

CLINICAL PRACTICE

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Community-Acquired Pneumonia

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

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A 66-year-old man with underlying chronic obstructive pulmonary disease (COPD) presents to the emergency department with a 2-day history of fever, dyspnea, and cough productive of green, purulent sputum. He had noted increasing dyspnea 3 days before the onset of fever. He describes one episode of acute exacerbation of COPD that occurred 6 months earlier. The physical examination is notable for mild respiratory distress and confusion, with disorientation to time. His temperature is 38.6°C, heart rate 100 beats per minute, blood pressure 140/85 mm Hg, respiratory rate 24 breaths per minute, and oxygen saturation 92% while he is breathing ambient air. Auscultation of the lungs reveals coarse rhonchi over the right midlung field. Chest radiography reveals right upper-lobe consolidation (Fig. 1). His white-cell count is 14,000 per cubic millimeter, platelet count 159,000 per cubic millimeter, serum sodium 136 mmol per liter, blood urea nitrogen 19 mg per deciliter (6.8 mmol per liter), creatinine 1.1 mg per deciliter (97.2 μmol per liter), and procalcitonin 5.4 ng per milliliter (normal range, 0.00 to 0.05). A multiplex viral panel was positive for respiratory syncytial virus. How would you further evaluate and treat this patient?

THE CLINICAL PROBLEM

Community-acquired pneumonia is an acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community (as distinguished from an infection acquired in a hospital). In the United States, community-acquired pneumonia is one of the leading causes of hospitalization and death, with approximately 6 million cases reported each year.¹⁻⁶ The annual incidence of hospitalization for community-acquired pneumonia in the United States is approximately 650 adults per 100,000 population, corresponding to 1.5 million unique hospitalizations for the disease each year.⁶ Factors that increase the risk of community-acquired pneumonia include advanced age, chronic lung disease, chronic heart disease, cardiovascular disease, diabetes mellitus, malnutrition, viral respiratory tract infections, immunocompromising conditions, and lifestyle factors such as smoking and excessive alcohol consumption.

The development of pneumonia is influenced by a combination of factors, including host susceptibility, pathogen virulence, and the inoculum of microorganisms reaching the lower airways. Respiratory pathogens must overcome several defense mechanisms of the respiratory system before reaching the alveoli. These defenses include mucus trapping, mucociliary clearance, coughing, and swallowing. Pathogens can reach the alveoli by means of microaspiration (aspiration of small amounts of oropharyngeal secretions that often occurs during sleep), inhalation, macroaspira-

KEY CLINICAL POINTS

COMMUNITY-ACQUIRED PNEUMONIA

- The diagnosis of community-acquired pneumonia is made on the basis of compatible symptoms and signs, with evidence of a new infiltrate on an imaging study.
- Most outpatients with mild community-acquired pneumonia can be treated empirically without diagnostic testing for bacteria. However, testing for SARS-CoV-2 and influenza should be considered.
- A comprehensive approach to microbiologic testing for hospitalized patients is recommended for determining the appropriate pathogen-directed therapy.
- The choice of antimicrobial therapy for community-acquired pneumonia varies according to severity, coexisting conditions, and the likelihood of antimicrobial-resistant organisms.

tion (aspiration of a large amount of oropharyngeal or upper gastrointestinal contents), or hematogenous spread. Microaspiration is the primary path for microorganisms into the lungs, and macroaspiration may lead to aspiration pneumonia.⁷ The alveolar macrophage is the primary defense mechanism in the lung. The lung microbiome may also contribute to defense mechanisms by producing antimicrobial molecules or competing for nutrients.⁸

If pathogens overcome the alveolar defense mechanisms, they will multiply and cause local tissue damage. Injured host cells then produce damage-associated molecular patterns that further stimulate alveolar macrophages to produce cytokines and chemokines, triggering a local inflammatory response. Cytokine spillover into the bloodstream produces a systemic inflammatory response. The local and systemic inflammatory responses constitute a physiologic response to lung

infection. The inflammatory responses explain most of the host patient's signs and symptoms as well as laboratory and imaging abnormalities (Fig. 2). In some patients, the initial systemic inflammatory response can become dysregulated and result in tissue injury and eventual organ dysfunction.⁹

Numerous microorganisms can cause community-acquired pneumonia. The bacteria and viruses that are considered to be likely etiologic agents in all patients with community-acquired pneumonia are described as core respiratory pathogens (Table 1).¹⁰⁻¹² Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is now a predominant viral pathogen in patients with community-acquired pneumonia. Uncommon or infrequent causes of community-acquired pneumonia should be considered as likely agents in patients who present with risk factors for a particular pathogen (e.g., travel or animal exposure) (Table S3 in

