Treatment of community-acquired pneumonia in adults who require hospitalization

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INTRODUCTION — Community-acquired pneumonia (CAP) is defined as an acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community, as distinguished from hospital-acquired (nosocomial) pneumonia. A third category of pneumonia, designated "healthcare-associated pneumonia," is acquired in other healthcare facilities such as nursing homes, dialysis centers, and outpatient clinics.

CAP is a common and potentially serious illness. It is associated with considerable morbidity and mortality, particularly in elderly patients and those with significant comorbidities [1,2] . (See "Prognosis of community-acquired pneumonia in adults").

The treatment of CAP in adults who require hospitalization will be reviewed here. A variety of other important issues related to CA are discussed separately. These include:

- The diagnostic approach to patients with CAP. (See "Diagnostic approach to community-acquired pneumonia in adults").
- How one makes the decision to admit patients with CAP to the hospital. (See "Community-acquired pneumonia in adults: Risk stratification and the decision to admit").
- Treatment recommendations for CAP in patients treated in the outpatient setting. (See "Treatment of community-acquired pneumonia in adults in the outpatient setting").
- The evidence for efficacy of different antibiotic medications in the empiric treatment of CAP and issues related to drug resistance. (See "Antibiotic studies for the treatment of community-acquired pneumonia in adults").
- The epidemiology and microbiology of CAP. (See "Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults").
- Pneumonia in special populations, such as aspiration pneumonia, immunocompromised patients, and hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. (See "Aspiration pneumonia in adults" and see "Common pulmonary infections in immunocompromised patients" and see "Treatment of hospital-acquired (nosocomial); ventilator-associated; and healthcare-associated pneumonia in adults").

INDICATIONS FOR HOSPITALIZATION — Determination of whether a patient with CAP can safely be treated as an outpatient or requires hospitalization is essential before selecting an antibiotic regimen. Severity of illness is the most critical factor in making this determination, but other factors should also be taken into account. These include ability to maintain oral intake, likelihood of compliance, history of substance abuse, cognitive impairment, living situation, and patient functional status. These issues with appropriate references are discussed in detail elsewhere. (See "Community-acquired pneumonia in adults: Risk stratification and the decision to admit").

Summarized briefly, prediction rules have been developed to assist in the decision of site of care for CAP. The two most commonly used prediction rules are the Pneumonia Severity Index (PSI) and CURB-65. The PSI is better studied and validated, but requires a more complicated assessment.

CURB-65 uses five prognostic variables:

- Confusion (based upon a specific mental test or disorientation to person, place, or time)
- Urea (blood urea nitrogen in the United States) >7 mmol/L (20 mg/dL)
- Respiratory rate >30 breaths/minute
- Blood pressure [BP] (systolic <90 mmHg or diastolic <60 mmHg)
- Age >65 years

The authors of the original CURB-65 report suggested that patients with a CURB-65 score of 0 to 1, who comprised 45 percent of the original cohort and 61 percent of the later cohort, were at low risk and could probably be treated as outpatients. Those with a score of 2 should be admitted to the hospital, and those with a score of 3 or more should be assessed for ICU care, particularly if the score was 4 or 5.

A simplified version (CRB-65), which does not require testing for blood urea nitrogen, may be appropriate for decision-making in primary care practitioners' offices. With either version, admission to the hospital is recommended if one or more points are present.

Clinical judgment should be used for all patients, incorporating the prediction rule scores as a component of the decision for hospitalization or intensive care unit admission, but not as an absolute determinant [3] .

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PRINCIPLES OF ANTIMICROBIAL THERAPY —CAP can be caused by a variety of pathogens, with bacteria being the most common identifiable cause (show figure 1A-1C) [2,4,5] . The choice of initial therapy is complicated by the emergence of antibiotic resistance among Streptococcus pneumoniae, the most common bacterium responsible for CAP. (See "Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults" section on Microbiology, and see "Antibiotic studies for the treatment of community-acquired pneumonia in adults", section on Drug resistance and choice of therapy).

Empiric therapy — Antibiotic therapy is typically begun on an empiric basis, since the causative organism is not identified in an appreciable proportion of patients (show figure 1A-1C) [2,6] . In addition, the clinical features and chest radiographic findings are not sufficiently specific to determine etiology and influence treatment decisions. The Gram stain of respiratory secretions can be useful for directing the choice of initial therapy if performed on a good quality sputum sample and interpreted by skilled examiners using appropriate criteria [2] . (See "Diagnostic approach to community-acquired pneumonia in adults", section on Sputum).

Benefit from a pathogen-directed approach to treatment, particularly for moderate to severe CAP, may emerge as rapid diagnostic tests become more widely available. However, there has been some concern that narrowing the coverage spectrum of antibiotics when a specific pathogen is identified may undertreat patients who have concurrent infection with atypical organisms.

This concern was not borne out in a prospective randomized trial comparing pathogen-directed treatment (PDT) and empiric broad-spectrum antibiotic treatment (EAT) in 262 hospitalized patients with CAP [7] . PDT was based upon microbiologic studies (rapid diagnostic tests) or clinical presentation; EAT patients received a beta-lactam/beta-lactamase inhibitor plus erythromycin or if admitted to the intensive care unit, ceftazidime and erythromycin. Overall, clinical outcomes (length of stay, 30 day mortality, fever resolution, and clinical failure) were the same for both groups. Adverse events were more frequent in the EAT group, but were primarily related to the specific antimicrobial choice (ie, erythromycin).

Despite the general use of empiric therapy, testing for a microbial diagnosis is important in clinical or epidemiologic settings suggesting possible infection with an organism that requires treatment different from standard empiric regimens. These include Legionella species, influenza A and B or avian influenza, community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA), or agents of bioterrorism. (See "Diagnostic approach to community-acquired pneumonia in adults" and see "Sputum cultures", section on Community-acquired pneumonia).

The selection of antimicrobial regimens for empiric therapy is based upon a number of factors, including:

- The most likely pathogen(s). (See "Common pathogens" below).
- Clinical trials proving efficacy. (See "Antibiotic studies for the treatment of community-acquired pneumonia in adults").
- Risk factors for antimicrobial resistance. The choice of empiric therapy must take into account the emergence of antibiotic resistance among Streptococcus pneumoniae, the most common cause of CAP in adults who require hospitalization. (See "Risk factors for drug resistance" below).
- Medical comorbidities, which may influence the likelihood of a specific pathogen and may be a risk factor for treatment failure.

Additional factors that may affect the choice of antimicrobial regimen include the potential for inducing antimicrobial resistance, pharmacokinetic and pharmacodynamic properties, safety profile, and cost [8] .

The effectiveness of empiric antimicrobial regimens may be decreased by the emergence of newly recognized pathogens, such as community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA). (See "Epidemiology of methicillin-resistant Staphylococcus aureus infection in adults", section on CA-MRSA infection).

Common pathogens — Although a variety of bacterial pathogens can cause CAP, a limited number are responsible for the majority of cases. (See "Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults" , section on Microbiology).

