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Antimicrobial therapy of community-acquired pneumonia

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Community-acquired pneumonia (CAP) is a common disorder that is potentially life-threatening, especially in older adults and patients with comorbid disease. Despite substantial progress in therapeutic options, CAP remains a primary cause of death from infectious disease in the United States. The mainstay of treatment for most patients is appropriate antimicrobial therapy. This article reviews the principles for initial antimicrobial therapy, highlights some of the differences in approaches to antimicrobial drug selection in selected guidelines, and includes new recommendations for empiric and pathogen-directed therapy of CAP.

Principles of antimicrobial therapy

As an acute infection, pneumonia may be caused by a wide variety of pathogens. The major goals of therapy, along with support of oxygenation and other vital functions in severe cases, are eradication of the infecting organism and resultant resolution of clinical disease.

Until more accurate and rapid diagnostic methods are developed, the initial antimicrobial treatment for most patients is empirical. Recommendations for such therapy in this article apply to most of the cases encountered by clinicians; however, pneumonia can encompass many different diseases, and clinicians need to consider specific risk factors for each patient. These factors include aspiration risks, pneumonia occurring during a community epidemic, and pneumonia complicating possible or probable influenza.

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Epidemiologic association with specific pathogens always must be considered (eg, *Coccidioidomyces* spp in the southwestern United States, severe acute respiratory syndrome [SARS] in travelers from parts of Asia).

Although some authorities propose a syndromic approach to therapy (counting on the predictability of a cause based on the presenting clinical manifestations), most data indicate that the presenting clinical features are not specific enough to reliably predict the cause of CAP [1–3]. Some studies have shown that atypical pathogens (such as *Chlamydophila pneumoniae*, *Legionella* spp, viruses) may serve as co-pathogens with traditional bacteria, making it difficult to know when it is appropriate to treat only a bacterial pathogen [4–6].

The selection of specific antimicrobial regimens for empiric therapy is based largely on a number of principles, including the prediction of the most likely pathogens (aided by knowledge of commonly encountered pathogens in a geographic area and an appreciation of their usual susceptibilities patterns); and the presence of medical comorbidities that may influence the pathogen, increase likelihood for drug-resistant *Streptococcus pneumoniae* (DRSP), and potentially be a risk factor for clinical failure (Box 1). Other factors for consideration of specific antimicrobials include spectrum of activity, potential for inducing resistance, pharmacokinetics and pharmacodynamics, efficacy, safety profile, clinical trials showing proven efficacy, and cost.

Likely pathogens of community-acquired pneumonia

Although CAP may be caused by many possible pathogens, a limited number of common pathogens are responsible for most cases. The emergence of newly recognized pathogens, such as the novel coronavirus associated with SARS, continually increases the challenge for appropriate management of CAP.

Box 1. Principles of empiric antimicrobial therapy for community-acquired pneumonia

The most likely pathogens (including most common pathogens and pathogens of epidemiologic consideration)
Local antimicrobial-susceptibility patterns
Potential for inducing antimicrobial resistance
Risk factors for drug-resistant *S pneumoniae* (especially recent antimicrobial drug use)
Medical comorbidities
Pharmacokinetic and pharmacodynamic considerations
Safety profile
Cost efficacy
Clinical trials showing proven efficacy

Table 1 lists the most common pathogens associated with CAP based on the collective results of recent studies and based on the severity of illness as judged by the site of care (outpatient versus inpatient) [7]. Collectively, *S pneumoniae* is the most frequently isolated pathogen. Relative to other pathogens, *Mycoplasma pneumoniae, C pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, and respiratory viruses are also common. The atypical pathogens (with the exception of *L pneumophila*) are not identified often in clinical practice, however, because there is not a specific, rapid, or standardized test for their detection. Although influenza remains the most predominant viral cause of CAP in adults, other recognized pathogens include respiratory syncytial virus; parainfluenza virus; and less commonly, adenovirus, metapneumovirus, herpesvirus, varicella, SARS-associated coronavirus, and measles. In a study of nonimmunocompromised adults who were admitted for CAP, 18% of patients had evidence of a viral cause, and in 9% of patients, a respiratory virus was the only pathogen identified [8].

Staphylococcus aureus, Enterobacteriaceae, and *Pseudomonas aeruginosa* pathogens are found in a selected group of patients who have had influenza, previously have taken antimicrobial drugs, or have pulmonary comorbidities. [9] Identified risk factors for gram-negative bacteria include recent antibiotic therapy, pulmonary comorbidity, and recent hospitalization; the latter two risk factors also predict *P aeruginosa* as a likely gram-negative pathogen [9].

Pneumonia caused by community-associated methicillin-resistant *S aureus* (CA-MRSA) has been observed [10,11]. This type of pneumonia is uncommon, but it is important to recognize because of its potentially serious consequences. CA-MRSA strains seem to be distinct from hospital-acquired strains from epidemiologic, genotypic, and phenotypic perspectives [12]. They tend to be less resistant to antimicrobial drugs than are hospital-acquired MRSA strains and almost always contain a novel-type IV staphylococcal cassette chromosome (SCC*mec*) gene. Many of these strains have been found to contain the gene for Panton-Valentine leukocidin, which

Table 1
Cause of community-acquired pneumonia according to severity/site of care

Ambulatory patients	Hospitalized (non-ICU) patients	Patients with severe (ICU) pneumonia
S pneumoniae	*S pneumoniae*	*S pneumoniae*
M pneumoniae	*M pneumoniae*	*Legionella* spp
H influenzae	*C pneumoniae*	*H influenzae*
C pneumoniae	*H influenzae*	Gram-negative bacilli
Respiratory viruses[a]	*Legionella* spp	*S aureus*
	Aspiration	
	Respiratory viruses[a]	

[a] Influenza A and B, adenovirus, respiratory syncytial virus, parainfluenza.
Data from File TM Jr. Community-acquired pneumonia. Lancet 2003;362:1991–2001.

is responsible for a toxin that is associated with the clinical features of necrotizing pneumonia, shock, and respiratory failure, and the formation of abscess and empyema. Most of the cases published to date have been in children; however, the authors observed this strain in adults during the winter season of 2003 to 2004, and many cases were associated with preceding influenza.

