Position Paper: Recommended Design Features of Future Clinical Trials of Antibacterial Agents for Community-Acquired Pneumonia

Infectious Diseases Society of America[a]

EXECUTIVE SUMMARY

The efficacy of new antibiotics for the treatment of community-acquired pneumonia (CAP) typically has been compared with that of established antibiotics in noninferiority clinical trials. However, the US Food and Drug Administration (FDA) is reevaluating the appropriateness of a noninferiority trial design for CAP. The resulting regulatory uncertainty about appropriate trial design has contributed to uncertainty among industry sponsors of new antibiotics. The Infectious Diseases Society of America (IDSA) and its Antimicrobial Availability Task Force (AATF), as well as the FDA, recognized that clarity and consensus on appropriate trial designs for CAP were needed to reverse the trend of reduced investments in the development of new antibacterial agents. To this end, on 17–18 January 2008, the IDSA and the FDA jointly sponsored a workshop on the appropriate design of clinical trials of antibiotics for the treatment of CAP, to provide a forum for scientific discussion.

An exhaustive review of available, pertinent data confirms that there is an unequivocal and substantial treatment effect of antibiotic therapy for CAP. The evidence supporting a treatment effect of antibiotics for CAP includes the following:

1. Far higher mortality rates among patients with CAP, regardless of disease severity or age, in the preantibiotic era

2. An immediate decline in the mortality due to CAP for all age groups and disease severity categories within 1 year after the initiation of use of sulfa drugs for the treatment of CAP

3. Without exception, lower mortality rates with antibiotic treatment versus no specific therapy in every clinical trial for CAP

4. Higher rates of treatment failure among patients infected with organisms that are highly resistant to fluoroquinolones or macrolides

5. More treatment failures and increased mortality among patients who received delayed antibiotic therapy

6. A strong correlation between antibiotic exposure and clinical success rates

7. High rates of treatment failure among patients with CAP treated with daptomycin, an antibiotic that was found to be partially inactivated by surfactant, compared with rates among patients given effective antibiotic therapy in randomized, double-blinded, registration-quality studies.

8. Extensive evidence of more-rapid clinical improvement among patients with CAP treated with antibiotics, compared with placebo or no specific therapy.

In addition to mortality benefits, studies consistently demonstrate a treatment effect of antibiotics on time to resolution of fever, cough, chest pain, dyspnea, and malaise, and/or shortened duration of hospitalization. The magnitude of the antibiotic treatment effect for clinical response at 72 h after initiation of therapy among patients with CAP ranged from 35% to 95%, depending on disease severity and etiological agent.

On the basis of the reviewed data, the IDSA supports and encourages the following design features for registration trials for CAP:

1. A noninferiority design, with the margin of noninferiority determined by the specific outcome measure and the severity of pneumonia among the enrolled patients (as suggested in table 5 in the text below).

2. Use of the following severity-of-illness classification, to establish clear and consistent definitions of the populations enrolled and thereby to harmonize clinical practice, clinical trial enrollment, and regulatory assessment:

    a. Mild = pneumonia severity index (PSI) class I

    b. Moderate = PSI classes II–III

    c. Severe = PSI classes IV–V or PSI classes I–III plus a requirement for mechanical ventilation or other validated, physiological markers of severe disease (e.g., markers of severe sepsis or septic shock or the use of pressors) in individual patients

    d. Combination definitions: mild to moderate = PSI classes I–III; mild to severe = PSI classes I–V or PSI classes I–III plus validated, physiological markers of severe disease; moderate to severe = PSI classes II–V or PSI classes II–III plus validated, physiological markers of severe disease.

3. Sponsors may wish to enrich their study populations for specific pathogens by increasing the use of modern tools of molecular biology. The impact of this enrichment should be taken into consideration in the justificatin of noninferiority margins for individual trials.

4. The following outcome measures are proposed in the context of a noninferiority design:

    a. For trials exclusively enrolling patients with severe CAP (PSI classes IV–V), a 15-day, "all-cause" mortality outcome measure

    b. For trials in which patients with mild CAP (PSI class I) or moderate CAP (PSI classes II–III) are enrolled (with or without inclusion of patients with severe CAP), 15-day, "all-cause" mortality either as the lead outcome in a hierarchical end point or as a composite end point with morbidity variables that represent meaningful benefit to patients. Such variables may be assessed by patient-reported outcome (PRO) instruments. In a hierarchical end point, morbidity outcomes may be assessed by time-to-event or dichotomous

analyses. In a composite end point, mortality and morbidity outcomes should be assessed by dichotomous analyses at prespecified time points. Potential morbidity end points include resolution of fever, cough, pain, dyspnea, or malaise. Hospital discharge is also a potential, relevant end point.

5. Clinical trial assessment of procalcitonin level or other biomarkers of inflammation, to determine their validity or lack thereof.

The current uncertainty about acceptable designs for clinical trials for CAP is contributing to disincentives in the discovery and development of new drugs for treatment of CAP. This crisis will be mitigated by the rapid approval and dissemination of clear and defensible guidelines for future clinical trials of new antibacterial agents for the treatment of CAP.

INTRODUCTION

CAP is a leading cause of morbidity and mortality in the United States and throughout the world [1,2]. Four to six million cases of CAP occur per year in the United States, resulting in 10 million physician visits, 600,000 hospitalizations, and tens of thousands of deaths [1,3]. The total cost of CAP to the annual US health care budget exceeds $10 billion (in 2007-adjusted dollars) [4]. Furthermore, there is increasing resistance to antibiotics among common pathogens, with a resultant critical need for new antibiotics [5].

In recent years, clinical trials of new antibiotics for CAP have tested the hypothesis that the new drugs were not inferior to established antibiotics by a prespecified margin (i.e., noninferiority clinical trials). The FDA has initiated a reevaluation of the appropriateness of a noninferiority trial design for CAP. The resulting regulatory uncertainty about appropriate trial design has contributed to uncertainty among industry sponsors. In turn, industry uncertainty about regulatory standards has exacerbated the already fragile market for antibiotic research and development [5].

The IDSA and its AATF, as well as the FDA, recognized that clarity and consensus on appropriate trial designs for CAP were needed to reverse the trend of reduced investment in development of new antibacterial agents. To this end, on 17–18 January 2008, the IDSA and FDA jointly sponsored a workshop on the appropriate design of clinical trials of antibiotics for the treatment of CAP. The workshop was intended to allow experts from academe, industry, and the FDA to share pertinent knowledge.

This position paper is based on the data presented, discussions held, and opinions expressed at the workshop. Conclusions and suggestions presented in this document are those of the IDSA and its participating representatives. There is no intent to represent the views of industry or the FDA. The goal of the IDSA is to consider the data and represent the best interests of patients.

Herein, 6 specific aspects of clinical trial design for CAP are addressed: (1) the basis of selection of noninferiority versus superiority trials for CAP, (2) severity of illness stratification for enrolled patients, (3) the basis of selection of margins for noninferiority trials, (4) the value of microbiological confirmation of the etiological organism, (5) appropriate clinical trial outcome measures, and (6) safety and other trial design concerns.

NONINFERIORITY VERSUS SUPERIORITY TRIALS FOR CAP, INCLUDING THE ETHICS AND FEASIBILITY OF PLACEBO CONTROLS

Are Superiority Trials Feasible for CAP?

Higgins et al. [6] reviewed recent registration phase III clinical trials of antibiotics for CAP. There is a remarkable consistency of treatment effect across all trials and all drugs, with an

~90% ± 5% clinical response rate in both experimental and comparator arms. Similarly, meta-analyses of multiple randomized clinical trials of antibiotic therapy for CAP found no significant differences in mortality or clinical response, regardless of treatment activity versus atypical bacteria or duration of therapy [7–9].

