986 four major outbreaks of acute rheumatic fever in three states resulted in a heightened concern for optimal treatment of streptococcal pharyngitis [14-16].

Penicillin, given orally or intramuscularly, has generally been considered the drug of choice and the drug against which other regimens have most often been judged. A full 10 days of oral therapy or a single injection of benzathine penicillin is required [3-6]. Shortening a course of penicillin by even a few days has been shown to result in an appreciable increase in the rate of treatment failure. However, even with the recommended 10 days of oral therapy, the failure rate may still be high [3-6]. In recent studies, penicillin therapy, given orally or intramuscularly, has been associated with rates of microbiologic failure as high as 20%-30%, in contrast to the rates of 5%-10% seen 20 years ago. The reasons for this increase are not clear, although the presence of  $\beta$ -lactamase-producing organisms in the throat flora and an increase in the tolerance of streptococci to penicillin have been suggested as contributing causes. Resistance to erythromycin, a frequently used al-

ternative drug, has been high in some areas but is generally low (<5% of isolates) in the United States.

*(a) Scope of Guideline*

The clinical entity addressed in this guideline is group A  $\beta$ -hemolytic streptococcal pharyngitis and tonsillitis. Not included are clinical cases of pharyngitis due to other agents or cases in which streptococci have been isolated in cultures of throat specimens but have not been documented to be group A  $\beta$ -hemolytic streptococci.

*(b) Standards of Care for Patients with Group A  $\beta$ -Hemolytic Streptococcal Pharyngitis*

Group A  $\beta$ -hemolytic streptococcal pharyngitis can not be diagnosed accurately on clinical grounds alone because it is frequently difficult to differentiate this entity from pharyngitis caused by other organisms. Therefore, diagnosis requires a positive culture for group A  $\beta$ -hemolytic streptococci from a throat swab specimen in a patient with symptomatic pharyngitis. Alternatively, the diagnosis may be made by use of one of the rapid diagnostic kits that can detect group A  $\beta$ -hemolytic streptococcal antigen directly from a throat swab specimen [19-22]. For the purpose of the evaluation of new drugs, however, the diagnosis should be confirmed with a throat culture, since the sensitivity (37%-100%, most 60%-95%) and specificity (70%-100%, most >90%) of the rapid detection kits are quite variable [19-22].

Drugs used for the treatment of group A  $\beta$ -hemolytic streptococcal pharyngitis should have been shown to have bactericidal activity against group A  $\beta$ -hemolytic streptococci and to have undergone relevant phase 1 studies prior to the initiation of clinical investigations. The drug under consideration should have a low index of toxicity in both children and adults, since a number of other agents exist that offer acceptable therapy for group A  $\beta$ -hemolytic streptococci and since streptococcal pharyngitis is usually a minor disease. Furthermore, the drug should result in clinical improvement within 24-48 hours of the initiation of therapy, with resolution of fever within 48 hours in uncomplicated streptococcal pharyngitis, as can be expected with penicillin and other antimicrobial agents currently approved for treatment of streptococcal pharyngitis [3, 7-12].

The drug under consideration also should provide an acceptably low rate of microbiologic failure associated with recurrence or persistent carriage and a rate no greater than that associated with current standard therapy with penicillin (10%-20%) [3-6]. The drug should be capable of preventing the suppurative complications of group A streptococcal pharyngitis and, ideally, of preventing rheumatic fever. It would be desirable to have data indicating that the drug is capable of preventing rheumatic fever, but it is recognized that this goal may not be achievable.

### (c) *Future Trends*

A current concern in the treatment of acute streptococcal pharyngitis is whether the failure rate for penicillin therapy will continue to climb and whether penicillin should still be considered the standard therapy. In addition, there is controversy about when antimicrobial therapy should be initiated. Clinical differentiation of group A streptococcal pharyngitis from other causes of sore throat is not always possible, a problem that raises the question of whether antibiotic therapy should be initiated before bacteriologic confirmation is available. Furthermore, prompt treatment of group A  $\beta$ -hemolytic streptococcal pharyngitis has been shown to interfere with the antibody response and possibly to result in a higher rate of recurrence than that seen in patients whose therapy is delayed for a few days [17]. Last, controversy exists concerning whether post-treatment cultures should be obtained to detect bacteriologic failures and whether asymptomatic carriage necessitates treatment [18].

## 2. Clinical Definitions of the Disease

Patients eligible for study entrance are children or adults with symptomatic pharyngitis or tonsillitis of acute onset clinically consistent with infection with group A  $\beta$ -hemolytic streptococci and from whom group A  $\beta$ -hemolytic streptococci have been isolated in cultures of throat-swab specimen or for whom a rapid screening test has indicated the presence of streptococci. To be evaluable for efficacy, the screening test results must be confirmed by culture. The guideline generally applies to ambulatory patients.

### (a) *Clinical Criteria*

Signs and symptoms of acute pharyngitis or tonsillitis of acute onset include sore throat and evidence on physical examination of inflammation of the uvula and pharynx or tonsils, including erythema, often with edema of the tissues, with or without exudate. Fever may or may not be present.

### (b) *Microbiologic Criteria*

A single culture specimen should be obtained from the posterior pharynx prior to initiation of anti-infective therapy. At least 10 colonies of group A  $\beta$ -hemolytic streptococci should be present on the culture plate. A throat specimen for culture is obtained with use of a throat swab that is passed over both sides of the posterior pharynx and the uvula [3]. The preferred culture medium is sheep's-blood agar. All cultures negative at 24 hours should be reincubated for another 24 hours. Reduced oxygen tension may enhance identification of group A  $\beta$ -hemolytic streptococci. Such a reduction may be achieved in a simple manner by stabbing the agar after the sample is streaked or by using a coverglass pressed onto the primary zone of inoculation [19]. Group A streptococci are identified by the bacitracin method or by an-

other method of at least equal sensitivity and specificity [3, 19, 21]. If a rapid diagnostic test is used for identification of group A streptococci, the findings must be confirmed by culture [20–22]. The streptococci obtained on culture should be saved for subsequent typing when possible.

## 3. Information Needed Before Conducting Clinical Trials in Humans

The drug under consideration should be active *in vitro* against group A  $\beta$ -hemolytic streptococci.

## 4. Special Qualifications of Investigators and Institutions

The institution or the investigator should have access to a clinical microbiology laboratory where the following tests can be performed: culture of throat swabs on sheep's-blood agar and identification of group A  $\beta$ -hemolytic streptococci. Alternatively, a single laboratory may process samples referred from participating centers.

## 5. Design and Implementation of Phase 1, 2, and 3 Clinical Trials

### (a) *Demographic Characteristics of the Study Population*

Clinical studies should include patients of different age groups, since the clinical manifestations of group A streptococcal pharyngitis and tonsillitis may vary with age of the patient. Streptococcal pharyngitis is uncommon in children <3 years of age. Classic exudative pharyngitis is most frequently observed in school-aged children. Group A streptococcal pharyngitis in teenagers and adults is often atypical.

### (b) *Inclusion and Exclusion Criteria*

Children, adolescents, and adults of both sexes should be included. For other considerations, see General Guidelines, section IX.

### (c) *Selection of the Comparison Drug*

It is not considered ethical to use a placebo control. An active control drug should be used. The control agent should be selected on the basis of previous experience demonstrating that it is among the most effective agents for the treatment of group A  $\beta$ -hemolytic streptococcal pharyngitis at standardized and well-tolerated doses.

### (d) *Study Design*

The study should compare the trial drug with the active control drug. The treatment regimens should be randomized and of a double-blind design whenever possible.

### (e) Administration of the Study Drug

Phase 1 studies should provide adequate information concerning dose, dosage interval, and other pharmacokinetic characteristics. The usefulness of monitoring concentrations in serum or other body fluids or tissues should have been determined. The form of the drug (liquid, tablet, capsule) should be acceptable for patients of any age included in the study and should be an accurate dose (e.g., no cutting of tablets required). The usual treatment course with standard regimens (e.g., penicillin or erythromycin) is 10 days. The optimal duration of therapy with the study drug may be determined by additional studies. The initiation of therapy should be standardized, i.e., at the time of clinical diagnosis or at the time of culture confirmation.

### (f) Modifications During Conduct of the Study

If it proves necessary to add a second drug or to substitute a new antimicrobial drug, treatment is considered to have failed clinically. In the event of allergy to or failure of either drug being evaluated, the patient should be treated with an alternative, standard active drug.

### (g) Evaluability

Response should be evaluated by both clinical and bacteriologic assessment. Clinical assessment should include history and physical examination. Documentation of the clinical response with regard to symptoms and signs, including fever, should be obtained at 3–5 days after initiation of therapy and at weekly intervals ( $\pm 2$  days) thereafter until the patient is asymptomatic. The 3- to 5-day assessment may take the form of a telephone call. *Patients should be observed post-therapy for a sufficient time to permit detection of relapse of disease and/or post-streptococcal nephritis or carditis.* The period of post-treatment evaluation will vary with knowledge of the duration of anti-infective activity subsequent to termination of administration of the test drugs. As a general guide,

patients should be followed-up for 2–4 weeks after termination of therapy.

Evaluation of the bacteriologic response requires a repeated throat culture at the first follow-up visit, within 4–7 days after the end of therapy, and at any time clinical symptoms recur. Additional posttreatment throat cultures may be necessary for patients treated with drugs known to remain in serum or tissue for intervals beyond the initial 4- to 7-day evaluation. All organisms recovered should be saved for typing if possible. Group A streptococci recovered during therapy or at the time of the follow-up visit should be evaluated for their *in vitro* susceptibility to the study drug.

The serologic response to group A  $\beta$ -hemolytic streptococci may be evaluated in acute- and convalescent-phase sera for titers of antibody to streptolysin-O (ASO) or other streptococcal antigens. Serologic evaluation, however, is not required for evaluation of drug efficacy.

Compliance should be evaluated by the return of all medication containers and of any remaining drug at the end of therapy. Documentation of drug in the urine or blood may also be used to assess compliance.

(1) *Definition of clinical response.* *Clinical cure* is defined as complete disappearance of signs and symptoms without recurrence; *clinical cure with recurrence* is defined as the development of symptomatic pharyngitis documented to be caused by group A  $\beta$ -hemolytic streptococci before or during follow-up in patients who were asymptomatic at the initial follow-up assessment; and *clinical failure* is defined as lack of any response to therapy.

(2) *Definition of microbiologic response.* *Microbiologic eradication* is defined as eradication of group A  $\beta$ -hemolytic streptococci at the initial and subsequent follow-up examinations; *microbiologic persistence* is defined as failure to eradicate group A  $\beta$ -hemolytic streptococci at the time of initial follow-up; and *microbiologic relapse* is defined as initial suppression of group A  $\beta$ -hemolytic streptococci with subsequent positive cultures for group A  $\beta$ -hemolytic streptococci.

The final assessment of efficacy may be categorized according to both clinical and microbiologic criteria as in table 3.

**Table 3.** Clinical and microbiologic responses of streptococcal pharyngitis to treatment with anti-infective drugs.

Response	During treatment (3–10 d)		Posttreatment (as defined by individual protocol)	
	Clinical signs	Throat culture	Clinical signs	Throat culture
Clinical cure and microbiologic eradication	None	NN*	None	–
Clinical cure with microbiologic persistence	None	NN	None	+
Clinical cure with microbiologic relapse	None	NN	None	+
Clinical failure with microbiologic relapse	Present	+	Present	+
Clinical failure with microbiologic persistence	Present	+	...	...
Indeterminate	State reason			

\* NN = none necessary.