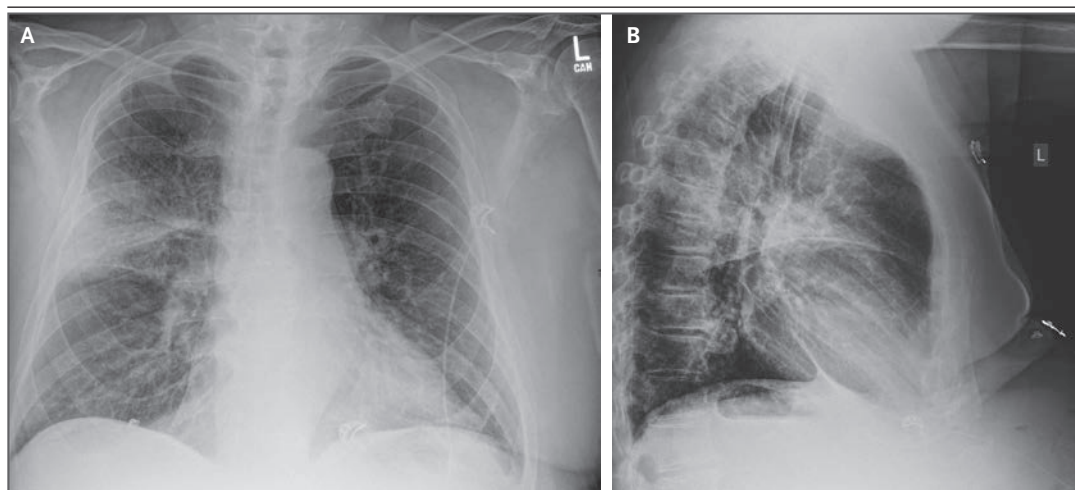
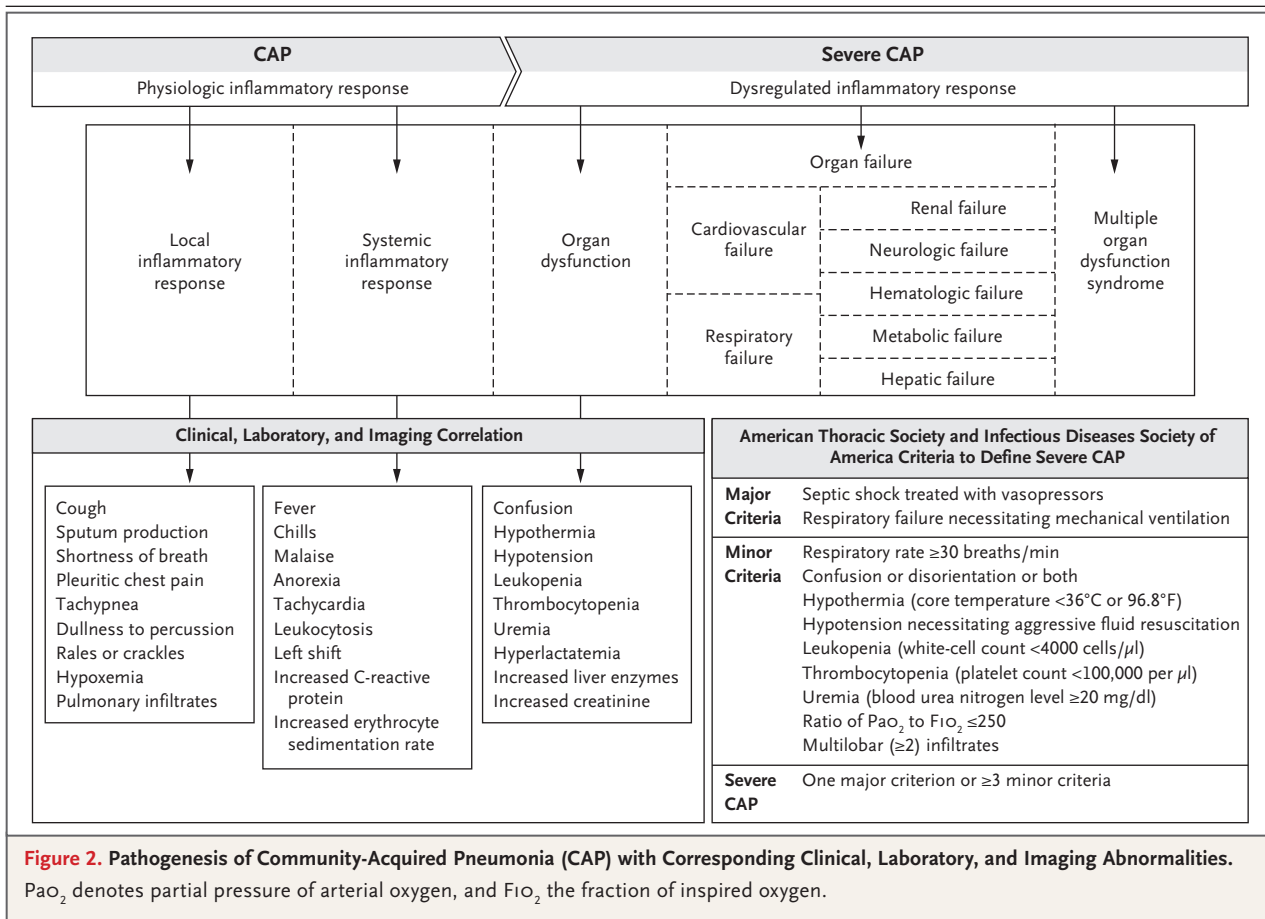