The frequency of other causes (eg, *Mycobacterium tuberculosis*, *Chlamydia psittaci* [psittacosis], *Coxiella burnetii* [Q fever], *Francisella tularensis* [tularemia], melioidosis, endemic fungi [histoplasmosis, coccidioidomycosis, blastomycosis]) vary with the epidemiologic setting (Table 2).

In patients admitted to the ICU with severe CAP, the predominant pathogens are pneumococcus, atypical pathogens, *H influenzae*, enteric gram-negative bacteria, and *S aureus* [13]. A carefully done bronchoscopic study of nursing-home patients with severe CAP in the setting of suspected aspiration identified enteric gram-negative bacteria as the predominant pathogens and found that anaerobes were uncommon, often were identified with other bacteria, and did not require specific therapy [14]. The atypical pathogens responsible for severe CAP may vary over time, accounting collectively for approximately 20% of pneumonia episodes, but the dominant pathogen from a pathogenic aspect is *Legionella* spp [15].

Although objective confirmation is often difficult, multiple organisms that infect a patient concurrently or sequentially may cause CAP [4,5]. Influenza A or *C pneumoniae* infection might be followed by a secondary infection with *S pneumoniae*. In one study of patients hospitalized with serologically diagnosed *C pneumoniae* pneumonia, 45% of patients were infected with other pathogens, the most common of which was the pneumococcus [6]. The importance of treating multiple infecting organisms has not been established; however, identification of one pathogen should not preclude evaluation for other causes, particularly when the case of CAP is not responding to therapy.

Drug-resistant Streptococcus pneumoniae

The emergence of resistant respiratory pathogens, particularly strains of DRSP, has influenced initial empirical management of CAP. The clinical relevance of DRSP for pneumonia is imprecise and has been the subject of several reviews [16–18]. Few well-controlled studies examine the impact of in vitro resistance on clinical outcomes of CAP. Published studies are limited by small sample sizes, biases inherent in observational design, and the relative infrequency of isolates showing high-level resistance among clinical isolates. Most studies suggest that current levels of β-lactam resistance generally do not result in treatment failures in patients with CAP when appropriate agents (ie, amoxicillin, ceftriaxone, cefotaxime) and doses are used. The available data suggest that the clinically relevant level of penicillin resistance is a minimal inhibitory concentration (MIC) of at least 4 mg/L.

Table 2
Epidemiologic conditions related to specific pathogens with selected community-acquired pneumonia

Condition	Commonly encountered pathogens
Alcoholism	*S pneumoniae*, oral anaerobes
Chronic obstructive pulmonary disease and/or smoking	*S pneumoniae, H influenzae, M catarrhalis, Legionella* spp, *Chlamydia pneumoniae*
Poor dental hygiene	Oral anaerobes
Aspiration/Lung abscess	Oral anaerobes
Exposure to bats or soil enriched with bird droppings	Histoplasma capsulatum
Exposure to birds	*Chlamydia psittaci*, avian influenza (poultry exposure)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnetti* (Q fever)
HIV infection (early)	*S pneumoniae, H influenzae, M tuberculosis*
HIV infection (late)	Above plus *J carinii,* Cryptococcus, Histoplasma
Travel to or residence of southwestern United States	*Coccidioides* spp
Travel to or residence of Asia	*Burkholderia pseudomallei*, severe acute respiratory disease
Influenza active in community	Influenza, *S pneumoniae, S aureus, H influenzae*
Structural lung disease (eg, bronchiectasis)	*Pseudomonas aeruginosa, Burkholderia cepacia, S aureus*
Injection drug use	*S aureus, S anserobes, M tuberculosis, S pneumoniae*
Endobronchial obstruction	Anaerobes, *S pneumoiae, H influenzae, S aureus*
Recent hospitalization, nursing home residence	DRSP, gram-negative bacilli, *S aureus*
In context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *F tularensis* (Tularemia)

Table 3
Comparison of recommendations of recently published guidelines for empirical antimicrobial therapy of community-acquired pneumonia in adults (from North America, United Kingdom, and Japan)