In contrast, 2 clinical trials reported superior clinical response rates among patients with CAP treated with a fluoroquinolone (levofloxacin or moxifloxacin) compared with rates among patients given treatment with a β-lactam with or without a macrolide [10,11]. However, the first trial was not double blinded, and the majority of patients in the control arm were treated with oral cefuroxime rather than intravenous ceftriaxone. Furthermore, subsequent comparisons of moxifloxacin [12] or gatifloxacin [13] versus ceftriaxone with or without erythromycin found no difference in response rates. Finally, multicentered, randomized comparisons of moxifloxacin or sparfloxacin versus amoxicillin also failed to show superiority of the fluoroquinolones [14,15]. Hence, the vast majority of randomized clinical trials of antibiotics for CAP have failed to show superiority of new antimicrobial agents to the comparative antibiotic regimens. In light of the high rate of clinical success and relatively low mortality for patients with CAP treated with standard antibiotics, demonstration of superiority of a new drug against an active comparator is unlikely. Hence, an active-comparator superiority trial for CAP poses a considerable risk of failing to meet primary efficacy end points, even for an efficacious drug.

The possibility of a placebo-controlled superiority trial was discussed at the workshop. Such a trial would establish a precise estimate of antibiotic treatment effect size. However, a placebo-controlled trial is ethical only if there is equipoise between the benefits of the treatment arms or if the withholding of active treatment poses minimal risk to enrolled patients. A majority of participants at the workshop—in particular, virtually all the physicians—concluded that it is unethical to use a placebo arm for a trial for moderate-to-severe CAP, on the basis of the risk to the participants randomized to the placebo arm. It was acknowledged that the potential sequelae of placebo-treated CAP caused by "atypical" organisms, other than *Legionella* species, were unlikely to cause serious harm. Nevertheless, most clinicians believed that even "atypical" pneumonia requiring hospitalization should be treated with antibiotics and that it is not ethical to administer a placebo to hospitalized patients with CAP.

Some workshop participants believed that a placebo-controlled trial might be justified among young, low-risk, clinically stable outpatients with mild CAP due to an atypical organism. Indeed, such trials have already been performed. The only 2 randomized, double-blind, placebo-controlled trials of CAP identified in the literature were performed with young healthy adults. In 1961, Kingston et al. [16] conducted a trial involving 290 healthy Marine recruits (aged 17–22 years) with mild CAP who were randomized to receive treatment with tetracycline or placebo. *Mycoplasma pneumoniae* was the etiological agent in 133 (46%) of the patients, no pathogen was identified in 122 (42%) patients, and respiratory viruses were the etiological agents in 35 (12%). Tetracycline significantly reduced the mean time to defervescence (temperature <37.2°C [99°F]), normalization of chest radiograph, and resolution of cough, both in patients who had a confirmed diagnosis of *M. pneumoniae* infection and in patients for whom no microbiological diagnosis was established (table 1). The percentage of patients remaining febrile on day 3 was dramatically lower among patients given treatment with tetracycline than among those given placebo, both in patients with confirmed *M. pneumoniae* infection (30% and 95% remained febrile in the tetracycline and placebo arms, respectively) and in patients for whom no microbiological diagnosis was established (30% and 65% remained febrile in the tetracycline and placebo arms, respectively). Statistically significant differences were also seen in Kaplan-Meier analyses of time to resolution of fever and time to normalization of chest radiograph, both in patients with confirmed *M. pneumoniae* infection and in patients with no microbiological diagnosis. In contrast,

tetracycline had no impact on the time to defervescence, normalization of chest radiograph, or any other clinical parameter in patients with confirmed viral infections.

In a subsequent double-blind trial involving 32 young, healthy Army recruits with CAP due to *M. pneumoniae*, patients were randomized to receive treatment with tetracycline, clindamycin, or placebo [17]. Patients receiving tetracycline had a significantly shorter time to defervescence than did those receiving either clindamycin or placebo. Clindamycin was of no benefit, compared with placebo. Thus, the superiority of active antibiotics over placebo has been demonstrated in 2 randomized trials involving patients with mild pneumonia. It is unclear what benefit would accrue by repeating a placebo-controlled trial in a similar population.

The efficacy of macrolides, as well as tetracyclines, for treatment of CAP caused by *M. pneumoniae* was supported by results from 3 other clinical trials involving US Air Force trainees [18–20]. In the first trial, CAP caused by *M. pneumoniae* was serologically confirmed in 317 healthy young men aged 18–21 years. Patients "were treated at random" with erythromycin stearate, erythromycin ethylsuccinate, tetracycline, methacycline, troleandomycin, demeclocycline, penicillin, or no antibiotics. In the second trial, CAP caused by *M. pneumoniae* was serologically confirmed in 105 trainees alternately given treatment with erythromycin or tetracycline. Their outcomes were compared with those of 170 patients with *M. pneumoniae* infection seen during the previous 5 years who had been given treatment with no antibiotics or penicillin. In the third trial, patients with CAP caused by *M. pneumoniae* were given treatment with tetracyclines ($n = 113$) or with no antibiotics ($n = 15$). In all 3 trials, the mean duration of fever among patients given treatment with tetracyclines or macrolides was significantly shorter than for those given treatment with penicillin or no antibiotics. Of note, in all 3 trials, the shortened duration of fever translated into significantly shorter hospital stays. Specifically, patients given treatment with demeclocycine, tetracycline, or erythromycin had an average hospital stay of 5–7 days, compared with 9–14 days for patients receiving penicillin or no antibiotic. A shorter time to resolution of abnormal chest radiograph was also seen in patients given treatment with a tetracycline or a macrolide. The authors of the first trial concluded, "The control group [of this trial] was not large because early in the investigation it was found that tetracycline and erythromycin reduced the length of illness, and thereafter it was considered inadvisable to withhold therapy" [18, p. 683].

In addition to ethics, placebo-controlled trials for CAP, of any severity, face 3 practical hurdles [21]. First, treating physicians are unlikely to agree to enroll their patients in such trials. Second, institutional review boards are unlikely to approve such protocols at individual sites, given the current standard of care and literature documenting the efficacy of antibiotics. Lastly, patients with CAP are unlikely to give informed consent for a trial in which they could be randomized to receive placebo. These 3 issues are particularly relevant to treatment trials involving infants and children with CAP [22].

Are Noninferiority Trials Appropriate for CAP?

According to International Congress on Harmonization (ICH) guidance, noninferiority trials are appropriate only when a comparator drug has been previously established to be superior to placebo for treatment of the disease in question (the "historical evidence of sensitivity to drug effect" standard) [23]. Furthermore, the clinical settings in which the efficacy of the comparator was previously established must be relevant to the planned noninferiority trial (the "constancy assumption" standard).

To determine whether data exist that demonstrate historical evidence of sensitivity to drug effect and the accuracy of the constancy assumption, Singer et al. [24] analyzed studies from the 1920s–1940s of antibiotic use for the treatment of CAP. Before the workshop, 7 studies were identified that compared the effect of antibiotics with that of no therapy for patients with

CAP (table 2). Three of these studies compared the outcomes for consecutive patients given treatment with antibiotics with the outcomes of historical, untreated control patients before the availability of antibiotics. We refer to these studies as "historical control" studies. The other 4 studies enrolled patients to receive antibiotic treatment and concurrent control patients who received no specific antibiotic therapy. We refer to these studies as "concurrent control" studies. Subsequent to the workshop, 1 additional concurrent control study and 3 additional historical control studies were identified, for a total of 11 studies that compared antibiotic treatment with no treatment for CAP (table 2). In addition, several other studies were identified that exclusively evaluated and confirmed the efficacy of antibiotics in pediatric CAP. The pediatric studies are discussed by Bradley and McCracken [22].

The concurrent control studies were not randomized in the modern sense, but rudimentary randomization strategies (e.g., enrollment by hospital ward, alternation of treatment regimen by patient, and alternation by day of enrollment) were used. The historical control studies predominantly evaluated patients with CAP caused by *Streptococcus pneumoniae*. In contrast, the concurrent control studies all included patients without confirmation of *S. pneumoniae* as the etiological agent, either because they enrolled patients with "lobar pneumonia" without specifying the microbial etiology, or they included patients whose cultures did not identify *S. pneumoniae* [31–34].