Figure 1. Chest Radiographs.

Posteroanterior (Panel A) and lateral (Panel B) views show right upper-lobe infiltrate.



the Supplementary Appendix, available with the full text of this article at NEJM.org) or in special populations, such as immunocompromised patients (Table 1).¹²

Although community-acquired pneumonia has traditionally been viewed as an acute disease of the lungs, the current understanding is that it is a multisystem disease that can result in acute and long-term sequelae (Fig. 3).^{13,14} Community-acquired pneumonia is associated with substantial long-term illness and death, with death at 1 year occurring in approximately 30% of all hospitalized patients and in approximately 50% of patients whose conditions had resulted in admission to the intensive care unit (ICU).^{6,15}

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

The diagnosis of community-acquired pneumonia is made on the basis of infiltrates shown on a

chest radiograph (or on computed tomography in a patient with symptoms if a chest radiograph is negative), plus supporting symptoms, signs consistent with airspace disease (e.g., rales, rhonchi, or egophony), or laboratory abnormalities resulting from the local and systemic inflammatory responses (Fig. 2). Testing for the inflammatory biomarker procalcitonin may supplement clinical judgment with regard to diagnosis and course of bacterial community-acquired pneumonia, since synthesis of procalcitonin is triggered by specific cytokines in response to bacteria. Although the procalcitonin level is typically elevated in bacterial community-acquired pneumonia, it is low in viral community-acquired pneumonia. Procalcitonin levels quickly decline with the resolution of bacterial infection, a response that can inform the decision to discontinue treatment with antimicrobials.¹⁶⁻¹⁸ However, procalcitonin levels are not definite indicators, since false positives can occur (e.g., in hemorrhagic shock or kidney injury),

and some bacteria (e.g., mycoplasma) may cause pneumonia in patients with normal procalcitonin levels. If access to chest radiography is limited, a diagnosis can be suggested by the findings from a comprehensive examination, including evidence of lung consolidation. Community-acquired pneumonia is considered to be severe if there are manifestations of organ dysfunction or organ failure. The American Thoracic Society and Infectious Diseases Society of America (ATS–IDSA) criteria for defining severe community-acquired pneumonia are shown in Figure 2.¹

SITE OF CARE

The decision regarding the site of care depends on many variables, including severity of illness, associated disease, presence of hypoxemia, adequacy of home support, and probability of adherence to treatment. The severity of a patient's illness is primarily a determination based on clinical judgment, which can be supplemented by the use of severity scores. The most commonly used severity scores are the Pneumonia Severity Index (PSI) and CURB-65, a score that incorporates confusion, urea, respiratory rate, blood pressure, and age ≥ 65 years.^{19,20} Calculations for determining PSI scores are provided in the Supplementary Appendix. The CURB-65 scale ranges from 0 to 5; scores are calculated by assigning 1 point each for the presence of new-onset confusion, blood urea nitrogen level greater than 19 mg per deciliter, respiratory rate greater than 30 breaths per minute, systolic blood pressure less than 90 mm Hg or diastolic blood pressure less than 60 mm Hg, and age of 65 years or older. Outpatient treatment is recommended for a patient with a CURB-65 score of 0 or 1, a short hospital stay or close observation should be considered for a patient with a score of 2, and hospitalization is recommended for a patient with a score of 3 to 5. Indications for ICU care are based on further criteria, including the use of mechanical ventilation and the presence of shock (Fig. 2). Severity score thresholds have not been defined for the treatment of patients who are immunocompromised; thresholds for admission should be based on clinical judgment.¹²

MICROBIOLOGIC TESTING

The identification of the causative agents of community-acquired pneumonia was limited in the past because there were no rapid, easily performed,

