

# Update of Practice Guidelines for the Management of Community-Acquired Pneumonia in Immunocompetent Adults

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## INTRODUCTION

The Infectious Diseases Society of America (IDSA) produced guidelines for community-acquired pneumonia (CAP) in immunocompetent adults in 1998 and again in 2000 [1, 2]. Because of evolving resistance to antimicrobials and other advances, it was felt that an update should be provided every few years so that important developments could be highlighted and pressing questions answered.

We addressed those issues that the committee believed were important to the practicing physician, including suggestions for initial empiric therapy for CAP. In some cases, only a few paragraphs were needed, whereas, in others, a somewhat more in-depth discussion was provided. Because many physicians focus on the tables rather than on the text of guidelines, it was decided that all of the information dealing with the initial empiric treatment regimens should be in tabular format with footnotes (tables 1–3). The topics selected for updating have been organized according to the headings used in the August 2000 CAP guidelines pub-

lished in *Clinical Infectious Diseases* [2]. The major headings were “Epidemiology,” “Diagnostic Evaluation,” “Special Considerations,” “Management,” “Prevention,” and “Performance Indicators,” and each section had a number of subentries. Our current topics are either updates of specific subheadings or are new contributions, and the committee’s recommendations are given at the beginning of each section. A summary of prior IDSA recommendations presented in 2000 and the updated and new recommendations can be found in table 4. Ratings of the strength of the supporting evidence and the quality of the data are given in parentheses after each recommendation, and the grading system used to categorize them is in table 5.

The next guidelines for the treatment of CAP will be a joint effort by the IDSA and the American Thoracic Society (ATS). A working group representing both societies has been formed and is already at work on the next CAP treatment guidelines.

## UPDATE ON THE INITIAL SITE OF TREATMENT DECISION

**Recommendation 1.** The initial site of treatment should be based on a 3-step process: (1) assessment of preexisting conditions that compromise safety of home care; (2) calculation of the pneumonia PORT (Pneumonia Outcomes Research Team) Severity Index (PSI) with recommendation for home care for risk classes I, II, and III; and (3) clinical judgment (A-II).

**Recommendation 2.** For discharge criteria, during the 24 h prior to discharge to the home, the patient should have no more than 1 of the following characteristics (unless this represents the baseline status): tem-

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**Table 1. Initial empiric therapy for suspected bacterial community-acquired pneumonia (CAP) in immunocompetent adults.**

Patient variable	Preferred treatment options
Outpatient	
Previously healthy	
No recent antibiotic therapy	A macrolide <sup>a</sup> or doxycycline
Recent antibiotic therapy <sup>b</sup>	A respiratory fluoroquinolone <sup>c</sup> alone, an advanced macrolide <sup>d</sup> plus high-dose amoxicillin, <sup>e</sup> or an advanced macrolide plus high-dose amoxicillin-clavulanate <sup>f</sup>
Comorbidities (COPD, diabetes, renal or congestive heart failure, or malignancy)	
No recent antibiotic therapy	An advanced macrolide <sup>d</sup> or a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone <sup>c</sup> alone or an advanced macrolide plus a $\beta$ -lactam <sup>g</sup>
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial superinfection	A $\beta$ -lactam <sup>g</sup> or a respiratory fluoroquinolone
Inpatient	
Medical ward	
No recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a $\beta$ -lactam <sup>h</sup>
Recent antibiotic therapy	An advanced macrolide plus a $\beta$ -lactam or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy)
ICU	
<i>Pseudomonas</i> infection is not an issue	A $\beta$ -lactam <sup>h</sup> plus either an advanced macrolide or a respiratory fluoroquinolone
<i>Pseudomonas</i> infection is not an issue but patient has a $\beta$ -lactam allergy	A respiratory fluoroquinolone, with or without clindamycin
<i>Pseudomonas</i> infection is an issue <sup>i</sup>	Either (1) an antipseudomonal agent <sup>l</sup> plus ciprofloxacin, or (2) an antipseudomonal agent plus an aminoglycoside <sup>k</sup> plus a respiratory fluoroquinolone or a macrolide
<i>Pseudomonas</i> infection is an issue but the patient has a $\beta$ -lactam allergy	Either (1) aztreonam plus levofloxacin, <sup>l</sup> or (2) aztreonam plus moxifloxacin or gatifloxacin, with or without an aminoglycoside
Nursing home	
Receiving treatment in nursing home	A respiratory fluoroquinolone alone or amoxicillin-clavulanate plus an advanced macrolide
Hospitalized	Same as for medical ward and ICU

**NOTE.** COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

<sup>a</sup> Erythromycin, azithromycin, or clarithromycin.

<sup>b</sup> That is, the patient was given a course of antibiotic(s) for treatment of any infection within the past 3 months, excluding the current episode of infection. Such treatment is a risk factor for drug-resistant *Streptococcus pneumoniae* and possibly for infection with gram-negative bacilli. Depending on the class of antibiotics recently given, one or other of the suggested options may be selected. Recent use of a fluoroquinolone should dictate selection of a nonfluoroquinolone regimen, and vice versa.

<sup>c</sup> Moxifloxacin, gatifloxacin, levofloxacin, or gemifloxacin (oral gemifloxacin only, which was approved by the US Food and Drug Administration on 4 April 2003 and which is the only fluoroquinolone approved for multidrug-resistant *S. pneumoniae*; not yet marketed).

<sup>d</sup> Azithromycin or clarithromycin.

<sup>e</sup> Dosage, 1 g po t.i.d.

<sup>f</sup> Dosage, 2 g po b.i.d.

<sup>g</sup> High-dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime.

<sup>h</sup> Cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem; ertapenem was recently approved for such use (in once-daily parenteral treatment), but there is little experience thus far.

<sup>i</sup> The antipseudomonal agents chosen reflect this concern. Risk factors for *Pseudomonas* infection include severe structural lung disease (e.g., bronchiectasis), and recent antibiotic therapy or stay in hospital (especially in the ICU). For patients with CAP in the ICU, coverage for *S. pneumoniae* and *Legionella* species must always be assured. Piperacillin-tazobactam, imipenem, meropenem, and cefepime are excellent  $\beta$ -lactams and are adequate for most *S. pneumoniae* and *Haemophilus influenzae* infections. They may be preferred when there is concern for relatively unusual CAP pathogens, such as *Pseudomonas aeruginosa*, *Klebsiella* species, and other gram-negative bacteria.

<sup>j</sup> Piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime.

<sup>k</sup> Data suggest that elderly patients receiving aminoglycosides have worse outcomes [47].

<sup>l</sup> Dosage for hospitalized patients, 750 mg q.d.

perature, >37.8°C; pulse, >100 beats/min; respiratory rate, >24 breaths/min; systolic blood pressure, <90 mm Hg; blood oxygen saturation, <90%; and inability to maintain oral intake (B-I).

**Comment.** Selection of the initial site of treatment, whether home or hospital, continues to be one of the most

important clinical decisions made in the treatment of patients with CAP, often determining the selection and route of administration of antibiotic agents, intensity of medical observation, and use of medical resources. This decision is often made in the emergency department, the portal of entry for

**Table 2. Empiric antibacterial selection for community-acquired pneumonia (CAP): advantages and disadvantages.**

Patient group, drug(s)	Advantages	Disadvantages
Outpatients		
Macrolides (azithromycin, clarithromycin, and erythromycin)	<p>Active against most common pathogens, including atypical agents.</p> <p><i>S. pneumoniae</i> resistance in vitro may be deceptive, because the M phenotype may not be clinically relevant [137], and alveolar lining fluid or intracellular levels may be more important than serum levels used to determine in vitro activity [189, 190].</p> <p>Clinical trial data have shown consistently good results [191–194], including activity against strains resistant in vitro [195].</p> <p>Azithromycin and clarithromycin have the advantage of once-daily therapy and are well tolerated.</p>	<p>Macrolide resistance is reported for 20%–30% of <i>Streptococcus pneumoniae</i> [137–140, 146–148], and in vitro resistance has emerged during therapy [144].</p> <p>Breakthrough pneumococcal bacteria with macrolide-resistant strains appear to be more common than with <math>\beta</math>-lactams or fluoroquinolones [150, 151, 196, 197].</p> <p>Erythromycin is poorly tolerated and is less effective against <i>Haemophilus influenzae</i>.</p>
Amoxicillin	<p>Amoxicillin is the preferred drug for oral treatment of susceptible strains of <i>S. pneumoniae</i>.</p> <p>Active against 90%–95% of <i>S. pneumoniae</i> strains when used at a dosage of 3–4 g/day [138, 198, 199].</p> <p>Standard in many European CAP guidelines for empiric treatment of outpatients [200], as well as CDC guidelines [26].</p>	<p>Lacks activity against atypical agents and <math>\beta</math>-lactamase-producing bacteria.</p> <p>High dosages (3–4 g/day) required to achieve activity against &gt;90% of <i>S. pneumoniae</i> [138, 198].</p> <p>The number of recent publications documenting efficacy is modest.</p>
Amoxicillin-clavulanate	<p>Compared with amoxicillin, spectrum in vitro includes <math>\beta</math>-lactamase-producing bacteria, such as most <i>H. influenzae</i>, methicillin-susceptible <i>Staphylococcus aureus</i>, and anaerobes [201].</p> <p>Clinical trials reported to document efficacy [202, 203].</p> <p>Standard in many European CAP guidelines for empiric treatment of outpatients [200], as well as CDC guidelines [26].</p>	<p>Lacks activity against atypical agents.</p> <p>More expensive and more gastrointestinal intolerance, compared with amoxicillin.</p> <p>The number of recent publications documenting efficacy is relatively modest.</p>
Oral cephalosporins (cefepodoxime, cefprozil and cefuroxime axetil)	<p>Active against 75%–85% of <i>S. pneumoniae</i> and virtually all <i>H. influenzae</i> [198, 204].</p> <p>Clinical trial data support efficacy in outpatients with CAP [203, 205].</p>	<p>All cephalosporins (and all <math>\beta</math>-lactams) are inactive against atypical agents.</p> <p>Amoxicillin is more predictably active against <i>S. pneumoniae</i> [198, 204, 205] (cefprozil and cefpodoxime are more active than cefuroxime).</p>
Doxycycline	<p>Active against 90%–95% of strains of <i>S. pneumoniae</i> [138]; also active against <i>H. influenzae</i>, atypical agents, and category A bacterial agents of bioterrorism [91, 92, 97, 103].</p> <p>At least 1 recent report showing good outcomes in hospitalized patients with CAP [206].</p> <p>Generally well tolerated and inexpensive.</p>	<p>Very limited recent published clinical data on CAP, and few clinicians use it [207].</p>
Fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin, and gemifloxacin)	<p>Active against &gt;98% of <i>S. pneumoniae</i> strains in United States, including penicillin-resistant strains [138, 140, 178, 208–211].</p> <p>Substantial comparative clinical trial data to confirm equivalence or superiority to alternative commonly used regimens [212–214], and a meta-analysis of trials showed significantly better outcomes than for <math>\beta</math>-lactams or macrolides [215].</p> <p>Active against <i>H. influenzae</i>, atypical agents, methicillin-susceptible <i>S. aureus</i>, and category A bacterial agents of bioterrorism [91, 92, 95, 97, 102, 106].</p>	<p>Concern for abuse with risk of increasing resistance by <i>S. pneumoniae</i> [165–168, 170–179]; this includes clinical failures attributed to emergence of resistance during therapy [216, 217] and selection of resistant strains such as 23F that may be prevalent in selected areas [218–220] and are usually resistant to macrolides and <math>\beta</math>-lactams as well [220].</p> <p>Expensive compared with some alternatives, such as doxycycline or erythromycin.</p>

(continued)

