PAKISTAN CHEST SOCIETY
GUIDELINES FOR THE MANAGEMENT OF
COMMUNITY ACQUIRED PNEUMONIA IN ADULTS
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Message from the President Pakistan Chest Society

Governing Council of Pakistan Chest Society has mandated the Guideline Committee to develop evidence-based guidelines for all the important diseases & issues related to respiratory medicine. It is a matter of great pleasure, pride and satisfaction that guidelines for the “Management of Community Acquired Pneumonia” have been developed and are being launched on the occasion of 9th Biennial Conference of Pakistan Chest Society at Bhurban. Beside this document guidelines on Management of Asthma, Tuberculosis, MDR-TB and COPD have already been circulated and during this conference two other guidelines on important issues of “Tobacco cessation” and “Ethical protocol for doctors and pharma interface and working” are also being launched.

It is very encouraging to note that Pakistan Chest Society has taken up the challenge of developing guidelines. These guidelines provide a highly valuable resource for practicing physicians. Most national guidelines are extrapolated from the literature published in developed countries and thus may not be applicable to large populations due to variation in resources, available interventions, and lack of relevant investigations. These guidelines are local in context, guided by the resources and problems we have in our clinical practice. I hope that PCS will continue to improve these guidelines and review them from time to time, as new information and evidence becomes available.

Finally I would like to thank Prof. Nazim Bokhari and the other members of the working group who have worked very hard into preparing this document. PCS remains committed to always endeavor for the achievement of the best possible clinical practice.

Professor Arshad Javaid  
Chairman Guidelines Committee PCS  
President Pakistan Chest Society (Centre)
INTRODUCTION
Improving the care of patients with community-acquired pneumonia (CAP) has been the focus of many different organizations. Such efforts at improvement in care are warranted, because CAP, together with influenza, remains the seventh leading cause of death in developed countries. In countries such as the United States, despite advances in antimicrobial therapy, rates of mortality due to pneumonia have not decreased significantly since penicillin became routinely available.

There are two important issues; (1) an increased risk of infection with drug-resistant isolates of usual CAP pathogens, such as Streptococcus pneumoniae, and, (2) an increased risk of infection with less common, usually hospital-associated pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas and Acinetobacter species.

Pneumonia in long-term care facilities epidemiologically resembles hospital-acquired pneumonia but they are better managed in accordance with CAP guidelines with concern for specific pathogens. For example, long-term dialysis alone is a risk for MRSA infection but does not necessarily predispose patients to infection with other health care associated pneumonia (HCAP) pathogens, such as Pseudomonas aeruginosa or Acinetobacter species. On the other hand, certain patients with chronic obstructive pulmonary disease (COPD) are at greater risk for infection with Pseudomonas species but not MRSA.

The Guideline Committee understands that mortality due to CAP can be decreased. Greatest emphasis has, therefore, been placed on aspects which are associated with decrease in mortality. For this reason, the document focuses mainly on management rather than discussions of such factors as pathophysiology, pathogenesis, merits of different antibiotics.

The committee recognizes that the majority of patients with CAP are cared for by family physicians, hospital doctors, and emergency medicine physicians including postgraduate residents. These guidelines are, therefore, directed primarily at them. The expertise of the committee and review of literature suggest that these guidelines are also an appropriate starting point for consultation by pulmonary physicians, those involved in critical care as well as internists.

Methodology: The process of guideline development started with the selection of guideline coordinator by Governing Council (GC) of Pakistan Chest Society Centre. The guideline coordinator (Chairman) was responsible for selection of the rest of the committee members. The general outline of the topics to be covered was prepared by the principal coordinator with assistance from an associate coordinator. The draft was then circulated to committee members for review and updates with new information from the literature. Before publication this document will be submitted to the GC Pakistan Chest Society for final approval.

RECOMMENDATIONS ON IMPLEMENTATION OF GUIDELINES
Enthusiasm for developing this set of CAP guidelines derives, in large part, from evidence that all previous international CAP guidelines have led to improvement in clinically relevant outcomes. A decrease in mortality with the introduction of guideline-based protocols has been found in several studies including Pakistan.
We recognize that these guidelines may be used as a measure of quality of care for hospitals and family physicians. Although these guidelines are evidence based as much of the core knowledge has been derived from the existing international guidelines like ATS, ERS, BTS and IDSA guidelines. The committee strongly believes that the caring physicians can modify various regimens depending upon local knowledge and experience of susceptibility.

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SUMMARY
The guidelines are intended primarily for use by emergency medicine physicians, hospitalists, postgraduate students and primary care practitioners; however, in view of the literature review they are also an appropriate starting point for consultants in any medical discipline.
Almost all of the major decisions regarding management of community acquired pneumonia (CAP), including diagnostic and treatment issues, revolve around the initial assessment of severity. Site-of-care decisions (e.g., hospital vs. outpatient, general ward vs. intensive care unit) are important areas for the better management of CAP.

Hospital admission decision
Severity-of-illness scores, such as the CURB-65 (or CRB) criteria (confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater), or prognostic models, such as the Pneumonia Severity Index (PSI), can be used to identify patients with CAP who may be candidates for outpatient treatment. Physicians often admit patients to the hospital who could be well managed as outpatients and who would generally prefer to be treated as outpatients. Objective scores can assist in identifying patients who may be appropriate for outpatient care, but the use of such scores must be influenced by other factors such as compliance and reliability of taking oral medication as well as the availability of family support.

ICU admission decision
Direct admission to an ICU is required for patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation. Direct admission to an ICU or high-level monitoring unit is recommended for patients with 3 of the minor criteria for severe CAP (table 2). Significant percentage of patients with CAP are transferred to the ICU within first 24–48 h after hospitalization. Mortality and morbidity among these patients appears to be greater than among those admitted directly to the ICU. On the other hand ICU resources are often limited in many institutions, and the admission of patients with CAP who would not directly benefit from ICU care is also problematic.

Diagnostic Testing
In addition to suggestive clinical features, a demonstrable infiltrate by chest radiograph or other imaging technique, with or without supporting microbiological data, is required for the diagnosis of pneumonia.

Recommended diagnostic tests for etiology
Patients with CAP should be investigated for specific pathogens that would significantly alter standard (empirical) management decisions, when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues. Recommendations for diagnostic testing remain controversial. The overall low yield and infrequent positive impact on clinical care argue against the routine use of common tests, such as blood and sputum cultures. On the other hand these cultures may have a major impact on the care
of an individual patient, and are important for epidemiologic reasons, including the antibiotic susceptibility patterns used to develop treatment guidelines. *Routine diagnostic tests to identify an etiologic diagnosis are optional for patients with CAP being managed in OPD.*

Blood samples for culture and an expectorated sputum sample for stain and culture should be obtained from hospitalized patients. Pretreatment Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained. Patients with severe CAP, as defined above, should at least have blood samples drawn and expectorated sputum samples collected for culture wherever facilities are available. For intubated patients, an endotracheal aspirate sample should be obtained. The most clear-cut indication for extensive diagnostic testing is in the critically ill CAP patient.

**Antibiotic Treatment**

Empirical antibiotic recommendations (table 1) have not changed significantly from those in previous international guidelines. Increasing evidence has strengthened the recommendation for combination empirical therapy for severe CAP. Recommendations are generally for a class of antibiotics rather than for a specific drug, because overall efficacy remains good for many classes of agents.