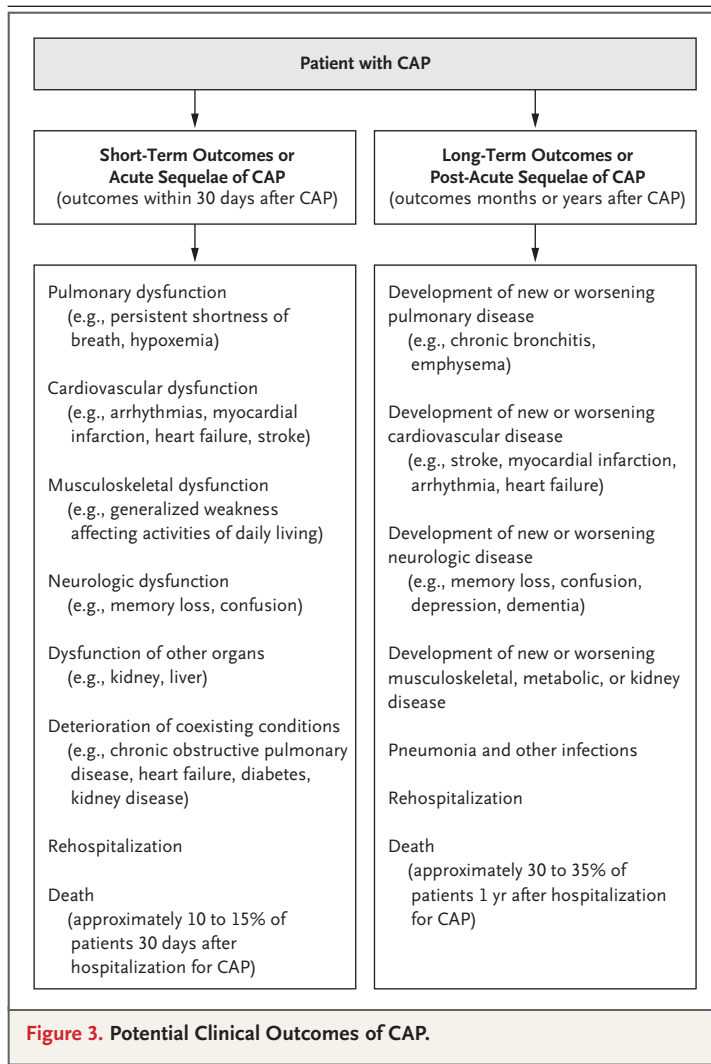
Table 1. Respiratory Pathogens in Community-Acquired Pneumonia (CAP).*

Pathogen Group	Pathogen
Common or core	
Gram-positive bacteria	<i>Streptococcus pneumoniae</i> , methicillin-susceptible <i>Staphylococcus aureus</i> , <i>Strep. pyogenes</i> , other streptococci
Gram-negative bacteria	<i>Hemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , Enterobacteriaceae (e.g., <i>Klebsiella pneumoniae</i>)
Atypical bacteria	<i>Legionella pneumophila</i> , <i>Mycoplasma pneumoniae</i> , <i>Chlamydophila pneumoniae</i>
Respiratory viruses	Influenza virus, SARS-CoV-2, respiratory syncytial virus, parainfluenza virus, human metapneumovirus, rhinoviruses, common human coronaviruses
Uncommon or infrequent	
Gram-positive bacteria	Methicillin-resistant <i>Staph. aureus</i> , nocardia species, <i>Rhodococcus equi</i>
Gram-negative bacteria	Enterobacteriaceae, including extended-spectrum beta-lactamases or carbapenem-resistant enterobacteriaceae; nonfermenting bacilli (e.g., pseudomonas or acinetobacter); <i>Francisella tularensis</i>
Atypical bacteria	<i>Chlamydia psittaci</i> , <i>Coxiella burnetii</i>
Mycobacteria	<i>Mycobacterium tuberculosis</i> , nontuberculous mycobacteria
Viruses	Cytomegalovirus, herpes simplex, varicella zoster, MERS-CoV
Fungi	<i>Pneumocystis jirovecii</i> , aspergillus species, mucorales species, histoplasma species, cryptococcus species, blastomyces species, coccidioides species
Parasites	<i>Strongyloides stercoralis</i> , <i>Toxoplasma gondii</i>

* Risk factors associated with specific pathogens are shown in Table S3. MERS-CoV denotes Middle East respiratory syndrome coronavirus, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

accurate, and cost-effective methods of obtaining results for most patients at the point of service. However, molecular diagnostic techniques that combine sensitivity, specificity, and a rapid turnaround time are becoming increasingly available.^{21–23} The coronavirus disease 2019 (Covid-19) pandemic has illustrated the etiologic importance of respiratory viruses that are primarily identified by molecular testing.