**Table 2. (Continued.)**

Patient group, drug(s)	Advantages	Disadvantages
Clindamycin	Regimens have advantage of once-daily administration and are well tolerated. Active against 90% of <i>S. pneumoniae</i> [138, 204].  Good in vitro activity and established efficacy in anaerobic bacterial infections [221, 222] and favored for toxic shock associated with pneumonia due to group A streptococci [223].	Not active against <i>H. influenzae</i> or atypical agents.  Limited published data on use for CAP.  High rates of diarrhea and <i>Clostridium difficile</i> -associated colitis.
Macrolide plus amoxicillin-clavulanate	Macrolide adds activity against atypical agents to spectrum of amoxicillin-clavulanate (described above).	Limited published data for outpatients.  Requires high dosages of amoxicillin-clavulanate (4 g/day). High rates of gastrointestinal intolerance anticipated. Unlikely to be effective against fluoroquinolone-resistant strains of <i>S. pneumoniae</i> [178, 219]. Escalating rates of resistance to both macrolides and penicillin by <i>S. pneumoniae</i> [224].
Hospitalized patients		
Fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin, and gemifloxacin)	Broad spectrum of activity against likely agents of CAP (summarized above).  Extensive published data, including retrospective analysis of hospitalized Medicare patients, showing significantly lower mortality than for macrolides alone or cephalosporins alone [47].  Efficacy in serious infections, including bacteremic pneumococcal pneumonia, established [150, 215].  Available in oral and parenteral formulations (except for gemifloxacin, for which only oral formulations are available), facilitating intravenous-to-oral switch.	Concern for increasing resistance, as summarized above [165–168, 170–179, 218].  Clinical failures attributed to resistant strains reported [216, 217].
Macrolides (azithromycin and erythromycin)	In vitro spectrum summarized above.  Extensive clinical trial data and clinical experience to document efficacy for CAP [191–194].  Azithromycin is included as an appropriate choice in many current CAP guidelines [200], including the guidelines of the American Thoracic Society [225].	Retrospective analysis of 14,000 hospitalized Medicare recipients for 1998–1999 shows mortality rate for macrolide alone was significantly greater than that for cephalosporin plus a macrolide or a fluoroquinolone alone [47].  Increasing in vitro resistance by <i>S. pneumoniae</i> , as summarized above [137–140, 146–148]. Breakthrough bacteremia due to resistant strains of <i>S. pneumoniae</i> is unusual but appears to be more common with macrolides than with other agents [150, 151, 196, 197].
Cephalosporins (ceftriaxone and cefotaxime)	Considered the parenteral drugs of choice (as well as penicillin G) for CAP caused by susceptible strains of <i>S. pneumoniae</i> .  Active in vitro against 90%–95% of <i>S. pneumoniae</i> [140, 148]; also active against <i>H. influenzae</i> and methicillin-susceptible <i>S. aureus</i> .	Not active against atypical agents or category A agents of bioterrorism.  Retrospective analysis of 14,000 Medicare patients showed higher mortality for cephalosporins alone than for cephalosporins plus macrolides or fluoroquinolones alone [47]. Increasing resistance by <i>S. pneumoniae</i> [224].
Fluoroquinolone plus cephalosporin	May increase antimicrobial activity against <i>S. pneumoniae</i> .	No documented benefit, compared with fluoroquinolone alone.
Macrolide plus cephalosporin	Cephalosporin provides better in vitro activity against <i>S. pneumoniae</i> , and macrolide adds activity against atypical agents.	Data suggesting that the macrolide-cephalosporin combination is superior to monotherapy in pneumococcal bacteremia are uncontrolled [48–50] and inconsistent (P. Houck, personal communication).

(continued)

**Table 2. (Continued.)**

Patient group, drug(s)	Advantages	Disadvantages
Penicillin G	Retrospective analyses show reduced mortality for this combination, compared with single-agent therapy, in patients with pneumococcal bacteremia [48–50] and for empiric treatment of pneumonia [47]. Preferred agent (along with ceftriaxone, cefotaxime, and amoxicillin) for proven penicillin-susceptible strains of <i>S. pneumoniae</i> [138, 200, 226]. Published experience to document clinical efficacy is extensive.	Limited spectrum of activity against common pulmonary pathogens other than <i>S. pneumoniae</i> .
New agents		
Telithromycin	Active in vitro against most <i>S. pneumoniae</i> , including macrolide-resistant strains; also active against <i>H. influenzae</i> and atypical agents [156–159, 227, 228]. Favorable pharmacokinetics [160, 161].	Available only in oral formulation. Clinical trial data are considered preliminary.
Gemifloxacin	Clinical trials in CAP show equivalence to high-dose amoxicillin, macrolides, and trovafloxacin [160–164], including CAP caused by $\beta$ -lactam-resistant strains of <i>S. pneumoniae</i> [228]. Most active of the “respiratory fluoroquinolone” against <i>S. pneumoniae</i> in vitro.	High rate of rash, especially in women aged <40 years and with use for >10 days. Available only in oral formulation.
Ertapenem	Clinical efficacy for empiric treatment of CAP comparable to ceftriaxone [232]. Once-daily parenteral dosing.	Parenteral formulation only. Inactive against atypical agents and less active than imipenem against <i>Pseudomonas aeruginosa</i> .
Linezolid	In vitro activity against <i>S. pneumoniae</i> is similar to ceftriaxone and cefotaxime [138]. Active in vitro against most gram-positive bacteria, including multidrug resistant <i>S. pneumoniae</i> and <i>S. aureus</i> [233]. Efficacy comparable to ceftriaxone for treatment of pneumococcal pneumonia [234, 235]. Oral and parenteral formulations.	Lacks established activity against atypical agents. Alternative antimicrobials have more established role in CAP. Concern about abuse, expense, drug-drug interaction, and toxicity [234].

**NOTE.** Durations of therapy are as follows: *S. pneumoniae*, until afebrile for 72 h (C-III); *M. pneumoniae*, duration of therapy for newer agents is not well established; *C. pneumoniae*, numerous clinical trials indicate good clinical response with 7–14 days of treatment (A-I); *Legionella*, 10–21 days (B-II); pathogens that potentially cause pulmonary necrosis (*S. aureus*, *P. aeruginosa*, *Klebsiella* species, or anaerobes),  $\geq 2$  weeks (B-II). CDC, Centers for Disease Control and Prevention.

75% of the 1 million annual pneumonia admissions in the United States.

Two recent articles suggest that the initial site of treatment decision be selected using a systematic 3-step process [3, 4]. Step 1 involves assessment of any preexisting conditions that compromise the safety of home care, including severe hemodynamic instability, active coexisting conditions that require hospitalization, acute hypoxemia or chronic oxygen dependency, and inability to take oral medications. The second step involves calculation of the pneumonia PSI, with a recommendation for home care for patients in risk classes I, II, or III. A description of how the PSI is derived is shown in Appendix A. The third step involves clinical judgment regarding the overall health of the patient and the suitability for home care. Miti-

gating factors for step 3 include frail physical condition, severe social or psychiatric problems compromising home care (including a history of substance abuse), and an unstable living situation or homelessness. Clinical judgment should supercede decisions made on the basis of PSI alone.

At the present time, 3 North American medical practice guidelines advocate use of the PSI as an objective measure of risk stratification to help determine the initial site of treatment for CAP [2, 5, 6]. Preliminary results from the Emergency Department Triage of Community-Acquired Pneumonia Study indicate that implementation of the PSI significantly increases the proportion of low-risk patients with pneumonia managed in the emergency department who are treated as outpatients without compromising outcomes, as measured by short-term

mortality or subsequent hospitalization [7]. In this randomized, controlled study that involved 32 hospital emergency departments and >3200 patients with CAP, implementation of the PSI with high- and moderate-intensity implementation strategies resulted in a statistically significantly greater proportion of low-risk patients being treated in the outpatient setting.

The committee continues to support use of the PSI as a means of risk stratification and urges that this process be combined with careful assessment of the patient and use of clinical judgment.

Although discharge criteria are not part of the initial site of treatment decision, there are data showing that appropriate use of recommended criteria can reduce mortality [8]. The recommended discharge criteria are that, during the 24 h before discharge to the home, the patient should have no more than 1 of the following characteristics (unless this represents the baseline status): temperature, >37.8°C; pulse, >100 beats/min; respiratory rate, >24 breaths/min; systolic blood pressure, <90 mm Hg; blood oxygen saturation, <90%; and inability to maintain oral intake.

## UPDATE ON DIAGNOSIS OF *CHLAMYDOPHILIA PNEUMONIAE*

**Recommendation.** Acceptable diagnostic methods for *C. pneumoniae* pulmonary infections are the demonstration of a 4-fold increase in IgG titer or a single IgM titer of  $\geq 1:16$  using a microimmunofluorescence (MIF) serologic test, isolation in tissue culture, or a PCR assay of respiratory secretions using reagents that satisfy optimal criteria for validation (B-II).

**Comment.** *C. pneumoniae* is an important respiratory pathogen, but it has also been associated with chronic conditions, such as atherosclerotic cardiovascular disease. Unfortunately, a “gold standard” for the diagnosis of infection with this organism is lacking; this accounts for the wide variation in the reported incidence and prevalence rates for *C. pneumoniae*.

To get a better idea of the significance of this pathogen, it is imperative that there is agreement with regard to standard diagnostic tests. The IDSA CAP Committee supports recommendations of the Centers for Disease Control and Prevention (CDC) in the United States and the Laboratory Center for Disease Control in Canada [9], which are that potential methods include serologic testing, culture, PCR, and tissue diagnostics or immunohistochemistry (IHC).

For the short-term treatment of patients with CAP, either the detection of IgM by MIF testing or the identification of the organism by culture or PCR of respiratory secretions is most likely to be useful. Four-fold increases in IgG antibody titers, determined by MIF testing, and tissue diagnostic tests may also provide an accurate diagnosis, but they are likely to be more useful in research or epidemiological settings.

For serologic testing, only MIF is acceptable. To document acute infection using serologic methods, a 4-fold increase in the IgG titer or an IgM titer of  $\geq 1:16$  must be demonstrated. Use of a single elevated IgG titer is discouraged. Because the reading may vary by 2- to 4-fold from day to day, acute- and convalescent-phase serum samples should be studied in the same run on the same ELISA plate.

Culture methods are important to document the viability of the organism and to provide samples for susceptibility testing. Documentation of a positive culture result requires either propagation of the isolate by means of subsequent passage or confirmation with the use of PCR. There are currently 18 PCR assays available for detection of *C. pneumoniae* in clinical specimens. Each has its own advantages and disadvantages, but only 4 satisfy the optimal criteria for a validated assay. There is no commercial assay that has been cleared by the US Food and Drug Administration (FDA), and, therefore, PCR is essentially not available except in research laboratories.

A variety of methods have been used to detect *C. pneumoniae* in tissue specimens, including immunofluorescence, in situ hybridization, and IHC. The main advantage of tissue diagnostic methods is that they allow localization of the pathogen to specific areas and cells within the tissue.

## PNEUMOCOCCAL URINARY ANTIGEN TEST: NEW ADDITION

**Recommendation.** The pneumococcal urinary antigen assay is an acceptable test to augment the standard diagnostic methods of blood culture and sputum Gram stain and culture, with the potential advantage of rapid results similar to those for sputum Gram stain (B-II).

**Comment.** An assay that has recently been cleared by the FDA for pneumococcal antigen detection using a urine sample is now available as a method for the diagnosis of pneumococcal pneumonia in adults. The assay is an immunochromatographic membrane test (ICT) used to detect pneumococcal cell-wall polysaccharide, which is common to all serotypes. Its main advantages are its rapidity (~15 min using unconcentrated urine samples) and simplicity.

When results of the ICT are compared with the results attained using conventional diagnostic methods for pneumococcal pneumonia in adults, the sensitivity ranges from 50% to 80%, and the specificity is ~90% depending on the standard of comparison [10–15]. The sensitivity in defining bacteremic pneumococcal disease in adults has been reported to be 70%–90%. In one of the largest published studies to date, Gutierrez et al. [15] performed ICT on concentrated urine samples obtained from 452 adults with CAP. Pneumococcal antigen was detected in 19 (70%) of 27 patients with proven pneumococcal pneumonia. Importantly, of the 269 patients who had pneu-

**Table 3. Susceptibility of *Streptococcus pneumoniae* isolates to commonly used antimicrobial agents, stratified by susceptibility to penicillin, according to 2001 data from the Center for Disease Control's Active Bacterial Core Surveillance ( $n = 3418$ ) and 2002 NCCLS susceptibility definitions.**

Agent	Percentage of pneumococcal isolates that are nonsusceptible (i.e., intermediate or resistant) to the agent, by susceptibility to penicillin			
	Susceptible <sup>a</sup> ( $n = 2555$ )	Intermediate ( $n = 331$ )	Resistant ( $n = 532$ )	All ( $n = 3418$ )
Amoxicillin <sup>b</sup>	0	0.3	47.7	7.5
Tetracycline	2.2	22.1	23.9	7.5
Erythromycin	4.9	44.7	73.7	19.5
Clindamycin	1.0	12.7	13.0	4.0
Trimethoprim-sulfamethoxazole	11.7	60.7	96.4	29.6
Cefuroxime sodium (parenteral)	0.4	48.9	100	19.5
Cefuroxime axetil (oral)	0.1	39.6	100	20.6
Cefotaxime (nonmeningitis) <sup>c</sup>	0	1.8	35.0	5.7
Levofloxacin	0.5	1.2	1.7	0.7
Meropenem	0	19.0	96.8	16.9
Vancomycin	0	0	0	0

<sup>a</sup> NCCLS defines penicillin-susceptible, penicillin-intermediate, and penicillin-resistant pneumococci as having MICs of  $\leq 0.1$   $\mu\text{g/mL}$ ,  $0.01$ – $1.0$   $\mu\text{g/mL}$ , and  $\geq 2$   $\mu\text{g/mL}$ , respectively.