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**TABLE- 1**

**Outpatient treatment**

- **Previously healthy and no risk factors for drug-resistant *S. pneumoniae* (DRSP) infection:**
  
  a. Amoxicillin (500-1000 mg TID) or
  
  b. A macrolide (erythromycin / clarithromycin or azithromycin,)

- **In the presence of comorbidities,** such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; absent spleen; immunosuppressed conditions or use of immunosuppressive drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
  
  a. A respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin, gemifloxacin)

  b. A β-lactam plus a macrolide High-dose amoxicillin [e.g., 1 g 3 times daily] or amoxicillin-clavulanate [1 g 2 times daily] is preferred; alternatives include ceftridine (500 mg QID), and cefuroxime [500 mg 2 times daily]; doxycycline is a weak alternative to the macrolide.)

**Inpatient, non-ICU treatment**

a. A β-lactam plus a macrolide.  
(Preferred β-lactam agents include ampicillin; 500mg-1 gm tid / Benzyle Penicillin 1.2-2.4 Gm qds (600 mg = one million units), cefotaxime, ceftriaxone. (A respiratory fluoroquinolone should be used for penicillin-allergic patients.)

b. A respiratory fluoroquinolone or a macrolide alone.
Increasing resistance rates have suggested that empirical therapy with single agent can be used only for the treatment of carefully selected hospitalized patients with no severe disease.

- **Inpatient, ICU treatment**
  A β-lactam (ampicillin-sulbactam, cefotaxime, ceftriaxone) *plus* either a fluoroquinolone or clarithromycin

  **For Pseudomonas infection**, use above β-lactam *plus* an aminoglycoside
  or the above β-lactam *plus* an aminoglycoside and an antipseudomonal fluoroquinolone
  or An antipseudomonal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) *plus* either ciprofloxacin or levofloxacin (750-mg dose)

For community-acquired methicillin-resistant Staphylococcus aureus infection (MRSA), add vancomycin or linezolid. Infections with the overwhelming majority of CAP pathogens will be adequately treated by use of the recommended empirical regimens. The emergence of MRSA as a CAP pathogen and the small but significant incidence of CAP due to *P. aeruginosa* are the exceptions. These pathogens occur in specific epidemiologic patterns and/or with certain clinical presentations, for which empirical antibiotic coverage may be necessary.

**Pathogens suspected on the basis of epidemiologic considerations.**
Risk factors for other uncommon etiologies of CAP are listed in table 5, and recommendations for treatment are included in table 6.

**Pathogen-directed therapy**
Once the etiology of CAP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen.

**Time to first antibiotic dose**
For patients admitted through the emergency department (ED), the first antibiotic dose should be administered while still in the ED. Rather than designating a specific window in which to initiate treatment, the committee felt that hospitalized patients with CAP should receive the first antibiotic dose in the ED.

**Switch from intravenous to oral therapy.**
Patients should be switched from intravenous to oral therapy when they are hemodynamically stable and improving clinically, are able to ingest medications, and have a normally functioning gastrointestinal tract. Patients should be discharged as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care. Inpatient observation while receiving oral therapy is not necessary.

**Duration of antibiotic therapy**
Patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48–72 h, and should have no more than one CAP-associated sign of clinical instability (table 7) before discontinuation of therapy. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as empyema, meningitis, or endocarditis.

**Other treatment considerations**
Patients with CAP who have persistent septic shock should be given adequate fluid and monitored through central venous line. Hypotensive patients who have been given adequate fluid should be screened for occult adrenal insufficiency. Those with hypoxemia or respiratory distress should receive a cautious trial of noninvasive ventilation unless they require immediate intubation because of severe hypoxemia (PaO2/FiO2 ratio, <150) and bilateral alveolar infiltrates. Low-tidal-volume ventilation (2 cm$^3$/kg of ideal body weight) should be used for patients undergoing ventilation who have diffuse bilateral pneumonia or acute respiratory distress syndrome.

Management of Nonresponding Pneumonia
As many as 15% of patients with CAP may not respond appropriately to initial antibiotic therapy. A systematic approach to these patients (table-8) will help to determine the cause. Because determination of the cause of failure is more accurate if the original microbiological etiology is known, risk factors for lack or response or deterioration are strong indications for more aggressive and/or extensive initial diagnostic testing.

Preventive Measures
All persons >50 years of age, others at risk for influenza complications, household contacts of high-risk persons, and health care workers should receive inactivated influenza vaccine. Health care workers in inpatient and outpatient settings and long-term care facilities should receive annual influenza immunization. Influenza vaccine should be advised at hospital discharge or during outpatient treatment during the fall and winter. Pneumococcal polysaccharide vaccine is recommended for persons >65 years of age and for those with selected high-risk concurrent diseases. Smoking cessation should be a goal for persons hospitalized with CAP who smoke. Smokers who will not quit should also be vaccinated for both pneumococcus and influenza.
Respiratory hygiene measures, including the use of hand hygiene and masks or tissues for patients with cough, should be used in outpatient settings and A&Es as a means to reduce the spread of respiratory infections.
MANAGEMENT OF PNEUMONIA

SITE-OF-CARE
Almost all of the major decisions regarding management of CAP, including diagnostic and treatment issues, revolve around the initial assessment of severity. The guidelines have, therefore, been organized to address this issue first.

Hospital admission decision The initial management decision after diagnosis is to determine the site of care—outpatient, hospitalization in a medical ward, or admission to an ICU. The decision to admit the patient is the most costly issue in the management of CAP, because the cost of inpatient care for pneumonia is up to 25 times greater than that of outpatient care and consumes the majority of the money spent yearly on treatment.

KEY POINTS-

HOW TO DIFFERENTIATE BETWEEN PNEUMONIA AND OTHER RESPIRATORY TRACT INFECTIONS?

A patient should be suspected of having pneumonia when the following signs and symptoms are present:

- an acute cough; and one of the following:
- new focal chest signs,
- dyspnoea,
- tachypnoea,
- fever > 4 days.

If pneumonia is suspected, a chest X-ray should be performed to confirm the diagnosis.

Severity-of-illness scores, such as the CURB-65 criteria or prognostic models, such as the PSI, can be used to identify patients with CAP who may be candidates for outpatient treatment. Significant variation in admission rates among hospitals and among individual physicians is well documented. Physicians often overestimate severity and hospitalize a significant number of patients at low risk for death.

The PSI stratifies patients into 5 mortality-risk classes, and its ability to predict mortality has been confirmed in multiple subsequent studies. On the basis of associated mortality rates, it has been suggested that risk class I and II patients should be treated as outpatients, risk class III patients should be treated in an observation unit or with a short hospitalization, and risk class IV and V patients should be treated as inpatients. In the initial study risk of death was increased 21-fold if a patient, at the time of admission, had at least 2 of the following 3 conditions: tachypnea, diastolic hypotension, and an elevated blood urea nitrogen (BUN) level. These criteria appear to function well except among patients with underlying renal insufficiency and among elderly patients.
**CURB 65.** The most recent modification of the BTS criteria includes 5 easily measurable factors. Analysis of studies has identified the following factors as indicators of increased mortality: confusion (based on disorientation to person, place, or time), BUN level 20 mg/dl, respiratory rate >30 breaths/min, low blood pressure (systolic <90 mm Hg; or diastolic <60 mm Hg), and age >65 years; this gave rise to the acronym CURB 65. A simplified version (CRB-65), which does not require testing for BUN level, may be appropriate for decision making in a family physician’s clinic. Whether the PSI or the CURB-65 score is superior is unclear. The PSI includes 20 different variables and, therefore, relies on the availability of scoring sheets, limiting its practicality in a busy emergency. In contrast, the CURB-65 criteria are easily remembered.

Making decisions regarding hospital admission only on a score is unsafe.