## B. Otitis Media

### 1. Background

Otitis media is the most frequent diagnosis recorded for infants and children who visit physicians because of illness [23]. Before 3 years of age more than two-thirds of children have had one or more episodes of acute otitis media (AOM) and more than one-third have had three or more episodes [24]. The highest incidence of AOM is in children 6–24 months of age. The incidence declines with age except for a limited reversal of the downward trend at the time of entry into day care or school. Although middle-ear infection is considered uncommon in adults, a recent survey identified almost 4 million visits to physicians by adults each year for this problem [25].

Males have a significantly increased risk for AOM, and Native Americans and Canadian and Alaskan Eskimos have high rates and severe disease. Incomplete data suggest that American blacks have fewer episodes of ear infection than do members of other racial groups in the United States. Early occurrence of the first episode of AOM, sibling history of recurrent AOM, not being breast fed, and attendance in day care are all associated with increased risk for recurrent AOM [24, 26].

Since AOM and secretory otitis media (SOM) are defined by the presence of middle-ear effusion (MEE), techniques to determine the presence of air or fluid in the middle ear are critical to diagnosis. Three methods are available: the standard technique of pneumatic otoscopy, tympanometry, and acoustic reflectometry. Tympanometry uses an electroacoustic impedance bridge to record compliance of the tympanic membrane (TM) and provides objective evidence of the status of the middle ear and the presence or absence of fluid. Technical difficulties limit the use of tympanometry in children during the first 6 months of life. The acoustic otoscope or reflectometer is a hand-held instrument that utilizes principles of reflected sound waves to diagnose the presence of air or fluid in the middle ear.

The microbiology of AOM has been documented by appropriate cultures of MEE obtained by needle aspiration. Many studies have been performed in the United States, Scandinavia, and Japan. The bacteriologic results are consistent in demonstrating the importance of *S. pneumoniae*, *H. influenzae* (90% nontypable, 10% type b), and *M. catarrhalis* [27]. *S. pneumoniae* is the most important bacterial cause of otitis media and is defined in MEE of about one-third of children with AOM. Otitis media due to *H. influenzae* has been associated with 20%–30% of cases of AOM, and ~20%–30% of these strains produce  $\beta$ -lactamase. *M. catarrhalis* has been isolated from MEE in 7%–20% of cases of AOM, and a majority of these strains produce  $\beta$ -lactamase. Virologic and epidemiologic data suggest that viral infection frequently is associated with AOM. *Mycoplasma pneumoniae* does not appear to play a role in AOM, although some patients with lower respiratory tract disease due to *M. pneumoniae* may have con-

comitant AOM. *C. trachomatis* is a cause of AOM but almost exclusively in infants <6 months of age.

The microbiologic diagnosis of AOM can be made only by aspiration of MEE. This procedure should be done only by persons skilled in the technique. Cultures of throat and nasopharyngeal swab specimens are of no value because they are neither sensitive nor specific when compared with cultures of isolates from the middle ear. The results of cultures of middle-ear fluids from the two ears are disparate in ~20% of cases of AOM (e.g., effusion from one ear may be sterile while the effusion from the other yields a bacterial pathogen, or different bacterial pathogens are isolated from the two ears). Therefore, for evaluation of new drugs or vaccines, it is important that each diseased ear be aspirated for a complete microbiologic assessment and that outcome for each ear be evaluated separately [28].

Suppurative sequelae such as mastoiditis and other infratemporal and intracranial complications occur but are uncommon in developed countries. Hearing loss is the most important complication of AOM and MEE. Patients with MEE suffer from hearing loss of variable severity. On average, a patient with fluid in the middle ear has a 25-decibel hearing loss. Since intellectual development is dynamic during infancy, when the incidence of AOM is highest, there is concern that any impediment to reception or interpretation of auditory stimuli might have an adverse effect on development of speech, language, and cognitive abilities. Some studies suggest that children with histories of recurrent AOM have lower scores in tests of linguistic and cognitive abilities than do their disease-free peers [29].

#### (a) Scope of Guideline

The clinical entity discussed in this guideline is limited to AOM (synonyms include acute suppurative OM and acute purulent OM). The microorganisms considered are *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Not included in this guideline are secretory otitis media and chronic suppurative otitis media. SOM is defined as the presence of MEE behind an intact TM without acute signs or symptoms (synonyms include chronic OM with effusion, persistent MEE, OM with effusion, and serous OM). Chronic suppurative OM is defined as chronic discharge from the middle ear through a perforation of the TM (synonym includes chronic OM).

#### (b) General Principles of Care for Patients with Acute Otitis Media

Tympanocentesis and culture of MEE is required for microbiologic diagnosis of AOM. Nose and throat cultures are of no value. Tympanocentesis is a safe procedure when performed by skilled and experienced persons. The procedure provides not only specific microbiologic diagnosis but also symptomatic relief of acute pain by decompressing the



middle-ear abscess. There is transient pain during the few seconds of the procedure. Rare untoward events may occur, including bleeding, tearing of the tympanic membrane, and ossicular dislocation. Approximately one-third of children with AOM caused by a bacterial pathogen improve without treatment with antibacterial drugs. Clinical resolution may occur because the contents of the middle ear are spontaneously discharged, either through the eustachian tube or by means of a spontaneous perforation of the TM. With appropriate antimicrobial therapy, however, signs and symptoms of AOM improve within 48–72 hours. MEE may persist (even though sterile) for weeks to months after onset of AOM. The goals of antimicrobial therapy for AOM are the rapid resolution of signs and symptoms of disease; sterilization of the MEE; prevention of suppurative sequelae; reduction of the occurrence of relapse and recurrences; and decrease in time spent with MEE.

The preferred antimicrobial agent for the patient with AOM must be active against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Group A streptococci, *Staphylococcus aureus*, gram-negative enteric bacilli, and anaerobic bacteria are infrequent causes of AOM and need not be considered in initial therapeutic decisions. Amoxicillin or an equivalent has been the standard regimen for AOM since it is effective against most strains of the three major pathogens and is well tolerated, producing limited adverse effects. However, since at present 20%–30% of *H. influenzae* strains and 50%–70% of *M. catarrhalis* strains in the United States produce  $\beta$ -lactamase, a  $\beta$ -lactamase-stable agent (such as amoxicillin plus a  $\beta$ -lactamase inhibitor, a second- or third-generation cephalosporin) or a combination such as trimethoprim-sulfamethoxazole or erythromycin/sulfisoxazole may also be used. Clinical trials with these agents indicate that all regimens are of approximately equal clinical efficacy when the bacterial pathogens are susceptible [30]. The control drug chosen for a clinical trial should be among the most effective and safe agents available for treatment. It is expected that an effective agent will sterilize the middle-ear fluid of bacterial pathogens in >80% of infected ears within 72 hours. A second aspiration of middle-ear fluid should be considered for any patient for whom the outcome at 72 hours is clinical failure.

Chemoprophylaxis has been shown to be of value in the prevention of acute illness in children who have had recurrent AOM [31]. More than 10 studies in which a penicillin, a sulfonamide, or erythromycin was used have identified protective efficacy against new episodes of AOM in 60%–90% of cases in comparisons with a placebo control group.

### (c) Future Trends

The changing susceptibility patterns of bacterial pathogens associated with AOM warrant consideration of new and effective drugs with activity against all major pathogens. New drugs

should have advantages over currently available agents, including (1) ease of administration to ensure compliance and greater convenience for the patient (e.g., once-a-day dosing, drug stability at room temperature, prolonged drug shelf-life); (2) reduced incidence of relapse and recurrence; and (3) reduced duration of MEE after resolution of acute signs and symptoms. New diagnostic instruments with improved capacity for examination of the middle ear (of most importance is diagnosis of the presence of fluid in the middle ear) also are needed. Even the most experienced otoscopists are accurate in diagnosing the presence of MEE in only ~80% of cases. Tympanometry and acoustic reflectometry are of value in assisting the otoscopist but are insufficiently sensitive and specific to assure accuracy of diagnosis for all children enrolled in clinical trials. A noninvasive technique for determining the organisms present in MEE is needed for the facilitation of appropriate microbiologic diagnosis and optimal use of approved drugs. Currently, only needle aspiration of the fluid from both middle ears assures definition of the etiologic agents of AOM.

## 2. Clinical Definitions of the Disease

### (a) General Definition

Patients eligible for inclusion in studies will be children or adults with symptoms and signs clinically compatible with AOM.

### (b) Minimal Diagnostic Criteria Permitting Inclusion in Trials

(1) *Clinical criteria.* AOM is defined as inflammation of the middle ear evidenced by the presence of fluid and accompanied by specific signs or symptoms such as ear pain, ear drainage, hearing loss, or nonspecific findings such as fever, lethargy, irritability, anorexia, vomiting, or diarrhea. The presence of MEE is defined by pneumatic otoscopy with or without use of tympanometry or acoustic reflectometry.

(2) *Microbiologic criteria.* Specific microbiologic diagnoses of AOM can be determined only by aspiration of MEE. Both ears should be aspirated when the patient has bilateral AOM. Tympanocentesis is a standard procedure and is described in various texts on otolaryngology [32]. The procedure should be performed only by qualified personnel with previous experience.

Nose and throat cultures are of no value in the microbiologic diagnosis of AOM since they are neither sensitive nor specific for predicting bacteria present in MEE. Specimens for such cultures may be obtained from selected patients for monitoring change in susceptibility patterns of nasopharyngeal or oropharyngeal isolates during the course of antimicrobial therapy.

### 3. Information Needed Before Conducting Clinical Trials in Humans

The drug under consideration should have proven *in vitro* activity against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Group A streptococci, *S. aureus*, gram-negative enteric bacilli, and anaerobic bacteria are infrequent causes of AOM and need not be considered in initial therapeutic decisions. *In vivo* evidence of sterilization of bacterial pathogens should be obtained with use of an appropriate dosage schedule in an animal model of AOM. The chinchilla has been used most frequently in assessments of pathogenesis and therapy and should be considered for such *in vivo* studies.

### 4. Special Qualifications of Investigators and Institutions

The investigator or the institution should have access to a clinical microbiologic laboratory where personnel can perform the following tests: culture of MEE for the isolation and identification of common pathogens in AOM and *in vitro* susceptibility testing, including tests for  $\beta$ -lactamase production. The institution should have appropriate facilities and investigators experienced in middle-ear examination and aspiration of MEE.

### 5. Design and Implementation of Phase 1, 2, and 3 Clinical Trials

#### (a) Demographic Characteristics of the Study Population

Clinical studies should be conducted with patients of different age groups and racial backgrounds. In newborns and infants up to 6 weeks of age, the bacterial pathogens in AOM differ from those in older children and include organisms acquired during delivery. In addition, pharmacologic considerations are different for older infants and children. The incidence of AOM is highest between the ages of 6 and 24 months. The risk for AOM is significantly increased in males, Native Americans, and Canadian and Alaskan Eskimos, and the risk may be lower for black Americans than for white Americans.

#### (b) Inclusion and Exclusion Criteria

Children, adolescents, and adults of both sexes should be included in studies. Phase 1 evaluations may include single-dose administration before tympanocentesis to assess the penetration of drug into middle-ear fluids. Initial clinical studies should not include children with focal anatomic, physiologic, or systemic immune defects; children who had received a systemic antimicrobial agent within the past 7 days for treatment of an illness other than AOM; and neonates or infants <12 weeks of age.

#### (c) Selection of the Comparison Drug

The control agent should be selected on the basis of expected patterns of *in vitro* susceptibility of the most common pathogens (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*) in the community.