<sup>b</sup> High-dose amoxicillin (1 g t.i.d., or 2 g b.i.d. for amoxicillin-clavulanate) should be effective against  $\geq 70\%$  of penicillin-resistant pneumococcal isolates.

<sup>c</sup> In 2002, NCCLS established different susceptibility criteria for certain  $\beta$ -lactam agents on the basis of whether they were to be used for treatment of meningitis versus other (nonmeningitis) syndromes. The data in this table for cefotaxime were based on the NCCLS definitions for nonmeningitis syndromes.

monia with no pathogen identified, antigen was detected in 69 (26%), suggesting that a significant percentage of cases that are not diagnosed by standard microbiological tests can be identified with ICT. However, 16 (10%) of 156 samples obtained from patients with pneumonia due to other causes were positive, indicating problems with specificity.

Studies involving children have documented the lack of specificity of ICT [16–18]. Dowell et al. [18] reported that the test result was no more likely to be positive among 88 children with pneumonia than among 198 control subjects, and it was significantly more likely to be positive among those who were nasopharyngeal carriers of pneumococci. Thus, this test is not likely to be useful for distinguishing children with pneumococcal pneumonia from those who are merely colonized, and although the specificity appears to be higher for adults, the colonization status has not been systematically evaluated. Other possible limitations include the possibility of a positive test result for patients with bacteremia due to *Streptococcus oralis* or *Streptococcus mitis*, because these pathogens contain a cell-wall polysaccharide antigen similar to that of *Streptococcus pneumoniae*, and the potential for variable interpretation of a weakly positive test result [19].

For adults, the ICT should increase the yield of identified pathogens for CAP, and a positive result of this test may allow administration of more-focused therapy directed against *S.*

*pneumoniae*. This test may be particularly helpful for patients receiving antimicrobial therapy at the time of evaluation. However, it should not be considered a substitute for culture, because susceptibility testing will be required to detect specific antimicrobial activity. Additional studies are required to establish the full clinical impact of ICT and to determine its effectiveness in clinical practice. Clinicians should be aware that false-positive results may result from detection of pneumococcal colonization in a patient with pneumonia caused by another agent.

On the basis of the present information, the panel considers this a possibly useful addition to blood culture and other standard tests for identifying pneumococcal pneumonia in adults. The committee believes that, at times, Gram staining of expectorated sputum may yield equally good results in the same time frame.

### NEW BREAKPOINTS FOR CEFOTAXIME AND CEFTRIAZONE FOR *S. PNEUMONIAE*: NEW ADDITION

**Recommendation 1.** Susceptibility of *S. pneumoniae* isolates to cefotaxime and ceftriazone in nonmeningeal infections should be defined as an MIC of  $\leq 1$   $\mu\text{g/mL}$ , intermediate should

**Table 4. Recommendations for management of community-acquired pneumonia (CAP) in immunocompetent adults: summary of prior Infectious Diseases Society of America (IDSA) recommendations of 2000 and updated and new recommendations for 2003 (in bold).**

Site of treatment decision

**The initial site of treatment should be based on a 3-step process: (1) assessment of preexisting conditions that compromise safety of home care; (2) calculation of the pneumonia PORT (Pneumonia Outcome Research Team) Severity Index with recommendation for home care for risk classes I, II, and III; and (3) clinical judgment (A-II).**

Hospitalized patients treated with intravenous antibiotics may be changed to oral antibiotics when the patient is clinically improving, is able to ingest drugs, is hemodynamically stable, and has a functioning gastrointestinal tract (A-I).

**Discharge criteria: during the 24 h prior to discharge to home, the patient should have no more than 1 of the following characteristics (unless this represents the baseline status): temperature, >37.8°C; pulse, >100 beats/min; respiratory rate, >24 breaths/min; systolic blood pressure, <90 mm Hg; blood oxygen saturation, <90%, and inability to maintain oral intake (B-I).**

Laboratory tests

Chest radiography: All patients with suspected pneumonia should have a chest radiograph (A-II).

General assessment: Patients hospitalized for pneumonia should have a complete blood count; serum blood urea nitrogen, glucose, electrolytes, and liver function testing; and assessment of oxygen saturation (B-II). Persons aged 15–54 years should undergo HIV testing with informed consent (B-II).

Tests for an etiologic agent in ambulatory patients: No tests for an etiologic agent are considered standard for patients who are not hospitalized for pneumonia, but an air-dried slide of a pretreatment deep-cough sputum sample may subsequently prove useful (C-III).

Tests for etiologic agent in hospitalized patients: Patients hospitalized for pneumonia should have 2 pretreatment blood cultures (A-II)<sup>a</sup> and expectorated sputum Gram stain and culture (B-II). The expectorated sputum specimen should be a deep-cough specimen obtained before antibiotic treatment that is rapidly transported and processed within a few hours of collection (B-II). Cytologic criteria should be used as a contingency for sputum culture, except with culture for *Mycobacteria* and *Legionella* species (A-I). Transtracheal aspiration, transthoracic aspiration, and bronchoscopy should be reserved for selected patients and done by physicians with appropriate expertise (B-III). Testing of induced sputum has established merit only for detection of *Mycobacterium tuberculosis* and *Pneumocystis carinii* (A-I).

Recommended agent-specific tests:

***Legionella*: Testing for *Legionella* species is appropriate for any patient hospitalized with enigmatic pneumonia (C-II). This test is recommended for patients with enigmatic pneumonia sufficiently severe to require care in the intensive care unit, in the presence of an epidemic, or failure to respond to a  $\beta$ -lactam (A-III).**

***Chlamydia pneumoniae*: Acceptable diagnostic methods for *C. pneumoniae* pulmonary infections are the demonstration of a 4-fold increase in IgG titer or single IgM titer of  $\geq 1:16$  using a microimmunofluorescence serologic test or isolation in tissue culture or a PCR assay of respiratory secretions using reagents that satisfy optimal criteria for validation (B-III).**

***Streptococcus pneumoniae*: Standard methods are blood culture and sputum for Gram stain and culture (B-II). The pneumococcal urinary antigen assay is an acceptable test to augment the standard diagnostic methods of blood culture and sputum Gram stain and culture, with the potential advantage of rapid results similar to those for sputum Gram stain (B-II).**

Influenza virus: A rapid antigen detection assay for influenza virus is recommended for rapid detection of this pathogen for epidemiologic purposes and/or treatment (CII). **Tests that distinguish between influenza A and B are generally preferred (CIII).**

**Respiratory syncytial virus: Antigen detection tests are readily available but are insensitive for detecting infections in adults and are not generally recommended for adults (C-III).**

**Means of diagnosis for category A agents of bioterrorism: for inhalation anthrax, blood culture (A-I) and chest CT scan (A-I); for pneumonic plague, blood culture and Gram stain and culture of sputum samples (A-I); and for tularemic pneumonia, culture of blood and sputum or pharynx in a biocontainment level 3 laboratory (A-I).**

**SARS: Diagnostic criteria include clinical and epidemiologic features and may include diagnostic studies for the coronavirus (A-I). Recommended virologic studies for laboratory confirmation are (1) culture for SARS coronavirus, (2) detection of antibody during the acute phase of illness or any time after onset, or (3) detection of SARS coronavirus RNA confirmed by second PCR assay by using a second aliquot of the specimen or a different set of primers. (The panel considers it premature to rate the use of virologic tests.)**

Interpretation of cultures

Etiologic diagnosis is established with recovery of a probable etiologic agent from an uncontaminated specimen (blood, pleural fluid, transtracheal aspirate, or transthoracic aspirate) or with recovery from respiratory secretions of a likely pathogen that does not colonize the upper airways (e.g., *M. tuberculosis*, *Legionella* species, influenza virus, respiratory syncytial virus, parainfluenza virus, adenovirus, **SARS coronavirus**, *P. carinii*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatidis*) (A-I).

Etiologic diagnosis is probable with a compatible clinical syndrome combined with detection by stain or culture of a likely pulmonary pathogen in respiratory secretions (expectorated sputum or bronchoscopic secretions); with culture, there should be significant growth with quantitative culture or moderate or heavy growth with semiquantitative culture (B-II).

Serologic tests are usually not helpful in the initial evaluation (C-III) but may be useful for epidemiologic surveillance.

DNA probes and nucleic acid amplification assays are under development especially for *C. pneumoniae*, *M. pneumoniae*, and *Legionella* species. These tests are not currently recommended because reagents have not had FDA clearance; availability is largely restricted to research laboratories, and studies show results that are variable (C-III).

(continued)



Table 4. (Continued.)

Antimicrobial treatment

Pathogen-specific therapy

**S. pneumoniae:** Susceptibility of *S. pneumoniae* isolates to cefotaxime and ceftriaxone in nonmeningeal infections should be defined as an MIC of  $\leq 1 \mu\text{g/mL}$ , intermediate should be defined as an MIC of  $2 \mu\text{g/mL}$ , and resistant should be defined as an MIC of  $\geq 4 \mu\text{g/mL}$  (A-III). Cefotaxime or ceftriaxone are the preferred parenteral agents for treatment of pneumococcal pneumonia without meningitis for strains with reduced susceptibility to penicillin but with MICs of cefotaxime or ceftriaxone of  $< 2 \mu\text{g/mL}$  (B-III). Amoxicillin is the preferred antibiotic for oral treatment of pneumococcal pneumonia involving susceptible strains (B-II).

Initial empiric therapy prior to availability of culture data for a patient ill enough to require admission to a hospital ward can be with a  $\beta$ -lactam plus macrolide combination or a respiratory fluoroquinolone alone (A-I). If sufficiently ill to need ICU management and if *Pseudomonas* infection is not a concern, a combination of a  $\beta$ -lactam plus either a macrolide or a respiratory fluoroquinolone should be used (B-III). Once culture data are available and it is known that the patient has pneumococcal pneumonia with bacteremia without evidence to support infection with a copathogen, treatment will depend upon in vitro susceptibility results. If the isolate is penicillin susceptible, a  $\beta$ -lactam (penicillin G or amoxicillin) alone may be used (B-II). If the isolate is penicillin resistant, cefotaxime, ceftriaxone, or a respiratory fluoroquinolone or other agent indicated by in vitro testing may be used (A-III).

**Legionella:** Treatment for legionnaires' disease is appropriate when there is epidemiologic evidence of this disease, despite negative diagnostic test results (B-III). The preferred treatment for legionnaires' disease for hospitalized patients is azithromycin or a fluoroquinolone (moxifloxacin, gatifloxacin, and levofloxacin; gemifloxacin is only available as an oral formulation) (B-II). For patients who do not require hospitalization, acceptable antibiotics include erythromycin, doxycycline, azithromycin, clarithromycin, or a fluoroquinolone (A-II). Treatment should be initiated as rapidly as is feasible (A-II).

**Influenza:** Early treatment (within 48 h after onset of symptoms) is effective in the treatment of influenza A using amantadine, rimantadine, oseltamivir, or zanamivir and is effective in the treatment influenza B using oseltamivir and zanamivir (B-I). Use of these drugs is not recommended for uncomplicated influenza with a duration of symptoms of  $> 48$  h (D-I), but these drugs may be used to reduce viral shedding in hospitalized patients or for influenza pneumonia (C-III).

**Herpes viruses:** Pneumonia caused by varicella zoster virus or herpes simplex virus should be treated with parenteral acyclovir (A-II).

**Other viruses:** There is no antiviral agent with established efficacy for the treatment of adults with pulmonary infections involving parainfluenza virus, respiratory syncytial virus, adenovirus, metapneumovirus, the SARS agent, or Hantavirus (D-I).

Empiric Therapy

See table 1 for recommendations and table 2 for details and rationale.

Empiric treatment of suspected bacterial superinfection of influenza should provide activity against *S. pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* with antibiotics such as amoxicillin-clavulanate, cefpodoxime, cefprozil, cefuroxime, or a respiratory fluoroquinolone (B-III).

Fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) are recommended for initial empiric therapy of selected outpatients with CAP (A-I). Other options (macrolides and doxycycline) are generally preferred for uncomplicated infections in outpatients (A-I). Fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) may be used as monotherapy for patients with CAP who are admitted to a hospital ward (A-I). With the exception of gemifloxacin (no intravenous formulation), they may be used as part of a combination for patients with CAP admitted to an ICU (C-III).

A macrolide is recommended as monotherapy for selected outpatients, such as those who were previously well and not recently treated with antibiotics (A-I). A macrolide plus a  $\beta$ -lactam is recommended for initial empiric treatment of outpatients in whom resistance is an issue and for hospitalized patients (A-I).

Telithromycin may have a role as an alternative to macrolides for treatment of patients with CAP. At this time, however, it is not yet FDA approved.