**KEY POINTS**

**WHO SHOULD BE ADMITTED TO HOSPITAL?**

*The decision to hospitalize remains a clinical decision; however, this decision should be validated against at least one objective tool of risk assessment.*

Both the Pneumonia Severity Index (PSI) and the CURB index are valid tools in this regard. In patients meeting a PSI of IV and V and/or a CURB of two or more, hospitalization should be seriously considered.

Additional requirements of patient management like social and family factors not related to pneumonia severity must be considered as well.

Reasons for the admission of low-mortality-risk patients fall into 4 categories:

1. complications of the pneumonia itself,
2. exacerbation of underlying diseases(s),
3. inability to reliably take oral medications or receive outpatient care, and/or
4. multiple risk factors falling just above or below thresholds for the score.

Use of the PSI score in clinical trials has demonstrated some of its limitations. The PSI score is based on a history of diseases that increase risk of death, whereas the CURB-65 score does not directly address underlying disease. However, pneumonia may exacerbate an underlying disease, such as obstructive lung disease, congestive heart failure, or diabetes mellitus, which, by themselves, may require hospital admission. For patients with CURB-65 scores >2, more-intensive treatment, that is, hospitalization or/and, intensive in-home health care services (if available) is recommended.

*The committee preferred the CURB-65 criteria because of ease of use and because they were designed to measure illness severity rather than the mortality risk.* Patients with a CURB-65 score >2 are not only at increased risk of death but also are likely to have additional complications.

**ICU admission decision**

Direct admission to an ICU is required for patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation.
Direct admission to an ICU or high-level monitoring unit is recommended for patients with 3 of the minor criteria for severe CAP. The second-level admission decision is whether to place the patient in the ICU or a high-level monitoring unit rather than on a general medical floor. Approximately 10% of hospitalized patients with CAP require ICU admission. Because respiratory failure is the major reason for delayed transfer to the ICU, simple cardiac monitoring units would not meet the criteria for a high-level monitoring unit for patients with severe CAP. One of the most important determinants of the need for ICU care is the presence of chronic comorbid conditions. However, approximately one-third of patients with severe CAP are previously healthy.

**KEY POINTS**

**WHO SHOULD BE CONSIDERED FOR ICU ADMISSION?**

Criteria of acute respiratory failure, severe sepsis or septic shock and radiographic extension of infiltrates indicate immediate consideration of admission to the ICU or an intermediate care unit

**The presence of at least two of:**

- Systolic blood pressure < 90 mmHg,
- Severe respiratory failure (PaO2/FIO2 < 250),
- Involvement of > 2 lobes on Chest radiograph (multilobar involvement)

**Or:**

- One of requirement for mechanical ventilation or
- Requirement of vasopressors > 4 hours (septic shock):

  *indicates severe CAP and can be used to guide ICU referral.*

**Severity of CAP**

The rationale for specifically defining severe CAP is 4-fold:

- Appropriate placement of patients optimizes use of limited ICU resources.
- Transfer to the ICU for delayed respiratory failure or delayed onset of septic shock is associated with increased mortality. About half of all patients with CAP who ultimately require ICU admission are initially admitted to a non-ICU setting. Many delayed transfers to the ICU represent rapidly progressive pneumonia that is not obvious on admission. However, some have subtle findings, including those included in the minor criteria, which might warrant direct admission to the ICU.
- The distribution of microbial etiologies differs from that of CAP in general, with significant implications for diagnostic testing and empirical antibiotic choices. Avoidance of inappropriate antibiotic therapy has also been associated with lower mortality.
- Patients with CAP appropriate for immunomodulatory treatment must be identified. The systemic inflammatory response/severe sepsis criteria which are typically used for sepsis syndrome may not be applicable specifically to severe CAP. For example, patients with unilateral lobar pneumonia may have hypoxemia severe enough to meet criteria for acute lung injury but not have a systemic response.
Table 2
Criteria for severe community-acquired pneumonia

**Minor criteria**
- Respiratory rate (b) >30 breaths/min
- PaO2/FiO2 ratio (b) <250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (BUN level, >20 mg/dL)
- Leukopenia (WBC count, <4000 cells/mm³)
- Thrombocytopenia (platelet count, <100,000 cells/mm³)
- Hypothermia (core temperature, <36 °C)
- Hypotension requiring aggressive fluid resuscitation

**Major criteria**
- Invasive mechanical ventilation
- Septic shock with the need for vasopressors

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NOTE. BUN, blood urea nitrogen; PaO2/FiO2, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.

a. Other criteria to consider include hypoglycemia (in nondiabetic patients), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.

b. A need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or a PaO2/FiO2 ratio <250.

c. As a result of infection alone.

Several criteria have been proposed to define severe CAP. Most case series have defined it simply as CAP that necessitates ICU admission. Objective criteria to identify patients for ICU admission include the initial definition of severe CAP and its subsequent modification, the CURB criteria, and PSI severity class V (or IV and V).

Three additional minor criteria were added. Leukopenia (white blood cell count <4000 cells/mm³), the coagulation system is often activated in CAP, and development of thrombocytopenia (platelet count <100,000 cells/mm³) is also associated with a worse prognosis, non-exposure hypothermia (core temperature <36 °C) also carries a bad prognosis in CAP.

**DIAGNOSTIC TESTING**
In addition to a variety of suggestive clinical features, a demonstrable infiltrate by chest radiograph or other imaging technique, with or without supporting microbiological data,
is required for the diagnosis of pneumonia. In the absence of radiological findings same clinical scenario will be labeled as Respiratory Tract Infection. The diagnosis of CAP is based on the presence of select clinical features (e.g., cough, fever, sputum production, and pleuritic chest pain) and is supported by imaging of the lung, usually by chest radiography. Physical examination to detect crepitations or bronchial breath sounds is an important component of the evaluation but is less sensitive and specific than chest radiographs.

**Both clinical features and physical exam findings may be lacking or altered in elderly patients.** All patients should be screened by pulse oximetry, which may suggest both the presence of pneumonia in patients without obvious signs of pneumonia and unsuspected hypoxemia in patients with diagnosed pneumonia. A chest radiograph is required for the routine evaluation of patients who are likely to have pneumonia, to establish the diagnosis and to aid in differentiating CAP from other common causes of cough and fever, such as acute bronchitis. Chest radiographs are sometimes useful for suggesting the etiologic agent, prognosis, alternative diagnoses, and associated conditions. Rarely, the admission chest radiograph is clear, but the patient’s toxic appearance suggests more than bronchitis. For patients who are hospitalized for suspected pneumonia but who have negative chest radiography findings, it may be reasonable to treat their condition presumptively with antibiotics and repeat the imaging in 24–48 h.

**Recommended Diagnostic Tests for Aetiology**

Patients with CAP should be investigated for specific pathogens (which may significantly change standard /empirical management decisions) when the presence of such pathogens is suspected on the basis of clinical and epidemiologic clues. The need for diagnostic testing to determine the etiology of CAP can be justified from several perspectives. The primary reason for such testing is if results will change the antibiotic management for an individual patient. The spectrum of antibiotic therapy can be broadened, narrowed, or completely changed on the basis of diagnostic testing. The benefit of changing therapy is very obvious when non responding infection is found to be tuberculous in nature.