In the historical control studies, the weighted average mortality rate was 38% without antibiotic treatment and 12% with antibiotic treatment, indicating a 26% (95% CI, 24%–28%) absolute reduction in mortality with antibiotic therapy (table 2). In the concurrent control studies, the weighted average mortality rate was 23% without antibiotics and 7% with antibiotics, indicating an absolute reduction in mortality of 16% (95% CI, 10%–22%) with antibiotics. These early studies established the efficacy of antibiotics for treatment of CAP, including CAP cases that are not confirmed to be caused by *S. pneumoniae*, and probably explain the absence of any recent placebo-controlled trials for this disease.

Stratification of the historical data by age demonstrates efficacy of antibiotics for treatment of CAP over a broad range of severity. For example, Tilghman and Finland [37] and Bullowa [38] reviewed the mortality among >2000 patients with CAP caused by *S. pneumoniae* in the preantibiotic era and stratified the results by age and the presence or absence of bacteremia. As expected, mortality was much lower among younger patients, in particular among those without bacteremia. Today, the majority of young patients with *S. pneumoniae* pneumonia but without bacteremia would be considered to have moderately severe disease, on the basis of numerous studies [26,38–45] and a standard and well-validated scoring system (the PSI, discussed more fully below) [42,46]. Nevertheless, patients aged 12–19 years and 20–29 years with untreated CAP, including those who were not bacteremic, had mortality rates of ~10% in the preantibiotic era (table 3), which is far higher than the <1% mortality rate expected for such patients in the antibiotic era [46].

In 1928, Park et al. [47] reported the results of a trial of antipneumococcal polysaccharide serum therapy among 223 consecutive patients with CAP caused by *S. pneumoniae*. Every other patient was administered serum therapy or supportive care, and patients receiving serum therapy had an absolute reduction in mortality of 14% (from 34% to 20%). Of note, patients who were in "good" baseline condition still had a mortality rate of 13% with no therapy, compared with a 52% mortality rate among patients in "fair" condition and a 100% mortality rate among patients in "poor" condition. Again, "good" condition at baseline likely reflected moderate CAP (i.e., PSI classes II–III), and the mortality rate with no treatment was far higher than that reliably achieved with antibiotics in the modern era (<1%).

In 1938, Evans and Gaisford [31] alternated patients with lobar CAP to receive sulfa treatment or no specific therapy. Of the cases, 22% were attributable to *S. pneumoniae*, on the basis of culture; no microbiological etiology was identified for the remaining 78%. The authors reported that sulfa treatment caused a 16% reduction in mortality among patients aged <30 years, a 21% reduction among patients aged 30–59 years, and a 55% reduction among patients aged ≥60 years. Finland [25] also compared the mortality among 1220 patients with pneumococcal pneumonia treated with sulfa drugs in 1938–1941, compared with that among 2832 patients given no therapy in 1929–1940. The results confirmed that antibiotics had significant treatment effects for all age groups, regardless of whether bacteremia was present. The treatment effect was greater for older patients and bacteremic patients. However, even among nonbacteremic patients aged 12–29 years, the mortality rate decreased from 10% to 5% with antibiotic treatment. Similarly, for patients aged <30 years, Dowling and Lepper [26] reported an 8% mortality rate among untreated patients, compared with a 1% mortality rate among patients given antibiotics.

In all the studies discussed above, the benefits of antibiotics were greater for patients with more-severe disease than for patients with moderate disease. Specifically, Finland [25] reported an absolute reduction in mortality of 40% among patients ≥50 years with CAP, including an ~50% reduction among bacteremic patients and an ~30% reduction among nonbacteremic patients. Similar rates were reported by Evans and Gaisford [31] and Dowling and Leper [26] (table 3).

Calculation of weighted averages from all 5 studies that reported the mortality among treated versus untreated patients stratified by age reveals 2 critical insights (table 3). First, specific estimates of antibiotic-mediated reduction in mortality can be generated for each age group. For patients aged <30 years, 30–59 years, and ≥60 years, the absolute reduction in mortality among patients given treatment with antibiotics was 11% (95% CI, 8%–13%), 27% (95% CI, 25%–30%), and 45% (95% CI, 39%–54%), respectively. Second, the mortality rates among treated patients in each age group show strong resemblances to the mortality rates among patients given antibiotic treatment and stratified by the PSI scoring system in contemporary data sets (table 4).

Collectively, these data establish a convincing reduction in mortality as a result of antibiotic for treatment of CAP and provide point estimates of efficacy that can be used as the basis for justifying noninferiority margins in CAP trials. Furthermore, the mortality rates among patient populations in historical data sets parallels closely the mortality rates among patients assigned specific PSI scores in contemporary data sets, providing evidence that the constancy assumption is valid for noninferiority trials for CAP. Additionally, although the historical control studies predominantly focused on CAP caused by *S. pneumoniae*, significant numbers of patients without confirmed *S. pneumoniae* infection were included in all the concurrent control trials.

Additional Data That Support a Benefit from Antibiotic Therapy for CAP

Adding credence to the historical data sets are recent studies of the effectiveness of antibiotic therapy in the circumstances of discordant therapy (i.e., use of an antibiotic against which the etiological agent is resistant, according to in vitro testing), delayed initiation of therapy versus more-rapid initiation of therapy, and subtherapeutic exposure to an antibiotic, either as a result of inadequate pharmacokinetic-pharmacodynamic parameters or in vivo drug inactivation.

Discordant therapy—In vitro resistance to macrolides and fluoroquinolones is associated with documented clinical failure and increased mortality among patients with CAP [3,48–57].

Delayed initiation of therapy—A delay in the initiation of active antibiotic therapy is associated with a higher mortality rate among patients with CAP [58–60]. A reduced mortality rate with rapid initiation of antibiotics is seen for both patients with moderate disease (PSI classes II–III) and severe disease (PSI classes IV–V) [58].

Subtherapeutic pharmacokinetic-pharmacodynamic parameters—As described in detail by Ambrose [61], data from pharmacokinetic-pharmacodynamic studies involving both animal models and patients with CAP demonstrate that serum area-under-the-inhibitory-curve (AUIC) ratios for antibiotics (e.g., fluoroquinolones or macrolides) strongly correlate with clinical outcome. Indeed, lower fluoroquinolone AUIC ratios are associated with a 25% absolute reduction in clinical response among patients with CAP, compared with higher AUIC ratios. In a multinational trial of antibiotic efficacy for acute exacerbations of chronic bronchitis, lower AUIC ratios predicted clinical progression to CAP [62]. Specifically, 92% of patients with antibiotic AUIC ratios of <100 had progression to CAP, compared with 35% of patients with antibiotic AUIC ratios >100. Furthermore, as discussed by File and Schentag [63], patients presenting with mild CAP caused by *S. pneumoniae* are at higher risk of progression to more-severe CAP when they are not given effective antibiotic therapy than when they are given initial effective antibiotic therapy.

In vivo drug inactivation—Finally, pooled data from 2 recent, phase III, double-blind, randomized clinical trials also demonstrate a treatment effect of antibiotics [64]. In the 2 trials, a combined 936 patients with CAP in PSI classes II–IV (1 patient was in PSI class V) were randomized to receive daptomycin or ceftriaxone. Of the 834 patients in the intention-to-treat (ITT) population, 24% had microbiological confirmation of *S. pneumoniae* as the etiological agent. It was not realized until after the results of the first trial became available that daptomycin is inactivated by pulmonary surfactant and thus loses considerable activity in lung tissue [65]. At that point, enrollment in the second trial was terminated, and the results were pooled with those of the first trial. Among the pooled ITT population, there were nearly twice as many clinical failures in the daptomycin arm than in the ceftriaxone arm (44 vs. 23 failures), resulting in a cure rate of 71% among the daptomycin recipient versus 77% among the ceftriaxone recipients (95% CI, −12.4% to −0.6%). Among the patients in the ITT population who did not have microbiological confirmation of a gram-positive organism as the cause of their CAP, the clinical response rates remained inferior in the daptomycin treatment group, compared with the ceftriaxone treatment group (69% vs. 77%). Thus, regardless of microbiological confirmation of the etiological agent and for a broad range of disease severity (PSI classes II–IV), standard antibiotic therapy was superior to a drug partially inactivated by surfactant.