Special populations and circumstances

**SARS:** Health care workers must be vigilant in recognizing SARS because of important epidemiologic implications, which include the potential for rapid spread to close contacts, including health care workers and household contacts (A-III). The major therapeutic intervention is supportive care (B-III). Preventive efforts include proper precautions in patients with suspected or established SARS. These include standard precautions (hand hygiene), contact precautions (use of gowns, goggles, and gloves), and airborne precautions (use of negative-pressure rooms and fit-tested N95 respirators) (A-I).

**Elderly patients:** Antimicrobial selection for elderly patients with CAP is the same as for all adults with CAP (B-III).

**Bioterrorism:** Physicians should know the clues to bioterrorism and the appropriate mechanisms to alert public health officials in cases of suspected bioterrorism (A-III). Recommended diagnostic tests and management guidelines are those of the Johns Hopkins Center for Biodefense Strategies and of the CDC, as modified for the specific outbreak (A-I).

(continued)

Table 4. (Continued.)

**Performance indicators**

Blood cultures prior to antibiotic therapy in patients hospitalized for pneumonia (B-III).

**Antibiotic therapy should be initiated within 4 h after registration for hospitalized patients with CAP (B-III).**

**Smoking cessation should be a goal for persons hospitalized with CAP who smoke (B-II).**

Legionella tests (culture and/or urinary antigen assay) for 50% of patients who are hospitalized in the ICU for severe enigmatic pneumonia (A-III).

Assessment of oxygenation by arterial blood-gas testing or pulse oximetry within 8 h after admission (A-III).

Demonstration of an infiltrate by chest radiograph or other imaging techniques in all patients who have an ICD-9 code diagnosis of CAP and who do not have AIDS or neutropenia (A-I).

**Prevention of CAP**

**All persons >50 years, others at risk for influenza complications, and household contacts of high-risk persons should receive inactivated influenza vaccine, as recommended by the ACIP (A-I). The injected inactivated vaccine is the preferred formulation for most persons at risk of complications associated with influenza, for household contacts of high-risk persons, and for health care workers (A-1). The intranasally administered live, attenuated vaccine (FluMist; Aventis) is an alternative vaccine formulation for some persons aged 5–49 years without chronic underlying diseases, including immunodeficiency, asthma, and chronic medical conditions (C-I). Influenza vaccine should be offered to persons at hospital discharge or during outpatient treatment during the fall and winter (C-III). Health care workers in inpatient and outpatient settings and long-term care facilities should receive annual influenza immunization (A-I).**

**Pneumococcal polysaccharide vaccine (Pneumovax; MedImmune [marketed by Wyeth in the United States]) is recommended for use, according to current ACIP guidelines, including use for persons aged >65 years and for those with selected high-risk concurrent diseases (B-II). Vaccination may be done either at hospital discharge or during outpatient treatment (C-III).**

**NOTE.** Prior IDSA recommendations from 2000 appeared in [2]. The IDSA–United States Public Health Service grading system for rating recommendations in clinical guidelines is shown in table 5. ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; FDA, US Food and Drug Administration; ICD-9, *International Classification of Diseases, Ninth Revision*; ICU, intensive care unit; SARS, severe acute respiratory syndrome.

<sup>a</sup> Represents a change in rating.

be defined as an MIC of 2 µg/mL, and resistant should be defined as an MIC of ≥4 µg/mL (A-III).

**Recommendation 2.** Cefotaxime or ceftriaxone are the preferred parenteral agents for treatment of pneumococcal pneumonia without meningitis for strains with reduced susceptibility to penicillin but with MICs of cefotaxime or ceftriaxone of <2 µg/mL (B-III).

**Recommendation 3.** Amoxicillin is the preferred antibiotic for oral treatment of pneumococcal pneumonia involving susceptible strains (B-II).

**Comment.** As of January 2002, the NCCLS increased the MIC breakpoints for cefotaxime and ceftriaxone. The new breakpoints apply to treatment of nonmeningeal infections caused by *S. pneumoniae* and state that isolates with MICs of ≤1 µg/mL are now considered to be susceptible, those with MICs of 2 µg/mL are intermediate, and those with MICs of ≥4 µg/mL are resistant. This is the first time that the NCCLS has provided different interpretive standards for isolates recovered from CSF and non-CSF isolates and should permit more cases of pneumococcal pneumonia to be treated with these agents.

Historically, MIC interpretive standards for pneumococci were derived largely from considerations for treating meningitis (table 3) [20]. Because the level of antibiotic in CSF is only a fraction of that in serum, to be considered susceptible, an or-

ganism must have a much lower MIC. The new breakpoints acknowledge that nonmeningeal infections caused by strains formerly considered to be intermediately susceptible and even some that were regarded as resistant can be treated successfully with the usual doses of β-lactam drugs [21–26]. Cefotaxime or ceftriaxone are the preferred agents for pneumococcal pneumonia involving the 95% of strains with an MIC of <2 µg/mL. The same could be said for use of amoxicillin for outpatients.

The IDSA committee endorses these changes and encourages clinicians to apply the new interpretive breakpoints as appropriate for the clinical setting. Similar considerations should be applied in the future to breakpoints for penicillin and other effective β-lactam antibiotics.

**SPECIAL CONSIDERATIONS: SEVERE ACUTE RESPIRATORY SYNDROME (SARS)—NEW ADDITION**

**Recommendation 1.** Health care workers must be vigilant in recognizing SARS because of important epidemiologic implications, which include the potential for rapid spread to close contacts, including health care workers and household contacts (A-III).

**Recommendation 2.** Diagnostic criteria include clinical and epidemiologic features and may include diagnostic studies

**Table 5. Infectious Diseases Society of America–United States Public Health Service grading system for rating recommendations in clinical guidelines.**

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from $\geq 1$ properly randomized, controlled trial
II	Evidence from $\geq 1$ well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from $>1$ center); from multiple time-series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

for the coronavirus (A-I). Recommended virologic studies for laboratory confirmation are (1) culture for SARS coronavirus, (2) detection of antibody during the acute phase of illness or any time after onset, or (3) detection of SARS coronavirus RNA confirmed by second PCR assay by using a second aliquot of the specimen or a different set of primers. (The panel considers it premature to rate the use of virologic tests.)

**Recommendation 3.** The major therapeutic intervention is supportive care (B-III).

**Recommendation 4.** Preventive efforts include proper precautions in patients with suspected or established SARS. These include standard precautions (hand hygiene), contact precautions (use of gowns, goggles, and gloves), and airborne precautions (use of negative-pressure rooms and fit-tested N95 respirators) (A-I).

**Comment.** “SARS” is the term used to describe outbreaks of pneumonia that were first recognized in Guangdong province in Southern China in late 2002 and that subsequently spread worldwide during March–June of 2003. As of July 2003,  $>8000$  probable cases have been reported from  $>28$  countries worldwide [27]. The heaviest concentrations of cases were identified in mainland China, Hong Kong, and Taiwan, with Singapore, Hanoi, and Toronto also experiencing severe outbreaks.

**Transmission and infection control.** A majority of early cases occurred among health care workers and family members reporting direct contact with patients who had SARS, and children were relatively spared. Subsequently, rapid international spread by infected airline passengers brought the disease to most continents. Most transmission has been from ill patients to their close contacts, with a relatively high degree of communicability. Direct contact with respiratory secretions and spread via respiratory droplets have been presumed to be the most important modes of transmission, and barrier nursing precautions (with hand washing) have been advocated as the

mainstay of control measures. However, the transmission to 13 persons staying in a Hong Kong hotel, to airline passengers, to  $>200$  residents of a single apartment block, and to a number of other persons without recognized close contact with a known case has raised the likelihood of more-remote transmission, whether by fomite or by airborne routes [28, 29].

Health care workers encountering a possible case of SARS should take meticulous safety precautions and should seek immediate advice from an expert in SARS infection control [30]. Protective measures should include standard precautions (hand washing and eye protection), contact precautions (use of gown and gloves), and airborne precautions (isolating the patient in a negative-pressure room and use of well-sealed N95 or greater respirators for all who enter the room). Additional precautions are advised for aerosol-generating procedures, which include many procedures routinely performed on patients undergoing ventilatory support, because of the evidence for transmission to health care workers in these settings, despite the routine use of airborne precautions [31]. This additional protection may include higher levels of respirators (N100 filters or powered air-purifying respirators), full-body isolation suits, and an outer disposable layer of equipment that can be discarded to reduce possible fomite spread [32]. Infection-control precautions should be continued for at least the duration of symptoms, and some precautions may be warranted for a longer period because of the possibility of more-prolonged viral shedding. Updated information should be sought from active reliable Web sites, such as those of the CDC (<http://www.cdc.gov>) and the World Health Organization (WHO; <http://www.who.int/csr/sars/en>).

**Pathogen.** Although a number of potential pathogens were initially identified in patients with SARS, including *C. pneumoniae*, influenza virus B, and human metapneumovirus, it is now clear that a novel coronavirus is the etiologic agent. Several

different laboratories identified an identical strain of this novel coronavirus in patients with SARS by culture of respiratory secretions and lung tissue specimens, electron microscopy, RT-PCR, and seroconversion [33, 34]. Inoculation of macaques with the novel coronavirus, but not with human metapneumovirus, produced a severe respiratory illness akin to SARS in humans [35]. The findings of preliminary reports of detection of the SARS coronavirus in civet cats and a number of other species are provocative, and a number of investigators are attempting to confirm the findings. The sequence of the viral genome has been completed, placing the agent in the coronavirus family and either as a distant member of 1 of the 3 previously described antigenic groups or in a fourth antigenic group [36].

*Diagnosis.* For surveillance purposes, using clinical and epidemiologic criteria, SARS has been categorized as suspect or probable cases, and the working definitions proposed by WHO have been modified for applicability to particular countries. To meet the CDC criteria for a suspected case, a patient must have fever (temperature,  $>38^{\circ}\text{C}$ ) and  $\geq 1$  clinical finding of moderate respiratory illness (e.g., cough, shortness of breath, and hypoxia), as well as epidemiologic criteria (travel within 10 days before onset of symptoms to an area with community transmission of SARS, or close contact within 10 days before onset of symptoms with a person known or suspected of having SARS infection) [37, 38]. A probable case is one that meets the definition for suspected cases and, in addition, has either radiographic evidence of pneumonia, respiratory distress syndrome, or autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause. Current versions of these definitions have changed as new information has become available; in particular, the updated definition of “areas with community transmission of SARS” should be obtained from the CDC or WHO Web sites [37, 39].

As of July 2003, the CDC case definition [37, 38] also incorporates laboratory criteria, although most cases reported in the United States and internationally have been defined using clinical and epidemiologic criteria alone [39]. Culture of the SARS coronavirus is considered solid evidence of infection. However, the various generations of RT-PCR assays have had problems, both with false-positive results and with inconsistent detection of viral genome in both the first days of illness and in the convalescent phase [40]. Because antibodies to SARS coronavirus have not been found in the general population, background SARS coronavirus antibodies do not appear to be a substantial concern [33, 34]. However, the current serologic assays (both ELISA and IFA formats) do not reliably detect antibodies until the titers increase substantially after the second week of illness [40]. According to the CDC, suspect or probable cases are considered to be laboratory confirmed if SARS coronavirus is isolated, if antibody to SARS coronavirus is detected, or if 2 different RT-PCR assays performed with different

specimen aliquots identify the coronavirus RNA. Because of the possibility of false-negative results of cultures and RT-PCR assays, only the absence of antibody in a serum specimen obtained  $>28$  days after symptom onset is considered by the CDC to be a negative laboratory test result for SARS coronavirus [37, 38].

These diagnostic tests are not yet available for routine use in clinical laboratories. Clinicians should conduct thorough diagnostic testing to rule out other etiologies in patients suspected of having SARS. Respiratory specimens and blood, serum, and stool samples should be saved for additional testing until a specific diagnosis has been made, and convalescent-phase serum samples should be obtained from patients whose cases meet the SARS case definition and forwarded to state and local health departments for testing at the CDC.

*Clinical features.* There is a characteristic clinical picture associated with the SARS in several well-described studies, although distinguishing SARS from other causes of pneumonia remains a challenge [39, 41, 42]. After an incubation period of  $\sim 2$ –10 days (median, 4 days), the most characteristic initial symptom is fever, with or without cough or dyspnea. Chills, myalgia, and progressive respiratory distress often accompany the persisting fever during the first week of illness, and mild gastrointestinal symptoms are present in some patients. The typical fever and the observation that pharyngitis, rhinorrhea, sneezing and conjunctivitis are unusual may help to distinguish patients with SARS from persons with more-common viral upper respiratory tract infections.