With respect to patients who require hospitalization but not admission to an intensive care unit (ICU), the most frequently isolated pathogens are Streptococcus pneumoniae, respiratory viruses (eg, influenza, parainfluenza, respiratory syncytial virus), and, less often, Mycoplasma pneumoniae, Haemophilus influenzae, Chlamydophila pneumoniae, and Legionella (show figure 2).

The distribution is different in patients with CAP who require admission to an ICU. S. pneumoniae is most common but Legionella, gram-negative bacilli, and Staphylococcus aureus are also important (show figure 3). Community-associated MRSA typically produces a necrotizing pneumonia with high morbidity and mortality. (See "Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults", section on S. aureus).

Risk factors for CAP due to gram-negative bacilli include previous antibiotic therapy, immunosuppression, pulmonary comorbidity (eg, cystic fibrosis, bronchiectasis, or repeated exacerbations of chronic obstructive pulmonary disease that require frequent glucocorticoid and/or antibiotic use), probable aspiration, and multiple medical comorbidities (eg, diabetes mellitus, alcoholism) [2,8,9] . (See "Epidemiology, pathogenesis, and microbiology of community-acquired pneumonia in adults" , section on Gram-negative bacilli)

The 2007 Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines on the management of community-acquired pneumonia recommend empiric antibiotic therapy directed against P. aeruginosa in patients with gram-negative bacilli on Gram stain, since such a regimen will also cover other gram-negative bacilli, such as Klebsiella pneumoniae [2] . (See "Pseudomonas aeruginosa pneumonia" and see "Overview of Klebsiella pneumoniae infection" , section on Community-acquired pneumonia).

Risk factors for drug resistance — Risk factors for and other issues related to drug resistance in patients with CAP are discussed in detail elsewhere. (See "Antibiotic studies for the treatment of community-acquired pneumonia in adults", section on Drug resistance and choice of therapy).

Summarized briefly, risk factors for drug-resistant S. pneumoniae in adults include:

- Age >65 years
- Beta-lactam, macrolide, or fluoroquinolone therapy within the past three to six months
- Alcoholism
- Medical comorbidities
- Immunosuppressive illness or therapy
- Exposure to a child in a day care center

Recent therapy or a repeated course of therapy with beta-lactams, macrolides, or fluoroquinolones is a risk factor for pneumococcal resistance to the same class of antibiotic.

The impact of discordant drug therapy, which refers to treatment of an infection with an antimicrobial agent to which the causativ organism has demonstrated in vitro resistance, appears to vary with antibiotic class and possibly with specific agents within a clas Most studies have been performed in patients with S. pneumoniae infection and suggest that current levels of beta-lactam resistance generally do not cause treatment failure when appropriate agents (eg, amoxicillin, ceftriaxone, cefotaxime) and doses are used. Cefuroxime is a possible exception with beta-lactams and there appears to be an increased risk of macrolide failure in patients with macrolide-resistant S. pneumoniae. (See "Antibiotic studies for the treatment of community-acquired pneumonia in adults", section on Outcomes with discordant drug therapy).

GUIDELINES — A number of medical societies have issued guidelines for the treatment of CAP [2,10,11] . The antibiotic regimen advocated by a collaboration between the Infectious Disease Society of America and the American Thoracic Society (IDSA/ATS) in 2007 [2] , and guidelines from the British Thoracic Society (BTS) in 2004 [10] are summarized in Table 1 (show table 1).

The following discussion will review antibiotic therapy in patients with CAP who require hospitalization. Guideline recommendations for therapy in patients with CAP treated in the outpatient setting are presented separately. (See "Treatment of community-acquired pneumonia in adults in the outpatient setting").

- For hospitalized patients on the general wards, the IDSA/ATS guidelines recommend an antipneumococcal fluoroquinolone (eg, levofloxacin, moxifloxacin) or the combination of a beta-lactam plus a macrolide (show table 1) [2] .
- For patients with severe CAP requiring intensive care unit (ICU) admission, the IDSA/ATS guidelines recommend a beta-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) plus either intravenous azithromycin or an antipneumococcal fluoroquinolone unless there is concern for Pseudomonas or methicillin-resistant S. aureus (MRSA) infection. If Pseudomona is a concern, an antipseudomonal agent (piperacillin-tazobactam, imipenem, meropenem, or cefepime) PLUS an antipseudomonal fluoroquinolone (ciprofloxacin or high-dose levofloxacin) should be used. If MRSA is a concern, either vancomycin or linezolid should be added (show table 1) (See "Admitted to an ICU" below) [2] .
- The BTS guidelines tend to select older antibiotics than those recommended in North America (show table 1) [10] .

In studies from different regions of the world, atypical pathogens account for 20 to 30 percent of cases of CAP in hospitalized patients [12] . However, the value of providing empiric coverage for atypical pathogens (eg, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila, and Haemophilus influenzae) is unclear.

This issue was addressed in a meta-analysis of 24 randomized trials of over 5000 patients with CAP requiring hospitalization; mos trials compared fluoroquinolone monotherapy to non-atypical monotherapy [13] . There was no significant difference in mortality (RR 1.13, 95% CI 0.82-1.54) or adverse effects between the atypical arm and non-atypical arm. There was a nonsignificant trend toward clinical success in the atypical arm, a difference that disappeared when only methodologically high quality trials were evaluated. Clinical success was significantly higher in the atypical arm for L. pneumophila. The trials were not designed to compar the time to response with different regimens.

An international observational study of over 4300 hospitalized patients with CAP published after the meta-analysis found that antimicrobial regimens with atypical coverage, compared to regimens that did not have atypical coverage, were associated with significant reductions in time to clinical stability (3.2 versus 3.7 days), length of stay in hospital (6.1 versus 7.1 days), and CAP-related mortality (3.8 versus 6.4 percent) [12] .

A well-designed prospective trial is required to more definitively determine the need to cover atypical pathogens in empiric regimens for CAP requiring hospitalization [13] .

TREATMENT REGIMENS —Antibiotic recommendations for hospitalized patients with CAP are divided by the site of care (ICU or non-ICU). Most hospitalized patients are initially treated with an intravenous regimen. However, many patients without risk factor for severe pneumonia can be treated with oral therapy, especially with highly bioavailable agents such as the fluoroquinolones [14] .

Hospitalized patients with CAP are initially treated with empiric antibiotic therapy. When the etiology of CAP has been identified based upon reliable microbiologic methods, and there is no laboratory or epidemiologic evidence of coinfection, treatment regimens may be simplified and directed to that pathogen. The results of diagnostic studies that provide identification of a specific etiology within 24 to 72 hours can be useful for guiding continued therapy. (See "Diagnostic approach to community-acquired pneumonia in adults").

Pathogen-specific therapy is discussed separately. (See "Pneumococcal pneumonia in adults" and see "Mycoplasma pneumoniae infection in adults" and see "Pneumonia caused by Chlamydophila (Chlamydia) species in adults" and see "Treatment and prevention of Legionella infection" and see "Pseudomonas aeruginosa pneumonia" and see "Overview of Klebsiella pneumoniae infection").