*The general recommendation of the committee is to strongly encourage diagnostic testing whenever the result is likely to change individual antibiotic management.* Those infections that are important to verify with diagnostic studies because of epidemiologic implications or because they require unique therapeutic intervention are SARS and avian influenza (H5N1), Legionella infection, community-acquired MRSA (CA-MRSA) infection, M. tuberculosis infection, or endemic fungal infection. Pretreatment blood samples for culture and an expectorated sputum sample for stain and culture (in patients with a productive cough) should be obtained from hospitalized patients with the clinical indications (like ICU admission, failed OPD treatment, cavitary lesion, pleural effusion, lukopenia, severe COPD, absent spleen, chronic liver disease) but are optional for patients without these conditions. Sputum should be performed only if a good-quality specimen can be obtained and quality performance measures for collection, transport, and processing of samples can be met. Patients with severe CAP, as defined above, should at least have blood samples drawn for culture. For intubated patients, an endotracheal aspirate sample should be obtained.
**Blood cultures**: Pretreatment blood cultures yielded positive results for a probable pathogen in 5–14% of patients hospitalized with CAP. The yield of blood cultures is, therefore, relatively low and, when management decisions are analyzed, the impact of positive blood cultures is minor. The most common blood culture isolate in all CAP studies is S. pneumoniae. Because this bacterial organism is always considered to be the most likely pathogen, positive blood culture results have not clearly led to better outcomes or improvements in antibiotic selection. Blood cultures should be optional for all hospitalized patients with CAP and performed selectively. The yield for positive blood culture results is halved by prior antibiotic therapy. Samples for blood culture should be obtained before antibiotic administration. However, when multiple risk factors for bacteremia are present, blood culture results after initiation of antibiotic therapy are still positive in up to 15% of cases and are, therefore, still warranted in these cases, despite the lower yield.

The yield of **sputum bacterial cultures** is variable and strongly influenced by the quality of the entire process, including specimen collection, transport, rapid processing, satisfactory use of cytologic criteria, absence of prior antibiotic therapy, and skill in interpretation.

The benefit of a sputum Gram stain is 2-fold. First, it broadens initial empirical coverage for less common etiologies, such as infection with S. aureus or gram-negative organisms. This indication is probably the most important, because it will lead to less inappropriate antibiotic therapy. Second, it can validate the subsequent sputum culture results.

Forty percent or more of patients are unable to produce any sputum or to produce sputum in a timely manner. The yield of cultures is substantially higher with endotracheal aspirates, bronchoscopic sampling, or transthoracic needle aspirates, although specimens obtained after initiation of antibiotic therapy are unreliable and must be interpreted carefully. Interpretation is improved with quantitative cultures of respiratory secretions from any source (sputum, tracheal aspirations, and bronchoscopic aspirations) or by interpretation based on semiquantitative culture results.

The fact that a respiratory tract culture result is negative does not mean that it has no value. Failure to detect S. aureus or gram-negative bacilli in good-quality specimens is strong evidence against the presence of these pathogens.

**Other cultures**: Patients with pleural effusions 15cm in height on a lateral upright chest radiograph should undergo thoracentesis to yield material for Gram stain and culture for aerobic and anaerobic bacteria. The yield with pleural fluid cultures is low, but the impact on management decisions is substantial, in terms of both antibiotic choice and the need for drainage.

**Nonbronchoscopic bronchoalveolar lavage** in the A&E has shown a high percentage (87%) of positive culture results, even in some patients who had already received their first dose of antibiotics. The best indications are for immunocompromised patients with CAP.

**Antigen tests**: Urinary antigen tests are commercially available and have been cleared by the US Food and Drug Administration.

**KEY POINTS**
WHAT CLASSIFICATION SHOULD BE USED FOR TREATMENT OF CAP?

- Antimicrobial treatment has to be empiric and should follow an approach according to the individual risk of mortality.
- The assessment of severity according to mild, moderate and severe pneumonia implies a decision about the most appropriate treatment setting (OPD, hospital ward, ICU).
- Antimicrobial treatment should be initiated as soon as possible.
- The guidance of empiric initial antimicrobial treatment should follow general patterns of expected pathogens according to pneumonia severity and additional risk factors, regional and local patterns of microbial resistance considerations of tolerability and toxicity of antimicrobial agents in the individual patient.

ANTIBIOTIC TREATMENT

A major goal of therapy is eradication of the infecting organism, with resultant resolution of clinical disease. As such, antimicrobials are a mainstay of treatment. Appropriate drug selection is dependent on the causative pathogen and its antibiotic susceptibility. Acute pneumonia may be caused by a wide variety of pathogens (table 3). However, until more accurate and rapid diagnostic methods are available, the initial treatment for most patients will remain empirical. Recommendations for therapy (table 4) apply to most cases; however, physicians should consider specific risk factors for each patient (table 5).

Table 3.
Most common etiologies of community-acquired pneumonia.

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Outpatient</td>
<td>Streptococcus pneumoniae</td>
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<tr>
<td></td>
<td>Haemophilus influenzae</td>
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<td></td>
<td>Respiratory viruses</td>
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<td></td>
<td>Mycoplasma pneumoniae</td>
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<td>Myc. Tuberculosis</td>
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<td>Chlamyphila pneumoniae</td>
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<td>Respiratory virusesa</td>
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<td></td>
<td>Legionella species</td>
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<td>Inpatient (ICU)</td>
<td>S. pneumoniae</td>
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<tr>
<td></td>
<td>H. influenzae</td>
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</tbody>
</table>
NOTE. Based on collective data from recent studies. ICU, intensive care unit. a Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

Even if a microbial etiology is identified, debate continues with regard to pathogen-specific treatment, because recent studies suggest coinfection by atypical pathogens (such as C. pneumoniae, Legionella species, and viruses). Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogen(s) and knowledge of local susceptibility patterns. Recommendations are generally for a class of antibiotics rather than a specific drug, unless outcome data clearly favor one drug. Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference.

Table 4
Recommended empirical antibiotics for community-acquired pneumonia.

**Outpatient treatment**

1. **Previously healthy and no use of antimicrobials within the previous 3 months**
   - Amoxicillin
   - A macrolide
2. **Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; use of immunosuppressive drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)**
   - A respiratory fluoroquinolone (levofloxacin 750 mg daily, moxifloxacin, or gemifloxacin)
   - b. A β-lactam plus a macrolide High-dose amoxicillin [e.g., 1 g 3 times daily] or amoxicillin-clavulanate [1 g 2 times daily] is preferred; alternatives include cef fixedine (500 mg QID), and cefuroxime [500 mg 2 times daily]; doxycycline is a weak alternative to the macrolide.)

**Inpatients, (non-ICU treatment)**
- A β-lactam plus a macrolide
- A respiratory fluoroquinolone (levofloxacin [750 mg daily], or moxifloxacin

**Inpatients, (ICU treatment)**
- A β-lactam (ampicillin-sulbactam, ceftriaxone or cefotaxime,)
  plus either clarithromycin or a respiratory fluoroquinolone
  (for penicillin-allergic patients, a respiratory fluoroquinolone is recommended)
Special concerns

**If Pseudomonas is a consideration**

The above β-lactam plus an aminoglycoside or antipneumococcal fluoroquinolone

**Or an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)**

**If Community Acquired - MRSA is a consideration, add vancomycin or linezolid**

---

**Likely Pathogens in CAP**

Although CAP may be caused by a variety of pathogens, a limited number of agents are responsible for most cases. Table 3 lists the most common causes of CAP, stratified for severity of illness as judged by site of care (OPD vs. hospitalized). *S. pneumoniae* is the most frequently isolated pathogen. Other bacterial causes include nontypeable Haemophilus influenzae and *Moraxella catarrhalis*, generally in patients who have underlying bronchopulmonary disease, and *S. aureus*, especially during an influenza outbreak. Risks for infection with *Enterobacteriaceae* species and *P. aeruginosa* as etiologies for CAP are; chronic oral steroid administration, severe underlying bronchopulmonary disease, alcoholism, and frequent antibiotic therapy, whereas recent hospitalization would define cases as HCAP. The “atypical” organisms, so called because they are not detectable on Gram stain or culturable on standard bacteriologic media, include *M. pneumoniae*, *C. pneumoniae*, Legionella species, and respiratory viruses. With the exception of Legionella species, these microorganisms are common causes of pneumonia, especially among outpatients. However, these pathogens are not often identified in clinical practice because, with a few exceptions, such as *L. pneumophila* and influenza virus, no specific, rapid, or standardized tests for their detection exist. Although influenza remains the predominant viral cause of CAP in adults, other commonly recognized viruses include RSV, adenovirus, and parainfluenza virus, as well as less common viruses, including human metapneumovirus, herpes simplex virus, varicella-zoster virus, SARS-associated coronavirus, and measles virus. The frequency of etiologic agents such as *M. tuberculosis* must not be underestimated.