Microbiologic testing for bacterial causes is generally not recommended for most patients who are treated in ambulatory settings, since empirical antibiotic therapy is largely successful. However, testing for viruses (e.g., SARS-CoV-2 and influenza) should be considered, since the results can affect the choice of therapy. Establishing an



etiologic diagnosis of community-acquired pneumonia in hospitalized patients is important for several reasons, including the appropriate selection of an antibiotic for use against a specific pathogen, promote good antimicrobial stewardship, and allow identification of pathogens associated with notifiable diseases such as SARS-CoV-2 infection or legionnaires' disease. Available recommended tests include sputum Gram's staining and culture, blood cultures, urine immunochromatographic analysis for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1, and molecular techniques such as multiplex assays that include SARS-CoV-2. In addition, if there is a risk of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, obtaining a nasal swab for a

MRSA polymerase-chain-reaction (PCR) assay can be useful, since a negative result can allow for discontinuation of anti-MRSA therapy.²⁴ A more comprehensive microbiologic workup should be performed on the basis of epidemiologic exposures as well as individual patient characteristics such as immunosuppression.¹²

TREATMENT

Empirical antimicrobial therapy targets common pathogens on the basis of risk factors.¹ Antiviral therapy for influenza or SARS-CoV-2 infection should be administered according to clinical factors, the results of diagnostic tests, or both.^{1,25} Therapy should be administered as soon as possible after community-acquired pneumonia is diagnosed. Therapy for patients who are immunocompromised is beyond the scope of this article and has been described elsewhere.¹²

Ambulatory Patients

For most patients who are younger than 65 years of age, otherwise healthy, and have not recently received treatment with antibiotics, recent ATS–IDSA guidelines recommend one of the following three oral medication options: amoxicillin (1 g three times daily), doxycycline (100 mg twice daily), or a macrolide (azithromycin at a dose of 500 mg on day 1, then 250 mg daily, or clarithromycin at a dose of 500 mg twice daily [extended-release, 1000 mg daily]). Macrolides should be considered only in areas where pneumococcal resistance to macrolides is less than 25% — which excludes the United States, where resistance exceeds 30%.

For patients who have taken antibiotics within the past 3 months, have serious coexisting conditions (e.g., chronic heart, lung, kidney, or liver disease; diabetes mellitus; or alcohol dependence), or who are smokers, amoxicillin–clavulanate (875 mg orally twice daily [extended-release, 2 g twice daily]) and either a macrolide (preferred) or doxycycline are recommended. Patients who cannot take beta-lactam agents owing to hypersensitivity or adverse effects can instead be treated with a respiratory fluoroquinolone (levofloxacin at a dose of 750 mg daily or moxifloxacin at a dose of 400 mg daily) or one of two more recently approved agents, lefamulin or omadacycline.^{26,27}