In summary, 4 different approaches in the modern era generated data that are in concordance with historical data demonstrating that antibiotics are more effective than no treatment for CAP.

Demonstration of Antibiotic Treatment Effect for CAP with Use of End Points Other Than Mortality

A classic medical text by Osler [66] indicated that, in the natural history of untreated CAP, clinical improvement and defervescence were "very uncommon" before 72 h. This opinion is concordant with data from a large cohort reported in a 1937 text by Bullowa [38]. The cohort consisted of 662 untreated patients with CAP who survived. Because these patients all survived in an era during which no effective therapy was available, they represent a population selected for less-severe disease, on average, than that represented by "all comers" with CAP. Nevertheless, only 1.4% of patients with CAP in this untreated cohort had defervesced by day 2 of therapy, and only 2.6% had defervesced by day 3. Furthermore, both Bullowa [38] and

Cecil [67] comment that the time course of normalization of pulse and respiratory rate parallel the time course to normalization of fever in patients with untreated CAP.

In contrast, shortly after the availability of antibiotics, clinical trials found significantly shorter times to resolution of signs and symptoms of infection than those found in the preantibiotic era. In 1939, only 2 years after Bullowa described his series of patients with untreated CAP, Flippin et al. [68] reported that 83% of 100 patients with CAP treated with sulfa drugs had defervesced by day 2 of treatment, and 99% of patients had defervesced by day 3. Raycraft et al. [69] reported that 90% of children with CAP treated with antibiotics had defervesced by day 2 of treatment. Also, in a previously mentioned trial of sulfa therapy versus no treatment for patients with lobar CAP, 54% of patients receiving sulfa drugs had defervesced by day 3, compared with only 4% of patients given no treatment [33]. Two decades later, Petersdorf et al. [70] reported that 74%–94% of patients with CAP had clinically improved (by a composite of defervescence and symptom scores, including chest pain, cough, appetite, general feeling, etc.) by 72 h after initiation of antibiotic therapy. Thus, data available almost immediately after the introduction of sulfa drugs indicate that antibiotic treatment dramatically reduced the time to defervescence and/or clinical improvement of CAP. These data are concordant with those from the previously mentioned trials of tetracyclines or macrolides versus placebo for mild CAP (PSI class I equivalent) in military recruits, in which the time to defervescence and clinical response rates were significantly shorter for patients receiving antibiotics than for those receiving placebo [16–20].

In individual studies, the superiority of antibiotics to an active comparator for the treatment of CAP has been demonstrable by use of time to resolution of signs and symptoms of infection. Specifically, short-course, high-dose (750 mg/day for 5 days) levofloxacin was shown to result in more-frequent resolution of fever and improvement of a variety of clinical symptoms by day 3 of treatment, compared with a then-standard dose (500 mg/day for 7 days) of levofloxacin [71]. In another trial, moxifloxacin treatment led to defervescence in a higher proportion of patients on days 2–5 of antibiotic therapy, improved time to resolution of clinical symptoms (e.g., cough, dyspnea, and chest pain), and a shortened hospital stay, compared with treatment with ceftriaxone with or without erythromycin [12]. Of note, in both fluoroquinolone trials, patients in PSI classes I–IV were enrolled. Thus, time to clinical improvement is a feasible end point and could be applied to trials that evaluate the full spectrum of severity of CAP.

Collectively, all the data reviewed support a treatment effect of antibiotics versus placebo in time to defervescence, time to other clinical response end points, and reduction of mortality. The antibiotic treatment effect for defervescence or clinical response at 72 h after initiation of therapy in patients with CAP ranges from 35% to 95%, depending on disease severity and etiological agent.

In summary, the evidence supporting a treatment effect of antibiotics for CAP includes the following:

1. Far higher mortality rates among patients with CAP, regardless of disease severity or age, in the preantibiotic era

2. An immediate decline in the mortality due to CAP for all age groups and disease severity categories within 1 year after the initiation of use of sulfa drugs for the treatment of CAP

3. Without exception, lower mortality rates with antibiotic treatment versus with no specific therapy in every clinical trial for CAP

4. Higher rates of treatment failure among patients infected with organisms that are highly resistant to fluoroquinolones or macrolides

5. More treatment failures and increased mortality among patients who received delayed antibiotic therapy

6. A strong correlation between antibiotic exposure and clinical success rates

7. High rates of treatment failure among patients with CAP treated with daptomycin, an antibiotic that was found to be partially inactivated by surfactant, compared with rates among patients given effective antibiotic therapy in randomized, double-blinded, registration-quality studies

8. Extensive evidence of more-rapid clinical improvement among patients with CAP treated with antibiotics, compared with placebo or no specific therapy.

SEVERITY-OF-ILLNESS STRATIFICATION

According to ICH guidances, the patient population in current or future noninferiority trials must be comparable to that in benchmark studies [23,72]. Comparability can be addressed in part by stratifying patients with use of a validated marker of disease severity.

The 2 most widely used prognostic scoring systems for CAP are the PSI, as mentioned above, and the CURB-65 score (confusion, urea level >7 mmol/L, respiratory rate ≥30 breaths/min, low systolic or diastolic blood pressure, and age ≥65 years). From the perspective of defining the disease severity in a CAP clinical trial, there are 3 advantages of using the PSI scoring system instead of the CURB-65 scoring system. First, and most important, as discussed above, the PSI correlates with mortality, despite antibiotic treatment, among patients in both historical and contemporary data sets (table 4). Thus, use of the PSI scoring system enables enrollment of populations that satisfy the patient population constancy requirement of noninferiority trials. Second, the PSI score separates disease severity into more categories than does the CURB-65 score; thus, the PSI is more flexible than is the CURB-65 score in stratifying patients by severity of disease. Third, the PSI scoring system takes into account a continuous range of age, whereas the CURB-65 score dichotomizes age to <65 years or ≥65 years.

From the prospective validation cohort of the PSI scoring system, mortality rates increased from 0.1% to 0.6% to 0.9% to 9.5% to 26.7% as the PSI class increased from I to V [46]. Note the 6-fold increase in mortality between classes I and II and the 10-fold increase between classes III and IV. Furthermore, as mentioned, there is a correlation between mortality rates among treated patients in the historical data sets and the average mortality rates for PSI classes II–III, III–IV, and IV–V in the validation cohort (table 4). Finally, the previously mentioned military studies of CAP due to *M. pneumoniae* were exclusively conducted involving patients with PSI class I–equivalent disease [16–20].

Therefore, the disease severity of patients enrolled in clinical trials can be defined by PSI class as follows: class I (mild), class II–III (moderate), and class IV–V (severe). In this context, trials that enroll patients across disease categories are concordantly designated as enrolling patients with mild-to-moderate disease (i.e., PSI classes I–III), mild-to-severe disease (i.e., PSI classes I–V), or moderate-to-severe disease (i.e., PSI classes II–V). These designations are relevant because historical data sets provide evidence of antibiotic efficacy for populations across these disease categories (table 2–table 5).