Pneumonia in patients admitted to the hospital from long-term care facilities is not considered community-acquired. It is

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categorized as "healthcare-associated pneumonia" and is discussed separately. (See "Epidemiology, pathogenesis, and microbiology of hospital-acquired (nosocomial); ventilator-associated; and healthcare-associated pneumonia in adults" and see "Important sites and pathogens causing infections in long term care facilities").

Not in the ICU — For patients admitted to a general ward, we suggest one of the following regimens:

- Combination therapy with ceftriaxone (1 to 2 g IV daily) or cefotaxime (1 to 2 g IV every 8 hours) plus azithromycin (500 mg IV or orally daily).
- Monotherapy with a respiratory fluoroquinolone given either IV or orally except as noted (levofloxacin 750 mg daily or moxifloxacin 400 mg daily or gemifloxacin 320 mg daily [only available in oral formulation]).

If the patient has risk factors for drug-resistant pathogens, such as Pseudomonas or methicillin-resistant Staphylococcus aureus, coverage for these organisms should be included, as discussed in the following section.

Admitted to an ICU

Empiric therapy — Patients requiring admission to an ICU are more likely to have risk factors for resistant pathogens, including community-associated MRSA and Legionella spp.

We recommend intravenous combination therapy with a potent anti-pneumococcal beta-lactam (ceftriaxone 2 g daily or cefotaxime 2 g every eight hours) plus either an advanced macrolide (azithromycin 500 mg daily) or a respiratory fluoroquinolone (levofloxacin 750 mg daily or moxifloxacin 400 mg daily).

In patients (particularly those with bronchiectasis or COPD and frequent antimicrobial or glucocorticoid use) who may be infected with Pseudomonas aeruginosa or other resistant pathogens, therapy should include agents effective against the pneumococcus, P. aeruginosa, and Legionella spp. Acceptable regimens include the following:

- Combination therapy with a beta-lactam antibiotic and fluoroquinolone:

Piperacillin-tazobactam (4.5 g every six hours) OR
Imipenem (500 mg IV every six hours) OR
Meropenem (1 g every eight hours) OR
Cefepime (2 g every eight hours) OR
Ceftazidime (2 g every 8 hours)

PLUS

Ciprofloxacin (400 mg every 8 hours) OR
Levofloxacin (750 mg daily) OR

For beta-lactam allergic patients, options include: aztreonam (2 g every 6 hours) plus levofloxacin (750 mg daily); or aztreonam plus moxifloxacin plus an aminoglycoside.

The fluoroquinolones may be administered orally when the patient is able to take oral medications. The dose of levofloxacin is the same when given intravenously and orally, while the dose of ciprofloxacin is 750 mg orally twice daily.

If the Gram stain suggests S. aureus, we recommend treatment for MRSA with the addition of vancomycin (15 mg/kg every 12 hours, adjusted for renal function) or linezolid (600 mg intravenously twice daily) until the results of culture and susceptibility testing are known. Linezolid may be given orally when the patient is able to receive oral medications. We also suggest empiric therapy of MRSA in patients with severe CAP who have risk factors for community-acquired (CA)-MRSA (prior antimicrobial therapy or recent influenza-like illness). If MRSA is not isolated, coverage for this organism should be discontinued.

CA-MRSA — The treatment of MRSA pneumonia has been best studied in patients with hospital-acquired pneumonia and is discussed in detail separately. (See "Treatment of hospital-acquired (nosocomial); ventilator-associated; and healthcare-associated pneumonia in adults", section on MRSA).

Although CA-MRSA is typically susceptible to more antibiotics than HA-MRSA, it appears to be more virulent, in part due to the presence of panton-valentine leukocidin (PVL). Optimal treatment is not well-defined. Vancomycin or linezolid is recommended, although there is a lack of data regarding therapy of this disease [15] . One concern with vancomycin is the increasing MICs of MRSA that have emerged over the past decade, which may reduce the efficacy of vancomycin in pulmonary infection. In addition, CA-MRSA causes a necrotizing pneumonia associated with PVL and other toxin production. Vancomycin does not decrease toxin production, whereas linezolid has been shown to reduce toxin production in experimental models [16,17] .

CA-MRSA as the cause of CAP should be suspected when pneumonia develops in a person known to be colonized with CA-MRSA or in those with risk factors for CA-MRSA colonization (eg, contact sport participants, injection drug users, those living in crowded conditions, men who have sex with men, prisoners). CA-MRSA pneumonia should also be suspected in young, previously healthy adults with a recent influenza-like illness.

Factors associated with rapid mortality include infection with influenza, the need for ventilator or inotropic support, onset of respiratory distress syndrome, hemoptysis, and leukopenia. In a report of 51 cases of CAP caused by S. aureus (79 percent of which were MRSA), 39 percent had a WBC count <4000/microL, and this finding was associated with a poor prognosis. In contrast, a WBC >10,000/microL appeared to be protective [18] .

Fluoroquinolone monotherapy — The role of monotherapy with a respiratory fluoroquinolone has not been established for severe CAP. In an observational study of 270 patients with CAP and shock, the 58 percent treated with combination antibiotic therapy (with a third-generation cephalosporin and a macrolide) had a significantly higher 28-day in-ICU survival than the 42 percent who received fluoroquinolone monotherapy (HR 1.69, 95% CI 1.09-2.60) [19] . Survival was not different comparing combination and monotherapy in ICU patients without shock. If the patient has pneumococcal meningitis, monotherapy with a

fluoroquinolone is not recommended. (See "Treatment and prevention of bacterial meningitis in adults", section on S. pneumoniae).

Timing of antimicrobial initiation — The benefit of prompt initiation of antimicrobial therapy has been evaluated, with more recent findings questioning if this is an independent risk factor for outcome:

- In a retrospective study of 13,771 Medicare patients, antibiotic administration within four hours of hospital arrival was associated with reductions in mortality (6.8 compared to 7.4 percent with delay in antibiotics) and length of stay (0.4 days shorter) [20] .
- A retrospective study of 603 patients with CAP at a single academic center found no difference in the time to clinical stability between those who received antibiotics within four hours and those whose treatment was later [21] .
- The time to first antibiotic dose was not independently associated with mortality in an observational study of 451 CAP patients from another tertiary center [22] . Delay in antibiotics was more common in patients with an altered mental status or signs of sepsis. Time to first antibiotic dose was possibly a marker of comorbidities driving both an atypical presentation and mortality rather than directly contributing to the outcome. Diagnostic uncertainty led to delay of initial antimicrobial therapy in another study [23] .
- A retrospective study of 548 patients found that when the required time to first antibiotic dose changed from eight hours to four hours, a reduction in the accuracy of the initial diagnosis of CAP occurred, although the mean time to first antibiotic dose was similar in both groups [24] .

The United States National Pneumonia Medicare Quality Improvement Project and the National Quality Forum have changed the recommended target for administration of antimicrobial therapy from four to six hours [25-27] . The previously recommended four hour window resulted in the unintended consequence of overuse of antimicrobials before the diagnosis of pneumonia could be definitively established [26,28,29] .