#### (d) Study Design and Stratification

Because of the difficulties in obtaining reliable cultural information in AOM even under protocol conditions, it may be appropriate to adopt a sequential study strategy:

(1) A small ( $\sim 100$  patients) phase 2 trial can be conducted in which MEE aspiration and culture is performed for all patients to document the unique microbiology of the population to be studied. *In vitro* antimicrobial susceptibility testing should be performed for all MEE isolates, and both clinical and presumed microbiologic outcome should be assessed (see definitions below). Repeat aspiration of MEE is required only if there is evidence of clinical failure. In the phase 2 trial, an "open" uncontrolled study may be conducted. Because the number of centers that perform tympanocenteses is presently limited and a second aspiration of MEE cannot be recommended for children who are clinically cured or improved, the microbiologic response is correctly termed presumptive eradication. Clinical and presumed microbiologic efficacy for a minimum of 60 patients with documented AOM, with 20 cases each due to the three major bacterial pathogens (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, respectively) should be sufficient to determine whether the drug is effective on an organism-specific basis. Both organism-specific and disease-specific responses should be evaluated. For the purpose of organism-specific evaluation, a minimum of 20 isolates from  $\geq 20$  patients is required for evaluation.

(2) If the preliminary assessment is favorable (i.e., a clinical and presumed microbiologic response rate of  $\geq 80\%$ ), a larger, comparative phase 3 trial with an active control should be conducted. A double-blind study design is desirable whenever feasible; in any event, the evaluator should be blinded. Aspiration of MEE for microbiologic diagnosis before treatment is desirable but not required, but aspirates from those patients who fail to respond clinically are required. *In vitro* susceptibility testing should be performed for all MEE isolates if cultures are performed. Concurrent therapy, such as with decongestants, should not be used. If the investigator believes such therapy is essential, it should be administered to all patients. If pretreatment cultures of MEE are not obtained, all clinical and presumed microbiologic responses of patient must be evaluated by a blinded observer. The sample size for the clinical trial should be specifically determined (see General Guidelines, section XVI and appendix).

### (e) Administration of the Study Drug

All drugs will be provided to the patient by the investigator or his or her designee. For young children unable to swallow tablets or for those with a small body mass, the use of a suspension or other acceptable formulation is necessary for accurate dosing.

### (f) Modifications During Conduct of the Study

It is not anticipated that addition of a new antimicrobial agent will be required. If there is clinical failure (see definition below) after 72 hours of therapy, tympanocentesis should be performed; modification of antimicrobial therapy will be based on the data obtained from culture and from susceptibility testing.

### (g) Evaluability

Both clinical and presumed microbiologic responses should be assessed. After enrollment, observations should be made 3–5 days after initiation of therapy and at least 2 and 4–6 weeks later. The precise period of posttreatment evaluation will vary according to knowledge of the anticipated duration of anti-infective activity subsequent to termination of administration of the test drugs. At each visit an interval medical history should be obtained and otoscopic examination, including tympanometry or acoustic reflectometry, should be performed to determine the status of the middle ear. During reexaminations, children should be assessed for other foci of infection and for adverse effects of the test drug.

The treatment outcomes for the study and control groups should be compared according to the proportion of patients in the following outcome categories: (1) clinical cure with presumed microbiologic eradication; (2) clinical failure with microbiologic persistence; and (3) clinical relapse or recurrence.

**(1) Definition of clinical response.** *Clinical cure* is defined as resolution of signs and symptoms (e.g., pain, fever, vomiting), exclusive of MEE, within 72 hours in a child who remains well throughout the course of therapy and follow-up. *Clinical failure* is defined as lack of resolution of signs and symptoms, exclusive of MEE, within 72 hours of onset of therapy. *Relapse* is defined as reappearance of signs and symptoms of AOM after initial response during or within 4 days of conclusion of therapy. *Recurrence* is defined as reappearance of signs and symptoms of AOM  $\geq 5$  days after the conclusion of therapy.

**(2) Definition of microbiologic response.** It is recognized that whereas the microbiologic response can be accurately assessed only by repeat aspirations of MEE during or after com-

pletion of antimicrobial therapy, repeat tympanocentesis in a patient who is clinically improving is generally not warranted. All patients for whom outcome is classified as clinical failure, relapse, or recurrence should undergo repeated aspiration of MEE before their antimicrobial regimens are changed. *Presumed microbiologic eradication* is defined as cases in which pretreatment cultures of MEE were performed and were positive. In these cases, posttreatment cultures are considered unwarranted because of the complete resolution of clinical signs and symptoms. *Microbiologic suppression* is defined as cases in which the causative organism is demonstrated to be eliminated in repeated culture of MEE aspirates after 72 hours of antimicrobial therapy. This response is likely to be seen only in the setting of clinical failure, when repeated aspiration of MEE is indicated. Definitive evidence of microbiologic eradication is not possible if concomitant antimicrobial therapy is provided. *Microbiologic persistence* is defined as a positive culture of MEE aspirates after at least 72 hours of antimicrobial therapy. If a pretreatment culture of MEE was performed and was positive, the isolation of the same organism after  $\geq 72$  hours of therapy is considered *confirmed microbiologic persistence*. If no pretreatment aspiration of MEE was performed, isolation of a pathogen in culture after  $\geq 72$  hours of treatment is considered *presumptive microbiologic persistence*. *Superinfection* is defined as identification of new organisms in repeated cultures of MEE aspirates after at least 72 hours of antimicrobial therapy. A superinfection can be demonstrated only if a pathogen was isolated from an earlier MEE aspirate.

## 6. Summary of Guideline

### (a) Baseline Assessment Should Include the Following Procedures:

(1) Initial clinical evaluation including otoscopic examination with pneumatic otoscopy, tympanometry, or acoustic reflectometry; (2) hematologic, hepatic, and renal function studies; and (3) aspiration of MEE and microbiologic studies for phase 2 trials and optionally for phase 3 trials.

### (b) Assessment During Course of Therapy Should Include:

(1) Clinical and otoscopic evaluation at 3–5 days and 10–14 days after initiation of antimicrobial therapy and at least bi-weekly thereafter (2 and 4–6 weeks later) until resolution of all symptoms and signs; (2) MEE aspiration for microbiologic studies in patients who fail to respond clinically after at least 72 hours of antimicrobial therapy to define microbio-

logic persistence, emergence of resistance, or superinfection and optional determinations of drug concentrations in MEE for such patients; (3) repeated hematologic, hepatic, and renal function studies as appropriate; (4) monitoring of change in susceptibility patterns of bacterial isolates in naso- or oropharyngeal culture specimens for selected patients; and (5) recording of allergic or toxic reactions or important adverse effects, which will be grounds for terminating the use of either the study drug or the standard drug.

*(c) Assessment After Completion of Therapy and Follow-up*

Patients should be followed up clinically and by otoscopy biweekly until MEE has completely resolved. Repeated aspiration of MEE should be performed for patients with clinical relapse or recurrence. The time to resolution of MEE should be recorded. Laboratory studies to monitor resolution of infection and adverse reactions should be repeated according to the protocol.

**C. Sinusitis**

**1. Background**

Sinusitis is a common disorder both in children and adults. Approximately 0.5% of upper respiratory infections in children are complicated by acute sinusitis, and 0.02% of adults have chronic sinusitis. Because of the location and rich vascular supply of the sinuses, these infections are potentially life-threatening in that intracranial suppurative complications may result, including epidural or subdural empyema, brain abscess, or cavernous sinus thrombosis. Early diagnosis and effective antimicrobial therapy are critical for the prevention of such complications as well as chronic sequelae. The paranasal sinuses are lined with ciliated pseudo-columnar epithelium and are connected to each other through small tubular openings, the sinus ostia, which drain into various regions of the nasal cavity. The paranasal sinuses are generally considered to be sterile, although transient colonization by the resident upper respiratory flora does occur [33]. Conditions that affect the patency of the sinus ostia, the normal mucociliary function of the sinus epithelium, or immune defenses of the upper airways or events that facilitate direct introduction of microorganisms into the paranasal sinuses are the key predisposing factors to sinus infection [34]. Such conditions include viral upper respiratory tract infections, respiratory allergies, alterations in mucus (e.g., cystic fibrosis), and selective deficiencies in immunoglobulins. Dental extraction or periapical infections of the maxillary molar teeth are a particularly important cause of maxillary and chronic sinusitis.

The clinical manifestations of sinusitis vary greatly depending on the duration of infection (i.e., acute or chronic) and the age of the patient (i.e., child or adult). In children, symp-

toms of acute sinusitis are often difficult to distinguish from those of the common cold or from allergic (vasomotor) rhinitis. The most common complaints are cough (80%) and nasal discharge (75%). Parents often notice a malodorous breath among preschoolers (50% of cases) who have neither signs of pharyngitis nor poor dental hygiene [34, 35]. In adults, postnatal purulent discharge and facial pain over the affected sinus that worsens with movement or percussion are the cardinal symptoms [36, 37]. Fever occurs in <50% of cases. Hyposmia, jaw pain with mastication, nasal congestion, and a history of recent upper respiratory infection are other manifestations. In patients with nosocomial sinusitis secondary to prolonged nasotracheal intubation, the clinical features, except for unexplained fever, may be relatively silent. Symptoms associated with chronic sinusitis are usually less intense but more protracted than those in acute sinusitis. Fever is uncommon. Fatigue, general malaise, and an ill-defined feeling of unwellness and irritability can be more prominent than local symptoms of nasal congestion, facial pain, or postnasal drip [38].

The precise microbial etiology of sinusitis can be determined only by direct aspiration of the sinus, since nasopharyngeal secretions are regularly contaminated by the indigenous flora and culture results correlate poorly with results for sinus aspirates [36, 39]. This difficulty may limit the ability to make a definitive assessment of the microbiologic response to anti-infective therapy. *S. pneumoniae* and unencapsulated *H. influenzae* are responsible for >50% of cases of acute sinusitis in adults, while *M. catarrhalis* in addition to *S. pneumoniae* and *H. influenzae* account for two-thirds of cases in children [34, 39, 40] (table 4). *S. aureus* is a common nasal contaminant and an infrequent cause of acute sinusitis. Obligate anaerobes are uncommonly isolated in acute sinusitis. In contrast, the microbiology of chronic sinusitis is usually

**Table 4.** Microbial causes of acute maxillary sinusitis.

Pathogen	Mean percentage of cases (range)	
	Adults	Children
<b>Bacteria</b>		
<i>S. pneumoniae</i>	31 (20-35)	36
<i>H. influenzae</i> (unencapsulated)	21 (6-26)	23
<i>S. pneumoniae</i> and <i>H. influenzae</i>	5 (1-9)	...
Anaerobes ( <i>Bacteroides</i> , <i>Fusobacterium</i> , <i>Peptostreptococcus</i> , <i>Veillonella</i> )	6 (0-10)	...
<i>S. aureus</i>	4 (0-8)	...
<i>S. pyogenes</i>	2 (1-3)	2
<i>M. catarrhalis</i>	2	19
Gram-negative bacteria	9 (0-24)	2
<b>Viruses</b>		
Rhinovirus, adenovirus, influenza, parainfluenza	3-15	0-2

Table is reprinted from [36].

polymicrobial, and anaerobes (*Bacteroides*, *Peptostreptococcus*, *Fusobacterium*, and *Veillonella*) are the predominant isolates [41, 42]. Viridans streptococci and nonencapsulated *H. influenzae* are the major aerobic isolates. Nosocomially acquired sinusitis secondary to head trauma or prolonged nasotracheal intubation is commonly caused by polymicrobial gram-negative bacilli and *S. aureus* as well as by anaerobes [43]. Fungal sinusitis is rare, but *Aspergillus*, *Mucor*, *Candida*, *Pseudoallescheria boydii* (*Scedosporium spiospermum*) and other saprophytic fungi can cause invasive disease—usually in the debilitated host. Although antecedent viral upper respiratory infection is an important cause of acute sinusitis, viruses (e.g., rhinovirus, influenza, parainfluenza, and adenovirus) are isolated only in 15% of antral aspirates [39].