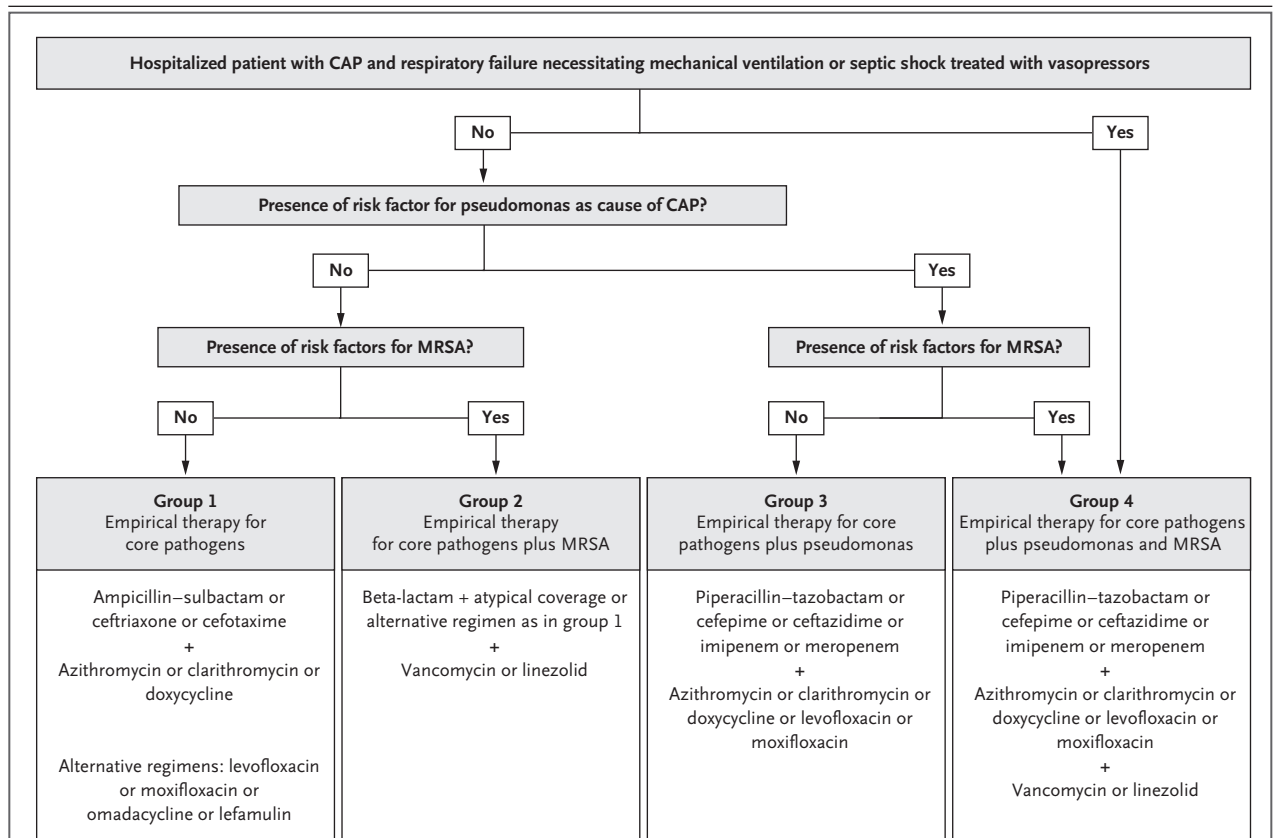


Figure 4. Empirical Therapy for Hospitalized Patients with CAP.

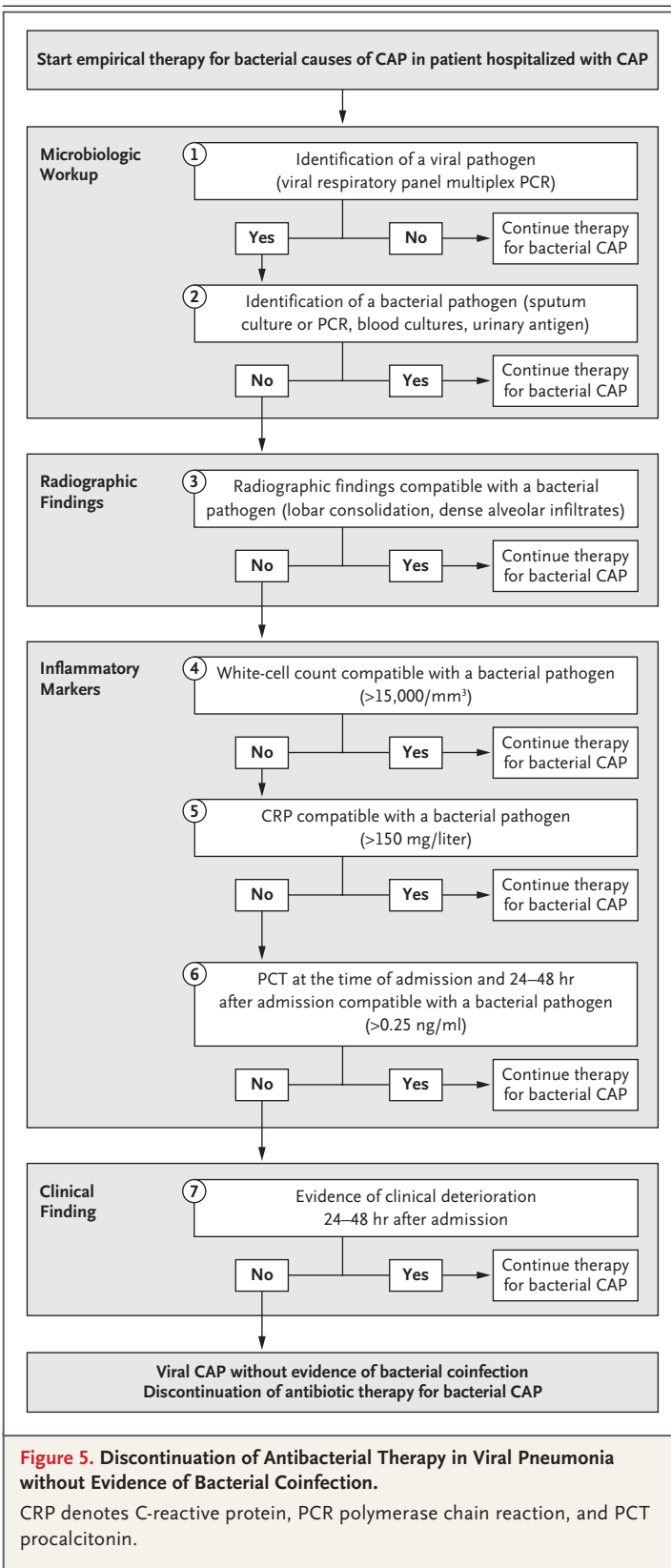
In the presence of severe CAP with respiratory failure necessitating mechanical ventilation or shock treated with vasopressors, initial therapy against methicillin-resistant *Staphylococcus aureus* (MRSA) and pseudomonas can be considered, pending assessment for risk factors and subsequent microbiologic test results. Strong risk factors for pseudomonas include known colonization or previous infection and gram-negative bacilli on Gram's staining; weak risk factors include receipt of intravenous (IV) antibiotics in the previous 3 months, bronchiectasis, and frequent exacerbations of chronic obstructive pulmonary disease necessitating glucocorticoid therapy or antibiotic use. Strong risk factors for MRSA include known colonization or previous infection and gram-positive cocci in clusters on Gram's staining; weak risk factors include receipt of IV antibiotics in the previous 3 months, recent influenza-like illness, cavitory infiltrate or empyema, and end-stage renal disease. In the presence of any strong risk factors, initiation of empirical therapy targeting MRSA or *Pseudomonas aeruginosa* is recommended. However, in patients with weak risk factors, the decision to initiate empirical therapy for multidrug-resistant pathogens should be based on clinical judgment and individual assessment. For patients in group 1 who are receiving care in the intensive care unit, combination therapy is recommended with a beta-lactam plus macrolide or a beta-lactam plus fluoroquinolone. The selection of an antipseudomonal antibiotic should be made on the basis of the susceptibilities of previous isolates or hospital antibiograms (or both), if available. Empirical therapy with two agents may be needed if the local prevalence of drug-resistant strains is high or in patients with a history of multidrug-resistant infection. The combination of piperacillin–tazobactam and vancomycin has been associated with acute kidney injury; we generally avoid this combination if possible. Recommended therapies and doses for patients with normal renal function are ampicillin–sulbactam (3 g IV every 6 hours), ceftriaxone (1 to 2 g IV daily), cefotaxime (1 to 2 g IV every 8 hours), azithromycin (500 mg IV or orally daily), clarithromycin (500 mg twice daily) or clarithromycin XL (two 500-mg tablets once daily), doxycycline (100 mg orally or IV twice daily), levofloxacin (750 mg IV or orally daily), moxifloxacin (400 mg IV or orally daily), omadacycline (200-mg IV loading dose on day 1 followed by 100 mg IV daily, or 300 mg orally twice daily on day 1 then 300 mg daily), lefamulin (150 mg IV every 12 hours or 600 mg orally every 12 hours), vancomycin (15 to 20 mg per kilogram of body weight IV every 8 to 12 hours or a loading dose of 20 to 35 mg per kilogram IV not to exceed 3000 mg for severe CAP; subsequent dose amounts should be based on area-under-the-curve values), linezolid (600 mg IV or orally twice daily), piperacillin–tazobactam (4.5 g IV every 6 hours), ceftazidime (2 g IV every 8 hours), imipenem (500 mg IV every 6 hours), and meropenem (1 g IV every 8 hours).