Guideline	Outpatient[a]	General ward[a]	ICU/Severe[a]
North American Guidelines (synthesis from Canadian, CDC, 2000; ATS, 2001, IDSA, 2003) [31,33,34]	If no significant risks for DRSP[b]: macrolide[c] or doxycycline If risks for DRSP[b]: antipneumococcal fluoroquinolone[d] or high-dose amoxicillin (3 g/d) or amoxicillin/clavulanate plus macrolide (if amoxicillin is used and there is a concern for *H influenzae*, use agent active for β-lactamase producing strains[c])	β-Lactam (ceftriaxone, cefotaxime, ampicillin/sulbactam) plus macrolide[c] (can use doxycycline if macrolide not tolerated) or antipneumococcal fluoroquinolone[d] alone	β-Lactam (ceftriaxone, cefotaxime, ampicillin/sulbactam, piperacillin/tazobactam) plus macrolide[c] or fluoroquinolone[d] (if β-lactam allergy, use fluoroquinolone[d] plus clindamycin) Modifying factors of structural lung disease: antipseudomonal agent (piperacillin/tazobactam, carbapenem, or cefepime) plus antipseudomonal fluoroquinolone (high-dose ciprofloxacin or levofloxacin)
Japanese Respiratory Society [36]	(Specified as mild or moderate pneumonia) When bacterial pneumonia is suspected: a penicillin-type drug (with a β-lactamase inhibitor) orally or penicillin-type drug (injection) or cepham-type drug	(Specified as severe pneumonia) For younger patients without underlying illness: injection use or fluoroquinolone	Not specified Consider as for inpatients, elderly patients, or patients with underlying illness

	When atypical pneumonia is suspected: macrolide or tetracycline	For elderly or underlying illness: Carbapenem plus tetracycline or macrolide or third-generation cepham plus clindamycin plus tetracycline or macrolide	
British Thoracic Society [35]	Amoxicillin 500–1000 mg three times a day (alternative: erythromycin or clarithromycin)	If admitted for nonclinical reasons or previously untreated in the community: amoxicillin (alternative: macrolide)	(Defined as severe)
		If admitted for pneumonia and oral therapy appropriate: amoxicillin plus erythromycin or clarithromycin (alternative: antipneumococcal fluoroquinolone)	Co-amoxiclav or $2^{nd}/3^{rd}$ gene ceph plus [iv erythro or clarithro, +/− rifampin] (fluoroquinolone with enhanced pneumococcal activity plus benzylpenicillin as alternative)
		If parenteral appropriate: ampicillin or benzylpenicillin plus erythromycin or clarithromycin (alternative: intravenous levofloxacin)	Second- or third-generation cepham plus intravenous erythromycin or clarithromycin, with or without rifampin

Abbreviations: ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America.

[a] Site of care.

[b] β-Lactam therapy within the past 3 months, hospitalization within the past month, alcoholism, immune-suppressive illness (including therapy with corticosteroids), multiple medical comorbidities, exposure to a child in a day care center.

[c] If chronic obstructive pulmonary disease, use a macrolide active against β-lactamase–producing *H influenzae* (ie, azithromycin, clarithromycin).

[d] Gatifloxacin, levofloxacin, moxifloxacin.

One report suggests that if cefuroxime is used to treat pneumococcal bacteremia and if the organism is resistant in vitro, the outcome may be worse than if other therapies are used. Other discordant therapies did not impact mortality [19]. Data suggest that resistance to macrolides and respiratory fluoroquinolones (levofloxacin) may result in clinical failure; however, interpretation is limited by the relatively small number of patients reported [20–22,23–25].

Risk factors for penicillin-resistant *S pneumoniae* have been identified: age <2 years or >65 years, β-lactam therapy within the previous 3 months, alcoholism, medical comorbidities, immunosuppressive illness or therapy, and exposure to a child in a day care center [16,19,26]. Although the relative predictive value of these risk factors is unclear, treatment with antimicrobial drugs is likely to be the most significant factor. Several sets of data have shown that recent therapy with β-lactams, macrolides or quinolones is a risk factor for pneumococcal resistance to the same class of antibiotic, and repeated courses of the same antibiotic class are a risk factor for pneumococcal resistance to that agent [27–30]. One study has found that in the presence of pneumococcal bacteremia, use of a β-lactam or macrolide within the past 6 months increased the likelihood of infection with a penicillin-resistant organism [30]. In that study, recent use of a quinolone did not predict an increased likelihood of penicillin resistance, but other studies have shown that repeated use of quinolones does predict an increased risk for quinolone-resistant pneumococci [25,29]. It remains uncertain if this risk applies equally to all quinolones or if it is more of a concern for less active pneumococcal agents (levofloxacin) than for more active agents (moxifloxacin, gemifloxacin) [23–25].

Different approaches to empiric antimicrobial drug selection

Numerous guidelines for recommended antimicrobial management of CAP have been published. Specific recommendations for empirical therapy for CAP as included in several published guidelines from North America, the United Kingdom, and Japan are listed in Table 3 [31–36]. A combined consensus guideline from the American Thoracic Society (ATS) and Infectious Diseases Society of America is being prepared (M. Niederman and T. File, personal communication, 2004).

Recommendations for empirical therapy of outpatients

North American (NA) guidelines variably recommend macrolides, doxycycline, an antipneumococcal fluoroquinolone (eg, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin), or the combination of a β-lactam plus macrolide as treatment options for patients who are mildly ill and can be treated as outpatients [31–34]. In general, the NA guidelines recommend a macrolide as first-line treatment for outpatients with no comorbidity or

risk factors for DRSP. The rationale is that macrolides provide effective therapy for the most common bacterial pathogens in such patients (ie, primarily *S pneumoniae*) and the atypical organisms, especially *M pneumoniae* and *C pneumoniae*, which are common in outpatients. The positioning of the macrolides as prominent first-line agents in the NA guidelines partially is based on the presumption that the new macrolides (azithromycin, clarithromycin) can be effective against MRSP strains, in which lower-level resistance results from increased drug efflux and resulting MICs that often are less than 8 μg/mL. Because data indicate that *mef*-mediated resistance is becoming associated with higher MICs (from a median of 4 μg/mL to a median of 8 μg/mL), it is reasonable to consider an alternative therapy (ie, respiratory fluoroquinolone, ketolide, or high-dose amoxicillin [≥3 g/d for adults] plus a macrolide) if risk factors for DRSP are present.