#### (a) Scope of Guideline

The clinical entities included in this guideline are acute sinusitis (symptoms present for  $\leq 4$  weeks) and chronic sinusitis (symptoms present for  $\geq 3$  months). Not included in this guideline are subacute cases (symptoms lasting 1–3 months), which have a variable natural history and in which the bacterial etiology is poorly defined.

#### (b) General Principles of Care for Patients with Acute and Chronic Sinusitis

The goals of antimicrobial therapy for acute sinusitis are (1) the eradication of the causative pathogens; (2) the provision of symptomatic relief; (3) the restoration and improvement of sinus function; and (4) the prevention of intracranial complications and chronic sequelae.

Although many management options are available, antimicrobial agents are the mainstay of therapy for acute sinusitis. The therapeutic efficacy of anti-infective agents for acute sinusitis has been established by placebo-controlled clinical trials [44] and in studies that employed sinus aspiration before and after treatment [39, 45]. Standard therapy is usually selected on an empiric basis and directed against the most likely pathogens, including *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* (see table 4). Oral therapy with a  $\beta$ -lactam agent such as ampicillin for 10–14 days is generally prescribed and is considered the standard regimen for acute sinusitis in both children and adults. A favorable rate of clinical response of 70%–80% can be expected with this regimen. In penicillin-allergic patients, a second-generation cephalosporin (e.g., cefaclor), a macrolide/sulfonamide (e.g., erythromycin/sulfisoxazole) or trimethoprim/sulfonamide (such as trimethoprim-sulfamethoxazole) combinations have yielded comparable results. Penicillins (such as amoxicillin plus a  $\beta$ -lactamase inhibitor) or cephalosporins that have a more-extended spectrum have not yielded superior results in controlled trials [44–46] even though the prevalence of  $\beta$ -lactamase-producing

strains among respiratory pathogens appears to be increasing (up to 20% of *H. influenzae* strains, 50%–70% of *M. catarrhalis* strains, and 20%–30% of respiratory anaerobes) [47].

In patients with chronic sinusitis, surgical procedures to facilitate sinus drainage through the creation of an artificial ostium and submucosal resection of diseased tissue appear to be the mainstays of treatment. The role of anti-infective agents in chronic sinusitis is not as clear as that in acute sinusitis. Conservative therapy with anti-infective agents or sinus irrigation without surgical intervention is successful in only one-third of cases [36, 48]. With combined medical and surgical treatment, the cure rate for chronic maxillary sinusitis is  $>60\%$  after 3 years of follow-up [48]. Anti-infective agents useful for chronic sinusitis should have broad-spectrum activity against respiratory anaerobes as well as against viridans streptococci, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

#### (c) Future Trends

Several issues in the management of acute and chronic sinusitis remain controversial. These include: (1) the optimal duration of therapy for acute and chronic sinusitis; (2) the clinical relevance of the increasing prevalence of in vitro resistance to  $\beta$ -lactam agents among upper respiratory pathogens; (3) the role of respiratory allergy in recurrent or chronic sinusitis; (4) the value of adjunctive measures such as oral or topical decongestants, antihistamines, and intranasal steroids in the treatment of acute and chronic sinusitis (such measures must be standardized in both study and control groups during initial assessment of new antibiotic regimens for both acute and chronic sinusitis); (5) the optimal mode of surgical management in chronic sinusitis (i.e., preservation of sinus epithelium vs. radical mucosal resection); (6) avoidance of the need for sinus puncture by the use of endoscopic sinuscopy for performing quantitative cultures.

## 2. Clinical Definitions of the Disease

#### (a) General Definition

Patients eligible for study will be children or adults with symptoms and signs clinically compatible with acute or chronic sinusitis.

#### (b) Minimum Diagnostic Criteria Permitting Inclusion in Trials

(1) *Clinical criteria.* Acute sinusitis is defined as inflammation of the sinuses associated with symptoms lasting  $\leq 4$  weeks. Clinical findings such as fever, headache, malar tenderness, and nasal discharge (which are often nonspecific) should be supported by objective localizing studies such as radiography, ultrasonography, or CT. Transillumination of the

sinuses has a relatively low sensitivity (74%) and specificity (47%) for acute sinusitis [39] and should not be used as the sole diagnostic criterion. Transillumination is also less informative in children <6 years of age (40% concordance and 20% discordance compared with radiographic findings) because of either poor cooperation of the child in performing the test or the developmental variations of the sinuses in this age group [34]. Anterior rhinoscopy may reveal hyperemic and edematous nasal turbinates, often with purulent discharge from the middle meatus where the orifices of the maxillary, frontal, and anterior ethmoidal sinuses enter the intranasal cavity [49]. Imaging studies (roentgenography, ultrasonography, or CT) should be performed in all cases. Other laboratory studies such as neutrophil count, erythrocyte sedimentation rate, and C-reactive protein should also be performed.

*Chronic sinusitis* is defined as inflammation of the sinuses associated with symptoms lasting >3 months that are compatible with radiographic abnormalities (determined by roentgenography, ultrasonography, or CT). If possible, chronic sinusitis should be confirmed by endoscopic sinuscopy with direct visualization of the sinus mucosa, appropriate microbiologic sampling, and histopathologic evaluation [49, 50].

(2) *Microbiologic criteria.* The precise microbial etiology of sinusitis can be determined only by direct aspiration or injection wash of the sinus cavity. Cultures of the surface of the nasal vestibule or the nasopharynx are unreliable because of their regular contamination by the resident microflora and should not be used for assessment of microbiologic efficacy of study regimens. Access to the maxillary sinus can be obtained intranasally through a puncture below the inferior turbinate and to the frontal sinus through a puncture below the infraorbital rim of the eye. Thorough cleansing of the puncture site with an appropriate antiseptic is important to minimize contamination of the specimen with surface bacteria. If no fluid is obtained, 1 mL of sterile normal saline without bactericidal preservative should be instilled and the washings reaspirated. Specimens should be sent to the laboratory for leukocyte counting, gram staining, and culture for aerobes, anaerobes, fungi, and mycobacteria. Viral cultures are of investigational interest. With the appropriate technique, >76% of such specimens will yield positive cultures in acute maxillary sinusitis [40]. Furthermore, if organisms are seen on gram-stained preparations of antral secretions, a presumptive diagnosis can be made by assessing the bacterial morphology in up to 90% of cases [51]. Quantitative cultures ( $\geq 10^3$  cfu/mL of aspirate) are useful in distinguishing true infection from colonization or contamination [39, 52], but such studies are labor-intensive and are not required for microbiologic diagnosis in clinical trials.

In chronic sinusitis, microbiologic diagnosis can be confirmed by culture of diseased mucosa obtained by biopsy during endoscopic sinuscopy or surgery. In such cases, the culture results should be correlated with the histopathologic findings to exclude the possibility of specimen contamination.

### 3. Information Needed Before Conducting Clinical Trials in Humans

For a pathogen-specific evaluation, the drug under consideration should have proven *in vitro* activity against the specific bacteria prevalent in sinusitis, and for a disease-specific evaluation (i.e., acute vs. chronic, pediatric vs. adult), the drug should have a broad range of activity against the most prevalent pathogens.

### 4. Special Qualifications of Investigators and Institutions

The investigator or subinvestigator should have the necessary skills to perform sinus puncture for microbiologic evaluations of acute and chronic sinusitis and endoscopic sinuscopy for studies of chronic sinusitis. The institution should have the facilities and personnel with expertise to perform and interpret radiographs, ultrasonography, or CT and microbiologic studies of the paranasal sinuses.

### 5. Design and Implementation of Phase 1, 2, and 3 Clinical Trials

#### (a) Demographic Characteristics of the Study Population

Clinical evaluation of new treatment regimens should be conducted with patients grouped by specified age, underlying disease, duration of symptoms, and presence or absence of respiratory allergy. Since these factors appear important both in predicting the microbial etiology and in overall prognosis, their contribution to treatment outcome should be carefully controlled by appropriate randomization during patient enrollment or by stratification either prospectively or post hoc during analysis of results.

#### (b) Inclusion and Exclusion Criteria

Children, adolescents, and adults of both sexes are eligible for inclusion. Patients who have received other antimicrobial therapy within the preceding 2 weeks, patients with hypersensitivity reactions to drugs of a similar class, and patients with other concurrent, acute infectious illnesses should be excluded.

#### (c) Selection of the Comparison Drug

In acute sinusitis, an active control regimen with proven efficacy against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* should be used. In chronic sinusitis, a placebo-controlled trial is considered justified since the role of antimicrobial therapy for this condition remains unclear at this time.

#### (d) Study Design and Stratification

Because of the difficulties in obtaining reliable cultural information about sinusitis even under protocol conditions, it may be appropriate to adopt the following sequential study strategy.

(1) Conduct a small (~100 patients) phase 2 trial in which sinus puncture and culture is performed for all patients to document the unique microbiology of the intended study population, with at least 20 cases of each of three major bacterial pathogens implicated (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*). In vitro antimicrobial susceptibility testing of all sinus isolates should be performed. Both clinical and presumed microbiologic outcomes are assessed (see definitions below). Repeated aspiration of the sinus is required only if there is evidence of clinical failure. In the phase 2 trial, an "open" uncontrolled study may be conducted, although a randomized comparative double-blind trial with an active control is still desirable despite the clearly inadequate size of the sample for meaningful comparisons of clinical response rates. A controlled comparison provides additional information regarding the expected response rate in a particular community. Both organism-specific and disease-specific responses should be evaluated. For purposes of organism-specific evaluation, a minimum of 20 isolates from  $\geq 20$  patients is required for evaluation.

(2) If the preliminary assessment is favorable (i.e., a clinical and presumed microbiologic response rate of  $\geq 70\%$ ), it is reasonable to conduct a larger, comparative phase 3 trial with an active control. Sinus puncture for microbiologic diagnosis and sinus radiography before treatment are desirable but not required, but examination of aspirates and sinus radiographs is necessary for those patients who fail to respond clinically. In vitro antimicrobial susceptibility testing should be performed for all isolates from cultures. Use of adjunctive medications such as oral or nasal decongestants, antihistamines, or intranasal steroids should be standardized such that they are used either in both the study and control groups or in neither of the groups. Similarly, in studies of chronic sinusitis, the mode of concomitant surgical therapy (i.e., endoscopic sinuscopy with limited mucosal curettage vs. a more conventional approach of radial mucosal resections) should also be standardized or stratified.

The projected sample size must include consideration of the expected difference in efficacy of the study and control regimens, the expected proportion of cases due to each of the major bacterial pathogens (and that one-fourth of all cases of acute sinusitis are due to nonbacterial causes that would not be affected by either antibacterial agent), and an anticipated rate of spontaneous clinical cure of ~30% among children with acute sinusitis [34].

#### (e) Administration of Study Drug

The treatment course is usually 10–14 days for acute sinus-

itis. Since the optimal duration of therapy has not been clearly established for either acute or chronic sinusitis, this could be the main focus of evaluation in phase 4 trials. Patients should be assigned randomly to the test or "control" group, and if pretreatment cultures of the sinuses are not performed, the clinical and presumed microbiologic response should be evaluated by a blinded observer. For children unable to swallow tablets or whose body mass is small, either a suspension or an acceptable alternative formulation of the study drug or the control drug is necessary for precise dosing.

#### (f) Modifications During Conduct of the Study

Modification of the study by the addition of a new antimicrobial agent may be necessary if the clinical response after 3–5 days of therapy is suboptimal. In such instances, sinus aspiration for documentation of the microbiologic response is required before the therapeutic regimen is modified. Addition of a new antimicrobial agent constitutes a clinical failure of the initial treatment regimen.