Clinical response to therapy — With appropriate antibiotic therapy, some improvement in the patient's clinical course is usually seen within 48 to 72 hours (show table 2). Patients who do not demonstrate some clinical improvement within 72 hours are considered nonresponders. (See "The nonresponding patient" below).

The time course of the clinical response to therapy is illustrated by the following observations:

- In a prospective, multicenter cohort study of 686 adults hospitalized with CAP, the median time to becoming afebrile, defined as 38.3 ºC (101 ºF), was two days, and three days if defined as either 37.8 ºC (100 ºF) or 37.2 ºC (99 ºF) [30] . However, fever in patients with lobar pneumonia may take three days or longer to improve.
- In a second prospective, multicenter trial of 1424 patients hospitalized with CAP, the median time to stability (defined as resolution of fever, heart rate <100 beats/min, respiratory rate <24 breaths/min, systolic blood pressure of ≥ 90 mmHg, and oxygen saturation ≥ 90 percent for patients not receiving prior home oxygen) was four days [31] .

Although a clinical response to appropriate antibiotic therapy is seen relatively quickly, the time to resolution of all symptoms and radiographic findings is more prolonged. With pneumococcal pneumonia, for example, the cough usually resolves within eight days and auscultatory crackles clear within three weeks. (See "Pneumococcal pneumonia in adults").

In addition, as many as 87 percent of inpatients with CAP have persistence of at least one pneumonia-related symptom (eg, fatigue, cough with or without sputum production, dyspnea, chest pain) at 30 days compared to 65 percent by history in the month prior to the onset of CAP [32] . Patients should be told that some symptoms can last this long so that they are able to set reasonable expectations for their clinical course. (See "Prognosis of community-acquired pneumonia in adults", section on Mortality and symptom resolution).

Radiographic response — Radiographic improvement typically lags behind the clinical response [33-36] . This issue was addressed in a prospective multicenter trial of 288 patients hospitalized for severe CAP; the patients were followed for 28 days in order to assess the timing of resolution of chest x-ray abnormalities [33] . The following findings were noted:

- At day 7, 56 percent had clinical improvement but only 25 had resolution of chest x-ray abnormalities.
- At day 28, 78 percent had attained clinical cure but only 53 percent had resolution of chest x-ray abnormalities. The clinical outcomes were not significantly different between patients with and without deterioration of chest x-ray findings during the follow-up period.
- Delayed radiographic resolution was independently associated with multilobar disease. In other studies, the timing of radiologic resolution of the pneumonia varied with patient age and the presence of underlying lung disease [34,35] . The chest x-ray usually cleared within four weeks in patients younger than 50 years of age without underlying pulmonary disease. In contrast, resolution could be delayed for 12 weeks or more in older individuals and in those with underlying lung disease.

Switch to oral therapy — Patients requiring hospitalization for CAP are generally begun on intravenous therapy. They can be switched to oral therapy when they are improving clinically, hemodynamically stable, able to take oral medications, and have a normally functioning gastrointestinal tract [2] .

Two prospective observational studies in 253 patients evaluated the clinical outcome of an early switch from intravenous to oral therapy in the treatment of CAP [37,38] . Patients met the following criteria prior to switching: resolution of fever, improvement in respiratory function, decrease in white blood cell (WBC) count, and normal gastrointestinal tract absorption. Only two patients failed treatment and the protocol was associated with high patient satisfaction [38] .

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Similar outcomes were noted in a multicenter randomized trial in the Netherlands of 265 patients with CAP (mean age 70) admitted to non-intensive care wards [39] . Patients were initially treated with three days of intravenous antibiotics and, when clinically stable, were assigned either to oral antibiotics to complete a total course of ten days, or to a standard regimen of seven days of intravenous antibiotics. There was no difference in 28 day mortality (4 versus 2 percent) or clinical cure rate (83 versus 8 percent), while the length of hospital stay was reduced in the oral switch group by a mean of 1.9 days (9.6 versus 11.5 days).

If the pathogen has been identified, the choice of oral antibiotic therapy is based upon the susceptibility profile. If a pathogen is not identified, the choice of antibiotic for oral therapy is either the same as the intravenous antibiotic, or in the same drug class. I patients who are treated with the combination of intravenous beta-lactam/macrolide, a switch to oral therapy with a macrolide alone is reasonable if there is no risk for DRSP, the prevalence of DRSP is low in the community, and a gram-negative enteric bacillus is not isolated or considered likely based on epidemiologic factors. (See "Risk factors for drug resistance" above and see "Treatment of community-acquired pneumonia in adults in the outpatient setting", section on Treatment regimens).

Documentation of pneumococcal bacteremia does not appear to alter the effect of switching to oral therapy early (no clinical failures in 18 such patients switched based upon the above criteria in one report) [40] .

Duration of hospitalization — Several studies have shown that it is not necessary to observe stable patients overnight after switching from intravenous to oral therapy, although this has been common practice [2,41,41,42] . As an example, a retrospective review of the United States Medicare National Pneumonia Project database compared outcomes between patients hospitalized for CAP who were not (n = 2536) and were (n = 2712) observed overnight after switching to oral therapy [42] . The following findings were noted:

- No significant difference in 14-day hospital readmission rate (7.8 versus 7.2 percent)
- No significant difference in the 30-day mortality rate (5.1 versus 4.4 percent).

The importance of clinical stability at discharge was illustrated in a prospective observational study of 373 Israeli patients discharged with a diagnosis of CAP [43] . On the last day of hospitalization seven parameters of instability were evaluated (temperature >37.8 ºC [100 ºF], respiratory rate >24/min, heart rate (HR) >100 beats/min, systolic BP ≤ 90 mmHg, oxygen saturation <90 percent on room air, inability to receive oral nutrition, and change of mental status from baseline). At 60 days pos discharge, patients with at least one parameter of instability at discharge were significantly more likely to have died or required readmission than patients with no parameters of instability (death rates, 14.6 versus 2.1 percent; readmission rates, 14.6 versus 6.5 percent).

Duration of therapy — Based upon the available data, we agree with the recommendation of the IDSA/ATS guidelines that patients with CAP should be treated for a minimum of five days [2] . Support for this recommendation comes from a meta-analysis of 15 randomized controlled trials of almost 2800 patients with mild to moderate CAP, which found comparable clinical outcomes with less than seven days compared to more than seven days of antimicrobial therapy; however, only two of these trials were specifically about hospitalized patients [44] . (See "Antibiotic studies for the treatment of community-acquired pneumonia in adults", section on Duration of therapy).

Before stopping therapy, the patient should be afebrile for 48 to 72 hours, breathing without supplemental oxygen (unless require for preexisting disease), and have no more than one clinical instability factor (defined as heart rate [HR] >100 beats/min, respiratory rate [RR] >24 breaths/min, and systolic blood pressure [SBP] ≤ 90 mmHg) [2] .

Longer durations of therapy are needed in the following settings:

- If the initial therapy was not active against the subsequently identified pathogen (see "The nonresponding patient" below)
- If extrapulmonary infection is identified (eg, meningitis or endocarditis)
- If the patient has documented S. aureus bacteremia, P. aeruginosa pneumonia, or pneumonia caused by some unusual and less common pathogens (eg, Burkholderia pseudomallei, fungus)

The duration of therapy in these patients should be individualized based upon the clinical response to treatment and patient comorbidities.