On initial presentation, there are typically few physical findings, with a normal chest examination or mild crackles without wheezing, and no rash. The chest radiograph may appear normal or show only mild abnormalities during the first few days, but progression to a bilateral lower lobe interstitial infiltrate is most characteristic. Other radiographic findings are also described, including lobar pneumonia, shifting atelectasis, and multiple focal areas of consolidation, particularly in the periphery of the lungs [43]. Routine laboratory findings include normal-to-low leukocyte counts, with absolute lymphopenia in approximately one-half the patients. Platelet counts are also normal to low. Mild to moderately elevated transaminase, lactate dehydrogenase, and creatinine phosphokinase levels are seen in 30%–70% of cases.

In most probable SARS cases, symptoms resolve spontaneously after the first week. In  $\geq 20\%$  of patients, symptoms progress over 2–3 weeks to the more-severe respiratory distress syndrome, and the patients require intensive care and ventilatory support. Approximately 10%–15% of cases have died of progressive respiratory failure. Mortality is strongly age-dependent, with mortality of  $>50\%$  for patients older than 65 years. Patients with underlying chronic heart or lung disease also appear to be at elevated risk for severe disease, although pre-

viously healthy younger adults have also died. The most prominent pathological findings in lung tissue samples on autopsy have been diffuse alveolar damage with hyaline membrane formation, interstitial mononuclear infiltration, and desquamation of pneumocytes; in some cases, tissues have shown intra-alveolar hemorrhage, necrotic debris within small airways, organizing pneumonia, or the presence of multinucleated giant cells without viral inclusions [33].

**Therapy.** A variety of treatments have been attempted, but there are no data from controlled studies, and the available anecdotal evidence is not persuasive that any of the treatment approaches thus far have demonstrated efficacy. Most patients have been treated throughout the illness with supplemental oxygen, intravenous fluids, and other supportive measures; broad-spectrum antibacterial agents have also been given, but these would not be expected to have any effect on the coronavirus infection itself. Early in vitro testing of ribavirin and other antiviral compounds against the novel coronavirus has not produced persuasive evidence of in vitro activity [44, 45]. Corticosteroids and a number of antiviral compounds, including the neuraminidase inhibitors and ribavirin, have been used empirically, but, in the future, use of antiviral compounds for SARS should be done within the context of a controlled clinical trial, because of the importance of identifying efficacious treatments and the lack of evidence of efficacy for any treatment to date.

SARS progressed rapidly from a localized outbreak in southern China to an epidemic with global reach. As of this writing, the epidemic has waned in most of the heavily affected areas, in association with vigorous public health interventions, including community mobilization and quarantine measures on a scale not seen during the past half-century or more. A second wave of infections in Toronto and isolated clusters of new cases elsewhere highlight the dangers of complacency as the acute phase of the epidemic passes. The impact of the epidemic on regional economies, international travel, and medical care is only beginning to be recognized, and the future of SARS is uncertain. It seems possible that SARS will be an important cause of pneumonia in the future, and the screening of outpatients at risk for SARS may become part of the pneumonia evaluation. Infectious diseases physicians will need to ensure that they maintain awareness and that triage procedures adequately provide for the standard, contact, and airborne precautions necessary to protect their fellow workers from infection.

## **SPECIAL CONSIDERATIONS: TREATMENT OF BACTEREMIC PNEUMOCOCCAL PNEUMONIA—NEW ADDITION**

**Recommendation 1.** Initial empiric therapy prior to availability of culture data for a patient ill enough to require ad-

mission to a hospital ward can be with a  $\beta$ -lactam plus macrolide combination or a respiratory fluoroquinolone alone (A-I). If sufficiently ill to need intensive care unit (ICU) management and if *Pseudomonas* infection is not a concern, a combination of a  $\beta$ -lactam plus either a macrolide or a respiratory fluoroquinolone should be used (B-III).

**Recommendation 2.** Once culture data are available and it is known that the patient has pneumococcal pneumonia with bacteremia without evidence to support infection with a co-pathogen, treatment will depend upon in vitro susceptibility results. If the isolate is penicillin susceptible, a  $\beta$ -lactam (penicillin G or amoxicillin) alone may be used (B-II). If the isolate is penicillin resistant, cefotaxime, ceftriaxone, or a respiratory fluoroquinolone or other agent indicated by in vitro testing may be used (A-III).

**Comment.** The mortality rate for bacteremic pneumococcal pneumonia is 6%–20%, yet it was always assumed that monotherapy in such cases was sufficient. The guidelines from the IDSA, the ATS, and the Canadian Infectious Diseases Society and Canadian Thoracic Society recommend a macrolide and  $\beta$ -lactam regimen or a fluoroquinolone alone for empiric treatment of patients admitted to a hospital ward and a macrolide or fluoroquinolone plus a  $\beta$ -lactam for patients admitted to the ICU for whom *Pseudomonas aeruginosa* infection has been excluded. In the former instance, therapy was based on the results of studies that showed that such a regimen was associated with a shorter length of stay and reduced mortality [46, 47]. For ICU patients, this recommendation was based on a lack of efficacy data about fluoroquinolones as monotherapy for severe CAP, as well as concerns about infection with a resistant pathogen.

Three retrospective studies have suggested that dual therapy that included a macrolide given empirically reduced mortality associated with bacteremic pneumococcal pneumonia [48–50]. However, the fact that they were neither prospective nor randomized studies meant that they had significant design limitations. It is important to note that these studies evaluated the effects of initial empiric therapy before the results of blood cultures were known. They did not examine effects of pathogen-specific therapy after the results of blood cultures were available, and the panel believes that the results of these studies do not contradict the principles of pathogen-directed therapy.

Two possible explanations for the improved results with a macrolide are the concurrent presence of atypical pathogens (*Mycoplasma pneumoniae*, *C. pneumoniae*, or *Legionella* species) and the immunomodulating effects of macrolides [51]. A prospective, randomized trial is ultimately needed to determine the best regimen without bias or confounding variables distorting the answer.

A retrospective analysis of Medicare data involving >700 patients aged  $\geq 65$  years with severe pneumococcal pneumonia

by the Fine criteria showed that monotherapy with a third-generation cephalosporin was as effective as any other regimen involving a single drug or combination therapy. The end points were in-hospital mortality and 30-day mortality (P. Houck, personal communication).

Empiric therapy for patients with CAP admitted to a hospital ward can be with either a  $\beta$ -lactam plus macrolide regimen or a respiratory fluoroquinolone alone. For those ill enough to require admission to the ICU and in whom *Pseudomonas* infection is not an issue, initial empiric treatment started before any culture data are available should be with a  $\beta$ -lactam plus either a macrolide or a fluoroquinolone. However, if blood cultures subsequently reveal a pathogen such as *S. pneumoniae* and there is no evidence of infection with a copathogen, the decision to continue with combination therapy or to switch to a single agent is probably best determined on an individual basis [52]. Variables to consider include the patient's age and any comorbid conditions, as well as the clinical, bacteriological, and radiographic response to therapy.

If a single agent is to be used, the committee believes that bacteremic pneumococcal pneumonia should be treated with penicillin G or ampicillin if the pathogen is penicillin susceptible, and it should be treated with cefotaxime, ceftriaxone, a respiratory fluoroquinolone, or other agent indicated by in vitro testing, if the pathogen is penicillin resistant.

### **SPECIAL CONSIDERATIONS: UPDATE ON LEGIONNAIRES' DISEASE**

**Recommendation 1.** Preferred diagnostic tests are the urinary antigen assay and culture of respiratory secretions on selective media (A-II).

**Recommendation 2.** Testing for *Legionella* species is appropriate for any patient hospitalized with enigmatic pneumonia (C-II). This test is recommended in patients with enigmatic pneumonia sufficiently severe to require care in the ICU, in the presence of an epidemic, or if there is failure to respond to a  $\beta$ -lactam (A-III).

**Recommendation 3.** Treatment for legionnaires' disease is appropriate when there is epidemiologic evidence of this disease, despite negative diagnostic test results (B-III).

**Recommendation 4.** The preferred treatment for legionnaires' disease for hospitalized patients is azithromycin or a fluoroquinolone (moxifloxacin, gatifloxacin, and levofloxacin; gemifloxacin is only available as an oral formulation) (B-II). For patients who do not require hospitalization, acceptable antibiotics include erythromycin, doxycycline, azithromycin, clarithromycin, or a fluoroquinolone (A-II). Treatment should be initiated as rapidly as is feasible (A-II).

**Comment.** *Legionella* is implicated in 0.5%–6% of CAP cases in most hospital-based series [53–57]. Risk is related to

exposure, increasing age, smoking, and compromised cell-mediated immunity, such as occurs in transplant recipients [58]. Epidemiologic risk factors include recent travel with an overnight stay outside of the home, exposure to spas, recent changes in domestic plumbing, renal or hepatic failure, diabetes, and systemic malignancy [58–60]. Mortality rates are 5%–25% among immunocompetent hosts [57, 59, 61]. *Legionella* was 1 of 2 major respiratory tract pathogens in patients with CAP who required admission to the ICU, according to 7 of 9 recent reviews [62].

Some authorities feel that the following constellation of clinical features suggests this diagnosis: high fever, hyponatremia, CNS manifestations, lactate dehydrogenase levels of >700 U/mL, or severe disease [57]. However, several studies have demonstrated difficulty in distinguishing individual cases of legionnaires' disease from other causes of CAP on the basis of initial clinical findings, nonspecific laboratory findings, or radiograph findings [63–65]. A clinical scoring system that uses a combination of clinical and nonspecific laboratory findings is neither sufficiently specific nor sensitive to enable accurate diagnosis, although a high score may help direct cost-effective specific laboratory testing [57].

Methods of laboratory detection include culture, serologic tests, direct fluorescent antibody (DFA) staining, urinary antigen assay, and PCR [66]. DFA stains require substantial expertise for interpretation, and selection of reagents is critical. PCR is expensive, and there are no FDA-cleared reagents. The 2 recommended tests are the urinary antigen assay and culture of respiratory secretions. The urinary antigen assay for *Legionella pneumophila* serogroup 1 is not technically demanding and reliably and rapidly detects up to 80%–95% of community-acquired cases of legionnaires' disease, but it is substantially less sensitive for nosocomial cases because of frequent involvement of serogroups other than serogroup 1 [60]. Culture on selective media detects all but very rare strains but is technically demanding and requires 3–7 days [58, 67]. Testing for *Legionella* species is appropriate for any patient hospitalized with enigmatic pneumonia sufficiently severe to require hospitalization in an ICU, pneumonia in a compromised host, in the presence of an epidemic, and failure to respond to treatment with a  $\beta$ -lactam. It should also be emphasized that no laboratory test for legionnaires' disease detects all patients with the disease. In the appropriate clinical and epidemiologic settings, therapy for legionnaires' disease should be given or continued even if the results of *Legionella*-specific tests are negative [58, 67].

The preferred therapy for legionnaires' disease depends upon the severity of illness, the underlying health of the patient, and patient drug tolerance. Otherwise healthy patients with mild pneumonia not requiring hospitalization may be treated with a wide variety of antimicrobial agents, including erythromycin,

tetracycline, doxycycline, azithromycin, clarithromycin, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin [57, 68, 69]. Azithromycin or a fluoroquinolone (moxifloxacin, gatifloxacin, or levofloxacin) are recommended for severe disease (gemifloxacin is only available in an oral formulation). A delay in therapy is associated with an increased mortality rate, and treatment should be started as soon as possible [70]. The duration of treatment should be 10–21 days, but it should be less for azithromycin because of its long half-life [57, 68].

## SPECIAL CONSIDERATIONS: VIRAL CAUSES OF CAP—NEW ADDITION

**Recommendation 1.** Respiratory syncytial virus (RSV) antigen detection tests are readily available but are insensitive for detecting infections in adults and are not generally recommended for adults (C-III).

**Recommendation 2.** A rapid antigen detection assay for influenza virus is recommended for rapid detection of this pathogen for epidemiologic purposes and/or treatment (C-II). Tests that distinguish between influenza A and B are generally preferred (C-III).

**Recommendation 3.** Early treatment (within 48 h after onset of symptoms) is effective in the treatment of influenza A using amantadine, rimantadine, oseltamivir, or zanamivir and is effective in the treatment influenza B using oseltamivir and zanamivir (B-I). Use of these drugs is not recommended for uncomplicated influenza with a duration of symptoms of >48 h (D-I), but these drugs may be used to reduce viral shedding in hospitalized patients or for influenza pneumonia (C-III).

**Recommendation 4.** Empiric treatment of suspected bacterial superinfection of influenza should provide activity against *S. pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* with antibiotics such as amoxicillin-clavulanate, cefpodoxime, cefprozil, cefuroxime, or a respiratory fluoroquinolone (B-III).

**Recommendation 5.** Pneumonia caused by varicella zoster virus (VZV) or herpes simplex virus (HSV) should be treated with parenteral acyclovir (A-II).

**Recommendation 6.** There is no antiviral agent with established efficacy for the treatment of adults with pulmonary infections involving parainfluenza virus, RSV, adenovirus, metapneumovirus, the SARS agent, or Hantavirus (D-I).