Hospitalized Patients

The choice of the appropriate antibiotic agent for treatment of a patient who has been admitted to the hospital is based on the presence of risk factors for MRSA or pseudomonas (or both), as shown in Figure 4. In patients admitted to a general ward without risk factors for MRSA or pseudomonas, combination therapy with a beta-lactam plus a macrolide or doxycycline or monotherapy with a fluoroquinolone is recommended (see group 1 in Fig. 4). Although data from randomized trials are lacking, many observational studies have suggested that macrolide combination regimens are associated with better clinical outcomes in patients with severe community-acquired pneumonia, possibly owing to the immunomodulatory effects of macrolides.²⁸⁻³¹ If risk factors for MRSA, pseudomonas, or other gram-negative pathogens not covered by the standard community-acquired pneumonia regimens outlined above are present, coverage should be expanded (see groups 2, 3, and 4 in Fig. 4).

Patients with severe community-acquired pneumonia who are admitted to the ICU are more likely to be at risk for resistant pathogens, including MRSA and pseudomonas.^{1,32,33} The establishment of an etiologic diagnosis is important in the treatment of these patients. Evidence to guide appropriate therapy in patients with severe community-acquired pneumonia is limited, but common practice is to administer anti-MRSA therapy and antipseudomonas therapy to patients in the ICU who have shock that is being treated with vasopressors or respiratory failure that necessitates mechanical ventilation, pending results of cultures and PCR tests (group 4 in Fig. 4).³⁴

Therapies that modify the host response, such as dexamethasone, interleukin-6 inhibitors, and kinase inhibitors, have been established for patients with community-acquired pneumonia due to SARS-CoV-2 infection.²⁵ The use of glucocorticoids in the treatment of other causes of community-acquired pneumonia is evolving, with recent evidence showing a benefit of survival among patients with severe community-acquired pneumonia (i.e., patients who had been admitted to the ICU and had received mechanical ventilation) and patients at high risk for respiratory failure who had been treated with hydrocortisone at a dose of 200 mg daily initially, followed by a taper.³⁵ Glucocorticoid therapy should be avoided in patients with influenza or aspergillus pneumonia.