In contrast, the primary agents recommended in the British Thoracic Society (BTS) guidelines are β-lactams, primarily penicillins, rather than macrolides [35]. The rationale is that these agents are effective against *S pneumoniae* and, when given in high doses, are even effective for most strains with decreased sensitivity to penicillin. Because most of the macrolide resistance in Europe is *erm*-mediated, high-level resistance, the macrolides are not regarded as optimal first-line empirical agents to treat this pathogen if *S pneumoniae* infection is considered likely. The British guidelines place less significance in the need to treat empirically patients who are infected with atypical pathogens and are ambulatory (mild disease). The guidelines suggest that because *M pneumoniae* exhibits epidemic periodicity every 4 to 5 years and largely affects younger patients, a policy for initial empirical therapy that aims always to cover this pathogen is unnecessary.

The two approaches represented by the NA and BTS guidelines differ primarily because of the greater emphasis in North America to routinely treat the atypical pathogens and the fact that MRSP in Europe is of higher-level resistance than in North America. More studies are needed to answer the question regarding the need to routinely treat atypical pathogens. The Japanese guidelines advocate initial therapy based on a syndromic approach (ie, macrolides or tetracycline treatment for likely atypical pneumonia and penicillin-type therapy for bacterial pneumonia) [36].

Recommendations for empirical therapy of inpatients

The NA guidelines recommend treatment with a β-lactam plus a macrolide or monotherapy with a fluoroquinolone for patients who are admitted to the general ward. This rationale partly results from studies showing that these regimens are associated with a significant reduction in the mortality rate, compared with the mortality rate associated with cephalosporin treatment alone [37–40]. Although limited by their retrospective design, these studies have found that the use of macrolides as part of an initial combination therapy (usually with a cephalosporin agent) or

fluoroquinolone monotherapy in patients who require hospitalization seems to be associated with decreased mortality rates or shorter hospital stays, compared with the use of a cephalosporin alone [37–40]. The specific cause of infection was not determined in these studies; however, the added coverage for atypical pathogens partly may explain this observation. The recommendations in the BTS guidelines are similar to in the NA guidelines. The Japanese guidelines stratify patients based on age and presence of underlying illness, and use of an "injection use fluoroquinolone" is recommended for younger patients with less serious disease. A combination regimen is recommended for other patients.

For patients with severe CAP who require ICU admission, all of the guidelines recommend comprehensive antimicrobial therapy to cover infection with *S pneumoniae* (including DRSP), *Legionella* spp, and potentially gram-negative bacilli, including *Pseudomonas* spp in selected-cases.

Updated recommendations for empirical antimicrobial therapy

The authors' recommendations for empiric therapy of CAP in outpatients, patients admitted to a general ward, and patients requiring ICU admission are listed in Box 2. These therapeutic regimens are considered to be effective for most patients (ie, patients who are likely to have one of the more common causes, which are listed in Table 1). The authors recognize that a significant minority of patients has epidemiologic risk factors for which other pathogens, and other antimicrobial therapy is warranted in such patients. Such epidemiologic factors and associated pathogens are listed in Table 2.

Outpatients

For patients who have mild (ambulatory) pneumonia, do not have significant medical comorbidities (ie, diabetes, chronic inflammatory lung disease, liver or renal insufficiency, malignancy, congestive heart failure), and have not been recently treated with antimicrobial agents, treatment with an extended-spectrum macrolide (clarithromycin, azithromycin) or doxycycline is appropriate.

In recent studies, the most common pathogens in such patients were *S pneumoniae*, *M pneumoniae*, *C pneumoniae*, and *H influenzae* [41,42]. *Mycoplasma* spp most commonly were found in patients younger than 50 years and without significant comorbid conditions or abnormality of vital signs. *S pneumoniae* was the most common pathogen in older patients and patients with significant underlying disease. *H influenzae* was found in 5% of patients and mostly in patients with comorbidities, such as cigarette smoking. The importance of therapy for *Mycoplasma* spp and *Chlamydia* spp infection in mild CAP has been the subject of some conjecture, because

many infections are self-limiting. Studies from the 1960s indicate that treatment of mild *M pneumoniae* CAP reduces the morbidity of pneumonia and shortens the duration of symptoms [43].

The macrolides constitute a long-standing class of antimicrobials in the treatment of outpatients with CAP in the United States. This class includes the erythromycin-type agents (including dirithromycin), the extended-spectrum macrolide and clarithromycin and the azalide azithromycin. These agents have had a significant role in the management of CAP because of their activity against *S pneumoniae* and the atypical pathogens. Although erythromycin is the least expensive drug, it is not used as often because of gastrointestinal intolerance and lack of activity against *H influenzae*. In light of this activity against *H influenzae*, an advanced macrolide-and-azalide combination should be used when considering treatment for outpatients with comorbidities such as chronic obstructive pulmonary disease.

Numerous randomized clinical trials document the efficacy of the advanced macrolide-and-azalide combination as monotherapy (azithromycin, clarithromycin) for outpatients [44–50]. Despite the reports of clinical failures of macrolides in the treatment of outpatients with pneumococcal pneumonia, the numbers are relatively small in light of the large number of patients treated. When such patients were hospitalized and treated with a β-lactam and a macrolide, they generally survived [21,22,51]. Most of these patients had risk factors for which monotherapy with a macrolide is not recommended in the guidelines. For patients without significant risks for DRSP or gram-negative bacilli, monotherapy with a macrolide still can be considered appropriate. Doxycycline is included as a cost-effective alternative, in part based on in vitro data, which indicate that the drug is at least as effective as erythromycin for treating pneumococcal isolates; however, little clinical trial data are available [52].