Follow-up chest radiograph — Chest x-ray findings usually clear more slowly than clinical manifestations (see "Radiographic response" above). Routine chest x-rays for follow-up of CAP patients who are responding clinically are unnecessary. Some authorities recommend a follow-up chest x-ray at 7 to 12 weeks after treatment for selected patients who are over age 40 years or are smokers, to document resolution of the pneumonia and exclude underlying diseases, such as malignancy [45] .

The nonresponding patient — Issues relating to nonresolving pneumonia are discussed in detail separately. This section will b limited to a general overview of nonresponding pneumonia in patients with CAP who require hospitalization. (See "Nonresolving pneumonia")

It has been estimated that 6 to 15 percent of hospitalized patients with CAP do not respond to initial antibiotic therapy, most withi the first 72 hours, and the failure rate may be as high as 40 percent in patients initially admitted to an ICU [2,46-48] . These patients have significantly increased mortality compared to responders [2,47,48] . (See "Prognosis of community-acquired pneumonia in adults", section on The nonresponding patient).

Two general patterns of nonresponse have been described in patients with CAP [2,46] :

- Progressive pneumonia or clinical deterioration, with requirement for ventilator support and/or septic shock usually occurrin in the first 72 hours. Deterioration after 72 hours is often due to an intercurrent complication, progression of the underlying infection, or a superimposed nosocomial infection. Many patients who ultimately require ICU admission for CAP are initially admitted to a non-ICU ward and then transferred because of clinical deterioration (59 of 113 in one report, 50 in the first 2

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hours) [49] .

- Persistent or nonresponding pneumonia, defined as the absence of or delay in achieving clinical stability after 72 hours of antibiotic therapy.

The most common causes of treatment failure are lack of or delayed response by the host despite appropriate antibiotics and infection with an organism that is not covered by the initial antibiotic regimen [2,46,50] . Patient-related factors include severity o illness, neoplasia, aspiration pneumonia, and neurologic disease (show table 3) [50] , while lack of responsiveness to initial therapy may be due to drug-resistant organisms, unusual pathogens (eg, Legionella spp, Pneumocystis jirovecii [formerly P. carinii] or Mycobacterium tuberculosis), or an infectious complication, such as postobstructive pneumonia, empyema, abscess, or superimposed nosocomial pneumonia [2,46] .

In a review of treatment failure in 49 hospitalized patients with CAP, a definite diagnosis was established in 32 and a probable diagnosis was made in nine [46] . The major causes were infection with a pathogen not detected in the initial evaluation (atypical or unusual pathogens or pathogens associated with the development of empyema), persistent infection with the same pathogen, usually reflecting resistance to initial empiric therapy, and nosocomial infection with a new pathogen, most often associated with ventilator-associated pneumonia.

In addition, treatment failure may be wrongly presumed when the infiltrates are responding slowly but the patient has developed a superimposed problem [2,36,46,51] . These include noninfectious entities, such as drug fever, malignancy, interstitial lung disease (eg, bronchiolitis obliterans organizing pneumonia), inflammatory conditions, or heart failure, or a hospital-acquired infection of another body system (eg, intravascular catheter infection, urinary tract infection due to an indwelling urinary catheter, or Clostridium difficile infection) (show table 3). Noninfectious causes were considered responsible for nine of the treatment failures in the above series of 49 patients [46] .

Treatment failure may also be incorrectly diagnosed in patients who have repeat sputum cultures that grow a new pathogen. The upper airway of hospitalized patients receiving antibiotics may become colonized, particularly with gram-negative bacilli and S. aureus, and may be misinterpreted as contributing to the pneumonia. Thus, repeat sputum cultures should be interpreted with caution.

Risk factors — A number of studies have evaluated risk factors for nonresponse in hospitalized patients with CAP [47,48,52] . The rate of treatment failure in different large series was 13 and 15 percent overall [47,52] , with early treatment failure (lack of response or worsening at 48 to 72 hours) occurring in 6 percent [48] .

A prospective multicenter study identified risk factors for treatment failure in CAP, which occurred in 15 percent of 1424 hospitalized patients [47] . Independent risk factors were multilobar pneumonia, cavitation on chest x-ray, pleural effusion, liver disease, leukopenia, and a high PSI. Three factors were protective: influenza vaccination, chronic obstructive pulmonary disease, and treatment with a fluoroquinolone.

A second observational analysis of 1383 hospitalized adults with CAP identified the following risk factors for early treatment failure (lack of response or worsening at 48 to 72 hours) [48] :

- Multilobar pneumonia
- Pneumonia caused by Legionella or gram-negative organisms
- Pneumonia Severity Index (PSI) >90
- Treatment with an antimicrobial agent to which the causative organism was not susceptible

Further evaluation — When evaluating a patient who is not responding to therapy, the initial approach may include repeating the history (including travel and pet exposures to look for unusual pathogens), chest x-ray, and sputum and blood cultures [2,46] . If this is unrevealing, then further diagnostic procedures, such as chest CT, bronchoscopy, and, lung biopsy can be performed. (See "Nonresolving pneumonia", section on Further evaluation of nonresolving pneumonia).

- Chest CT can detect pleural effusion, lung abscess, or central airway obstruction, all of which can cause treatment failure. It may also detect noninfectious causes such as bronchiolitis obliterans organizing pneumonia [2] . Since empyema and parapneumonic effusion can contribute to nonresponse, thoracentesis should be performed in all nonresponding patients wit significant pleural fluid accumulation.

- Bronchoscopy can evaluate the airway for obstruction due to a foreign body or malignancy, which can cause a postobstructive pneumonia. Protected brushings and bronchoalveolar lavage (BAL) may be obtained for microbiologic and cytologic studies; in some cases, transbronchial biopsy may be helpful. The microbiologic evaluation of the nonresponding patient can be complicated by the effect of the initial antimicrobial therapy that may reduce the yield of pathogen isolation, or select for colonization with resistant organisms. In addition, BAL may reveal evidence of noninfectious disorders or, if the is a lymphocytic rather than neutrophilic alveolitis, viral or Chlamydophila infection [53] .

Thoracoscopic or open lung biopsy may be performed if all of these procedures are nondiagnostic and the patient continues to be ill. The advent of thoracoscopic procedures has significantly reduced the need for open lung biopsy, and its associated morbidity.

Management — Failure to respond to antibiotics usually results in one or more of the following: patient transfer to a higher level of care; further diagnostic testing; and escalation of or change in treatment [2] . There is no convincing evidence of benefit from combination antibiotic therapy in patients with progressive disease [2] with the exception of severe bacteremic pneumococca pneumonia requiring admission to an ICU [54] . This is a presumed reflection of the primary importance of severe illness at presentation or delayed treatment response due to host factors. (See "Nonresolving pneumonia" and see "Pneumococcal pneumonia in adults", section on Bacteremic pneumonia).