**KEY POINTS**

**TREATMENT OPTIONS FOR HOSPITALIZED PATIENTS WITH MODERATE COMMUNITY-ACQUIRED PNEUMONIA**

(IN NO SPECIAL ORDER)

<table>
<thead>
<tr>
<th>PREFERRED</th>
<th>ALTERNATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminopenicillin ± macrolide</td>
<td>Levofloxacin</td>
</tr>
</tbody>
</table>
Aminopenicillin / β-lactamase inhibitor ± macrolide

<table>
<thead>
<tr>
<th>Cephalosporin II or III ± macrolide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Gemifloxacin</td>
</tr>
</tbody>
</table>

**KEY POINTS**

**TREATMENT OPTIONS FOR PATIENTS WITH SEVERE COMMUNITY-ACQUIRED PNEUMONIA**

<table>
<thead>
<tr>
<th>NO RISK FACTORS FOR <em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-antipseudomonal cephalosporin III + macrolide or Non-antipseudomonal cephalosporin III + (moxifloxacin or levofloxacin)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RISK FACTORS FOR <em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipseudomonal cephalosporin (ceftazidime) or Tazobactam/ β-lactamaseinhibitor or carbapenem Plus ciprofloxacin</td>
</tr>
</tbody>
</table>

*The need for specific anaerobic coverage for CAP is generally overestimated.*

Anaerobic bacteria cannot be detected by diagnostic techniques in current use. Anaerobic coverage is clearly indicated only in the classic aspiration in patients with a typical history of loss of consciousness as a result of alcohol/drug overdose or after seizures in patients with concomitant bad oral hygiene or esophageal motility disorders. Antibiotic trials have not demonstrated a need to specifically treat these organisms in the majority of CAP cases. Small-volume aspiration at the time of intubation is adequately handled by standard empirical severe CAP treatment and by the high oxygen tension provided by mechanical ventilation.

Table 5

Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Commonly encountered pathogen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>Streptococcus pneumoniae, oral anaerobes, Klebsiella pneumoniae, Acinetobacter species, Myc. tuberculosis</td>
</tr>
<tr>
<td>COPD and/or smoking</td>
<td>H.influenzae, Pseudomonas aeruginosa, Legionella species, S. pneumoniae, Moraxella cararrhalis, Chlamydophila pneumoniae</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Gram-negative enteric pathogens, oral anaerobes</td>
</tr>
<tr>
<td>Lung abscess</td>
<td>CA-MRSA, oral anaerobes, Mycobacteria, fungus</td>
</tr>
<tr>
<td>HIV infection (early)</td>
<td>S. pneumoniae, H. influenzae, M. tuberculosis</td>
</tr>
<tr>
<td>HIV infection (late)</td>
<td>Pathogens for early infection plus Pneumocystis</td>
</tr>
</tbody>
</table>
Structural lung disease (e.g., bronchiectasis) jirovecii, Aspergillus, atypical mycobacteria, P. aeruginosa, H. influenzae, Cryptococcus, Histoplasma
Injection drug abuse Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus
Endobronchial obstruction S. aureus, anaerobes, M. tuberculosis, S. pneumoniae
Travel to or residence in SE and East Asia Anaerobes, S. pneumoniae, H. influenzae, S. aureus
Influenza active in Avian influenza, SARS Burkholderia pseudomallei
Community S. pneumoniae, Staphylococcus aureus H. influenzae
Exposure to bat/ bird droppings Histoplasma capsulatum
Exposure to birds Chlamydia psittaci (if poultry: avian influenza)
Exposure to rabbits Francisella tularensis
Exposure to farm animals Coxiella burnetti (Q fever)
Hotel or cruise ship stay Legionella species
in previous 2 weeks
Cough x 12 weeks with whoop or posttussive vomiting Bordetella pertussis
In context of bioterrorism Bacillus anthracis (anthrax), Yersinia pestis (plague), Francisella tularensis (tularemia)

**NOTE.** CA-MRSA, community-acquired methicillin-resistant Staphylococcus aureus; COPD, chronic obstructive pulmonary disease; SARS, severe acute respiratory syndrome.

**Antibiotic Resistance Issues**
The emergence of drug-resistant pneumococcal (DRSP) isolates is well documented. The incidence of resistance appears to have stabilized somewhat in the past few years. Resistance to penicillin and cephalosporins may even be decreasing, whereas macrolide resistance continues to increase. Data exist that resistance to macrolides and older fluoroquinolones (ciprofloxacin and levofloxacin) results in clinical failure. To date, no failures have been reported for the newer fluoroquinolones, (moxifloxacin and gemifloxacin).

Risk factors for infection with β-lactam–resistant S. pneumoniae include 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. Although the relative predictive value of these risk factors is unclear, recent treatment with antimicrobials is likely to be the most significant. Recent therapy or repeated courses of therapy with β-lactams, macrolides, or fluoroquinolones are risk factors for pneumococcal resistance to the same class of antibiotic.

CA-MRSA. Recently, an increasing incidence of CAP to MRSA has been observed. CA-MRSA appears in 2 patterns: the typical hospital-acquired strain and, recently, strains that are epidemiologically, genotypically, and phenotypically distinct from hospital-acquired strains. Many of the former may represent HCAP, because these earlier studies did not differentiate this group from typical CAP. The latter are resistant to fewer
antimicrobials than are hospital-acquired MRSA strains. In addition, most contain the gene for a toxin associated with clinical features of necrotizing pneumonia, shock, and respiratory failure, as well as formation of abscesses and empyemas. The large majority of cases published to date have been skin infections in children. This strain should also be suspected in patients who present with cavitary infiltrates without risk factors for anaerobic aspiration pneumonia.

Empirical Antimicrobial Therapy

Outpatient treatment: The following regimens are recommended for outpatient treatment on the basis of the listed clinical risks.

**Previously healthy and no risk factors for DRSP infection:**
- An Aminopenicillin
- A macrolide (erythromycin, or clarithromycin, Azithromycin)

**Presence of comorbidities,** such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection:
  - 1. A β-lactam plus a macrolide (High-dose amoxicillin [e.g., 1 g 3 times daily] or amoxicillin-clavulanate [1 g 2 times daily] is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime [500 mg 2 times daily]; (doxycycline is an alternative to the macrolide.)
  - 2. A respiratory fluoroquinolone ( levofloxacin [750 mg]) moxifloxacin, or gemifloxacin,
  - 3. In regions with a high rate (>25%) of infection with high-level (MIC>16 mg/ml) macrolide-resistant S. pneumoniae, consider the use of alternative agents listed above.

The most common pathogens identified from recent studies of mild CAP were S. pneumoniae, M. pneumoniae, and H. influenzae. Mycoplasma infection was most common among patients <50 years of age without significant comorbid conditions or abnormal vital signs, whereas S. pneumoniae was the most common pathogen among older patients and among those with significant underlying disease. Hemophilus infection was found in 5%—mostly in patients with comorbidities.