The PSI scoring system provides the foundation for identification of populations with differing disease severity, but the PSI does not capture all elements contributing to disease severity [43,44,73]. In individual clinical studies, protocol designers should have the ability to modify the definition of severe CAP on the basis of well-validated factors not accounted for in the PSI scoring system. For example, CAP with severe hemodynamic compromise or with a requirement of mechanical ventilation should be considered severe even in young, otherwise

healthy persons who might not have enough comorbidities to be in PSI classes IV–V. Care must be taken in the creation of such modifications to the scoring of disease severity, so as not to undermine the predictive power of the PSI scoring system. Therefore, if the criteria are modified for individual studies, the modifications should be justified for the projected clinical trial patient population. Finally, the PSI scoring system is not validated for use in children, and additional research is needed to better define populations for enrollment in trials of pediatric CAP.

IDSA-SUGGESTED MARGINS OF NONINFERIORITY

As summarized above, there is compelling evidence of a mortality benefit of antibiotic treatment for CAP. The overall effect size is an absolute reduction in mortality of 26% (95% CI, 24%–28%) for CAP due to *S. pneumoniae* and 16% (95% CI, 10%–22%) for all patients with CAP (table 2). Furthermore, historical data indicate mortality reductions among patients given antibiotic treatment of 11% (95% CI, 8%–13%), 27% (95% CI, 25%–30%), and 45% (95% CI, 39%–54%) with CAP disease severities equivalent to PSI classes II–III, III–IV, and IV–V, respectively (table 3).

According to the ICH guidance document E10, "The margin chosen for a noninferiority trial cannot be greater than the *smallest effect size that the active drug would reliably be expected to have* compared with placebo in the setting of the planned trial" [23, p. 9; italics in the original]. Therefore, the lower bound of the noninferiority margin in a clinical trial for a new antibiotic is set, in part, on the basis of the previously reported lower limits of efficacy for the comparator drug. Furthermore, the ICH guidance states, "In practice, the noninferiority margin chosen usually will be smaller than that suggested by the smallest expected effect size of the active control because of interest in ensuring that some clinically acceptable effect size (or fraction of the control drug effect) was maintained" [23, p. 9].

Thus, the data justify conducting noninferiority trials for CAP with an end point of mortality and a noninferiority margin of 5%–10%, depending on the severity of disease among the enrolled population (table 5). These proposals are based on the lower limit of the 95% CI of effect sizes in historical data sets, taking into consideration the need to preserve a significant effect size, particularly for more-ill patients who have a higher risk of death. Furthermore, available data also support use of a noninferiority trial design to evaluate time to resolution of clinical end points, such as fever and cough, or resolution of clinical end points as a dichotomous outcome for patients with the full spectrum of CAP severity, from mild to severe (PSI classes I–V) (table 5).

It is emphasized that resolution of fever, cough, chest pain, dyspnea, malaise, or hypoxia are important clinical end points because (1) faster resolution is closely linked to faster time to hospital discharge [12,18,19,33] and (2) they cause patients substantial discomfort and distress. Multiple clinical trials have demonstrated that achievement of "clinical stability," including defervescence and resolution of hypoxia, can be used to determine when it is safe to switch a patient from intravenous to oral antibiotic therapy and/or when it is safe to discharge a hospitalized patient with CAP [74–79]. These studies underscore the close link between time to defervescence and/or clinical improvement and time to hospital discharge. Furthermore, use of clinical improvement to guide decisions about the switch from oral to intravenous antibiotics and hospital discharge has been incorporated into national guidelines on the treatment of CAP [3].

Because the treatment effect of antibiotics for these clinical end points is so large, compared with no treatment or placebo, and because the treatment effect is based on clinical and/or symptomatic responses rather than mortality, the precision with which the noninferiority margin is selected for future trials is less critical. For example, a 20% noninferiority margin

for a dichotomous end point of defervescence at day 3 of treatment is reasonable, because it is far below the treatment effect, and therefore is sufficient to maintain a substantial treatment effect, relative to placebo.

Finally, we emphasize that table 5 serves as a guideline for reasonable choices for noninferiority margins in different clinical trial settings. However, the margins used may differ from one trial to another. Justification of specific end points should be performed for each specific trial design, because the patient population and range of pathogens may alter the effect size and/or risk-to-benefit ratio, thereby affecting the appropriate noninferiority margin.

THE VALUE OF MICROBIOLOGICAL IDENTIFICATION OF THE ETIOLOGICAL ORGANISM OF CAP

A prominent theme of the workshop was the value of identification of the microbiological etiology (or etiologies) of pneumonia in patients enrolled in clinical trials. Although it is not always necessary to know the microbiological etiology of pneumonia to administer rational and effective empirical therapy for CAP in clinical settings, it is important to know for a noninferiority trial for CAP. The data that document a mortality benefit of antibiotic therapy for CAP are derived, in large part, from trials that enrolled populations enriched for patients with CAP caused by *S. pneumoniae*. Therefore, for noninferiority trials using mortality as an end point, it may be desirable to similarly enrich the enrolled population for patients with CAP caused by *S. pneumoniae*.

However, as mentioned, there is substantial evidence of a treatment benefit for patients with "lobar pneumonia" or pneumonia of unclear microbial etiology, as well as for patients with proven *M. pneumoniae* infection. Furthermore, in standard clinical practice, treating physicians almost never know the etiological organism when they choose empirical antibiotic therapy for CAP. Therefore, restriction of the primary end-point analysis to patients who are later confirmed to have an infection caused by a specific microbe does not reflect "real-world" practice. Thus, although appropriate for some trials, it may not be necessary—and in some cases may be undesirable and misleading—to restrict the primary analysis to patients eventually confirmed to have pneumococcal pneumonia.

Nevertheless, another advantage of enriching the enrolled population in a CAP trial for patients infected with *S. pneumoniae* is that the greater the homogeneity of the patient population, the greater the likelihood of clear clinical end points and reduced mortality. Pneumonia caused by viruses does not respond to antibiotics, and most other bacterial causes of CAP, with the exception of *Legionella* species, are less likely to lead to infectious complications. In a superiority trial, dilution of the population most likely to derive benefit from the therapeutic intervention biases the trial away from rejection of the null hypothesis (i.e., biases the trial away from the finding of superiority versus the comparator drug). In contrast, in a noninferiority trial, dilution of the population most likely to derive benefit from the therapeutic intervention biases the trial toward rejection of the null hypothesis (i.e., biases the trial toward the finding of no difference between the 2 interventions). Enrichment for patients infected with *S. pneumoniae*—the patients most likely to benefit from antibiotic therapy—can therefore mitigate bias toward rejection of the null hypothesis in a noninferiority trial.

Klugman and Madhi [80] and Nolte [81] reviewed recent advances in the rapid, precise identification of the pathogens most often implicated in the etiology of CAP. Use of such methods could facilitate enrichment of an analyzable population for a target pathogen. Multiplex real-time PCR is evolving rapidly and allows identification of bacteria and viruses in respiratory specimens in a few hours. Presently, the technology is not generally available, but improved access is likely to emerge in a short time. The National Institutes of Health could

help by facilitating an investigation of a wide range of diagnostic tests designed to identify the specific microbial etiology of CAP.

In short, even if they are not, at present, generally available clinically, the emerging methods of molecular diagnostics could, and perhaps should, be used in future clinical trials. However, to the degree that these methods provide greater sensitivity than do classic microbiological methods, they may identify patient cohorts different from those defined in the historical clinical trials that have been used to define effect sizes for the active-comparator arms. Thus, the impact of molecular diagnostics on the anticipated event rate and enrolled population should be taken into consideration when a noninferiority margin for an individual trial is justified.

Other microbiological tests are readily available and should be performed—for example, Gram stain and culture of sputum specimens, blood cultures, urinary pneumococcal antigen tests, and *Legionella* urinary antigen tests. *Mycoplasma* IgM antibody tests have reasonable sensitivity and specificity. *M. pneumoniae* and *Chlamydophila pneumoniae* can be identified by probing respiratory secretions with PCR. A positive result of Gram stain or culture of sputum specimen or blood culture in the appropriate clinical circumstances (i.e., with an abnormal chest radiograph with relevant signs or symptoms) is sufficient to identify patients with pneumococcal pneumonia. Although serological or antigen test results positive for atypical pathogens do not exclude the possibility of pneumococcal pneumonia (because dual infection is well described), they do allow a greater understanding of the pathogen distribution in the trial population.