**Comment.** Respiratory tract viruses are common causes of often serious cases of pneumonia, particularly in elderly patients, patients with chronic obstructive lung disease, and patients with comorbidities. One prospective study of 1029 chronically ill adults found respiratory viral infections in 35%–48% (depending on age) of those hospitalized for an acute respiratory condition (i.e., pneumonia, tracheobronchitis, exacerbations of asthma, or chronic obstructive lung disease) and

that influenza, RSV, or parainfluenza virus accounted for 75% of these viral infections [71]. A review of influenza and RSV for the 1976–1977 through 1998–1999 seasons suggested that influenza was responsible for an average of 36,155 respiratory- and circulatory-associated deaths per year in the United States. Particularly vulnerable were persons with cardiopulmonary disease and persons aged >65 years, especially the “elderly elderly,” defined as persons >85 years of age [72]. RSV was implicated in an average of 11,321 cardiopulmonary deaths per year, with most deaths occurring among elderly persons and persons with chronic cardiac or pulmonary diseases. Other viral causes of respiratory tract infections are parainfluenza virus and, less commonly, adenovirus, metapneumovirus, HSV, VZV, and measles. (SARS is discussed in a separate section in this guideline.) Metapneumovirus is a recently described paramyxovirus, which appears to be a potentially important viral respiratory tract pathogen, causing pneumonia in both children and adults [73, 74].

The clinical presentations of viral pneumonias and the spectrum of associated agents are highly dependent on patient age, comorbidities, and immune status. Approximately 10% of immunocompetent adults hospitalized with CAP have evidence of viral infection, but this varies from 4%–39% in different studies [75]. A recent report from the United Kingdom showed serologic evidence of a viral infection in 23% of 267 patients hospitalized with CAP, with influenza and RSV in 20% and 4%, respectively, of the total [76].

Influenza and other viruses can cause primary viral pneumonias; secondary bacterial infections are common in hospitalized adults, and the reported frequency has ranged widely, from 26% to 77% in different studies [75]. The most common cause of bacterial superinfection is *S. pneumoniae*, but *S. aureus* has been found in up to one-quarter of patients in earlier studies. In the absence of a characteristic exanthem, no clinical or radiographic criteria are able to reliably distinguish persons with viral infection from persons with bacterial infection. Cultures for respiratory viruses (except for shell vial methods, which can yield a diagnosis the next day) and serologic studies are usually too slow to be useful in individual patient treatment. Rapid antigen detection aimed at influenza can provide a diagnosis in 15–30 min, but test performance varies with the specific test used, sample type, duration of illness, and patient age. Sensitivity is ~50%–70% in adults [77, 78], so that negative test results do not exclude the diagnosis; these tests have not generally proven to be superior to physician diagnosis based on the presence of fever and typical symptoms in the presence of an epidemic [79], but some rapid tests can distinguish between influenza A and B strains, which may have therapeutic implications. Antigen tests for RSV detection are insensitive (<15%) with use of upper respiratory samples from adults. One nucleic acid detection assay for multiple respiratory viruses is

commercially available, and, in general, such assays offer the possibility of a rapid, highly sensitive means of a specific viral diagnosis.

No prospective controlled studies of antiviral treatment of viral pneumonias involving adults have been reported, but antiviral therapy is warranted for infection with influenza virus, VZV, HSV, and other viruses in selected circumstances. The M2 inhibitors amantadine and rimantadine are active only for influenza A virus, whereas the neuraminidase inhibitors are inhibitory for both influenza A and B viruses [80]. Amantadine appears to be as effective as the other agents for influenza A infections and is less expensive, but it is associated with higher rates of toxicity. All are effective for chemoprophylaxis and early treatment (<2 days) of uncomplicated influenza A, but their relative efficacies have not been directly compared, except in 1 study, which found that inhaled zanamivir (which has not been approved by the FDA for prophylaxis) was more effective than oral rimantadine in protection of nursing home residents during influenza A outbreaks, in part because of emergence of resistance to the M2 inhibitor [81]. Early treatment of influenza in ambulatory adults with inhaled zanamivir or oral oseltamivir may reduce the likelihood of lower respiratory tract complications [82–84]. The use of influenza antiviral medications may reduce the likelihood of respiratory tract complications, as reflected by reduced use rates of antibacterial agents in ambulatory patients with influenza. In hospitalized adults with influenza, a minority of whom had radiographically documented pneumonia, no obvious benefit was found in one retrospective study of amantadine treatment [85]. Because such patients often have recoverable virus (median duration, 4 days after hospitalization) after hospitalization, antiviral treatment seems reasonable. Because of its broad influenza spectrum, low risk of resistance emergence, and lack of bronchospasm risk, oseltamivir is an appropriate choice for hospitalized patients. For severely ill persons with influenza viral pneumonia, combined antiviral therapy with an M2 inhibitor and neuraminidase inhibitor deserves consideration, but this approach has not yet been shown to improve clinical outcomes in such a scenario [86].

Parenteral acyclovir is indicated for treatment of VZV [87] or HSV pneumonia. No antiviral treatment of proven value is available for other viral pneumonias in immunocompetent adults. Intravenous ribavirin has been used in adenovirus infection, but its efficacy has not been established; this drug appears ineffective for *Hantavirus* infection [88, 89]. Pleconariv is available for compassionate use for management of picornavirus pneumonias in immunocompromised patients.

## SPECIAL CONSIDERATIONS: UPDATE ON PNEUMONIA IN THE CONTEXT OF BIOTERRORISM

**Recommendation 1.** Physicians should know the clues to bioterrorism and the appropriate mechanisms to alert public health officials in cases of suspected bioterrorism (A-III).

**Recommendation 2.** Recommended diagnostic tests and management guidelines are those of the Johns Hopkins Center for Biodefense Strategies and of the CDC, as modified for the specific outbreak (A-I). Means of diagnosis for category A agents of bioterrorism: for inhalation anthrax, blood culture (A-I) and chest CT scan (A-I); for pneumonic plague, blood culture and Gram stain and culture of sputum samples (A-I); and for tularemic pneumonia, culture of blood and sputum or pharynx in biocontainment level 3 (BL-3) laboratory (A-I).

**Comment.** A number of microbes can be disseminated by aerosol as biological weapons that can potentially afflict thousands of people. The etiologic agents most likely to cause severe pulmonary infection are *Bacillus anthracis*, *Francisella tularensis*, and *Yersinia pestis* [90, 91]. Inhalation anthrax always indicates bioterrorism; pneumonic tularemia and pneumonic plague might or might not be associated with bioterrorism.

The greatest experience with inhalation anthrax was the 11 cases that followed established or suspected exposure to contaminated mail in 2001 in the United States [92, 93]. Clinical clues to facilitate the distinction of inhalation anthrax from CAP have been reported [94]. Features of this disease included a median incubation period of 4 days (range, 4–6 days), non-specific initial symptoms (fever, gastrointestinal complaints, and cough without coryza) and some highly characteristic epidemiologic clues and laboratory findings (a wide mediastinum on chest radiograph, hyperdense mediastinal nodes on chest CT scan, and bloody pleural effusions). Blood cultures were positive for 8 of 8 untreated patients, usually within 18 h [92, 93]. The mortality rates in this and prior inhalation anthrax cases in the antibiotic era were 45%–80% [95]. The most important therapeutic interventions are rapid institution of antibiotic treatment and adequate drainage of pleural effusions. Antibiotic selection should be based on the epidemic strain, which may have an unusual resistance pattern due to genetic modification. Treatment and prophylaxis should be prolonged, because animal studies have shown in vivo persistence of spores [95]. Prophylaxis in the 2001 epidemic consisted of 60–100-day courses of oral doxycycline or ciprofloxacin for 10,000 persons with suspected exposure; none subsequently developed anthrax [93]. It should be emphasized that the last case of naturally occurring inhalation anthrax in the United States occurred in 1976, so any case of established or suspected inhalation anthrax should prompt notification of public health authorities [95].



*F. tularensis* causes <200 infections per year in the United States but caused hundreds of thousands of infections in Europe in World War II [96]. Its potential as a biological weapon was substantiated by extensive studies performed by the US biological weapons program in the 1960s [97]. The most common form of bioterrorism with *F. tularensis* after aerosol exposure is “typhoidal” or “pneumonic” tularemia. Clinical features include an incubation period of 3–5 days, nonspecific symptoms (fever, malaise, pleurisy, and nonproductive cough), and a chest radiograph showing pneumonia, often with mediastinal adenopathy. If tularemia is suspected, the organism may be cultured from blood samples, sputum samples, or pharyngeal exudates, but only with difficulty, using media containing cysteine or other sulfhydryl compounds, such as thioglycolate broth or charcoal-yeast agar. This organism represents a hazard to laboratory personnel, and culture should be attempted only in a BL-3 laboratory [98]. There are multiple diagnostic methods, including antigen detection, PCR, EIA, immunoblot assay, and pulsed-field gel electrophoresis; these are generally available only in research or public health laboratories. Standard treatment is streptomycin, which is preferred, although gentamicin is more generally available, can be given intravenously, and is an acceptable alternative [99–101]. Tetracycline and chloramphenicol are also alternatives, but treatment failures and relapses are more common with these agents [99]. Ciprofloxacin is not FDA-approved for tularemia, but has been used successfully in animals and people [99, 102]. The usual duration of treatment is 14 days. Compared with inhalation plague or anthrax, tularemia progresses more slowly and has a lower mortality rate. The experience with 1409 cases reported during 1985–1992 showed that mortality was 1.4% [99]. There is minimal risk of person-to-person spread, and the recommendation for prophylaxis for exposed persons is ciprofloxacin or doxycycline for 2 weeks.

*Y. pestis* is also a potential biological weapon of great concern because it has a fulminant course, causes death in the absence of antibiotic treatment, and can be spread from person to person [103]. Clinical features of infection include high fever, chills, headache, cough, bloody sputum, prominent gastrointestinal symptoms, leukocytosis, and radiographic changes that show bilateral pneumonia. There is rapid progression to septic shock and death. The acutely swollen, tender lymph node or bubo that is characteristic of bubonic plague is unlikely to be present with aerosol dissemination. A review of 390 cases of plague in the United States for 1947–1996 showed that only 6 cases (2%) were of the pneumonic form [104]. The diagnosis is established with culture of sputum or blood samples; sputum Gram stain shows typical safety-pin-shaped, bipolar-staining, gram-negative coccobacilli. Growth occurs within 24–48 h, but identification often takes up to 6 days; if this diagnosis is suspected, the specimen

should be split in half for incubation at 28°C for one half (for rapid growth) and at 37°C for the other (for identification of the capsular antigen). Health care workers are at risk of aerosol exposure, so respiratory precautions should be taken until patients have undergone therapy for 48 h. The standard treatment for plague pneumonia is administration of streptomycin or gentamicin in standard doses for 10 days [105]. Doxycycline may be given for treatment or prophylaxis, although resistance has been described elsewhere [106]. Ciprofloxacin appears to be as effective as aminoglycosides in mice with experimental pneumonic plague [107] and may be given for treatment or prophylaxis. Administration of tetracyclines or fluoroquinolones for 7 days is the preferred prophylaxis when face-to-face contact has occurred or exposure is suspected.

## PNEUMONIA IN ELDERLY PERSONS—NEW ADDITION

**Recommendation.** Antimicrobial selection for elderly patients with CAP is the same as for all adults with CAP (B-III).

**Note.** Recommendations for pneumococcal and influenza vaccines in the elderly population are included as part of the recommendations given in the following section, Update on Prevention of CAP.

**Comment.** In the United States, CAP is the fifth-leading cause of death in people aged  $\geq 65$  years, and an estimated 60,000 seniors die annually [108]. Residents of long-term care facilities, a distinct subpopulation of elderly people, are at particularly high risk of developing pneumonia [109].

**Etiology.** Determining the relative importance of the various etiologic agents of pneumonia in older adults is challenging. In a Finnish study involving 345 CAP episodes, *S. pneumoniae* was the etiologic agent in 48% of patients aged  $\geq 60$  years, *C. pneumoniae* was detected in 12%, *M. pneumoniae* in 10%, *H. influenzae* in 4%, and respiratory viruses in 10% [110]. The incidence of gram-negative bacterial pneumonia in elderly persons living in the community is uncertain, but it is greater in those with comorbidities [111]. For nursing home residents, data are even more scant. The proportion of cases of pneumonia in long-term care facilities that are attributable to pneumococcus is 0%–39% [109]. The proportions of cases due to gram-negative bacteria and *S. aureus* were 0%–55% and 0%–33%, respectively. *Legionella* and *Mycoplasma* species were infrequently detected.