VACCINATION — Patients with CAP should be appropriately vaccinated for influenza and pneumococcal infection [2] . Screening for influenza vaccination status is warranted from October through February in patients age 50 and older or with other indications

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for vaccination. Screening for pneumococcal vaccination status is warranted in patients age 65 or older or with other indications fo vaccination. Vaccination can be performed at hospital discharge or during outpatient treatment. (See "Influenza vaccination in adults" and see "Pneumococcal vaccination in adults").

SMOKING CESSATION — Smoking cessation should be a goal for hospitalized patients with CAP who smoke [2] . (See "Management of smoking cessation").

PERFORMANCE MEASURES — The Centers for Medicare and Medicaid Services (CMS), as part of the National Pneumonia Medicare Quality Improvement Project [25] and Joint Commission on Accreditation of Healthcare Organizations (JCAHO), have established performance indicators to assess the quality of hospital care for pneumonia patients (show table 4). These indicators are also endorsed by the National Quality Forum [25] .

The primary intent of these indicators is to implement evidence-based processes of care to maximize survival rates for pneumonia patients. These performance measures are based on studies demonstrating effectiveness for individual components, but data are lacking on the effect of the measures taken as a composite.

Compliance with these measures has been linked to reimbursement (ie, Pay for Performance). Concern has been raised that this may drive pressure for hospitals and physicians to act based on these measures rather than on what may be best for an individua patient [55] , or for triaging other patients in an emergency department [27] . Specific performance measures cannot cover all host and epidemiological settings, especially when the presentation of pneumonia is atypical [56] , and deviation from the performance measurement criteria may be reasonable in particular circumstances [26] ; the reason for deviation should be documented in the chart.

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "Patient information: Pneumonia in adults"). We encourage you to print or e-mail this topic review, or to refer patients to our public web site, www.uptodate.com/patients , which includes this and other topics.

SUMMARY AND RECOMMENDATIONS

- Most initial treatment regimens for hospitalized patients with community-acquired pneumonia (CAP) are empiric. A limited number of pathogens are responsible for the majority of cases (show figure 2 and show figure 3). (See "Principles of antimicrobial therapy" above).
- Emerging drug-resistant S. pneumoniae (DRSP) complicates the use of empiric treatment. Treatment failures have been demonstrated with use of macrolides for macrolide-resistant organisms. Most pneumococci respond to higher dose beta-lactams, other than cefuroxime. (See "Risk factors for drug resistance" above).
- For hospitalized patients not requiring ICU admission, we suggest initial combination therapy with a third-generation cephalosporin (ceftriaxone or cefotaxime) plus azithromycin, or monotherapy with a quinolone (levofloxacin, moxifloxacin, or gemifloxacin) (**Grade 1B**). Coverage for drug-resistant pathogens, such as Pseudomonas or methicillin-resistant Staphylococcus aureus, should be included in patients with risk factors. (See "Not in the ICU" above).
- For hospitalized patients requiring ICU care, we suggest initial combination therapy with a third-generation cephalosporin (ceftriaxone or cefotaxime) plus either intravenous therapy with azithromycin or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) (**Grade 2B**). Coverage for drug-resistant pathogens, such as Pseudomonas or methicillin-resistant Staphylococcus aureus, should be included in patients with risk factors. (See "Admitted to an ICU" above).
- We suggest that empiric treatment regimens be modified when results of diagnostic studies indicate a specific pathogen, an coinfection is unlikely based upon clinical or epidemiological data (**Grade 2B**).
- Patients should demonstrate some improvement in clinical parameters by 72 hours, although fever may persist with lobar pneumonia. Cough from pneumococcal pneumonia may not clear for a week; abnormal chest x-ray findings usually clear within four weeks but may persist for 12 weeks in older individuals, and those with underlying pulmonary disease. (See "Clinical response to therapy" above).
- We suggest switching from intravenous to oral therapy when patients are hemodynamically stable, demonstrate some clinical improvement (in fever, respiratory status, white blood count) and are able to take oral medications (**Grade 2A**). (See "Switch to oral therapy" above).
- We suggest hospital discharge when the patient can take oral medication; we suggest not keeping the patient overnight for observation following the switch (**Grade 2B**). (See "Duration of hospitalization" above).
- Routine follow-up chest x-rays for patients who are responding clinically within the first week are unnecessary. We suggest a follow-up chest x-ray at 7 to 12 weeks after treatment for patients who are over age 40 years or are smokers, to document resolution of the pneumonia and exclude underlying diseases, such as malignancy (**Grade 2C**). (See "Follow-up chest radiograph" above).
- The most common cause of treatment failure is the lack of response by the host despite appropriate antibiotics. Risk factors for treatment failure include neoplasia, aspiration pneumonia, neurologic disease, multilobar pneumonia, Legionella or gram-negative infection, high pneumonia severity index (>90), antibiotic-resistant pathogen, cavitation, pleural effusion, liver disease, and leukopenia. (See "The nonresponding patient" above).

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GRAPHICS

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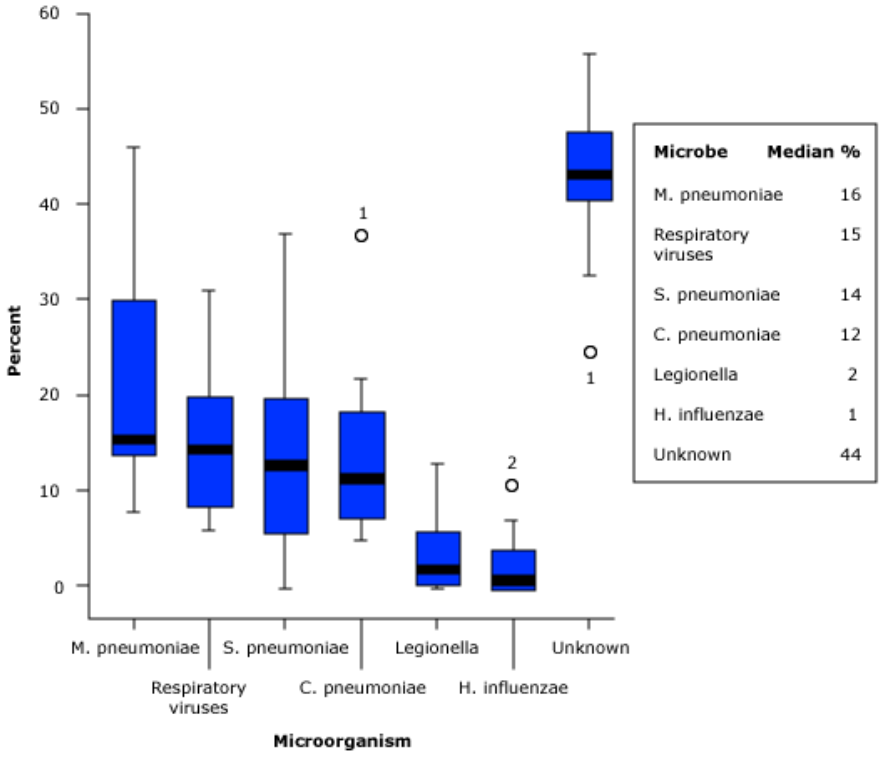
Causes of community-acquired pneumonia in ambulatory patients