As discussed by Bradley and McCracken [22], the sensitivity, specificity, and clinical significance of diagnostic tests for pathogens of CAP may differ between adult and pediatric populations, and distinct tests may be required to assess infection in different age groups [82].

APPROPRIATE OUTCOME MEASURES FOR CAP TRIALS

Primary end points

In accordance with ICH guidances, the primary end points in noninferiority trials for CAP should reflect the end points of the trials used to justify the noninferiority margin. Potential end points include mortality and/or clinical morbidity outcomes as hierarchical or composite end points, as discussed more fully below. Clinical outcomes could be time to event or dichotomous end points at a specific time point, including resolution of fever, cough, dyspnea, chest pain, malaise, or hypoxia, as well as duration of hospitalization. If defervescence is used as an end point, factors that can affect the temperature curve and validation of the definition of defervescence must be considered prospectively. For example, control of the use of antipyretics must be built into the protocol. Similarly, prospective definition of the duration of normal temperature required to achieve the "defervescence" end point is necessary (i.e., for how long must a patient maintain a normal temperature before he or she is considered to have defervesced?).

In a superiority trial design, because there is no need to match end points with historical precedents, selection of a primary end point for a superiority trial should follow ICH guidance E9: "The primary variable ('target' variable, primary end point) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial" [72, p. 5]. It is recommended that time-to-event analyses be considered for superiority trials. Time-to-event outcomes increase statistical power and informative analysis, compared with dichotomous outcomes. Analyses might include time to death, hospital discharge, transfer from the intensive care unit, defervescence, cessation of pressors, cessation of supplemental oxygen, and so forth.

Mortality as an end point

It is difficult to accurately assign cause of death for individual patients. Attempts to determine "attributable mortality" would likely introduce unmeasurable bias into the analysis. Thus, analysis of "all-cause mortality" is recommended in lieu of attributable mortality.

Historical data sets and recent evaluations of pneumonia demonstrate that deaths among patients with CAP typically occur within the first 7–14 days after presentation [24,39]. Deaths occurring after 14 days are more likely due to comorbidities. Therefore, it is recommended that the primary mortality end point apply to all deaths occurring within 15 days after presentation, rather than deaths occurring after ≥30 days.

PRO instruments (standardized questionnaires)

A PRO instrument is a tool used to measure a patient's health and well being. Information recorded on the PRO is provided by the patient, rather than by the health care provider, with no interpretation of the patient's answers by the health care provider. An advantage of PRO instruments is that they "offer a structured interview technique that minimizes measurement error and ensures consistency, ultimately providing a more reliable measurement than one that can be obtained by informal interviews" [83]. There is considerable enthusiasm for increasing the use of PRO instruments to objectively quantify clinical response, especially in the context of time-to-event analyses. If a PRO is used, it should be appropriately validated [84], and the interview process must be standardized, to remove interviewer bias from the results.

Surrogate markers

In the context of CAP, clinical signs of infection, such as fever, are both biomarkers and surrogate markers for infection. An elevated WBC count is a laboratory surrogate marker for infection. Fever and elevated WBC count lack, by themselves, specificity to pneumonia. Neither separates bacterial from other causes of CAP (e.g., viral or fungal). Nonetheless, laboratory tests that indicate a bacterial infection, as opposed to a viral infection, could improve clinical trials by excluding from enrollment patients who have a very high likelihood of viral infection.

Elevated procalcitonin levels may increase the likelihood of a bacterial etiology of pneumonia. As discussed by Niederman [85], prospective clinical trials involving adults demonstrate that antibiotics may be safely withheld from patients with pulmonary infiltrates who have serum procalcitonin levels of <0.1 ng/mL. If validated, procalcitonin levels may exclude patients with nonbacterial pneumonia from enrollment or the primary end-point analysis, thereby improving the population homogeneity and increasing the signal-to-noise ratio in the analysis of the primary end point.

Hierarchical primary end-point testing

Multiple primary end points are generally not appropriate for a clinical trial, because of the concern about multiple comparisons testing. However, if multiple end points are hierarchically ranked such that the most important end point is tested first and subsequent end points are tested only if significance is achieved with the preceding end points, the issue of multiple comparisons is obviated [86].

Hierarchical testing may be particularly advantageous for a CAP clinical trial because it allows assessment of both noninferiority and superiority primary end points in the same trial. Hierarchical testing can also allow sequential assessment of a dichotomous end point and time-to-event end points. For example, the first primary end point tested could be a dichotomous noninferiority analysis of mortality. If statistical noninferiority was met with the first primary end point, the second primary end point could be a superiority analysis of time to defervescence,

time to clinical improvement as a PRO, time to hospital discharge, and so forth. Thus, the use of hierarchical testing enables superiority testing while still enabling a successful trial on a noninferiority basis, in case superiority is not achieved (i.e., the risks of not achieving superiority are mitigated).

If hierarchical primary end-point testing is to be used in a clinical trial, 3 principles apply. First, the hierarchy of the end points must be predetermined in the trial protocol, before initiation of the trial, and cannot be subsequently switched, or bias will be introduced. Second, the hierarchy should set clinically more important and/or relevant end points to a more important hierarchical position (e.g., mortality should be tested before time to defervescence). Aside from clinical relevance, the hierarchical order should reflect loss of available information at each step in the hierarchy. For example, in a trial that assesses both all-cause mortality and clinical end points (e.g., symptoms), mortality must be the first end point tested, because dead patients are not available for assessment of the clinical end points [87]. Third, if the initial end point does not meet statistical significance, the trial is considered failed per the primary end point, and subsequent end points in the hierarchy can no longer be considered primary end points. In the latter scenario, subsequent end points either should not undergo statistical testing, or, if testing does occur, the results should be considered as secondary, hypothesis-generating end points, rather than confirmatory end points.

Composite outcome measures

As stated in the Introduction, CAP results in considerable morbidity, in addition to mortality. It is reasonable to determine the efficacy of antibiotics at reducing both mortality and morbidity due to CAP. For inclusion in a composite outcome measure, markers of morbidity must be clinically meaningful. Furthermore, evidence should be available that demonstrates that antibiotics mitigate the severity of the individual components of the composite end point. On the basis of these criteria, a composite primary outcome measure for a noninferiority CAP trial could include all-cause, 15-day mortality and ≥1 dichotomous clinical morbidity end point, such as defervescence or other patient health status variables (e.g., cough, pain, and shortness of breath) assessed by PRO instruments.

However, use of a composite end point has the potential to mask unfavorable mortality effects if the efficacy of the new antibiotic is driven by morbidity components. Therefore, if a composite end point is used, a secondary analysis of all-cause mortality should be performed to determine whether the mortality effect is concordant or discordant with the overall composite end point and the other individual components of the end point.

Composite end points may be appropriate for CAP trials enrolling patients with mild (PSI class I) or moderate (PSI classes II–III) CAP, with or without inclusion of patients with severe CAP (PSI classes IV–V) in the study population. However, antibiotics mediate a very large reduction in mortality among patients with severe CAP (table 3), making assessment of noninferiority with respect to mortality critical for any new drug directed at this population. Therefore, the preferred primary outcome assessment for trials that exclusively enroll patients with severe CAP (PSI classes IV–V) is all-cause, 15-day mortality. In trials that include CAP populations that include, but are not limited to, patients with severe CAP, a secondary analysis should examine mortality in this subgroup, to explore consistency with the expected benefit (recognizing that the trial will not be powered to draw a definitive conclusion on this analysis).