Numerous randomized clinical trials have documented the efficacy of clarithromycin and azithromycin as monotherapy for outpatient CAP, although several studies have demonstrated that clinical failure can occur with a resistant isolate. When such patients were hospitalized and treated with a β-lactam and a macrolide, however, all survived and generally recovered without significant complications. At present for patients with a significant risk of DRSP infection, monotherapy with a macrolide is not recommended.

The use of fluoroquinolones to treat ambulatory patients with CAP without comorbid conditions, risk factors for DRSP, or recent antimicrobial use, is discouraged because of concern that widespread use may lead to the development of fluoroquinolone resistance. More concerning is the observation that many patients treated in OPD given a
fluoroquinolone may not have even required an antibiotic, and that the dose and duration of treatment are often incorrect.

**Comorbidities or recent antimicrobial therapy** increase the likelihood of infection with DRSP and enteric gram-negative bacteria. For such patients, recommended empirical therapeutic options include

1. a respiratory fluoroquinolone (levofloxacin: 750 mg daily), moxifloxacin, gemifloxacin

2. Combination therapy with a β-lactam effective against S. pneumoniae plus a macrolide

On the basis of present pharmacodynamic principles, high-dose amoxicillin (1 g 3 times daily) or amoxicillin-clavulanate [1 g 2 times daily]) should target >93% of S. pneumoniae and is the preferred β-lactam. Ceftriaxone is an alternative to high-dose amoxicillin when parenteral therapy is feasible.

Selected oral cephalosporins (cefixime and cefuroxime) can be used as alternatives, but these are less active in vitro than high-dose amoxicillin or ceftriaxone. Agents in the same class as the patient had been receiving previously should not be used to treat patients with recent antibiotic exposure.

**Inpatient, non-ICU treatment:** The following regimens are recommended for hospital ward treatment.

- A β-lactam plus a macrolide (Preferred β-lactam agents include ampicillin, cefotaxime, or ceftriaxone, and; for selected patients as an alternative to the macrolide, a respiratory fluoroquinolone should be used. The recommendations of combination treatment with a β-lactam plus a macrolide or monotherapy with a fluoroquinolone were based on various studies demonstrating a significant reduction in mortality compared with that associated with administration of a cephalosporin.

- A respiratory fluoroquinolone

Preferred β-lactams are those effective against S. pneumoniae and other common, nonatypical pathogens without being overly broad spectrum. Other “antipneumococcal, antipseudomonal” β-lactam agents are appropriate when resistant pathogens, such as Pseudomonas, are likely to be present.

Initial therapy should be given intravenously for most admitted patients, but some without risk factors for severe pneumonia could receive oral therapy, especially with highly bioavailable agents such as fluoroquinolones. When an intravenous β-lactam is combined with coverage for atypical pathogens, oral therapy with a macrolide or doxycycline is appropriate for selected patients without severe pneumonia risk factors.

**Inpatient, ICU treatment:** The following regimen is the minimal recommended treatment for patients admitted to the ICU.

- A β-lactam (or ampicillin-sulbactam, cefotaxime, or ceftriaxone,) plus either clarithromycin or a fluoroquinolone

(For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.)

Because septic shock and mechanical ventilation are the clearest reasons for ICU admission, the majority of ICU patients would still require combination therapy.
For all patients admitted to the ICU, coverage for S. pneumoniae and Legionella species should be ensured by using a potent antipneumococcal β-lactam and either a macrolide or a fluoroquinolone. Therapy with a respiratory fluoroquinolone alone is not established for severe CAP. Various studies and retrospective analyses have found that combination therapy for bacteremic pneumococcal pneumonia is associated with lower mortality than monotherapy. Therefore, combination empirical therapy is recommended for at least 48 hours or until results of diagnostic tests is known.

In critically ill patients with CAP, a large number of microorganisms other than S. pneumoniae and Legionella species must be considered. **The recommended standard empirical regimen should routinely cover the 3 most common pathogens that cause severe CAP, all of the atypical pathogens, and most of the relevant Enterobacteriaceae species.** Treatment of MRSA or P. aeruginosa infection is the main reason to modify the standard empirical regimen. The following are additions or modifications to the basic empirical regimen recommended above if these pathogens are suspected.

For Pseudomonas infection, use
- The above β-lactam **plus** an aminoglycoside and an antipneumococcal fluoroquinolone.
- **Or** an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) **plus** either ciprofloxacin or levofloxacin (750-mg dose)

Pseudomonal CAP requires combination treatment to prevent inappropriate initial therapy, just as Pseudomonas nosocomial pneumonia does. Once susceptibilities are known, treatment can be adjusted accordingly. Alternative regimens are provided for patients who may have recently received an oral fluoroquinolone, in whom the aminoglycoside-containing regimen would be preferred.

Other clinical risk factors for infection with Pseudomonas species include structural lung diseases, such as bronchiectasis, or repeated exacerbations of severe COPD leading to frequent steroid and/or antibiotic use, as well as prior antibiotic therapy. These patients do not necessarily require ICU admission for CAP, so Pseudomonas infection remains a concern for them even if they are only hospitalized in a general ward.

The major risk factor for infection with other serious gram-negative pathogens, such as Klebsiella pneumoniae or Acinetobacter species, is chronic alcoholism.

- For CA-MRSA infection, add vancomycin or linezolid.

The best indicator of S. aureus infection is the presence of gram-positive cocci in clusters in a tracheal aspirate or in an adequate sputum sample. The same findings on preliminary results of blood cultures are not as reliable, because of the significant risk of contamination.

Clinical risk factors for S. aureus CAP include end-stage renal disease, injection drug abuse, prior influenza, and prior antibiotic therapy (especially with fluoroquinolones). For methicillin-sensitive S. aureus, the empirical combination therapy recommended above, which includes a β-lactam and sometimes a respiratory fluoroquinolone, should be adequate until susceptibility results are available and specific therapy with penicillinase-resistant semisynthetic penicillin or first-generation cephalosporin can be initiated. Both
also offer additional coverage for DRSP. Neither linezolid nor vancomycin is an optimal drug for methicillin-sensitive S. aureus. The majority of CA-MRSA strains are more susceptible in vitro to non-β-lactam antimicrobials, including trimethoprim-sulfamethoxazole (TMP-SMX) and fluoroquinolones, than are hospital-acquired strains.

**Pathogens Suspected on the Basis of Epidemiologic Considerations**

Clinicians should be aware of epidemiologic conditions and/or risk factors that may suggest that alternative or specific additional antibiotics should be considered. These conditions and specific pathogens, with preferred treatment, are listed in tables 8 and 9.

**Pathogen-Directed Therapy**

Once the etiology of CAP has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be directed at that pathogen. Treatment options may be simplified (table 9) if the etiologic agent is established or strongly suspected. Diagnostic procedures that identify a specific etiology within 24–72 h can still be useful for guiding continued therapy.