Fluoroquinolone treatment of ambulatory CAP without comorbid conditions or recent antimicrobial use is discouraged for fear that widespread use may lead to the development of fluoroquinolone resistance among respiratory pathogens and to the colonization of other pathogens. Studies of outpatients have shown that many quinolone recipients could receive other agents as preferred first-line therapy, that some quinolone recipients may not require antibiotic treatment, and that the doses and durations employed are often incorrect. This type of usage pattern has raised concerns about promoting the rapid development of antibiotic resistance to the quinolone class of antibiotics [52].

The likelihood for the development of DRSP and enteric gram-negative bacteria is increased in patients with comorbidities or recent antimicrobial therapy. For such patients, recommended empiric therapeutic options include a respiratory fluoroquinolone (gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin), a ketolide alone (ie, telithromycin) if enteric gram-negative bacteria are not a concern, or combination therapy with a beta-lactam plus a macrolide (with doxycycline as alternative) is effective for

Box 2. Empirical selection of antimicrobial agents for treating patients with community-acquired pneumonia

Outpatients

A. Previously healthy and no use of antimicrobial drugs within the previous 3 months[a]:
   - An extended-spectrum macrolide (clarithromycin or azithromycin) or doxycyline

B. Presence of comorbidities (ie, diabetes, liver disease, renal insufficiency, malignancy, chronic inflammatory lung disease, congestive heart disease) or use of antimicrobial drugs within the previous 3 months (depending on the class of antibiotics recently given, an alternative option from a different class should be selected)[a]:
   - A respiratory fluoroquinolone (gatifloxacin, levofloxacin, moxifloxacin, gemifloxacin)
   - Telithromycin if no risks for enteric gram-negative organisms
   - A β-lactam (high-dose amoxicillin [eg, 1 g three times daily; or 2 g of amoxicillin/clav 2 twice daily is preferred]. Alternatives: cefpodoxime, cefuroxime, cefprozil, and cefdinir) plus a macrolide (alternative: doxycycline)
   - Ceftriaxone (intramuscular or intravenous) plus macrolide, or doxycyline

Inpatients in the general ward
   - Respiratory FQ or β-lactam (preferred agents include cefotaxime, ceftriaxone, ampicillin/sulbactam; consider ertapenem in selected patients) plus macrolide or doxycycline
   - For carefully selected patients with no risk factors for DRSP or gram-negative organisms, the use of monotherapy with azithromycin can be considered
   - Consider risk factors for other pathogens (see Table 1).

Inpatients in the ICU
   - Pseudomonas not a consideration
     - A β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam, ertapenem) plus azithromycin or a respiratory FQ. For patients with penicillin allergy, a respiratory fluoroquinolone, with or without clindamycin
   - Pseudomonas is a consideration (severe structural lung diseases, such as bronchiectasis, chronic obstructive pulmonary disease with repeated antimicrobial or steroid use)

An antipneumococcal, antipseudomonal β-lactam (piperacillin, cefepime, imipenem, meropenem) plus ciprofloxacin or levofloxacin (750 mg)
An antipneumococcal, antipseudomonal β-lactam plus an aminoglycoside and an intravenous macrolide or intravenous antipneumococcal quinolone
For patients with penicillin allergy, aztreonam plus levofloxacin (750 mg); or aztreonam plus moxifloxacin or gatifloxacin, with or without aminoglycoside
Consider risk factors for other pathogens (see Table 1).

[a] Consider regimens listed in B for any patient in regions with a high rate of high-level macrolide-resistant *S pneumoniae*.

S pneumoniae infection. These regimens may be appropriate for use in patients who are without comorbidities or recent antimicrobial and who live in places where there is a high prevalence of *S pneumoniae* infection with high-level macrolide resistance. Based on pharmacodynamic principles, high-dosage amoxicillin (1 g of amoxicillin three times daily or 2 g of amoxicillin and potassium clavulanate two times daily) should be effective for more than 93% of cases of *S pneumoniae* infection, and amoxicillin is the preferred β-lactam [53]. For patients without type I penicillin allergy [53], a selected cephalosporin (cefpodoxime, cefuroxime) can be used as an alternative, but these drugs are less active in vitro than is high-dose amoxicillin.

Telithromycin is the first ketolide approved for the treatment of mild-to-moderate CAP and is useful when DRSP is a risk. This agent has shown efficacy in some patients with bacteremia and with higher pneumonia severity of illness (PSI) scores [54,55]. In vitro, telithromycin is active against *S pneumoniae* which is resistant to other antimicrobials, including penicillin, macrolides, and fluoroquinolones. Data from several controlled, double-blind CAP trials suggest that telithromycin is as effective as the comparators, including amoxicillin, clarithromycin, and trovafloxacin [56–58]. Available information suggests that telithromycin, which is only available as an oral agent, will have an important role in the treatment of CAP caused *S pneumoniae* or the common atypical pathogens. The efficacy of this agent in *H influenzae* infection is similar to that of the new macrolides, but more data involving patients with such infection are needed.

Another possible option for empiric treatment of outpatients with modifying factors, depending on the setting, is the use of parenteral intramuscular or intravenous ceftriaxone that is given with an oral macrolide, ketolide, or doxycyline. Outpatient services are increasingly available, and

parenteral antimicrobial therapy may be appropriate for selected patients with mild disease [59].