**Risk factors.** In another Finnish study, independent risk factors for pneumonia included alcoholism (relative risk [RR], 9.0; 95% CI, 5.1–16.2), bronchial asthma (RR, 4.2; 95% CI, 3.3–5.4), immunosuppression (RR, 3.1; 95% CI, 1.9–5.1), lung disease (RR, 3.0; 95% CI, 2.3–3.9), heart disease (RR, 1.9; 95% CI, 1.7–2.3), institutionalization (RR, 1.8; 95% CI, 1.4–2.4),

and increasing age (for age of  $\geq 70$  vs. 60–69 years: RR, 1.5; 95% CI, 1.3–1.7) [112]. In a cohort study to assess risk factors for pneumonia in residents of long-term care facilities, older age (OR, 1.7; 95% CI, 1.1–2.6 per 10-year interval;  $P = .01$ ), male sex (OR, 1.9; 95% CI, 1.1–3.5;  $P = .03$ ), difficulty swallowing (OR, 2.0; 95% CI, 1.2–3.3;  $P = .01$ ), and the inability to take oral medications (OR, 8.3; 95% CI, 1.4–50.3;  $P = .02$ ) were found to be significant [113].

**Clinical presentation.** The clinical presentation of CAP has frequently been described as being more subtle in elderly individuals; however, there have been relatively few systematic evaluations to confirm this. A study of 1812 patients found that persons aged 65–74 years and  $\geq 75$  years had 2.9 and 3.3 fewer symptoms, respectively, than did those aged 18–44 years [114]. The reduced prevalence of symptoms was most pronounced for those related to febrile response (chills and sweats) and pain (chest, headache, and myalgia). When 71 long-term care facility residents admitted to hospital with pneumonia were compared with 93 seniors admitted with CAP, it was noted that nursing home residents were less likely to experience chills, pleuritic chest pain, headache, anorexia, myalgia, and productive cough [115].

**Management.** Guidelines for the antibacterial management of CAP in the elderly population have not been assessed in randomized, controlled trials. Antimicrobial selection recommendations for elderly patients with CAP are the same as for all adults with CAP (table 1).

A discussion of immunoprophylaxis of elderly persons against influenza and pneumococcus infection is included in the following section, Update on Prevention of CAP.

## UPDATE ON PREVENTION OF CAP

**Recommendation 1.** All persons  $>50$  years, others at risk for influenza complications, and household contacts of high-risk persons should receive inactivated influenza vaccine, as recommended by the Advisory Committee on Immunization Practices (ACIP) (A-I). The injected inactivated vaccine is the preferred formulation for most persons at risk of complications associated with influenza, for household contacts of high-risk persons, and for health care workers (A-1). The intranasally administered live, attenuated vaccine (FluMist; Aventis) is an alternative vaccine formulation for some persons aged 5–49 years without chronic underlying diseases, including immunodeficiency, asthma, and chronic medical conditions (C-I). Influenza vaccine should be offered to persons at hospital discharge or during outpatient treatment during the fall and winter (C-III). Health care workers in inpatient and outpatient settings and long-term care facilities should receive annual influenza immunization (A-I).

**Recommendation 2.** Pneumococcal polysaccharide vac-

cine (Pneumovax; MedImmune [marketed by Wyeth in the United States]) is recommended for use, according to current ACIP guidelines, including use for persons aged  $>65$  years and for those with selected high-risk concurrent diseases (B-II). Vaccination may be done either at hospital discharge or during outpatient treatment (C-III).

**Comment.** Vaccination against influenza and pneumococcus infection is the mainstay of prevention against pneumonia for older adults. A systematic review that included 1 randomized trial and 20 cohort studies showed that, for frail older adults, influenza vaccine had an efficacy (1-OR) of 53% for preventing pneumonia, 50% for preventing hospitalization, and 68% for preventing death [116]. A recent large observational study of adults  $>65$  years found that vaccination against influenza was associated with a reduction in the risk of hospitalization for cardiac disease (19% reduction), cerebrovascular disease (16%–23% reduction), and pneumonia or influenza (29–32% reduction), as well as a reduction in the risk of death due to all causes (48%–50% reduction) [117]. In long-term care facilities, vaccination of health care workers with influenza vaccine is an important preventive health measure. Data from 2 cluster randomized trials have shown benefit [118, 119]. Potter et al. [118] randomized 12 long-term facilities to either the offer of vaccination of health care workers or to no offer of vaccination. Vaccination of health care workers was associated with a reduction in total patient mortality rate, from 17% to 10%. Carman et al. [119] conducted a randomized trial involving 20 geriatric care hospitals in which they compared influenza vaccination of health care workers with no vaccination. Vaccination of health care workers significantly reduced mortality among elderly people who had a stay of  $>6$  months in hospitals where health care workers were vaccinated, compared with hospitals where they were not (OR, 0.58; 95% CI, 0.04–0.84;  $P = .014$ ). Influenza vaccine effectiveness varies among influenza seasons, with effectiveness being higher when the vaccine antigens are more closely matched to the circulating strains.

Pneumococcal polysaccharide vaccine has not been consistently effective in randomized, double-blind, controlled trials involving elderly individuals. Results of one randomized clinical trial suggested that the polysaccharide vaccine provided some protection against pneumococcal pneumonia among high-risk elderly persons [120]; 2 other trials did not demonstrate efficacy against pneumonia or bronchitis without bacteremia [121, 122], although the use of nonspecific diagnostic methods may have limited the studies' ability to find an effect [123]. Two open-label trials have suggested protection against pneumococcal pneumonia among elderly residents of long-term care facilities [124, 125].

Postlicensure epidemiological studies, including a recent large observational study, involving elderly persons and younger

adults with certain chronic medical conditions have documented effectiveness of pneumococcal polysaccharide vaccines for prevention of invasive infection (bacteremia and meningitis) but not for prevention of pneumonia without bacteremia [126–130]. The overall effectiveness against invasive pneumococcal disease among immunocompetent persons aged  $\geq 65$  years is 75% [126], although efficacy may decrease with advancing age [128].

Older adults may be benefiting from vaccination of children against pneumococcal disease because of decreased pneumococcal transmission. In 2000, a protein-polysaccharide conjugate vaccine targeting 7 pneumococcal serotypes (Prevnar; Wyeth Lederle Vaccines) was licensed for use in young children in the United States. According to data from the CDC's Active Bacterial Core Surveillance (ABCS), rates of invasive pneumococcal disease (e.g., primary bacteremia, pneumonia with bacteremia, and meningitis) among children aged  $< 2$  years—the vaccine's target population—were 69% lower in 2001, compared with baseline [131]. Invasive disease rates decreased by 18% among persons  $\geq 65$  years of age (49.5 cases per 100,000 persons vs. 60.1 cases per 100,000 persons) and 32% among adults aged 20–39 years (7.6 cases per 100,000 persons vs. 11.2 cases per 100,000 persons). To date, the pneumococcal conjugate vaccine is only licensed for children; the vaccine's safety and performance have not been adequately studied in adults.

If indicated, patients with CAP should receive pneumococcal and influenza vaccines as recommended by the CDC's ACIP. The optimal time for influenza vaccination is October and November, although vaccination in December and later is recommended for those who were not vaccinated earlier. Influenza and pneumococcal vaccines can be given at the same time in different arms. The vaccines should be provided either at hospital discharge or at the conclusion of outpatient treatment; standing orders can be used to simplify the process of ensuring that patients are vaccinated [132].

Recent ACIP influenza recommendations state that inactivated influenza vaccine should be given (by intramuscular administration) to all people  $> 6$  months of age who are at increased risk for complications from influenza [133]. Target groups for vaccination include persons aged  $\geq 50$  years; persons of any age who reside in a nursing home or other long-term care facility, who have a chronic disorder of the pulmonary or cardiovascular systems, including asthma, or who have a chronic illness that required regular outpatient follow-up or hospitalization in the prior year, such as chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by HIV); and women who will be in the second or third trimester of pregnancy during the influenza season. All health care workers or others whose work involves any patient contact, including contact with nurs-

ing home residents, should receive influenza vaccine annually to prevent possible transmission to patients. In addition, vaccination of all children 6–23 months and their caregivers is encouraged.

An intranasally administered, live, attenuated, influenza virus vaccine was approved in 2003 by the FDA. ACIP guidelines on use were published in September 2003 [134]. The live, attenuated vaccine is approved for use and is currently recommended as an option for vaccination of healthy persons aged 5–49 years. Advantages of the new vaccine include the potential to induce both mucosal and systemic immune responses and the acceptability of administration using the intranasal rather than intramuscular route. Because it is made from live, attenuated virus, however, care should be taken to avoid administering it to certain persons. Inactivated influenza vaccine (the injected formulation) rather than the intranasally administered, live, attenuated virus vaccine should be given to persons aged  $< 5$  years or  $\geq 50$  years; persons with asthma; persons with reactive airways disease or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including metabolic diseases, such as diabetes, renal dysfunction, and hemoglobinopathies; or persons who have immunodeficiency diseases or who are receiving immunosuppressive therapies; children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza infection); and pregnant women. Because data are lacking on transmission of live vaccine virus from vaccinated persons to immunocompromised persons, use of inactivated vaccine is preferred for vaccinating household members, health care workers, and others who have close contact with immunosuppressed people.

Chemoprophylaxis can be used as an adjunct to vaccination for prevention and control of influenza. Both amantadine and rimantadine have FDA indications for treatment and chemoprophylaxis of influenza A infection, and oseltamivir is indicated for prevention and treatment of both influenza A and B [133]. (Zanamivir is FDA-approved for the treatment of both influenza A and B but is not approved for prophylaxis). Developing an adequate immune response to the inactivated influenza vaccine takes  $\sim 2$  weeks in adults; chemoprophylaxis may be useful during this period for persons with household exposure to influenza, persons who reside or work in institutions with an influenza outbreak, and other persons at high risk for influenza-associated complications in the setting of a community outbreak. Chemoprophylaxis also may be considered for persons with contraindications to influenza vaccine or may be given in addition to vaccination to persons in whom the vaccine may not be effective. The use of influenza antiviral medications for treatment or chemoprophylaxis should not affect response to the inactivated vaccine. Because it is unknown whether administration of influenza antiviral medications af-

fects the performance of the new live, attenuated, intranasally administered vaccine, the live, attenuated vaccine should not be administered until 48 h after the end of any influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after the receipt of the live, attenuated vaccine.

Pneumococcal polysaccharide vaccine is recommended by the ACIP for all adults >65 years of age and for younger adults with certain chronic diseases (such as diabetes, cardiovascular disease, lung disease, alcohol abuse, liver disease, CSF leaks, or renal failure) or immune system disorders (such as sickle cell disease, nephrotic syndrome, HIV infection, hematologic malignancies, or long-term use of immunosuppressive medications) [135]. A second dose is recommended after 5 years for persons with immune system disorders and for persons aged >65 years whose first dose was received before the age of 65 years. The efficacy of revaccination is unknown. A recent model suggested that it may be cost-effective to vaccinate all adults aged  $\geq 50$  years, especially African American persons and those with comorbid conditions [136]. The ACIP is considering changes to the vaccine recommendations that would include vaccinating all adults aged  $\geq 50$  years and listing smokers among those with chronic illnesses who should be vaccinated at an earlier age.

## UPDATE ON MACROLIDES

**Recommendation 1.** A macrolide is recommended as monotherapy for selected outpatients, such as those who were previously healthy and not recently treated with antibiotics (A-I).

**Recommendation 2.** A macrolide plus a  $\beta$ -lactam is recommended for initial empiric treatment of outpatients in whom resistance is an issue and for hospitalized patients (A-I).

**Comment.** The macrolides constitute one of the most popular and long-standing classes of antibiotics in clinical use. The class includes 3 drugs in North America: erythromycin, azithromycin, and clarithromycin and has played a significant role in the management of CAP because of its activity against *S. pneumoniae* and the atypical pathogens. Although erythromycin is the least expensive of these 3 drugs, it is not used as often because of gastrointestinal intolerance and lack of activity against *H. influenzae*.

In the United States, pneumococci were uniformly susceptible to macrolides until the late 1980s [137]. As the result of a steady increase in the rate of resistance, at present, in the United States,  $\sim 25\%$  of all pneumococci show some level of resistance to macrolides [138–140], ranging from 17% in the Northeast to 35% in the Southeast [138]. There are 2 principal mechanisms of resistance: (1) an alteration of the macrolide binding site by methylation in the 23S rRNA, encoded by

*erm(B)*, and (2) an efflux pump, encoded by *mef(A)*, by which bacteria expel macrolides [141, 142]. The methylase causes high level resistance (MIC of erythromycin, 128 mg/mL), whereas the efflux pump produces lower-level resistance (MIC of erythromycin, 1–64 mg/mL) that some experts believe can be overcome by increasing antibiotic concentrations. Rarer mechanisms of (high-level) resistance include alterations of ribosomal proteins L4 or L22 that are adjacent to domain V [143, 144].