Exclusions from the analysis population

In the past, patients in CAP trials were often excluded from the primary end-point analysis if they received therapy for an insufficient number of days (usually ≤3 days), because of the assumption that patients who died within that time frame were sufficiently ill to have been

unlikely to have benefited from any antibiotic therapy. However, in today's environment of early goal-directed therapy and other critical-care supportive measures, it is not clear that this assumption is valid. Furthermore, early deaths in patients receiving therapy may reflect an exacerbation of underlying disease, toxicity of the trial drug, or worsening sepsis caused by sudden lysis of bacteria. Such data elements should not be excluded from the primary endpoint analysis. Therefore, it is recommended that the ITT population for the efficacy analysis consist of all randomized patients.

SAFETY, BLINDING, PRIOR ANTIBIOTIC THERAPY, AND PEDIATRICS

Safety issues

Patient safety should be a principal concern of all those participating in the design, conduct, and analysis of clinical trials, including trials for CAP [88,89]. The evaluation of known class or molecule toxicities is a standard component of this process. Antibiotic classes commonly used to treat CAP exhibit a number of known adverse events, such as prolongation of the corrected QT interval (e.g., fluoroquinolones) and gastrointestinal symptoms (e.g., macrolides). Furthermore, anyantibiotic has the potential to affect the risk of developing *Clostridium difficile* enterocolitis. Trials should be designed and conducted to evaluate thoroughly the potential for such events and to avoid them. Safety analyses should be conducted on an ITT basis with use of all patients randomized in the trial.

Patient safety also extends beyond the capture and analysis of adverse events [89]. Safety includes the impact of trial variables on efficacy. For example, suboptimal efficacy in a clinical trial can lead to many adverse patient "safety" outcomes—for example, prolonged hospitalization, increased cost, complications, and even death. To increase the likelihood of efficacy, proper dose selection for the new antibiotic must be a primary focus. Other areas requiring rigorous attention in this context include (1) the choice of active comparator, (2) the choice of adjunctive antibiotic therapy (i.e., antibiotics given as a part of the trial regimen but not including the primary trial drug), (3) protocol-defined adjunctive nonantibiotic therapy, (4) the impact of prior antibiotic therapy, and (5) patient inclusion and exclusion criteria.

Impartial data safety–monitoring boards and interim analyses are important to protect against a clearly inferior treatment or unexpected adverse events. Finally, postmarketing studies should conduct active surveillance for safety issues that were not uncovered in earlier trials, and such studies should involve appropriate, rigorous design to enable meaningful conclusions.

Blinding

Double blinding (i.e., blinding of the patient and all trial personnel who are involved with evaluations in the trial) should be incorporated into CAP clinical trials [90]. Double blinding may require a double-dummy design if comparator antibiotics are dosed with frequency or routes different from those of the trial drug or if adjunctive therapy is planned in case of resistant gram-negative bacilli or other drug-resistant organisms. Expectation of a substantial proportion of drug-resistant organisms, methicillin-resistant *Staphylococcus aureus* in particular, may require use of an unblinded trial pharmacist, microbiologist, or other personnel, to provide therapeutic interventions (e.g., dose-adjusting vancomycin) without unblinding the patient. However, the development of specific safety issues in individual patients may require unblinding, to discern treatment assignment. Development of other clinical scenarios may also mandate unblinding of the patient or discontinuation of a patient from the trial protocol. For example, development of staphylococcal bacteremia necessitates initiation of a series of interventions both diagnostic (e.g., echocardiography) and therapeutic (i.e., prolonged intravenous antibiotic treatments) that are beyond the scope of most CAP clinical trials.

Prior antibiotic therapy

The complexities involved in identifying, obtaining consent from, screening, and enrolling patients into clinical trials are such that enrollment within a few hours after presentation is extremely challenging. Because delayed initiation of therapy poses risks for patients with CAP, as well as for hospitals and individual physicians being monitored for compliance with national standards of quality care, clinical protocols may need to allow for a single dose of antibiotics or perhaps short periods of antibiotic therapy before enrollment [89]. Nevertheless, striving to enroll patients before administration of antibiotics is an important goal, to minimize the potential confounding effects of the prior antibiotic treatment.

Concerns about pediatric trial design

The incidence of CAP in infants exceeds that in adults. Inclusion of infants and children brings additional issues to the complexities of clinical trial design for CAP—for example, ethical issues of placebo-controlled trials, the increased difficulty of identifying bacterial pathogens in pediatric CAP, and age-related differences in drug kinetics. Nevertheless, the historical evidence of antibiotic effectiveness for pediatric patients with CAP is sufficient to justify noninferiority trials. These issues are discussed by Bradley and McCracken [22] in this supplement.

SUMMARY OF THE IDSA'S VIEWS

The following views and recommendations are those of the IDSA. The IDSA advocates for patients and their physicians. The positions presented are not motivated by advocacy for industry. IDSA leadership remains critically concerned about the converging problems of lack of antibiotic development and surging rates of antibiotic resistance among lethal bacterial pathogens [5]. As physicians and public health advocates, we emphasize that patients need new drugs for treatment of CAP to be in the discovery and development pipeline. Furthermore, because it takes, on average, ≥10 years to complete development of a new drug, it is essential that the pipeline be strengthened now to meet anticipated needs a decade or more from now. An important step to enhance the discovery and development of new antibiotics is clarification of FDA guidance for future clinical trials of antibacterial agents for CAP.

An exhaustive review of available, pertinent data confirms that there is an unequivocal and substantial treatment effect of antibiotic therapy for CAP. Antibiotic therapy results in a reduction in mortality among patients with moderate CAP (PSI classes II–III) and an even greater reduction in mortality among patients with severe CAP (PSI classes IV–V). As demonstrated by placebo-controlled trials, antibiotic therapy also accelerates improvement in relevant clinical markers of morbidity among patients with mild CAP (PSI class I). Thus, the ICH "historical evidence of sensitivity to drug effect" standard [23] is met for use of noninferiority trials of antibiotics for the treatment of CAP of all severities. Finally, the PSI scoring system enables correlation of mortality rates of patients given antibiotic treatment in contemporary CAP trials and those of historical data sets, thereby validating the constancy assumption needed for noninferiority trials of CAP.

Given the available data, the conduct of placebo-controlled trials of antibiotics for CAP is both unnecessary and, we suggest, unethical. The IDSA favors a rapid and clear delineation of FDA guidance to industry on the design options for future registration clinical trials for CAP. On the basis of the reviewed data, the IDSA supports and encourages the following design features:

1. A noninferiority design, with the margin of noninferiority determined by the specific outcome measure and the severity of pneumonia among the enrolled patients, as suggested in table 5.

2. Use of the following severity-of-illness classification, to establish clear and consistent definitions of the populations enrolled and thereby to harmonize clinical practice, clinical trial enrollment, and regulatory assessment:

    a. Mild = PSI class I

    b. Moderate = PSI classes II–III

    c. Severe = PSI classes IV–V or PSI classes I–III plus a requirement for mechanical ventilation or other validated, physiological markers of severe disease (e.g., markers of severe sepsis or septic shock or the use of pressors) in individual patients

    d. Combination definitions: mild to moderate = PSI classes I–III; mild to severe = PSI classes I–V or PSI classes I–III plus validated, physiological markers of severe disease; moderate to severe = PSI classes II–V or PSI classes II–III plus validated, physiological markers of severe disease.

3. Sponsors may wish to enrich their study populations for specific pathogens by increasing the use of modern tools of molecular biology. The impact of this enrichment should be taken into consideration in the justification of noninferiority margins for individual trials.

4. The following outcome measures are proposed in the context of a noninferiority design:

    a. For trials exclusively enrolling patients with severe CAP (PSI classes IV–V), a 15-day, "all-cause" mortality outcome measure

    b. For trials in which patients with mild CAP (PSI class I) or moderate CAP (PSI classes II–III) are enrolled (with or without inclusion of patients with severe CAP), 15-day, "all-cause" mortality either as the lead outcome in a hierarchical end point or as a composite end point with morbidity variables that represent meaningful benefit to patients. Such variables may be assessed by PRO instruments. In a hierarchical end point, morbidity outcomes may be assessed by time-to-event or dichotomous analyses. In a composite end point, mortality and morbidity outcomes should be assessed by dichotomous analyses at prespecified time points. Potential morbidity end points include resolution of fever, cough, pain, dyspnea, or malaise. Hospital discharge is also a potential, relevant end point.