DE-ESCALATION OF ANTIMICROBIAL THERAPY

If the etiologic cause of community-acquired pneumonia has been identified by means of reliable microbiologic methods and there is no laboratory or epidemiologic evidence of coinfection, treatment regimens should be simplified and directed toward that pathogen.^{36,37} If a causative pathogen is not identified, empirical treatment should be continued, provided the patient's symptoms are abating. If a screening nasal swab for MRSA is negative, empirical anti-MRSA therapy can usually be discontinued.

In patients in whom viral community-acquired pneumonia is suspected owing to the identification of a virus (including SARS-CoV-2) by means of a molecular test and in whom there is no evidence of concurrent bacterial infection or clinical deterioration, antibacterial treatment can be discontinued (Fig. 5). Most patients have some clinical improvement within 48 to 72 hours after the start of antibacterial treatment. Intravenous antibiotic regimens can be transitioned to oral regimens with a similar spectrum activity as the patient's condition improves.^{38,39}

DURATION OF THERAPY

Typically, patients continue to receive treatment until they have been afebrile and in a clinically stable condition for at least 48 hours. Treatment should usually continue for a minimum of 5 days; however, 3 days may be an adequate treatment duration for certain patients whose condition is completely stable.⁴⁰⁻⁴² Extended courses of therapy may be indicated for patients with immunocompromising conditions, infections caused by certain pathogens (e.g., *P. aeruginosa*), or complications such as empyema. Serial procalcitonin thresholds as an adjunct to clinical judgment may help guide the discontinuation of antibiotic therapy.^{17,18}

HOSPITAL DISCHARGE AND FOLLOW-UP

Hospital discharge is appropriate when the patient is in a clinically stable condition, is able to take oral medication, and has a safe environment for continued care; overnight observation after a switch to oral therapy is not necessary. Early discharge based on clinical stability and criteria for the switch to oral therapy is encouraged to reduce unnecessary hospital costs and risks associated with hospitalization.

Communication and coordination with the patient's primary care clinician for early outpatient

follow-up is encouraged to reduce the likelihood of readmission to the hospital.⁴³ A follow-up chest radiograph is indicated in only a minority of patients, such as those at risk for lung cancer on the basis of age, smoking history, or persistence of symptoms.^{1,44}

PREVENTION

Smoking and excessive alcohol consumption should be addressed. In addition, vaccines against influenza, Covid-19, and *Strep. pneumoniae* should be administered according to current Advisory Committee on Immunization Practices recommendations.⁴⁵

GUIDELINES

The recommendations we describe align with the most recent ATS-IDSA guidelines.¹ We agree with the recommendation that the addition of anaerobic coverage for suspected aspiration pneumonia should not be routine practice unless there is evidence of a lung abscess or empyema. The current guidelines were published before the Covid-19 pandemic and suggest selective microbiologic testing. However, we now advocate for a more comprehensive approach to microbiologic testing for all hospitalized patients with community-acquired pneumonia, including testing for SARS-CoV-2 infection.

AREAS OF UNCERTAINTY

The role of the lung microbiome in community-acquired pneumonia is an area of ongoing research.⁸ Further understanding of the lung microbiome may provide information regarding inflammatory response and susceptibility to specific pathogens.

Microbiologic diagnosis with the use of rapid multiplexed molecular platforms is a swiftly advancing technology.²² Further studies are needed to determine the clinical effect and cost-benefit ratio of these rapid molecular tests.

Although ATS-IDSA guidelines recommend monotherapy with amoxicillin as a first-line option for ambulatory patients at low risk, we often add a macrolide that targets atypical pathogens, since such pathogens are relatively common and not readily identified in low-risk patients, and treating such patients may hasten recovery.⁴⁶⁻⁴⁸

There is an observed association between com-

munity-acquired pneumonia and an increased risk of cardiovascular disease.^{49,50} Further studies are needed to gain a better understanding of this relationship and to develop interventions aimed at reducing cardiovascular risk as well as the risk of other sequelae of community-acquired pneumonia.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette was clinically stable, had a CURB-65 score of 2, and had only one minor criterion for severe community-acquired pneumonia (i.e., confusion); therefore, he should be admitted to a general ward. Although a viral pathogen was identified, we would be

concerned about secondary bacterial infection, particularly given the elevated procalcitonin level. In the absence of known risk factors for MRSA or pseudomonas, we would initiate treatment in the emergency department with intravenous azithromycin and ceftriaxone. If testing proved negative for atypical bacteria, we would discontinue azithromycin therapy. We would discharge him with continued oral therapy (e.g., amoxicillin-clavulanate if no bacterial pathogen was identified); if his condition had reached clinical stability in 48 to 72 hours, he should complete a 5-day course of the medication. Outpatient follow-up should be scheduled a week after discharge.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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