Inpatients in the general ward

Recommended regimens for inpatients in the general ward are a β-lactam plus a macrolide (alternatively, doxycyline or ketolide) or monotherapy with a fluoroquinolone that is considered effective for treating *S pneumoniae* infection. Numerous studies have shown that empiric treatment with either of these regimens is associated with a significant reduction in mortality rate and length of hospital stay, compared with treatment with cephalosporin alone [38–40]. The preferred β-lactams are effective in treating *S pneumoniae* infection and are not overly broad spectrum; however, treatment with other antipneumococcal, antipseudomonal agents (eg, cefepime, piperacillin, tazobactam) can be appropriate when more resistant pathogens are involved in the pneumonia or coexisting infections. In January 2002, the National Committee for Clinical Laboratory Standards (NCCLS) increased the MIC breakpoints for cefotaxime and ceftriaxone treatment of nonmeningeal *S pneumoniae* infections. These new breakpoints acknowledge that nonmeningeal infections caused by strains that formerly were considered to be intermediately susceptible, and even some strains that were regarded as resistant, can be treated successfully with the usual doses of these β-lactams. Ertapenem is included as a β-lactam option in light of two randomized, double-blind studies showing that such treatment has equivalent results compared with the results of ceftriaxone therapy [60,61]. This drug also has excellent activity for anaerobic organisms and most Enterobacteriaceae (including producers of extended-spectrum β-lactamase producers, but not *P aeruginosa*). It may be useful in patients with risks for these pathogens, particularly in elderly patients who are admitted from nursing homes and patients who have recently received antibiotic therapy. Clinical experience with ertapenem is limited, however. Doxycycline can be used as an alternative to a macrolide, based on minimal-to-moderate experience for treatment of *Legionella* infections [62].

Monotherapy with azithromycin can be considered in selected patients who have nonsevere disease (may be admitted for reasons other than CAP) and do not have risks for DRSP or gram-negative pathogens. Data from two randomized, double-blind studies of adults hospitalized for CAP have demonstrated that parenteral azithromycin monotherapy was as effective as intravenous cefuroxime therapy with or without intravenous erythromycin (the azalide monotherapy regimen had greater tolerability) [63,64]. Feldman et al [65] reviewed the records of patients with CAP who were admitted to a Veterans Affairs facility between December 1997 and July 2001 and compared the outcomes of patients who received azithromycin monotherapy with the outcomes of patients who received ATS-recommended antibiotics or non–ATS-recommended antibiotics. Outcomes included time

to stability, length of stay (LOS), and mortality and were adjusted for severity of illness (mean PSI score: 89.2 for azithromycin group versus 95.0 for the ATS groups; $P = 0.07$) and processes of care. Patients requiring ICU management were excluded. Mortality and re-admission rates were similar among the groups, but mean LOS was shorter in the azithromycin group. None of the 10 patients with erythromycin-resistant *S pneumoniae* infections died or was transferred to the ICU, including the six patients who received azithromycin. In a retrospective analysis of the impact of initial antibiotic choice on 30-day mortality rates in patients admitted to the hospital for CAP, Brown et al [66] observed that patients who received monotherapy with macrolides had the lowest mortality rate, but were the least ill. Such patients were younger and were more likely to be in low-risk groups.

Although most admitted patients initially are treated with an intravenous regimen, many patients, particularly those without risk factors for severe pneumonia, can receive oral therapy, especially with highly bioavailable agents such as the quinolones. When an intravenous β-lactam is combined with coverage for atypical pathogens, the addition of a macrolide, doxycycline, or ketolide can be achieved with oral therapy in carefully selected patients without severe pneumonia risk factors.

Patients in the intensive care unit

ICU patients are likely to be very ill and have risk factors for more resistant pathogens. In a review of nine studies that included 890 patients with CAP who were admitted to the ICU, the most common pathogens (in order of frequency) were *S pneumoniae*, *Legionella* spp, *H influenza*, Enterobacteriaceae, *S aureus*, and *Pseudomonas* spp. For patients without risks for *Pseudomonas* infection, coverage for *S pneumoniae* and *Legionella* species should be ensured [13]. The combination of a potent antipneumococcal β-lactam and an advanced macrolide or a respiratory fluoroquinolone should provide an effective spectrum for such patients. The role of monotherapy with a respiratory fluoroquinolone is not yet established for severe CAP, and if the patient has pneumococcal meningitis, the efficacy of quinolone monotherapy is uncertain. If risk factors for *Pseudomonas* infection are present (or if other infection sites coexist in which *Pseudomonas* spp or more resistant pathogens are considerations), therapy should include agents that are effective against pneumococcus, *Pseudomonas* spp, and *Legionella* spp. Piperacillin–tazobactam, imipenem, meropenem, and cefepime are the preferred β-lactams when there is concern for unusual pathogens, such as *P aeruginosa* or other gram-negative bacteria.

Switch from intravenous to oral therapy

Once the patient has a good clinical response to initial therapy, other coexisting medical problems are stabilized, and the patient can eat and drink

again, consideration should be given to switching from intravenous to oral antibiotic therapy. Ramirez et al [67] defined a set of criteria for an early switch from intravenous to oral therapy that included improved cough and dyspnea, fever less than 37.8°C for at least 8 hours, normalized white blood cell count, oral intake, and adequate intestinal function. These criteria are discussed further by Ramirez in another article in this issue.