#### (g) Evaluability

Both clinical and presumed microbiologic responses should be assessed. Clinical evaluation should be made 3–5 days after initiation of therapy and weekly or biweekly thereafter until the resolution of all symptoms and signs. Use of a scoring system, particularly a binomial (yes/no) objective scoring system, for signs and symptoms such as fever, pain, headache, tenderness, nasal discharge, and purulence is strongly encouraged. Imaging studies (roentgenography, ultrasonography, or CT) should be repeated at least at the completion of antimicrobial therapy. Patients with chronic sinusitis should be further assessed by repeated endoscopic sinuscopy before or after completion of therapy. Information about concentrations of drug in sinus aspirates or mucosal biopsies may be of value in studies of chronic sinusitis, but they are not critical to studies of efficacy in acute sinusitis and are not required for final evaluation.

Since a repeat of sinus puncture is generally not justified in patients who have responded clinically to therapy, the microbiologic response in such patients can only be judged presumptively.

Comparisons of treatment outcomes in the study and control groups should be made according to the proportion of patients in the following outcome categories: (1) clinical cure with presumed microbiologic eradication; (2) clinical failure with microbiologic persistence; (3) clinical and/or microbiologic relapse and recurrence; and (4) indeterminate.

(1) *Definition of clinical response.* *Clinical cure* is defined as complete resolution of signs and symptoms at the conclusion of antimicrobial therapy and at follow-up. *Clinical failure* is defined as lack of improvement in signs and symptoms within a defined period of therapy (72 hours for acute sinusi-

tis and 2 weeks for chronic sinusitis). *Early relapse* is defined as reappearane of signs and symptoms or new clinical findings of sinusitis within 14 days after the conclusion of therapy. *Late relapse* is defined as the reappearance of signs and symptoms or new clinical findings of sinus infection after 14 days but within 1 month after the conclusion of therapy.

(2) *Definition of microbiologic response.* *Presumed microbiologic eradication* is defined as cases in which pretreatment cultures of sinus aspirates were positive, clinical signs and symptoms resolve completely, and posttreatment cultures are not performed because clinical response is complete. *Confirmed microbiologic response* is defined as cases in which the causative organism cannot be isolated in cultures of sinus aspirates performed after 72 hours of antimicrobial therapy. Such repeated cultures of sinus aspirates are likely to be performed only in the setting of clinical failure. A statement as to microbiologic eradication is not possible because of the influence of concomitant antimicrobial therapy. *Microbiologic persistence* is defined as a positive culture of sinus aspirates after at least 72 hours of antimicrobial therapy. If a pretreatment culture of sinus aspirate was performed and was positive, the isolation of the same organism after  $\geq 72$  hours of therapy is considered confirmed microbiologic persistence. If no pretreatment culture of sinus aspirates was performed, isolation of a pathogen after  $\geq 72$  hours of treatment is considered presumptive microbiologic persistence. *Superinfection* is defined as the emergence of new or resistant organisms in cultures of sinus aspirates after  $\geq 72$  hours of antimicrobial therapy.

## 6. Summary of Guideline

### (a) Baseline Assessment Should Include the Following Procedures:

(1) Initial clinical evaluation and imaging (roentgenography, ultrasonography, or CT) of the paranasal sinuses; (2) hematologic, hepatic, and renal function studies; (3) sinus puncture and microbiologic studies for phase 2 trials and optionally for phase 3 trials; and (4) endoscopic sinuscopy, bacterial cultures, and optional tissue biopsy for studies of chronic sinusitis.

### (b) Assessment During the Course of Therapy Should Include:

(1) Clinical evaluation at 2–3 and 5–7 days after initiation of antimicrobial therapy, and weekly or biweekly thereafter until resolution of all symptoms and signs; (2) aspiration of sinuses for microbiologic studies for patients who fail to respond clinically after at least 72 hours of antimicrobial therapy to define microbiologic persistence, emergence of resistance, or superinfection; and (3) repeated imaging, hematologic, hepatic, and renal function studies as appropriate.

### (c) Assessment After Completion of Therapy and Follow-up

Patients should be followed up clinically and with imaging for at least 2 weeks after completion of antimicrobial therapy to assess relapse or recurrence, clinical complications, and adverse effects of the antimicrobial regimen. Sinus aspiration should be performed for those patients with clinical relapse or recurrence.

## D. Acute Exacerbations of Chronic Bronchitis

### 1. Background

Bronchitis is an inflammatory condition of the tracheobronchial tree. It is both acute and chronic and is caused by a variety of irritants and infectious agents. Productive cough is the common denominator of this condition, and the sputum produced ranges from mucoid to frankly purulent.

Acute bronchitis is generally an infectious process. It occurs in all age groups and is most common in the winter months, when acute respiratory infections are prevalent. Most cases are thought to be due to respiratory viruses, including those associated with the common cold and other respiratory viruses involved in infections of the lower respiratory tract (e.g., adenovirus, rhinovirus, coronavirus, influenza, parainfluenza, respiratory syncytial virus, coxsackievirus). *M. pneumoniae*, *C. pneumoniae*, and *Legionella* species have also been implicated in some cases. The frequency of infection due to these pathogens is not certain.

Chronic bronchitis generally is defined as a condition characterized by cough and excessive secretion of mucus in patients who have coughed up sputum on most days during 3 consecutive months for  $>2$  successive years. This disease is caused by prolonged exposure to pulmonary irritants, the most prominent of which is cigarette smoke. Atmospheric pollution also plays some role, as do recurrent episodes of infection. Chronic bronchitis results in widely ranging degrees of respiratory embarrassment. In its most severe forms, obstructive pulmonary disease, emphysema, and respiratory failure occur.

Patients with chronic bronchitis frequently experience episodes of acute disease superimposed on the chronic process. These exacerbations are characterized by some combination of increasing cough, sputum volume and purulence, and respiratory distress. The role of infection in these episodes has been difficult to define. The bacterial species most often mentioned as potential etiologic pathogens include *S. pneumoniae*, typable (especially type B) and nontypable *H. influenzae*, and *M. catarrhalis*. However, the same organisms, particularly *Haemophilus* species, can be isolated from the respiratory secretions of patients with chronic bronchitis who do not present with evidence of acute exacerbation [53]. Gump et al. did report an association between purulence of sputum and an increase in the number of pneumococci in the sputum



of patients with acute exacerbations [54]. *Haemophilus parainfluenzae*, viridans streptococci, and strains of *Enterobacteriaceae* also are isolated from patients with acute exacerbations of bronchitis, but their pathogenic role is even less well defined. Viruses, *M. pneumoniae*, *C. pneumoniae*, and perhaps *Legionella* species play an etiologic role in some cases of acute exacerbations.

#### (a) Scope of Guideline

The only clinical entity included in this guideline is acute exacerbation of chronic bronchitis.

#### (b) Standards of Care for Acute Exacerbations of Chronic Bronchitis

Considerable controversy surrounds the use of antibacterial agents for patients with acute exacerbations of chronic bronchitis [55, 56]. Tager and Speizer [57] reviewed the existing studies in 1975 and concluded that the role of antimicrobial agents in the management of these patients needed reassessment and that respiratory infections appeared to contribute to worsening of episodes of cough and production of sputum. A recent double-blind randomized placebo-controlled study by Anthonisen et al. [58] showed a significant clinical benefit in association with antibacterial therapy. The recovery of peak air flow was more rapid and the rate of clinical deteriorations requiring therapeutic intervention was lower in antibiotic-treated patients. Response to treatment was evidenced by the trilogy of decreased dyspnea, sputum volume, and sputum purulence. Treatment success was defined as resolution within 21 days of all symptoms that accompanied the exacerbation. No attempt at microbiologic confirmation was performed in this study. Antibacterial agents utilized in the treatment group included trimethoprim-sulfamethoxazole, amoxicillin, and doxycycline.

Although controversy about possible microbial pathogenesis persists, most clinicians elect to treat the acute exacerbations as infectious events and direct that therapy at *S. pneumoniae* and *H. influenzae* and, more recently, at *M. catarrhalis*. The duration of therapy is generally 7–10 days. It should be recognized that up to 25% of strains of *H. influenzae* and 50%–70% of *M. catarrhalis* strains produce  $\beta$ -lactamase.

#### (c) Future Trends

The etiologic role of viruses, *M. pneumoniae*, *C. pneumoniae*, and *Legionella* in acute exacerbations of chronic bronchitis needs clarification. Determination of their role will be facilitated by the application of more sensitive and specific microbiologic diagnostic techniques (e.g., nucleic acid probes, polymerase chain reactions, antigen detection).

## 2. Clinical Definitions of the Disease

### (a) General Definition

Patients eligible for study will primarily be adults with symptoms and signs compatible with acute exacerbations of chronic bronchitis.

### (b) Minimal Diagnostic Criteria Permitting Inclusion in Trials

(1) *Clinical criteria.* Patients must (a) have had a chronic cough and sputum production for >2 consecutive years and on most days for 3 consecutive months and (b) have evidence of acute exacerbation as indicated by some combination of increased cough and/or dyspnea, increased sputum volume, or increased sputum purulence.

(2) *Microbiologic and other laboratory criteria.* These criteria include (a) negative chest roentgenogram to rule out pneumonia; (b) production of purulent sputum as defined by the presence on a gram-stained preparation of >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per low-power magnification ( $\times 10$ ) field (the presence of predominant bacterial morphology may be noted); (c) documentation of the presence or absence of potential bacterial pathogens and monitoring of emergence of resistant isolates during antimicrobial therapy by sputum culture and susceptibility tests.

## 3. Information Needed Before Conducting Clinical Trials in Humans

The drug under consideration should have proven in vitro activity against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Dosage of the study drug must be determined by means of pharmacokinetic and in vitro studies.

## 4. Special Qualifications of Investigators and Institutions

The investigator or subinvestigator should have the necessary skills to assess pulmonary function and interpret radiographic studies. The institution should have adequate facilities for performance of laboratory studies, including hematologic, hepatic, and renal function tests and studies of pulmonary function, especially arterial blood gas analysis, forced vital capacity, FEV<sub>1</sub> (forced expiratory volume in 1 sec), total lung capacity, and peak flow spirometry.

## 5. Design and Implementation of Phase 1, 2, and 3 Clinical Trials

### (a) Demographic Characteristics of the Study Population

Only adult patients ( $\geq 18$  years) with stable chronic pulmonary disease should be included.

### (b) Inclusion and Exclusion Criteria

Patients who are experiencing an acute exacerbation of chronic bronchitis are eligible. Patients with cystic fibrosis, patients unable to give informed consent, and patients with a known history of hypersensitivity to the study or control drug should be excluded. Steroid use is not necessarily a criterion for exclusion.

### (c) Selection of the Comparison Drug

Even though the use of antibacterial agents for treatment of acute exacerbations of chronic bronchitis is controversial, the presence of *S. pneumoniae* and other potential pathogens in some patients and the concomitant need for corticosteroids in some patients suggest the need for an active control drug. Both control and study drugs should be active in vitro against *S. pneumoniae*, *H. influenzae* type b, and *M. catarrhalis*. Placebo-controlled trials may be conducted.

### (d) Study Design and Stratification

In phase 1 studies, human pharmacologic and pharmacokinetic studies should demonstrate sufficient absorption and achievement of peak serum concentrations that exceed the MIC<sub>90</sub> for the major respiratory pathogens. In phase 2 and 3 trials, study patients should be stratified according to major host factors (e.g., history and duration of smoking).