---

**Table 6**

Recommended antimicrobial therapy for specific pathogens.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Preferred and Alternative antimicrobials (Alt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td><strong>Penicillin nonresistant</strong>; (MIC &lt; 2 mg/ml) Penicillin G, amoxicillin, / Alt: Macrolides, cephalosporins (e.g; oral cefpodoxime, cefuroxime) or parenteral [cefauroxime, ceftriaxone, cefotaxime, clindamycin, doxycycline, respiratory fluoroquinolonea (a) <strong>Penicillin resistant</strong>; (MIC &gt; 2 mg/mL) Agents chosen on the basis of susceptibility, like cefotaxime, ceftriazone (3 g/day) Alt: high dose amoxicillin(3 g/day)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td><strong>Non–β-lactamase producing</strong> Amoxicillin Alt: Fluoroquinolone, doxycycline, azithromycin, clarithromycinb (b) <strong>β-lactamase producing</strong> Second-or third-generation cephalosporin, amoxicillin-clavulanate Alt: Fluoroquinolone, doxycycline, azithromycin, clarithromycin (b)</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae/ Chlamydomphila pneumoniae</td>
<td>Macrolide, a tetracycline Alt: Fluoroquinolone</td>
</tr>
<tr>
<td>Legionella species</td>
<td>Fluoroquinolone, azithromycin Alt: Doxycycline</td>
</tr>
<tr>
<td>Chlamydomphila psittaci</td>
<td>A tetracycline Alt: Macrolide</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>A tetracycline Alt: Macrolide</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>Streptomycin, gentamicin Alt: Doxycycline, fluoroquinolone</td>
</tr>
</tbody>
</table>
### Bacillus anthracis (inhalation)

Ciprofloxacin, levofloxacin, doxycycline (usually with second agent)  
**Alt:** Other fluoroquinolones; β-lactam (if susceptible); rifampin; clindamycin; chloramphenicol

### Enterobacteriaceae

Third-generation cephalosporin, carbapenam (c) (drug of choice if extended-spectrum β-lactamase producer),  
**Alt:** β-lactam/β-lactamase inhibitor (d) or fluoroquinolone.

### Pseudomonas aeruginosa

Antipseudomonal β-lactam (e) plus (ciprofloxacin / levofloxacin (f) / aminoglycoside)  
**Alt:** Aminoglycoside plus (ciprofloxacin or levofloxacin (f))

### Burkholderia pseudomallei

Carbapenem, ceftazadime  
**Alt:** Fluoroquinolone, TMP-SMX

### Acinetobacter species

Carbapenem  
**Alt:** Cephalosporin-aminoglycoside, ampicillin-sulbactam, colistin

### Staphylococcus aureus

**Methicillin susceptible** Antistaphylococcal penicillin (g)  
**Alt:** clindamycin, Cefazolin

**Methicillin resistant** Vancomycin or linezolid  
**Alt:** TMP-SMX

### Bordetella pertussis

Macrolide  
**Alt:** TMP-SMX

### Anaerobe (aspiration)

β-lactam/β-lactamase inhibitor (d) clindamycin  
**Alt:** Carbapenem

### Influenza virus

Oseltamivir or zanamivir

### Myc. tuberculosis

Isoniazid plus rifampin plus ethambutol plus pyrazinamide

### Coccidioides species

For uncomplicated infection in a normal host; no therapy, when needed; itraconazole, fluconazole / Amphotericin B

### Histoplasmosis

Itraconazole  
**Alt:** Amphotericin B

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**NOTE.** Choices should be modified on the basis of susceptibility test results and advice from local specialists. Refer to local references for appropriate doses.  

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

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

c. Imipenem-cilastatin, meropenem, ertapenem.  

d. Piperacillin-tazobactam for gram-negative bacilli, ticarcillin-clavulanate, ampicillin-sulbactam or amoxicillin-clavulanate.  

e. Piperacillin, ceftazidime, cefepime, aztreonam, imipenem, meropenem.  

f. 750 mg daily.  

g. Oxacillin flucloxacillin. Nafcillin

---

This information is often available at the time of consideration for a switch from parenteral to oral therapy and may be used to direct specific oral antimicrobial choices.  

Early treatment (within 48 h of onset of symptoms) with oseltamivir or zanamivir is recommended for influenza. The use of influenza antiviral medications appears to reduce the likelihood of respiratory tract complications.
Parenteral acyclovir is indicated for treatment of varicella-zoster virus infection or herpes simplex virus pneumonia. No antiviral treatment of proven value is available for other viral pneumonias—that is, parainfluenza virus, RSV, adenovirus, metapneumovirus, the SARS agent, or hantavirus. For all patients with viral pneumonias, a high clinical suspicion of bacterial superinfection should be maintained.

**Time to First Antibiotic Dose**

For patients admitted through the A&E, the first antibiotic dose should be administered while still in the A&E. The initial study suggested a breakpoint of 8 h, whereas the subsequent analysis found that 4 h was associated with lower mortality. The committee feels that therapy should be administered as soon as possible after the diagnosis is considered likely. On the other hand, a delay in antibiotic therapy has adverse consequences in most of the situations.

**Switch from Intravenous to Oral Therapy**

Patients should be switched from intravenous to oral therapy when they are hemodynamically stable and improving clinically, are able to ingest medications, and have a normally functioning gastrointestinal tract. Patients should be discharged as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care. Inpatient observation while receiving oral therapy is not necessary.

---

**Table 7**

Criteria for clinical stability

<table>
<thead>
<tr>
<th>Temperature &lt;37.8°C</th>
<th>Heart rate &lt;100 beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate &lt;24 breaths/min</td>
<td>Systolic blood pressure &gt;90mm Hg</td>
</tr>
<tr>
<td>Arterial oxygen saturation &gt;90% or pO2 &gt;60 mm Hg on room air</td>
<td>Ability to maintain oral intake (a)</td>
</tr>
<tr>
<td>Normal mental status (a)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE**: a. Important for discharge or switching to oral decision; but not necessarily a sign of instability.

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**KEY POINTS - WHEN SHOULD IV BE USED AND WHEN SHOULD THE SWITCH TO ORAL OCCUR?**

- In mild pneumonia, treatment can be started orally from the beginning.
- In patients with moderate pneumonia, sequential treatment should be considered in all patients except the most severely ill.
- The optimal time to switch to oral treatment is unknown.
- It seems reasonable to target this decision according to the resolution of the most prominent clinical features at admission.

The need to keep patients in the hospital once clinical stability is achieved has been questioned, even though physicians commonly choose to observe patients receiving oral
therapy for >1 day. Even in the presence of pneumococcal bacteremia, a switch to oral therapy can be safely done once clinical stability is achieved and prolonged intravenous therapy is not needed.

Discharge should be considered when the patient is a candidate for oral therapy and when there is no need to treat any comorbid illness, no need for further diagnostic testing and social environment is conducive. Patients in higher PSI classes take longer to reach clinical stability than do patients in lower risk classes. This finding may reflect the fact that elderly patients with multiple comorbidities often recover more slowly. Arrangements for appropriate follow-up care, including rehabilitation, should therefore be initiated early for these patients.

In general, when switching to oral antibiotics, either the same agent as the intravenous antibiotic or the same drug class should be used. Switching to a different class of agents simply because of its high bioavailability (such as a fluoroquinolone) is probably not necessary for a responding patient.

**Duration of Antibiotic Therapy**

Patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability (table 10) before discontinuation of therapy. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis, or empyema. Most patients with CAP have been treated for 7–10 days or longer. On the basis of studies, 5 days appears to be the minimal overall duration of therapy documented to be effective in usual forms of CAP.

**KEY POINTS—**

**WHAT SHOULD BE THE DURATION OF TREATMENT?**

| The appropriate duration of antimicrobial treatment has not been settled. |
| In comparative studies, the usual duration of treatment is around seven to ten days. |
| Intracellular pathogens such as Legionella spp. should be treated for at least 14 days |

Patients with **sepsis-induced leukopenia** are at extremely high risk of death and ARDS. Hypotensive, fluid-resuscitated patients with severe CAP should be screened for occult adrenal insufficiency. A large, multicenter trial has suggested that stress-dose (200–300 mg of hydrocortisone per day or equivalent) steroid treatment improves outcomes of vasopressor-dependent patients with septic shock who do not have an appropriate cortisol response to stimulation. If corticosteroids are used, close attention to glucose control is required even if the patient is non-diabetic.