A box plot depicting the causes of CAP in immunocompetent adults as reported by workers from several studies in worldwide locations whose data could be abstracted by site of care (see text for full references). The bottom and top horizontal lines mark the boundaries of the 5th and 95th percentiles for each microorganism. The box encompasses the 25th through the 75th percentiles. Within the box, the horizontal line represents the median (50th percentile) for each organism. O with number (reference, see below) represents the percent for outlying studies. *1. Chest 2003; 123:1512.*
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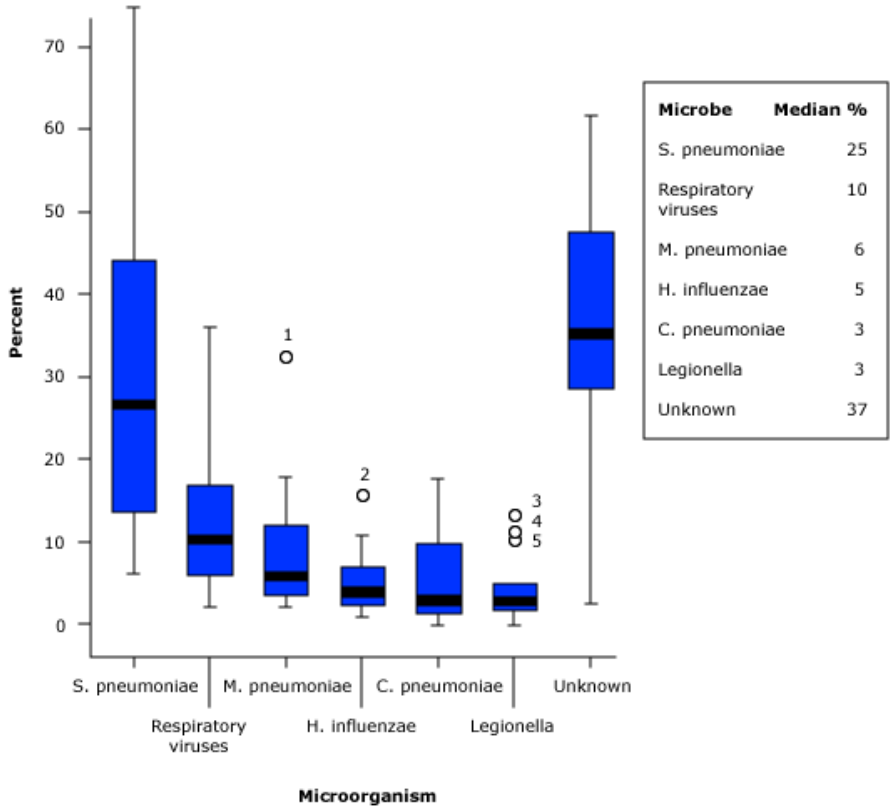
Causes of community-acquired pneumonia in hospitalized patients (non-ICU)



A box plot depicting the causes of CAP in immunocompetent adults as reported by workers from several studies in worldwide locations whose data could be abstracted by site of care (see text for full references). The bottom and top horizontal lines mark the boundaries of the 5th and 95th percentiles for each microorganism. The box encompasses the 25th through the 75th percentiles. Within the box, the horizontal line represents the median (50th percentile) for each organism. O with number (reference, see below) represents the percent for outlying studies. *1. Arch Intern Med 1997; 157:1709.*
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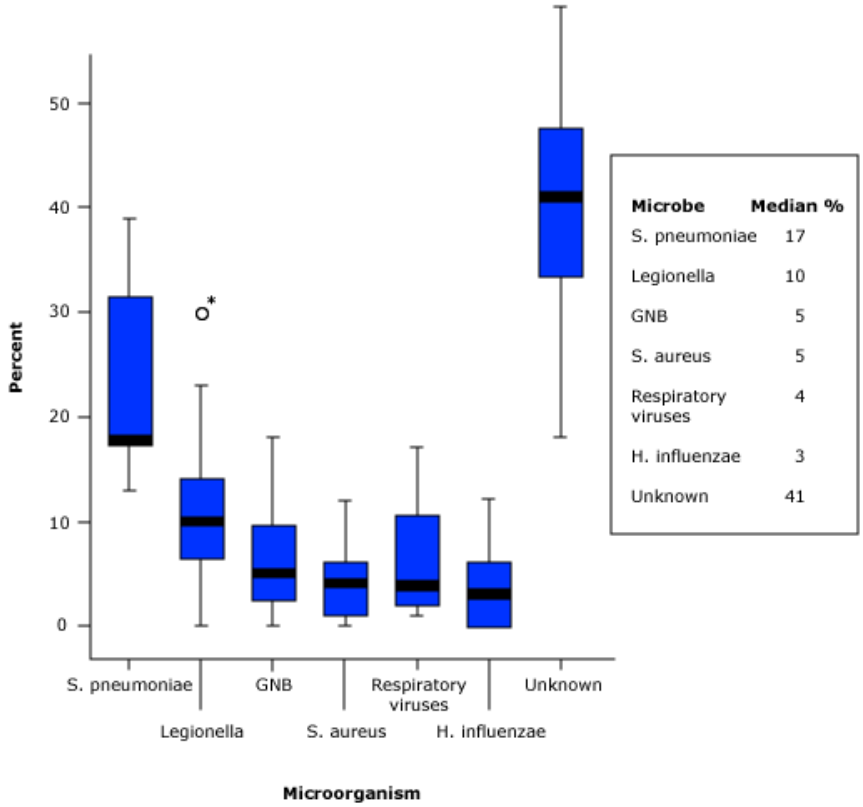
Causes of community-acquired pneumonia in ICU patients (severe CAP)



A box plot depicting the causes of CAP in immunocompetent adults as reported by workers from several studies in worldwide locations whose data could be abstracted by site of care (see text for full references). The bottom and top horizontal lines mark the boundaries of the 5th and 95th percentiles for each microorganism. The box encompasses the 25th through the 75th percentiles. Within the box, the horizontal line represents the median (50th percentile) for each organism. O with number (reference, see below) represents the percent for an outlying study.
GNB: Gram negative bacilli.
** J Infect 1985; 10:204.*

Comparison of recommendations of published guidelines for empiric antimicrobial therapy of community-acquired pneumonia in adults (from North America, United Kingdom)

Guideline	Site of care		
	Outpatient	**General ward**	**ICU/severe**
North American Guideline (ATS/IDSA; 2007) [1]	If no significant risks for DRSP*: Macrolide∆ or doxycycline If risks for DRSP*: Antipneumococcal fluoroquinolone• **OR** High-dose amoxicillin (3 gm/day) or high dose amoxicillin/clavulanate (4 gm/day) **plus** macrolide (if amoxicillin is used and there is a concern for H. influenzae, use macrolide active for β-lactamase producing strains∆)	β-lactam (ceftriaxone, cefotaxime, ampicillin/sulbactam, ertapenem) **plus** macrolide (can use doxycycline if macrolide not tolerated) **OR** Antipneumococcal fluoroquinolone• alone	β-lactam (ceftriaxone, cefotaxime, ampicillin/sulbactam) **plus** IV azithromycin or IV fluoroquinolone• If concern for Pseudomonas (eg, presence of structural lung disease such as bronchiectasis): antipseudomonal agent (piperacillin/tazobactam, imipenem, meropenem, or cefepime) **plus** antipseudomonal fluoroquinolone (ciprofloxacin or high dose levofloxacin); If concern for MRSA (see text): add vancomycin or linezolid