Whenever feasible, studies should be prospective, randomized, and of double-blind design. No additional antimicrobial agent is permitted. Concurrent medications (e.g., bronchodilators) should be administered in the same manner to study and control groups.

The study patients may be stratified according to the use of concomitant steroid therapy. Another strategy might be to design a four-arm randomized comparison: (1) study drug with steroids; (2) control drug with steroids; (3) study drug with no steroids; and (4) control drug with no steroids.

In projecting a sample size, consideration must be given to the expected difference in efficacy of the study and control regimens and the desirability of undertaking poststudy subset analysis of pertinent patient variables. Variables include (1) the presence or absence of adjunctive treatment; (2) the presence or absence of fever; (3) status of pulmonary function; and (4) characteristics of sputum.

### (e) Administration of the Study Drug

Duration of treatment is generally 7–10 days. However, the optimal duration of therapy could be a main focus of evaluation. In comparative studies, patients should be assigned randomly to the test or “control” group, and insofar as possible, the study should be blinded.

### (f) Modification During Conduct of the Study

For patients who do not demonstrate clinical improvement (i.e., decreased dyspnea, cough, and volume and purulence of sputum production) or whose clinical conditions worsen after 3–5 days of treatment, clinical failure will be declared and such patients will be removed from the study. The addition of an antimicrobial agent that is not a study drug will also result in a designation of clinical failure.

### (g) Evaluability

Clinical response and results of pulmonary function tests and/or arterial blood gas analyses can be used to assess efficacy. The effect of treatment on sputum microbiology will be monitored. Failure to eradicate a potential pathogen in a patient with a complete clinical response is common in this disease. The bronchial secretions of many patients remain “colonized” after the acute episode resolves. All patients entered into the study should be assessed on the basis of intent to treat. The clinical response in both the study and control group will be classified as (1) clinical cure, (2) clinical improvement (which requires measurement of an objective end point, e.g., volume and/or purulence of sputum), (3) clinical failure, and (4) indeterminate. Patients will be evaluated at 3–5 days after initiation of treatment, and weekly thereafter.

(1) *Definitions of clinical response.* *Clinical cure* is the resolution of acute symptoms and signs to a baseline level of dyspnea, cough, sputum production, and, if elevated at enrollment, resolution of fever. *Clinical improvement* is the subjective improvement in dyspnea, with reduction in cough, a quantified reduction in 24-hour volume or purulence of sputum, and a return of the temperature to normal if the patient is initially febrile. *Clinical failure* is the lack of any resolution in the magnitude of the dyspnea, sputum purulence, or fever (if present) that prompted enrollment of the patient in the study. *Clinical response indeterminate* should be substantiated by stated reasons. The clinical response definition may be supported by improvement or lack of improvement in sequential measurements of the patient's white blood cell count, oxygen saturation, and/or pulmonary function tests.

(2) *Definitions of microbiologic response.* The categories of microbiologic response commonly encountered include *eradication*, *persistence*, *relapse*, *reinfection*, and *superinfection*. Consult General Guidelines, section XIII.C, for detailed definitions.

## 6. Summary of Guidelines

### (a) Baseline Assessment

(1) Initial history and physical examination should be performed just before enrollment. (2) Chest radiography should be performed to rule out pneumonia. (3) Hematologic, hepatic, renal, pulmonary function, and arterial blood gas studies (with room air) should be performed. (4) Gram stain and

culture of sputum plus determination of 24-hour sputum volume should be performed; nucleic acid probes and culture for *Mycoplasma* and *Legionella* may be included.

#### (b) Assessment During Course of Therapy

(1) At a minimum, patients should undergo clinical evaluation 3–5 days after initiation of therapy and weekly thereafter until completion of therapy. (2) For febrile patients the body temperature should be determined a minimum of four times daily. (3) Quantitation of the volume of sputum produced daily and/or daily assessments of the degree of sputum purulence may assist in assessment of the patient's clinical response. (4) It is helpful to monitor patient's arterial blood gases and/or expiratory flow rates at periodic intervals. The precise frequency depends on the individual protocol (e.g., every 3–5 days for hospitalized patients and perhaps once during therapy for outpatients). (5) Repeated chest radiographic, hematologic, hepatic, and renal studies are appropriate at 3–5 days after treatment has begun and within 48 hours after the end of treatment. (6) A sputum culture during therapy is indicated if there is evidence of clinical failure. In individual patients, such cultural data may be useful in identifying the emergence of bacterial resistance or in documenting failure to eradicate a potential bacterial pathogen (e.g., *S. pneumoniae*).

#### (c) Assessment After Completion of Therapy and Follow-up

Patients should undergo clinical and microbiologic assessment within 48 hours, 7–14 days, and 21–28 days after completion of therapy.

The clinical assessment should include assessment of cough, dyspnea, sputum volume, and sputum purulence. Oximetry to determine oxygen saturation and spirometry should be performed. A chest radiograph is not required unless clinically indicated, since the presence of a pulmonary infiltrate precludes enrollment.

Sputum should be submitted for gram staining, culture, and sensitivity testing, or—in the case of mycoplasma or legionella infections—for nucleic acid probe tests.

## E. Infectious Pneumonia

### 1. Background

Lower respiratory tract infections include bronchitis, bronchiolitis, and pneumonia and its complications. The relative frequency of isolation of various etiologic agents that cause community-acquired pneumonia differ according to age group, socioeconomic status, underlying disease, time of year, and possible concomitant viral illnesses. Prospective studies of the causes of community-acquired pneumonia are often difficult to interpret because of imprecise methods of microbio-

logic diagnosis, such as reliance on sputum culture and/or serologic testing. However, it is generally accepted that in North America viral agents (e.g., respiratory syncytial virus and parainfluenza virus type 3) are most important for children <5 years of age. The inability to obtain sputum from infants and children is a major deterrent to microbiologic diagnosis of pneumonia in this population. *M. pneumoniae* is considered to be a major cause of community-acquired pneumonias in North Americans 5–25 years of age. In older individuals, mycoplasmas and viruses are less common causes, while bacterial agents are more prevalent. A majority (50%–90%) of cases of pyogenic pneumonia with acute onset in middle-aged or older adults are due to *S. pneumoniae* [59, 60].

Pneumonias due to *H. influenzae* (either ampicillin-susceptible or ampicillin-resistant), *S. aureus*, mixed aerobic-anaerobic bacteria, and aerobic facultative gram-negative bacilli such as *Klebsiella pneumoniae*, in rank order, are less common.

*Legionella* species, (determined primarily on the basis of serologic studies) account for a variable proportion of cases of community-acquired pneumonia in adults (e.g., in 1% of patients not requiring hospitalization and in 5%–20% of those hospitalized). *Legionella* species probably account for 10%–15% of cases of so-called atypical pneumonia [61, 62]. Other agents that cause nonpyogenic, or atypical, pneumonia include *M. pneumoniae*, *C. burnetii*, *C. pneumoniae*, and, rarely, *Chlamydia psittaci*.

In classic pneumonias, the isolation of certain pathogens can often be linked to certain specific conditions of the host (e.g., infection with group A  $\beta$ -hemolytic *S. pyogenes*, *S. aureus*, *H. influenzae*, or *S. pneumoniae* following influenza). Both typable and nontypable strains of *H. influenzae* are pathogenic primarily among smokers, patients with chronic obstructive pulmonary disease (COPD), and some patients with lymphoma or other malignancies. Aspiration pneumonia in the community is believed to involve mostly the normal oropharyngeal aerobic and anaerobic flora. In the nursing home or nosocomial setting, infections with aerobic gram-negative bacilli and *S. aureus* are additional considerations in aspiration pneumonia.

Data for nosocomial pneumonias prior to 1988 from the Centers for Disease Control (CDC) may not be completely reliable because they appear to be based primarily on results of sputum cultures and cultures of endotracheal suction specimens. Nonetheless, the rank order of pathogens in the last reported CDC survey of nosocomial infections is *Pseudomonas aeruginosa* (16.9%), *S. aureus* (12.9%), *Klebsiella* species (11.6%), and *Enterobacter* species (9.4%), followed by *Escherichia coli*, *Serratia marcescens*, and *Proteus* species [63, 64].

Data based on the results of transtracheal aspiration performed on members of a high-risk population of elderly men in a Veterans Administration hospital and nursing home in

the 1970s give a different perspective on nosocomial pneumonia. Bartlett et al. [65] relied only on isolates from blood cultures, pleural fluid, and transtracheal aspirates. They found gram-negative bacilli in about one-half of 159 patients studied, anaerobes (*Peptostreptococcus* species were the most common isolates) in about one-third, and *S. pneumoniae* in about one-fourth. *Klebsiella* species were the most commonly isolated gram-negative aerobic bacilli. The isolates were polymicrobial in about one-half of the patients.

Gram-negative bacilli are more likely to be involved in nosocomial pneumonia in high-risk populations, such as those in intensive care units, than in other patients. Outbreaks of nosocomial pneumonia due to some organisms, including aerobic gram-negative bacilli and organisms not usually appreciated as nosocomial pathogens, may present particular problems. The latter group includes *S. pneumoniae*, ampicillin-resistant *H. influenzae*, and *M. catarrhalis* [66-68].

The timely use of appropriate systemic antibacterial therapy should eradicate the pathogen in a large number of cases of pneumonia and lead to a reduction in morbidity as well as mortality. Efficacy of new agents should at least equal those of established regimens when evaluated in prospective, randomized, controlled trials (active treatment concurrent control) [69, 70]. If  $\beta$ -lactamase-producing pathogens are suspected (e.g., *H. influenzae*), both the study and control drugs should have *in vitro* activity against such pathogens. The efficacy rates for a new drug for etiologic agents and clinical syndromes in which there is no established therapy should at least equal those in recent historical controls. Data from open studies may be useful in these instances.

Data obtained from parts of the world other than the United States may be considered supporting evidence of efficacy. However, possible regional differences in resistance patterns must be noted and may preclude direct comparison (e.g., appreciably higher resistance to penicillin G among *S. pneumoniae* strains isolated in South Africa and to erythromycin in Spain than in North American isolates). The local antimicrobial susceptibility patterns will clearly be the predominant influence on the choice of concurrent active treatment control regimens.

#### (a) Scope of Guideline

(1) Clinical entities to be included are common community-acquired or nosocomial bacterial pneumonias. Clinical entities not included are bronchitis, bronchiolitis, lower respiratory tract infections in patients with cystic fibrosis, lower respiratory tract infections caused by infrequent and/or difficult-to-diagnose entities (e.g., infections with anaerobic bacteria; psittacosis, Q fever, tularemia, and plague; and infections with mycobacteria, viruses, or fungi).

(2) Microorganisms included in the guideline are *S. pneumoniae* (prototype), *H. influenzae*, *S. aureus*, facultative

aerobic gram-negative bacilli, *Pseudomonas* species, *M. pneumoniae*, and *Legionella* species.

#### (b) General Principles of Care for Patients with Infectious Pneumonia

The diagnosis of infectious pneumonia combines clinical, laboratory, and microbiologic data. A compatible clinical picture (fever, cough, and/or auscultatory findings such as rales and/or evidence of pulmonary consolidation) together with confirmatory chest radiographic findings and isolation of the causative pathogen(s) from suitable respiratory specimens (e.g., expectorated sputum, transtracheal aspirate, bronchial washings or lavage, pleural fluid) or blood establishes the diagnosis of bacterial pneumonia. Pneumonia due to *M. pneumoniae* is identified by culture or nucleic acid probe and/or by documentation of a fourfold or greater rise in titer of complement-fixing antibody. Detection of cold agglutinins does not establish the diagnosis. The diagnosis of legionella pneumonia requires isolation of the organism from sputum, a bronchoalveolar lavage specimen, pleural fluid, or blood. Alternatively, *Legionella* antigen may be detected by immunofluorescence in respiratory secretions or by radioimmunoassay in urine. Also, *Legionella* may be detected in respiratory secretions with nucleic acid probes. Testing for antibody in acute- and convalescent-phase sera, except for antibody to *L. pneumophila* serogroup 1, is not specific enough for reliable diagnosis of legionellosis, especially in areas of low disease prevalence. Diagnostic methods for detection of *C. pneumoniae* are under development.