Alternative or additional antimicrobial therapy of pathogens based on epidemiologic considerations

For several patients, clinicians should be aware of other potential pathogens that are separate from or in addition to the most common organisms for which the empiric therapies in Box 2 are directed. Among these pathogens are respiratory viruses.

Although no prospective, controlled studies of antiviral treatment of viral pneumonias have been reported in adults, antiviral therapy is warranted for influenza, varicella, herpesvirus, and other viruses in selected circumstances (Table 4). In ambulatory adults with influenza, early treatment with inhaled zanamivir or oral oseltamivir seems to reduce the likelihood of lower respiratory tract complications [68–70]. The use of influenza antiviral medications seems to reduce the likelihood of respiratory tract complications as reflected by reduced rates of antibacterial agent use in ambulatory patients with influenza. In one retrospective study of hospitalized adults with influenza, a minority of whom had radiographically documented pneumonia, no obvious benefit of amantadine treatment was found [71]; however, because such patients often have recoverable virus after hospitalization (median duration, 4 days), antiviral treatment seems reasonable. Because of its broad influenza spectrum, low risk for resistance emergence, and lack of bronchospasm risk, oseltamivir is an appropriate treatment choice in hospitalized patients.

Antimicrobial therapies for infection with other pathogens that are associated with epidemiologic conditions are listed in Table 4. Clinicians should consider the importance of the epidemiologic association when choosing these agents and consider the need to provide effective therapy for the core group of pathogens (eg, *S pneumoniae* and atypical pathogens).

Pathogen-directed therapy

Once the cause of the infection has been identified through reliable microbiologic methods, most experts recommend that antimicrobial therapy be directed to that pathogen and not to the possibility of atypical pathogen co-infection; however, some authorities question this approach in light of recent data [72–74].

Treatment options may be simplified if the etiologic agent is established or strongly suspected (see Table 2). Diagnostic procedures that provide

identification of a specific cause within 24 to 72 hours still can be useful for guiding continued therapy. If an appropriate culture reveals the isolation of penicillin-susceptible *S pneumoniae*, therapy can be specified by selecting a narrow-spectrum agent, such as penicillin or amoxicillin. It is hoped that this approach reduces the selective pressure for resistance. This information is often available for consideration if the patient is switched from parenteral to oral therapy and may be used to direct specific antimicrobial choices.

Several studies suggest that dual therapy that includes an empiric macrolide reduces the mortality rate associated with bacteremic pneumococcal pneumonia. It is uncertain what the impact of these findings is on the principle of narrowing the regimen to effective monotherapy once the results of susceptibilities are known [72–74]. The results of these studies have led to the suggestion that these observations might result from the presence of unknown coinfection with an atypical pathogen. An alternative explanation is the immunomodulatory effects of macrolides. These studies have significant design limitations, as they are not prospective or randomized. They evaluated the effects of initial empiric therapy before the results of blood cultures were known and did not examine the effects of pathogen-specific therapy after the results of blood cultures were available.

The need to provide pathogen-specific therapy for anaerobic pathogens in patients with suspected aspiration pneumonia is uncertain. Some studies have shown that in this setting, patients improve without specific therapy directed at these pathogens [14].

As MRSA becomes more common in CAP, the most effective therapy will need to be defined. Most CA-MRSA strains reportedly have been associated with skin infections, but they also have been associated with pneumonia (primarily in children, although the authors have observed such cases in adults during the winter of 2003 to 2004). In general, these strains are more susceptible in vitro to non–β-lactam antimicrobial drugs than are hospital-acquired strains. They are often susceptible in vitro to trimethoprim/sulfamethoxazole and to the fluoroquinolones, although pockets of fluoroquinolone-resistant strains exist. They are often susceptible to clindamycin, but the emergence of resistance during therapy has been reported (especially in erythromycin-resistant strains). There is insufficient data on the use of these agents to treat adults with CA-MRSA pneumonia. Until such data become available, the authors recommend vancomycin or linezolid for initial therapy of such patients.

Recommendations for duration of therapy

Most patients with CAP receive treatment for at least 7 to 10 days, but few well-controlled studies have evaluated the optimal duration of therapy for these patients, both in and out of the hospital. Duration is difficult to define in a uniform fashion, because some antibiotics are administered for a short time, but have a long half-life at respiratory sites of infection

Table 4
Recommended antimicrobial therapy for specific pathogens

Organism	Preferred antimicrobial drugs	Alternative antimicrobial drugs
S pneumoniae Penicillin-nonresistant (MIC <2 μg/mL)	Pencillin G, amoxicillin	Macrolide, telithromycin, cephalosporins (oral cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren, parenteral cefuroxime, ceftriaxone, cefotaxime), clindamycin, doxycyline, respiratory fluoroquinolone[a]
S pneumoniae Penicillin-resistant MIC ≥2 μg/mL	Agents based on susceptibility, including, cefotaxime, ceftriaxone, fluorquinolone[a]; telithromycin (orally, only for mild infections)	Vancomycin, linezolid (high-dose amoxicillin, 3 g/d, should be effective for strains with penicillin [MIC ≤4 μg/mL])
H influenzae	Non–β-lactamase producing: amoxicillin β-Lactamase producing: second- or third-generation cephalosporin, amoxicillin/clavulanate	Fluoroquinolone,[a] doxycycline; azithromycin,[b] clarithromycin[b]
M pneumoniae/*C pneumoniae*	Macrolide, a tetracycline	Telithromycin, fluoroquinolone[a]
Legionella spp	Fluorquinolone,[a] azithromycin, clarithromycin	Doxycyline
C psittaci	A tetracycline	Macrolide
C burnetii	A tetracycline	Macrolide
Francisella tularensis	Doxycycline, Gentamicin, streptomycin	
Yersinisa pestis	Streptomycin, gentamicin	Doxycyline, fluoroquinolone
Anthrax (inhalation)	Ciprofloxacin	Other fluoroquinolones, doxycycline; penicillin, if susceptible
Enterobacteriaceae	Third-generation cephalosporin, carbapenem (drug of choice if extended spectrum β-lactamase producer)	β-lactam–β-lactamase inhibitor,[c] fluoroquinolone
P aeruginosa	Antipseudomonal β-lactam[d] plus ciprofloxacin or levofloxacin (750 mg daily) or aminoglycoside	Aminoglycoside plus ciprofloxacin or levofloxacin (750 mg daily)
B pseudomallei	Imipenem, ceftazidime	Fluoroquinolone, TMP/SMX
S aureus	Methicillin-susceptible: antistaphylococcus penicillin[e]	Cefazolin, clindamycin