5. Clinical trial assessment of procalcitonin level or other biomarkers of inflammation, to determine their validity or lack thereof.

The current uncertainty about acceptable designs for clinical trials for CAP is contributing to disincentives in the discovery and development of new drugs for treatment of CAP. This crisis will be mitigated by the rapid approval and dissemination of clear and defensible guidelines for future clinical trials of new antibacterial agents for the treatment of CAP.

Acknowledgments

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Table 1

Effect of tetracycline on mean time to resolution of symptoms in patients with community-acquired pneumonia.

Symptom	Patients with confirmed *Mycoplasma* infection (*n* = 133)		Patients with no microbiological diagnosis (*n* = 122)		Patients with confirmed viral infection (*n* = 35)	
	Placebo group	Tetracycline group	Placebo group	Tetracycline group	Placebo group	Tetracycline group
Fever (temperature >37.2°C [99°F])	10	3[a]	7	3[a]	6	4
Abnormality on chest radiograph	20	9[a]	15	11[a]	16	15
Cough	22	10[a]	15	9[a]	18	14
Fatigue and/or malaise	9	3[a]	4	3	4	5

NOTE. Data are mean days to resolution. From [16].

[a] $P<.05$.

Table 2

Historical studies demonstrating antibiotic-mediated reduction in mortality among patients with community-acquired pneumonia.

Study	Non-*Streptococcus pneumoniae* infections included[a]	Mortality among patients		
		No treatment	Antibiotic treatment	Absolute reduction[b] (95%CI), %
Historical control studies				
Finland [25]	No	1161/2832 (41)	207/1220 (17)	
Dowling and Lepper [26]	No	331/1087 (31)	47/920 (5)	
Austrian and Gold [27]	No	405/480 (84)	90/527 (17)	
Heinztelman et al. [28]	No	8/10 (80)	2/9 (22)	
Anderson and Cairns [29]	No	86/462 (19)	26/217 (12)	
Gaisford [30]	Yes	193/876 (22)	26/400 (7)	
Total (weighted average)	…	2184/5747 (38)	398/3293 (12)	26 (24–28)
Concurrent control studies				
Evans and Gaisford [31]	Yes	27/100 (27)	8/100 (8)	
Graham et al. [32]	Yes	7/30 (23)	4/80 (5)	
Agranat et al. [33][c]				
Population 1	Yes	16/86 (19)	6/71 (8)	
Population 2	Yes	6/27 (22)	2/27 (7)	
Ormiston et al. [34]	Yes	2/11 (18)	1/30 (3)	
Total (weighted average)	…	58/254 (23)	21/308 (7)	16 (10–22)

NOTE. Data are no. of patients who died/total no. of patients (%), unless otherwise indicated.

[a]Patients were included in the trial who did not have laboratory-confirmed *S. pneumoniae* infection.

[b]The reduction in mortality is summarized across the studies as the difference between the group receiving antibiotics and the group not receiving antibiotics, weighted by the numbers of patients. The 95% CIs were calculated using standard linear combination variance formulas [35]. This method allows inclusion of 1-arm studies and nonrandomized 2-arm studies, which is not possible with meta-analytic techniques [36].

[c]Two distinct patient populations were considered separately in this trial.

Table 3

Historical mortality rates among patients with pneumonia, according to age or baseline status of the severity of their condition.

Study	Mortality among patients aged <30 years or with "good" status[a]			Mortality among patients aged 30–59 years or with "fair" status[a]			Mortality among patients aged ≥60 years or with "poor" status[a]		
	No antibiotics	Antibiotic treatment	Absolute reduction[b] (95% CI), %	No antibiotics	Antibiotic treatment	Absolute reduction[b] (95% CI), %	No antibiotics	Antibiotic treatment	Absolute reduction[b] (95% CI), %
Tilghman and Finland [37]	32/301 (11)	NA		154/563 (27)	NA		96/140 (69)	NA	
Bullowa [38]	103/739 (14)	NA		371/1090 (34)	NA		80/135 (59)	NA	
Heinztelman et al. [28]	NA	NA		5/7 (71)	0/7 (0)		3/3 (100)	2/2 (100)	
Evans and Gaisford [31]	6/34 (18)	1/51 (2)		18/52 (35)	6/44 (14)		3/4 (75)	1/5 (20)	
Dowling and Lepper [26]	23/287 (8)	3/226 (1)		199/613 (32)	24/565 (4)		109/187 (58)	20/129 (16)	
Weighted average	164/1361 (12)	4/277 (1)	11 (8–13)	747/2325 (32)	30/616 (5)	27 (25–30)	291/469 (62)	23/136 (17)	45 (39–54)

NOTE. Data are no. of patients who died/total no. of patients (%), unless otherwise indicated. NA, not available.

[a] Some studies scored the baseline status of the severity of illness as "good" (i.e., pneumonia severity index [PSI] classes II–III equivalent), "fair" (i.e., PSI classes III–IV equivalent), or "poor" (i.e., PSI classes IV–V equivalent); if scoring was not available, age was used.

[b] The reduction in mortality is summarized across the studies as the difference between the group receiving antibiotics and the group not receiving antibiotics, weighted by the numbers of patients. The 95% CIs were calculated using standard linear combination variance formulas [35]. This method allows inclusion of 1-arm studies and nonrandomized 2-arm studies, which is not possible with meta-analytic techniques [36]. One small trial (by Heinzelman et al. [28]; $n = 19$) was not included in the summary statistics because of the 0% and 100% mortality rates among some subgroups. Also, the large, historical control study by Finland [25] was not included, because he reported only the percentage mortality according to age and did not list the numerator and denominator of patients in each age group.

Table 4

Comparison of the influence of age on mortality rates among patients given antibiotic treatment, on the basis of historical and contemporary data sets.

Age, years	Mortality rate based on historical data,[a] %	Mortality rate among PORT validation cohort,[b] % (PSI classes)
<30	1	0.75 (II–III)
30–59	5	5.3 (III–IV)
≥60	17	18.1 (IV–V)

NOTE. PORT, Patient Outcomes Research Team; PSI, pneumonia severity index.

[a] Historical data are from table 3.

[b] The mortality rate for age <30 years is the average of 0.6% and 0.9% for PSI classes II and III, respectively; for age 30–59 years, the average of 0.9% and 9.5% for PSI classes III and IV, respectively; and for age ≥65 years, the average of 9.5% and 26.7% for PSI classes IV and V, respectively [46].

Table 5

Examples of possible noninferiority margins for clinical trials of treatments for community-acquired pneumonia.

End point, population	Established lower limit of antibiotic effect,[a] %	Proposed noninferiority margin, %
Mortality		
PSI classes II–V with *Streptococcus pneumoniae* only	24	10
PSI classes II–V	10	10
PSI classes II–III	8	5
PSI classes III–IV	25	10
PSI classes IV–V	39	10
Defervescence by day 3 (dichotomous)		
PSI class I with *Mycoplasma pneumoniae* only	65	20
PSI class I	35	15
PSI classes II–V	50	20
Composite clinical response[b]	Varied	10–20

NOTE. PSI, pneumonia severity index.

[a] Based on data reviewed in table 2 and table 3 and in the text.

[b] Composite clinical responses could include either time-to-event or dichotomous end points at a specific time point. Data exist to support components, including mortality, defervescence, resolution of cough, resolution of dyspnea, resolution of chest pain, resolution of malaise, and duration of hospitalization. Patient-reported outcome instruments should be considered for clinical response end points. The appropriate patient population and selection of noninferiority margin should be appropriately justified on the basis of available data and the principles outlined in the text above and in International Conference on Harmonisation guidance documents E9 and E10.