The bacterial pathogens isolated should be tested for susceptibility to antimicrobial agents by standardized methods. Determinations of MBCs, postantibiotic effect, or effect of subinhibitory concentrations of antibiotics are not done routinely and are not generally required for assessment of efficacy. When *Mycoplasma* or *Legionella* is isolated, antimicrobial susceptibility testing is not done routinely.

Selection of empiric antimicrobial therapy is based on the suspected pathogens and their anticipated susceptibility *in vitro*. Penicillin G remains the drug of choice for almost all *S. pneumoniae* infections in the United States [71]. Ampicillin or a cogener is the drug of choice for pneumonia due to non- $\beta$ -lactamase-producing *H. influenzae*. Aspiration pneumonia acquired in the community is treated with penicillin G, usually without the benefit of culture results. A lincosamide or a combination of a penicillin and a  $\beta$ -lactamase inhibitor are alternatives. A macrolide (e.g., erythromycin) or tetracycline is preferred for pneumonia due to *M. pneumoniae* or *C. pneumoniae*, and erythromycin is the choice for legionella infections [61, 72]. A semisynthetic penicillinase-resistant penicillin is the treatment of choice for pneumonia due to methicillin-sensitive *S. aureus*. A combination of a suitable cephalosporin or penicillin and an aminoglycoside is

frequently employed for infections due to facultative gram-negative rods or to *Pseudomonas*. In most other instances of community-acquired pneumonia, combination therapy is usually not required. Oral preparations of the aforementioned parenteral compounds or oral drugs with comparable in vitro activity can be used in milder cases. The optimal duration of therapy varies, but uncomplicated *S. pneumoniae* pneumonia is usually treated for 7–10 days [71].

For treatment of nosocomial pneumonias (e.g., associated with ventilator use), combination therapy with an extended-spectrum penicillin or cephalosporin and an aminoglycoside is commonly employed. Initial therapy must be directed at the suspected pathogens in a given hospital and their known susceptibility profile. Determination of the concentration of antimicrobial agent(s) in serum, other bodily fluids, or tissues is not done routinely. Most often, cure is defined by clinical criteria alone. With resolution of the inflammatory process, the patient is unable to provide secretions from the lower airway for documentation of eradication of the causative pathogen. Patients requiring tracheostomy or endotracheal intubation may have persistent, presumably tracheal, colonization with an etiologic organism after the criteria for clinical cure of pneumonia are met. Relief of endobronchial obstruction and/or drainage of empyema fluid remains a mainstay of therapy for lower respiratory tract infections.

The probability of cure for *S. pneumoniae* pneumonia is variable and ranges from 95% in uncomplicated infection to ~50%–80% with bacteremic disease [71]. Relapse is not a significant problem with *S. pneumoniae*.

### (c) Future Trends

Newer methods for more precise microbiologic diagnosis of pneumonia, such as the use of semiquantitative cultures of protected endoscopic brushings or bronchoalveolar lavage specimens, are promising. The practice of changing parenteral therapy to therapy with an oral agent such as a fluoroquinolone after 5–7 days is gaining increasing acceptance, as is the use of intravenous antimicrobial therapy in the home for follow-up management. It is likely that the number and precision of diagnostic techniques that rely on antigen detection or nucleic acid detection will increase.

## 2. Clinical Definitions of the Disease

### (a) General Definition

Patients eligible for study are adults and children of both sexes with confirmed or presumptive diagnosis of community-acquired or nosocomial pneumonia. These guidelines may be adapted to treatment of patients in either a hospitalized or ambulatory setting or for patients that progress from hospital to an outpatient setting.

### (b) Minimal Diagnostic Criteria Permitting Inclusion in Trials

(1) *Clinical criteria.* Patients must have signs and symptoms consistent with bacterial pneumonia (chest pain, cough, and/or auscultatory findings such as rales and/or evidence of pulmonary consolidation) with or without fever (oral temperature  $>38^{\circ}\text{C}$  [ $100.4^{\circ}\text{F}$ ]) or leukocytosis (blood leukocyte count  $>10,000/\text{mm}^3$  or  $>15\%$  band forms), and there must be radiographic or other laboratory evidence that supports the diagnosis (see below).

(2) *Microbiologic and other etiologic (noncultural) criteria.* Specimens obtained by expectoration or by endotracheal aspiration should be screened microscopically for suitability of culture (presence of  $>25$  polymorphonuclear leukocytes and  $<10$  squamous epithelial cells/low-magnification field [ $\times 10$ ]). Suitable specimens should be cultured aerobically in appropriate media. Blood specimens should be cultured for all patients, and pleural fluid, if present, should be aspirated, examined by microscopy, and cultured for both aerobes and anaerobes. The microbiologic diagnosis of infectious pneumonia is confirmed by the following criteria:

(a) *Purulent expectorated sputum*—identification of a predominant suspected pathogen by culture and/or microscopy (e.g., with *S. pneumoniae* by finding an average of  $>10$  lancet-shaped diplococci/oil-immersion field [ $\times 1,000$ ] for 10 fields examined) (material from endotracheal suctioning may also be used, and slides should be saved and made available as part of the case record) or (b) *transtracheal aspirate, bronchial brushings, or biopsy material* (obtained under direct visualization with a fiberoptic bronchoscope, preferably double-sheathed)—gram stain reveals neutrophils and a predominant pathogen is suspected by smear or culture; quantitative cultures of endobronchial brushes from potentially infected ventilator-dependent patients may be of value; (c) *pleural fluid or direct lung aspirate*—identification of a predominant pathogen on gram stain or by culture; (d) *positive blood culture*—yields a pathogen in a patient with a compatible clinical syndrome of bacterial pneumonia in the absence of another source of bacteremia. If an organism is isolated, it should be susceptible to both the study and the control drug. Clinical improvement or stabilization must be documented by 72 hours to permit retention in the study. (e) *Surrogate markers*—detection of antigen or specific nucleic acid by non-culture methods may be used as a surrogate marker of infection. Culture or other non-cultural methods for confirmation of the diagnosis of pneumonia must follow within 24–72 hours of starting therapy to retain the patient in the study. Isolation by culture is not required for the diagnosis of pneumonia due to *M. pneumoniae*, *Legionella*, or *C. pneumoniae*.

(3) *Radiographic criteria.* The presence of new infiltrate(s) on chest radiograph within 48 hours of institution of therapy.

### 3. Information Needed Before Conducting Clinical Trials in Humans

#### (a) *In Vitro* Studies

See General Guidelines, section II.D.

#### (b) *In Vivo* Studies

Use of accepted animal models for pneumonia caused by specific pathogens is desirable for evaluations of dosage, duration of therapy, achievable serum concentrations, and comparisons with other agents for efficacy and relative toxicity, as described in General Guidelines, section II.E. Determinations of levels of antimicrobial agents in respiratory tract secretions and tissue are optional since there is a lack of accepted interpretation of results

### 4. Special Qualifications of Investigators and Institutions

Physicians should be available who are competent in the following procedures: bronchoscopy, endobronchial protected-brush sampling, bronchoalveolar lavage, and thoracentesis.

In addition to standard clinical microbiology, the laboratory should have access to nucleic acid probes for detection of *Legionella* and *Mycoplasma*, detection of *Legionella* species antigen, and determination of titers of specific antibody to *Mycoplasma* and *Legionella*.

### 5. Design and Implementation of Phase 1, 2, and 3 Clinical Trials

#### (a) *Demographic Characteristics of Study Population*

For most studies, adults (18–65 years of age) and elderly patients ( $\geq 65$  years of age) will be the prototype groups to be studied. Additional potential study populations are neonates, infants, children, and immunosuppressed patients.

#### (b) *Inclusion and Exclusion Criteria*

Male and female patients will be included. Pregnant or lactating women will be excluded. Patients with severe underlying diseases (e.g., AIDS, metastatic tumor, shock) will be excluded. Patients are excluded if they have received prior therapy with a potentially effective anti-infective agent for  $\geq 24$  hours. See General Guidelines, section IX, for additional details.

#### (c) *Selection of the Comparison Drug*

It is not considered ethical to use a placebo control in studies evaluating the efficacy of a new anti-infective drug for treatment of pneumonia. Active or historical controls are needed to assess the relative value of the new drug. The historical cure

rate of uncomplicated (nonbacteremic) pneumonia due to *S. pneumoniae* in healthy hosts is  $\sim 95\%$ .

Whenever feasible, the use of a control drug is desirable. The control anti-infective agent should be a drug, or one of several drugs, approved for pneumonia and still recognized by authoritative publications as "standard" treatment. Other considerations are discussed in the General Guidelines, section X.

#### (d) *Study Design*

Whenever possible, the study design should be randomized, prospective, and double-blind. See General Guidelines, sections X and XI, for details.

#### (e) *Patient Selection and Stratification*

The spectrum of organisms that cause pneumonia is the result of the interplay of multiple host factors and environmental factors. Only some determinant factors in the host-parasite relationship are understood, e.g., the presence or absence of oropharyngeal binding sites for microorganisms, patient age, immune status prior to infection, aspiration of oropharyngeal secretions, concomitant chronic diseases and/or organ failure, or damage to nonspecific or specific portions of the host defenses against microbial invasion. In a given patient, one or more factors may apply.

(1) *Community-acquired vs. hospital-acquired pneumonia.* The traditional distinction between community-acquired and hospital-acquired pneumonia has blurred. Traditional community-acquired pathogens, such as *S. pneumoniae* or *L. pneumophila*, are now recognized as causes of hospital-acquired pneumonia. Patients with chronic diseases, e.g., lung, heart, renal, and/or hepatic failure, are cared for with increasing frequency outside of the hospital. These disease states increase the likelihood of colonization of the oropharyngeal secretions with facultative gram-negative bacilli and, hence, increase the risk of pneumonia due to this class of organisms traditionally associated with nosocomial pneumonia.

(2) *Patient selection based on clinical category.* Because of this blurring between community- and hospital-acquired pneumonia, it is reasonable to select patients as trial candidates on the basis of the clinical picture. The greater the homogeneity of the randomized population of patients with pneumonia, the greater the likelihood the trial results will have clinical import. Some patients may fit in more than one category. Suggested categories for patients with pneumonia are presented in table 5. By necessity, the categories are arbitrary and will require periodic revision as new insights into pathogenesis emerge. In clinical trials of patients who present with signs and symptoms of atypical pneumonia, most patients enrolled will be ambulatory. In trials of acute bacterial pneumonia, most patients will be hospitalized. At the time of patient

**Table 5.** Clinical categories of pneumonia that might be used for inclusion criteria for enrollment and/or stratification of patients. All patients are febrile and have radiographic evidence of pulmonary infiltrates.