Table 4 (*continued*)

Organism	Preferred antimicrobial drugs	Alternative antimicrobial drugs
	Methicillin-resistant[f]: vancomycin or linezolid	Trimethoprim/ sulfamethoxazole
Anaerobe (aspiration)	β-Lactam-β-lactamase inhibitor,[c] clindamycin	Carbapenem[g]
Influenza	Oseltamivir or zanamivir (influenza A or B); amantadine or rimantadine (influenza A)	For avian influenza: oseltamivir
Mycobacterium tuberculosis	Isoniazid plus rifampin plus ethambutol plus pyrazinamide	Refer to ATS/CDC/IDSA guidelines 2003 for specific recommendations
Coccidioides immitis	Uncomplicated infection in normal host: no therapy generally recommended For therapy: itraconazole, fluconazole	Amphotericin B
Histoplasma	Itraconazole	Amphotericin B

Choices should be modified based on susceptibility, test results, and advice from local specialists. Refer to local references for appropriate doses.

Abbreviations: ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America; TMP/SMX, trimethoprim/ sulfamethoxazole.

[a] Levofloxacin, gatifloxacin, moxifloxacin (not a first-line choice for penicillin-susceptible strains); ciprofloxacin is appropriate for *Legionella* spp, and most gram-negative bacilli (including *H influenza*).

[b] Azithromycin is more active in vitro than clarithromycin for *H influenza*.

[c] Ticarcillin/clavulanate; piperacillin/tazobactam for gram-negative bacilli; ampicillin/ sulbactam or amoxicillin/clavulanate is appropriate for oral anaerobes.

[d] Ticarcillin, piperacillin, ceftazidime, cefepime, aztreonam, imipenem, meropenem.

[e] Nafcillin, oxacillin flucloxacillin.

[f] See text regarding community-acquired MRSA.

[g] Imipenem/cilastatin, meropenem, ertapenem.

(eg, azithromycin). Most patients become clinically stable within 3 to 7 days, so longer durations of therapy are rarely necessary; however, patients with persistent clinical instability are often readmitted to the hospital and may not be candidates for short-term therapy. Short-term therapy may not be optimal for patients with bacteremic *S aureus* pneumonia because of the risks for associated endocarditis and deep-seated infection; patients with meningitis-complicating pneumonia; patients with *P aeruginosa* pneumonia, which is often a necrotizing pneumonia; and patients with infection caused by other less common pathogens. In one study, 8-day therapy of nosocomial pneumonia with *P aeruginosa* led to relapse more commonly than did 15-day therapy [75]. Studies that defined the duration of therapy focused on patients receiving accurate empiric therapy, and no data exist that well define the duration of treatment in patients who initially received an ineffective therapy regimen.

In trials of antibiotic therapy for CAP, azithromycin was used for 7 to 10 days as monotherapy in admitted patients (intravenous azithromycin for the initial 2–3 days of treatment, with the option of changing to oral treatment to complete the course) and for 3 to 5 days as oral therapy in outpatients. Some reports used one-dose therapy for patients with atypical pathogen infection [44,63,64,76]. The ketolide telithromycin has been used for 5 to 7 days to treat outpatients, including some patients with pneumococcal bacteremia or PSI classes of at least III [77]. The antipneumococcal quinolones have been used for 7 to 14 days in inpatients and outpatients, but most patients have a good clinical response within 2 to 3 days. Two studies of quinolones have shown that using quinolone doses that result in high antipneumococcal activity can lead to a rapid clinical response. In one study, more recipients of 750-mg levofloxacin than recipients of 500-mg levofloxacin became afebrile by day 3 (49.1% versus 38.5%; $P = 0.03$). In that study, the 750-mg dose was successful after only 5 days of therapy [78]. In another study, 58.9% of patients receiving 400 mg of moxifloxacin became afebrile by day 2 (this rate was higher than that for the comparator agent in the study), and 50% of these patients were switched to oral therapy by day 3 [79].

Based on the available data, the authors believe that patients with CAP should be treated for a minimum of 5 days, and therapy should not be stopped until patients are afebrile for 48 to 72 hours and have no more than one clinical instability. Longer durations of therapy may be needed if initial therapy was not active against the identified etiologic pathogen, and longer durations of therapy are needed if there is an extrapulmonary infection, such as meningitis or endocarditis. Patients with documented *S aureus* bacteremia, *P aeruginosa* pneumonia, or infection caused by several other less common pathogens (eg, *Burkholderia pseudomallei*, fungus) may need longer durations of therapy.

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