British Thoracic Society (2004) [2]	Amoxicillin 500-1000 mg thrice daily; (Alternative therapy: erythromycin or clarithromycin)	If admitted for non-clinical reasons or previously untreated in the community: Amoxicillin (macrolide as alternative) If admitted for pneumonia and oral therapy appropriate: Amoxicillin **plus** (erythromycin or clarithromycin); (Alternative therapy: antipneumococcal fluoroquinolone•) If parenteral therapy appropriate: Ampicillin or benzylpenicillin **plus** (erythromycin or clarithromycin); (Alternative therapy: IV levofloxacin, note IV moxifloxacin not available in UK)	Co-amoxiclav or 2nd/3rd generation cephalosporin **plus** (IV erythromycin or clarithromycin, +/- rifampin); (IV levofloxacin **plus** IV benzylpenicillin as alternative)

ICU: intensive care unit; DRSP: drug resistant S. pneumoniae; UK: United Kingdom; IV: intravenous.
* Antimicrobial 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.
• Gemifloxacin, Levofloxacin, Moxifloxacin (Gemifloxacin is only available in oral formulation).
Δ Azithromycin or clarithromycin.
1. Clin Infect Dis. 2007.
2. British Thoracic Society. Pneumonia Guidelines Committee (John MacFarlane, Chair). Guidelines for the management of community-acquired pneumonia-2004 Update. www.Brit-thoracic.org/guideline.

Usual duration of findings in treated community-acquired pneumonia

Abnormality	Duration (days)
Fever	2 to 4
Cough	4 to 9
Crackles	3 to 6
Leukocytosis	3 to 4
C-reactive protein elevation	1 to 3

Comorbidities associated with delayed resolution of pneumonia

Condition	Effects
Chronic obstructive pulmonary disease	Impaired cough and mucociliary clearance
Alcoholism	Aspiration, malnutrition, impaired neutrophil function
Neurologic disease	Aspiration, impaired clearance of secretions and cough
Heart failure	Edema fluid, impaired lymphatic drainage
Chronic kidney disease	Hypocomplementemia, impaired macrophage and neutrophil function, reduced humoral immunity
Malignancy	Impaired immune function, altered colonization, effects of chemotherapy
Human immunodeficiency virus	Impaired cell-mediated and humoral immunity
Diabetes mellitus	Impaired neutrophil function and cell-mediated immunity

Performance measures for the treatment of patients hospitalized with community-acquired pneumonia

1. Assessment of arterial oxygenation by arterial blood gas or pulse oximetry
2. Screening and administration of pneumococcal vaccination if indicated for patients age 65 or older
3. Blood cultures performed in the emergency department should be obtained prior to initial antibiotic received in the hospital
4. Blood cultures performed within 24 hours prior to or 24 hour after hospital arrival for patients admitted or transferred to the intensive care unit within 24 hours of hospital arrival
5. Receipt of the first dose of antibiotic within six hours of arrival at hospital
6. Antibiotic selection consistent with current guidelines during the first 24 hours of hospitalization
7. Adult smoking cessation advice/counseling, if warranted
8. Screening for influenza vaccination status, administration of influenza vaccine if indicated, for patients age 50 and older, discharged during October-February

Grade 1B recommendation

A Grade 1B recommendation is a strong recommendation, and applies to most patients. Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Explanation:
A Grade 1 recommendation is a strong recommendation. It means that we believe that if you follow the recommendation, you will be doing more good than harm for most, if not all of your patients.
Grade B means that the best estimates of the critical benefits and risks come from randomized, controlled trials with important limitations (eg, inconsistent results, methodologic flaws, imprecise results, extrapolation from a different population or setting) or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimates of benefit and risk, and may change the estimates.

Recommendation grades
1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

Evidence grades
A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

For a complete description of our grading system, please see the UpToDate editorial policy which can be found by clicking "About UpToDate" and then selecting "Policies".

Grade 2B recommendation

A Grade 2B recommendation is a weak recommendation; alternative approaches may be better for some patients under some circumstances.
Explanation:
A Grade 2 recommendation is a weak recommendation. It means "this is our suggestion, but you may want to think about it." It is unlikely that you should follow the suggested approach in all your patients, and you might reasonably choose an alternative approach. For Grade 2 recommendations, benefits and risks may be finely balanced, or the benefits and risks may be uncertain. In deciding whether to follow a Grade 2 recommendation in an individual patient, you may want to think about your patient's values and preferences or about your patient's risk aversion.
Grade B means that the best estimates of the critical benefits and risks come from randomized, controlled trials with important limitations (eg, inconsistent results, methodologic flaws, imprecise results, extrapolation from a different population or setting) or very strong evidence of some other form. Further research (if performed) is likely to have an impact on our confidence in the estimates of benefit and risk, and may change the estimates.

Recommendation grades
1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

Evidence grades
A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

For a complete description of our grading system, please see the UpToDate editorial policy which can be found by clicking "About UpToDate" and then selecting "Policies".

Grade 2A recommendation

A Grade 2A recommendation is a weak recommendation, and the best action may differ depending on circumstances or patient or societal values.

Explanation:

A Grade 2 recommendation is a weak recommendation. It means "this is our suggestion, but you may want to think about it." It is unlikely that you should follow the suggested approach in all your patients, and you might reasonably choose an alternative approach. For Grade 2 recommendations, benefits and risks may be finely balanced, or the benefits and risks may be uncertain. In deciding whether to follow a Grade 2 recommendation in an individual patient, you may want to think about your patient's values and preferences or about your patient's risk aversion.

Grade A means that the best estimates of the critical benefits and risks come from consistent data from well-performed, randomized, controlled trials or overwhelming data of some other form (eg, well-executed observational studies with very large treatment effects). Further research is unlikely to have an impact on our confidence in the estimates of benefit and risk.

Recommendation grades
1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

Evidence grades
A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

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Grade 2C recommendation

A Grade 2C recommendation is a very weak recommendation; other alternatives may be equally reasonable.

Explanation:

A Grade 2 recommendation is a weak recommendation. It means "this is our suggestion, but you may want to think about it." It is unlikely that you should follow the suggested approach in all your patients, and you might reasonably choose an alternative approach. For Grade 2 recommendations, benefits and risks may be finely balanced, or the benefits and risks may be uncertain. In deciding whether to follow a Grade 2 recommendation in an individual patient, you may want to think about your patient's values and preferences or about your patient's risk aversion.

Grade C means the evidence comes from observational studies, unsystematic clinical experience, or from randomized, controlled trials with serious flaws. Any estimate of effect is uncertain.

Recommendation grades
1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

Evidence grades
A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

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