In the United States, one-third of macrolide-resistant strains carry *erm(B)*, and the other two-thirds carry *mef(A)* [138, 140]. The level of resistance among *mef(A)* strains has steadily increased in the past few years [139, 145]. In other words, even those organisms that historically had lower-level resistance have become increasingly resistant to achievable levels of macrolides [139, 146]. In Europe, a higher proportion of pneumococci are macrolide resistant, and *erm(B)* is responsible in the majority of isolates [147]. Rates of resistance are lower in Canada than in the United States, and they are higher in the Far East than in Europe [148].

Despite the reports of increasing resistance in vitro, the number of clinical failures has not kept pace. Reports of clinical failures in pneumococcal pneumonia by Dixon [149], Fogarty et al. [150], Kelley et al. [151], and Lonks et al. [152] have failed to provide convincing numbers to match the laboratory phenomena. Why is this?

There are a number of possible answers. First of all, mortality may be a relatively insensitive measure of the impact of resistance. Also, to detect treatment failures, one would have to use monotherapy with a drug to which the etiologic agent is known to be resistant.

In support of the IDSA approach is the relatively small number of reported failures and the fact that, when patients such as those described by Kelley et al. [151] and Lonks et al. [152] were hospitalized and treated with a  $\beta$ -lactam and a macrolide, they all survived.

What then is the role for macrolides in 2003? For outpatients, we believe that, for those who have previously been healthy and who have not been treated with antibiotics for any reason within the preceding 3 months, a macrolide alone is adequate (table 1). An advanced macrolide, such as azithromycin or clarithromycin, may be used alone for patients with comorbidities, such as chronic obstructive pulmonary disease, diabetes, renal or congestive heart failure, or malignancy, who have not been previously treated with antibiotics. For selected outpatients and inpatients, it is clear that, given together with a  $\beta$ -lactam, the macrolides still play an important role. If the infection is caused by macrolide-resistant *S. pneumoniae*, it is highly likely that the  $\beta$ -lactam will still be effective, and, if caused by one of the atypical pathogens, the macrolide will certainly have a role to play.

## THE KETOLIDES—NEW ADDITION

**Recommendation.** Telithromycin may have a role as an alternative to macrolides for treatment of patients with CAP. At this time, however, it is not yet FDA approved.

**Comment.** The ketolides, which are semisynthetic derivatives of 14-membered macrolides, were developed specifically to be effective against macrolide-resistant, gram-positive cocci. Structural modifications at the positions of 3, 6, and 11–12 have altered and improved the pharmacokinetic and antimicrobial activity of the parent compounds, and pharmaceutical manufacturers are seeking approval for their use in CAP, acute exacerbation of chronic bronchitis, and acute sinusitis.

The antibacterial activity of macrolides and ketolides is dependent on inhibition of bacterial protein synthesis. The main differences between them, however, are that, although macrolides bind to only 1 contact site within the 23S ribosomal subunit (domain V), ketolides bind more avidly to domain V and, in addition, bind to a second site on the 23S subunit (domain II). Telithromycin also has some affinity for the efflux pump [153–155]. These differences explain why ketolides remain active against pathogens with both *erm*- and *mef*-mediated resistance.

In vitro, telithromycin is active against *S. pneumoniae*, including macrolide-resistant strains, as well as *H. influenzae* and *Moraxella catarrhalis* [156, 157]. The drug also inhibits *Legionella*, *Mycoplasma*, and *Chlamydia* species [158, 159].

The drug is given once daily at a dose of 800 mg and appears to be well tolerated while achieving ratios of tissue to plasma of  $\geq 500$  and 16.8 in alveolar macrophages and epithelial lining fluid, respectively [160, 161].

Data from 3 randomized, controlled, double-blind CAP trials comparing telithromycin with amoxicillin, clarithromycin, and trovafloxacin suggest that the ketolide is as effective as the comparators [162–164]. Data available to date suggest that the ketolides may have an important role to play in the treatment of CAP caused by macrolide-resistant *S. pneumoniae*, but more studies involving sicker patients are required before its full value can be appreciated. The drug has not yet been approved by the FDA.

## S. PNEUMONIAE WITH REDUCED SUSCEPTIBILITY TO FLUOROQUINOLONES IN NORTH AMERICA—NEW ADDITION

**Recommendation 1.** Fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) are recommended for initial empiric therapy of selected outpatients with CAP (A-I). Other options (macrolides and doxycycline) are generally preferred for uncomplicated infections in outpatients (A-I).

**Recommendation 2.** Fluoroquinolones (gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) may be used as monotherapy for patients with CAP who are admitted to a hospital ward (A-I). With the exception of gemifloxacin (no intravenous formulation), they may be used as part of a combination for patients with CAP admitted to an ICU (C-III).

**Comment.** Since publication of the 2000 guidelines, fluoroquinolone agents have been more widely used to treat pneumonia, yet, at the same time, several compounds have been withdrawn because of serious safety concerns, and resistance to this class of drugs has been increasing. Emergence of *S. pneumoniae* with reduced susceptibility to the fluoroquinolones has been described in Canada, Spain, Hong Kong, eastern and central Europe, and, to a lesser extent, the United States [147, 165–171]. In some countries, resistance has been due to multiple serotypes, whereas, in others, it has resulted predominantly from a single serotype, such as the 23F clone in Hong Kong [165, 167]. Fluoroquinolone resistance in *S. pneumoniae* is primarily due to mutations in the genes encoding the target topoisomerase enzymes, namely *parC*, which encodes the A subunit of DNA topoisomerase IV, and/or *gyrA*, which encodes the A subunit of DNA gyrase. Resistance occurs in a stepwise fashion, with first-step mutations in one target gene (either *parC* or *gyrA*) resulting in low-level resistance and second-step mutations in the other target genes (either *parC* or *gyrA*) leading to higher levels of resistance. In Canada, Chen et al. [165] found that the prevalence of ciprofloxacin-resistant pneumococci (MIC,  $\geq 4$   $\mu\text{g/mL}$ ) increased from 0% in 1993 to 1.7% in 1997–1998 ( $P = .01$ ). In adults, the prevalence increased from 0% in 1993 to 3.7% in 1998. In addition to the increase in the prevalence of pneumococci with reduced susceptibility to fluoroquinolones, the degree of resistance also increased. From 1994 to 1998, there was a statistically significant increase in the proportion of isolates with an MIC of ciprofloxacin of  $\geq 32$   $\mu\text{g/mL}$  ( $P = .04$ ). In 2002, the Canadian Bacterial Surveillance Network reported that the prevalence of levofloxacin-resistant pneumococci (MIC, 8  $\mu\text{g/mL}$ ) was 4% in sputum isolates recovered from patients  $>65$  years of age [172].

Rates of resistance in the United States are  $<2\%$  [173–176]. Doern et al. [177] reported ciprofloxacin resistance (MIC,  $\geq 4$   $\mu\text{g/mL}$ ) rates of 1.4%, and the CDC's ABCS program performed during 1995–1999 reported levofloxacin nonsusceptibility rates of 0.2% [174]. The PROTEKT study (2000–2001), a surveillance study that examined the susceptibility of respiratory pathogens to a variety of antimicrobials, including levofloxacin, reported in vitro susceptibility test results for 10,103 respiratory tract isolates of *S. pneumoniae* recovered from patients in 154 cities and 44 states [178]. Overall, the study found that 0.8% of isolates were resistant to levofloxacin (MIC, 8  $\mu\text{g/mL}$ ); however, the resistance rates varied in some states (from 0% to

4.8%) and cities (from 0% to 22%). This wide divergence in the prevalence of resistance is similar to what occurred with  $\beta$ -lactam resistance to pneumococci in the 1980s, when overall resistance rates were <2% [179]. Extrapolating from what is known about the emergence and dissemination of resistance to  $\beta$ -lactams among pneumococci, the fluoroquinolones could possibly suffer the same fate, unless these agents are used appropriately. Local monitoring of susceptibility patterns of important pathogens to fluoroquinolones and, in fact, to all classes of antibiotics is important.

Clinical failures secondary to pneumococcal resistance to levofloxacin were recently reported [180]. It was shown that such resistance can develop de novo secondary to a point mutation while the patient is receiving therapy. Fluoroquinolone resistance appears to be more common among patients with pneumococcal pneumonia admitted from long-term care facilities [181].

The committee is concerned about misuse and overuse of fluoroquinolones and feels that, if abuse of this class of drugs continues unabated, we may see the demise of fluoroquinolones as useful antibiotics within the next 5–10 years.

## UPDATE ON PERFORMANCE INDICATORS

**Recommendation 1.** Antibiotic therapy should be initiated within 4 h after registration for hospitalized patients with CAP (B-III).

**Recommendation 2.** Smoking cessation should be a goal for persons hospitalized with CAP who smoke (B-II).

**Comment.** Timely antimicrobial therapy is important for patients who require hospitalization for acute pneumonia. The previous IDSA guidelines recommended initial administration within 8 h after arrival at the hospital. This recommendation was based on a retrospective analysis of 14,000 Medicare hospitalizations for pneumonia in 1994–1995 [182].

A more recent analysis of Medicare hospitalizations demonstrated an association between initiation of antimicrobial therapy within 4 h after arrival and improved outcomes [183]. In fact, the time to initiation of antibiotic therapy had a greater influence on patient outcome than did antibiotic selection itself. This study included >13,000 patients with pneumonia who were hospitalized in 1998 and 1999 and who had not received antibiotics before admission. Initial therapy within 4 h after arrival at the hospital was associated with reduced mortality in the hospital (severity-adjusted OR, 0.85; 95% CI, 0.76–0.95). Mean length of stay was 0.4 days shorter among patients who received antimicrobials within 4 h than among those whose initial therapy was given later. Improved outcomes were associated with timely therapy independent of PSI class and the presence of congestive heart failure. These findings are con-

sistent with those of several previous studies [182, 184–187]. The committee supports the early initiation of antibiotic therapy in patients requiring hospitalization for CAP.

Smoking has a well-established association with morbidity and mortality, especially in the form of chronic lung disease and cancer. It is also associated with a substantial risk of pneumococcal bacteremia; one report showed that smoking was the strongest of multiple risks for invasive pneumococcal disease in immunocompetent, nonelderly adults [188]. Smoking is also identified as a risk for *Legionella* infection [58]. Smoking cessation should be attempted when smokers are hospitalized; this is particularly important and relevant when these patients are hospitalized for pneumonia.

## CONFLICT OF INTEREST DISCLOSURE

Lionel A. Mandell has received research funding from Bayer, Bristol-Myers Squibb, and Pharmacia; has been a consultant for Bayer, Pfizer, Aventis, Ortho-McNeil, and Janssen-Ortho; and has been on the speakers' bureau for Pfizer, Aventis, Wyeth, Ortho-McNeil, and Bayer. Thomas M. File, Jr., has received research funding from Abbott, AstraZeneca, Bayer, Bristol-Myers Squibb, Cubist, GlaxoSmithKline, Pfizer, and Wyeth; has been a consultant for Aventis, Bayer, Cubist, GlaxoSmithKline, Ortho-McNeil, Pfizer, and Wyeth; and has been on the speakers' bureau for Abbott, Aventis, Bayer, GlaxoSmithKline, Merck, Ortho-McNeil, Pfizer, and Wyeth.

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## APPENDIX A

### HOW THE PNEUMONIA PORT SEVERITY INDEX (PSI) IS DERIVED

Patients are stratified into 5 severity classes by means of a 2-step process.

**Step 1.** Determination of whether patients meet the following criteria for class I: age <50 years, with 0 of 5 comorbid conditions (i.e., neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, and renal disease), normal or only mildly deranged vital signs, and normal mental status.

**Step 2.** Patients not assigned to risk class I are stratified into classes II–V on the basis of points assigned for 3 demo-

graphic variables (age, sex, and nursing home residency), 5 comorbid conditions (listed above), 5 physical examination findings (pulse,  $\geq 125$  beats/min; respiratory rate,  $\geq 30$  breaths/min; systolic blood pressure,  $< 90$  mm Hg; temperature,  $< 35^\circ\text{C}$  or  $\geq 40^\circ\text{C}$ ; and altered mental status), and 7 laboratory and/or radiographic findings (arterial pH,  $< 7.35$ ; blood urea nitrogen level,  $\geq 30$  mg/dL; sodium level,  $< 130$  mmol/L; glucose level,  $\geq 250$  mg/dL; hematocrit,  $< 30\%$ ; hypoxemia by  $\text{O}_2$  saturation,  $< 90\%$  by pulse oximetry or  $< 60$  mm Hg by arterial blood gas; and pleural effusion on baseline radiograph).

For classes I–III, hospitalization is usually not required. For classes IV and V, the patient will usually require hospitalization.

It should be noted that social factors, such as outpatient support mechanisms and probability of adherence to treatment, are not included in this assessment.

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