Clinical characteristics	Examples of potential etiologic organism(s)	Possible factors for stratification or poststudy subset analysis
Patient with no known immunologic deficiency or neutropenia		>40 or ≤40 y of age
Cough with minimal sputum production for ≥3 or more days Clinical diagnosis: <b>atypical pneumonia</b>	<i>M. pneumoniae</i> , <i>C. burnetii</i> , <i>L. pneumophila</i> , <i>C. psittaci</i> , <i>C. pneumoniae</i>	
Progressively severe dyspnea, nonproductive cough, diffuse radiographic abnormalities, and marked hypoxemia. Clinical diagnosis: <b>viral pneumonia</b>	Influenza, adenovirus	Presence or absence of congestive heart failure; secondary bacterial pneumonia
Acute onset of cough productive of large amounts of purulent sputum and <3 days of illness. Diagnosis: <b>acute bacterial pneumonia</b> due to etiologic organism(s) that stimulate exudative inflammatory response	<i>S. pneumoniae</i> Less often: <i>M. catarrhalis</i> , <i>H. influenzae</i> type b, <i>L. pneumophila</i> , facultative gram-negative bacilli	Associated chronic obstructive pulmonary disease; presence or absence of organ failure, e.g., heart, liver, kidney. Analysis by etiologic organism if number of patients sufficient
Mental obtundation due to metabolic encephalopathy, trauma, cerebrovascular disease, or other reasons with objective evidence of aspiration of oropharyngeal secretions. Diagnosis: <b>aspiration pneumonia</b>	Aerobic and anaerobic oral flora. Patient's oropharynx may or may not be colonized with <i>S. pneumoniae</i> or facultative gram-negative bacilli.	Presence or absence of teeth and/or health of existing teeth
Nasotracheal or orotracheal intubation or tracheostomy with need for mechanical ventilation. Diagnosis: <b>ventilator-associated pneumonia</b>	Facultative gram-negative bacilli, <i>S. aureus</i>	Facultative gram-negative bacilli vs. gram-positive cocci
Compromised hosts with immunodeficiency and/or neutropenia. Cough and variable degrees of hypoxia. Diagnosis: <b>pneumonia in immunocompromised and/or neutropenic host</b>	<i>S. pneumoniae</i> , <i>Staphylococcus</i> species, facultative gram-negative rods, <i>Pneumocystis carinii</i> , mycobacteria, <i>Nocardia</i> species, fungi, cytomegalovirus	Neutropenia vs. no neutropenia; presence or absence of T cell dysfunction, e.g., HIV infection

identification, cultural data will often not be available. Patients are considered for enrollment on the basis of clinical criteria.

For statistical considerations, it is strongly recommended that patients be stratified into no more than three clinical categories of pneumonia. For example, in a comparative trial of two parenteral drugs with an appropriate spectrum of activity, patients could be categorized in one of three categories, i.e., acute bacterial pneumonia, aspiration pneumonia, or respirator-associated pneumonia, and then randomized. Subsequent to the end of the study, patient response can be analyzed by type of infecting organism, presence of organ failure, severity of pneumonia, and other factors. Alternatively, a trial may be designed to study the response of only those patients who meet the clinical criteria for atypical pneumonia. In this example, no stratification would occur prior to randomization.

(3) *Compromised host.* Pneumonia, and other infections in the compromised host, is discussed in detail in the guide-

lines on infections in the febrile, neutropenic patient. The compromised host may or may not be neutropenic, have inadequate immunoglobulins, or exhibit abnormal lymphocyte function.

A wide variety of opportunistic pathogens cause pulmonary infection in the compromised patient. Development of a pulmonary infiltrate in a patient with a hematologic malignancy (e.g., leukemia or lymphoma) is a grave prognostic sign and requires an urgent, aggressive, and carefully planned approach to diagnosis and management. For example, local signs of infection in patients who are neutropenic often are fewer and less severe than those in the non-neutropenic person. Frequently, neutropenic patients have distant sites of infection from which organisms may have disseminated to the lungs. No symptoms, signs, or roentgenographic features are specific for a given opportunistic infection in the compromised patient.

Noninfectious pulmonary pathologic conditions are common in this population and may mimic infection. These include radiation pneumonitis, drug toxicity, involvement by the underlying malignancy, pulmonary hemorrhage, pulmo-

nary infarction, and congestive heart failure. Concurrent and sequential infections of the lung are common in this population, making the relationship of disease manifestations to a single pathogen difficult to ascertain.

Early diagnosis is often critical for these patients. Guidelines used for diagnosis by examination of pulmonary infiltrates in healthy patients may not be applicable for diagnosis in patients who are compromised. For example, severely neutropenic patients may not have neutrophils in their sputum despite having significant bacterial or fungal pneumonia, and for some pathogens the sputum culture may be negative despite the presence of invasive lung infection (e.g., aspergillus pneumonia). The diagnosis of pulmonary infection in the compromised host may require the performance of an invasive procedure, e.g., percutaneous needle aspiration of the lung, transtracheal aspiration, bronchial lavage and brushing for quantitative bacteriology, transbronchial biopsy, or open lung biopsy.

Pneumonia in the compromised patient may be rapidly fatal—hence, the need for empiric antimicrobial therapy. In addition, it is often necessary to reduce the dosage of the immunosuppressive therapeutic agent. Thus, the combined expertise of all involved physicians is desirable.

#### (f) Administration of the Study Drugs

The duration of treatment varies with the clinical category of pneumonia, with the results of blood cultures, and with the status of host defenses. For acute bacterial pneumonia in noncompromised hosts, it may be desirable to treat until the patient's temperature has returned to and remained in the normal range for a specific period, e.g., 3–5 days. The possible routes of administration and conversion from one route of administration to another are discussed in the General Guidelines, section XII.

#### (g) Modifications During Conduct of the Study

See General Guidelines, section XII.F.

#### (h) Conduct of Study

Clinical evaluation is based on resolution or improvement of clinical and laboratory signs of infection such as fever and leukocytosis, purulent sputum production, and radiographic lung infiltrates. Hospitalized patients will be assessed every day during treatment and within 5–7 days after completion of treatment. Body temperature will be measured at least every 8 hours during treatment, and the peak temperature for each day will be recorded. Measurements of vital signs (blood pressure, heart, and respiratory rates) will be obtained before enrollment and on each day at approximately the same time. The character of the sputum (color, consistency, volume, and number of neutrophils per low-magnification field [ $\times 10$ ]) will be recorded when the patient enters the study

and at regular intervals thereafter. Arterial blood gas determinations will be performed as clinically indicated. A chest radiograph will be obtained 3 days after initiation of therapy, within 72 hours of completion of therapy, and at any other time the investigator deems necessary. The location and extent of pneumonic involvement (e.g., segmental, lobar) and the presence of pleural effusion must be noted and recorded. Whenever possible, the same radiologist (or a panel of radiologists) from the same institution should interpret all radiographs. Other special radiographic studies (e.g., CT scan) will be obtained as clinically indicated.

Repeated cultures of respiratory tract secretions, if obtainable, will be performed at 48–72 hours after initiation of therapy, within 72 hours of the completion of therapy, and whenever clinically indicated. Standardized susceptibility testing (disk diffusion or broth dilution) will be performed on all isolates considered potentially significant. Blood cultures will be repeated if initially positive or if the patient fails to respond to treatment. Collection of specimens that require the use of semi-invasive techniques (e.g., collection of pleural fluid, transtracheal aspiration, bronchoscopy) should be repeated only if the clinical response is suboptimal. Tests for surrogate markers will be repeated if these were originally used for diagnosis.

For all patients a posttherapy evaluation is necessary for collecting information that will assist in making a precise assessment of the patient's clinical and microbiologic response to therapy.

#### (i) Evaluability

##### (1) Definition of clinical response

Patients who have received at least 5 days of therapy and at least 80% or more of prescribed medication will have an assessment of clinical response.

(1) *Clinical cure* is defined as complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on the chest radiograph. (2) *Clinical failure* is defined as any of the following conditions: persistence or progression of all signs and symptoms after 3–5 days of therapy; development of new pulmonary or extrapulmonary clinical findings consistent with active infection; persistence or progression of radiographic abnormalities; death due to pneumonia; or an inability to complete the study because of adverse effects. (3) *Indeterminate* indicates that extenuating circumstances preclude classification as cure or failure.

##### (2) Definition of microbiologic response

(1) *Microbiologic eradication* is defined as elimination of the original causative organism(s) from the same site (e.g., expectorated sputum or normally sterile body fluids such as pleural fluid or blood) during or upon completion of therapy.



(2) *Presumed microbiologic eradication* is defined as absence of appropriate material for culture (e.g., sputum or pleural fluid) for evaluation because the patient has improved clinically and does not produce sputum or because repeated aspiration of pleural fluid is not clinically justified.

(3) *Microbiologic persistence* is defined as failure to eradicate the original causative organism(s) from sites previously listed, whether or not signs or inflammation are present.

(4) *Microbiologic relapse* is defined as recurrence of pulmonary infection with the same organism(s) within 5 days after discontinuation of treatment or during treatment after two consecutive cultures have been negative.

(5) *Superinfection* is defined as development of a new lower respiratory tract infection (documented by fever, chest radiograph, and/or auscultatory findings) during treatment or within 3 days after treatment has been completed that is due to a new or resistant pathogen not recognized as the original causative organism(s).

(6) *Colonization* is defined as the development of a positive sputum culture that yields a bacterial strain other than the primary causative isolate that appears >48 hours after initiation of therapy, persists in at least two repeated cultures, and is not associated with fever, leukocytosis, persistence or progression of pneumonia, or evidence of infection at a distant site.

(7) *Eradication and reinfection* is defined as elimination of the initial infecting pathogen followed by its replacement with a new species or with a new serotype or biotype of the same organism in sputum, pleural fluid, or blood in the presence of signs or symptoms of infection after completion of therapy.

(8) *Presumed microbiologic persistence* is defined as need for new or additional antimicrobial therapy because of continued infection at the original site in the absence of microbiologic data.

(9) *Indeterminate* is defined as circumstances in which it is not possible to categorize the microbiologic response because of death and the lack of opportunity to perform further cultures, the withdrawal of the subject from the study before follow-up cultures can be obtained, incomplete microbiologic data, or concurrent treatment of the patient with a potentially effective anti-infective agent that is not part of the study protocol. The name of the agent and the dose and duration of this therapy must be recorded. The duration of therapy will affect decisions about patient evaluability and outcome.

(10) *Other considerations*—when more than one pathogen is present, a separate analysis must be made for each organism.

## 6. Summary of Guideline

### (a) Baseline Assessment

(1) Blood for initial cultures, respiratory tract secretions (sputum), and/or pleural fluid, and/or surrogate markers of infection will be obtained. A complete history and physical examination will be performed. (2) Tests of hematologic, re-

nal, hepatic, and pulmonary function will be performed. (3) Radiographic studies such as chest radiography or CT scanning will be performed. Arterial blood gas determinations and other tests, such as a diagnostic bronchoscopy, will be done if clinically indicated.

### (b) Assessment During Course of Therapy

(1) Culture of sputum will be repeated at 48–72 hours if available; blood cultures will be repeated at 48–72 hours if initially positive. Semi-invasive tests will be repeated only if there is a suboptimal clinical response. (2) Hematologic, renal, hepatic, and pulmonary function tests will be repeated on days 3–5 of therapy and at least every 5–7 days during therapy. (3) Antimicrobial concentrations in blood will be determined if possible, but pharmacokinetic studies of respiratory secretions and other body fluids are optional.

### (c) Assessment After Completion of Therapy and Follow-up

(1) If sputum is available, follow-up cultures should be done within 72 hours after completion of therapy.

(2) Hematologic, renal, hepatic, and pulmonary function tests will be repeated at 72 hours after completion of therapy.

(3) Chest radiography will be performed within 72 hours of completion of therapy, but other imaging (e.g., CT) and semi-invasive studies (e.g., bronchoscopy) will be performed only if the clinical response is suboptimal.

### (d) Overall Assessment

Response to therapy will be judged by a combination of clinical and microbiologic criteria and analyzed by intention to treat. Clinical response is paramount.

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