Patients with **hypoxemia or respiratory distress** should receive a cautious trial of noninvasive ventilation (NIV) unless they require immediate intubation because of severe hypoxemia (arterial oxygen pressure/fraction of inspired oxygen [PaO2/FiO2 ratio: <150]) and bilateral alveolar infiltrates. Patients who do not require immediate intubation but who have either hypoxemia or respiratory distress should receive a trial of NIV. Patients with underlying COPD are most likely to benefit. Inability to expectorate may limit the use of NIV, but intermittent application of NIV may allow for its use in patients with productive cough unless sputum production is excessive. Within the first 1–2 hours of
NIV, failure to improve respiratory rate and oxygenation or failure to decrease carbon dioxide partial pressure (pCO2) in patients with initial hypercapnia predicts NIV failure and warrants prompt intubation. NIV provides no benefit for patients with ARDS, which may be nearly indistinguishable from CAP among patients with bilateral alveolar infiltrates. Patients with CAP who have severe hypoxemia (PaO2/FiO2 ratio, <150) are also poor candidates for NIV.

**KEY POINTS**

**HOW SHOULD THE NONRESPONDING PATIENT BE ASSESSED?**

Two types of treatment failures, nonresponding pneumonia and slowly resolving pneumonia should be differentiated.

The evaluation of nonresponding pneumonia depends on the clinical condition; in unstable patients, full reinvestigation followed by a second empiric antimicrobial treatment regimen is recommended. The latter may be withheld in stable patients.

Slowly resolving pneumonia should be reinvestigated according to clinical needs according to the condition of the patient and his individual risk factors.

**MANAGEMENT OF NONRESPONDING PNEUMONIA**

Because of the limitations of diagnostic testing, the majority of CAP is still treated empirically. Critical to empirical therapy is an understanding of the management of patients who do not follow the expected normal response pattern. Although difficult to define, nonresponse is not uncommon. Overall, 6–15% of hospitalized patients with CAP do not respond to the initial antibiotic treatment. The incidence of treatment failure among patients with CAP who are not hospitalized is not well known. For patients initially admitted to the ICU, the risk of failure to respond is already high; as many as 40% will experience deterioration even after initial stabilization in the ICU.

**Definition and classification**

The term “nonresponding pneumonia” is used to define a situation in which an inadequate clinical response is present despite antibiotic treatment. Lack of response also varies according to the site of treatment. Lack of response in outpatients is very different from that in patients admitted to the ICU. The time of evaluation is also important. Persistent fever after the first day of treatment differs significantly from fever persisting (or recurring) at day 7 of treatment.

Table 8

Patterns and etiologies of types of failure to respond

1. **Failure to improve**
   A. Early (<72 h of treatment)
      Normal response
   B. Delayed
      Resistant microorganism
Uncovered pathogen
Inappropriate by sensitivity
Parapneumonic effusion/empyema
Nosocomial superinfection
Nosocomial pneumonia
Extrapulmonary
Noninfectious
Complication of pneumonia (e.g., BOOP)
Misdiagnosis: PE, CHF, vasculitis
Drug fever

2. Deterioration or progression
A- Early (<72 h of treatment)
  Severity of illness at presentation
  Resistant microorganism
  Uncovered pathogen
  Inappropriate by sensitivity
  Metastatic infection
  Empyema/parapneumonic
  Endocarditis, meningitis, arthritis
  Inaccurate diagnosis
  PE, aspiration, ARDS
  Vasculitis (e.g., SLE)
B-Delayed
  Nosocomial superinfection
  Nosocomial pneumonia
  Extrapulmonary
  Exacerbation of comorbid illness
  Intercurrent noninfectious disease
  PE Embolism
  Myocardial infarction
  Renal failure

NOTE. ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia; CHF, congestive heart failure; PE, pulmonary embolus; SLE, systemic lupus erythematosus.

Deterioration and development of respiratory failure or hypotension >72 h after initial treatment is often related to intercurrent complications, deterioration in underlying disease, or development of nosocomial superinfection. The second pattern is that of persistent or nonresponding pneumonia.

Nonresponse can be defined as absence of or delay in achieving clinical stability, using the criteria in table 10.

Finally, nonresolving or slow-resolving pneumonia has been used to refer to the conditions of patients who present with persistence of pulmonary infiltrates >30 days after initial pneumonia-like syndrome.

As many as 20% of these patients will be found to have diseases other than CAP when carefully evaluated. Specific causes that may be responsible for a lack of response in
CAP have been classified (table 11). This classification may be useful for clinicians as a systematic approach to diagnose the potential causes of nonresponse in CAP.

Management of nonresponding CAP
Nonresponse to antibiotics in CAP will generally result in one or more of 3 clinical responses: (1) transfer of the patient to a higher level of care, (2) further diagnostic testing, and (3) escalation or change in treatment. An inadequate host response, rather than inappropriate antibiotic therapy or unexpected microorganisms, is the most common cause of apparent antibiotic failure when guideline-recommended therapy is used. Mismatch between the susceptibility of a common causative organism, infection with a pathogen not covered by the usual empirical regimen, and nosocomial superinfection pneumonia are major causes of apparent antibiotic failure. Therefore, the first response to nonresponse or deterioration is to reevaluate the initial microbiological results. Culture or sensitivity data not available at admission may now make the cause of clinical failure obvious. In addition, a further history of any risk factors for infection with unusual microorganisms (table 8) should be taken if not done previously.

Viruses are relatively neglected as a cause of infection in adults but may account for 10%–20% of cases. Other family members or coworkers may have developed viral symptoms in the interval since the patient was admitted, increasing suspicion of this cause.

The evaluation of nonresponse is severely hampered if a microbiological diagnosis was not made on initial presentation. If cultures were not obtained, clinical decisions are much more difficult than if the adequate cultures were obtained but negative. Blood cultures should be repeated for deterioration or progressive pneumonia. Deteriorating patients have many of the risk factors for bacteremia, and blood cultures have still high yield even in the face of prior antibiotic therapy. Positive blood culture results in the presence of adequate antibiotic therapy should increase the suspicion of either antibiotic-resistant isolates or metastatic sites, such as endocarditis or empyema or arthritis.

Nonresponse may also be mimicked by concomitant or subsequent extrapulmonary infection, such as intravascular catheter, urinary, abdominal, and skin infections, particularly in ICU patients. Appropriate cultures of these sites should be considered for patients with nonresponse to CAP therapy.

- **Chest CT.** In addition to ruling out pulmonary emboli, a CT scan can disclose other reasons for antibiotic failure, including pleural effusions, lung abscess, or central airway obstruction. The pattern of opacities may also suggest alternative noninfectious disease, such as bronchiolitis obliterans organizing pneumonia.
- **Thoracentesis.** Empyema and parapneumonic effusions are important causes of nonresponse, and pleurocentesis should be performed whenever significant pleural fluid is present.
- **Bronchoscopy:** If the differential diagnosis of nonresponse includes other pneumonia like conditions bronchoscopy will provide more diagnostic information than routine microbiological cultures.

**KEY POINTS**
HOW SHOULD RESPONSE BE ASSESSED AND WHEN TO REPEAT CHEST RADIOGRAPH?

Response to treatment should be monitored by simple clinical criteria including body temperature, respiratory and haemodynamic parameters.

The same parameters should be applied to judge the ability of hospital discharge.

Complete response including radiographic resolution requires longer time periods.

Discharge decisions should be based on strong evidence of clinical stabilization

PREVENTION

All persons >50 years of age, others at risk for influenza complications, household contacts of high-risk persons, and health care workers should receive inactivated influenza vaccine

Table 9

Recommendations for vaccine prevention of community-acquired pneumonia

Recommendation for Vaccination:

- All persons >65 years age, including health care providers and household contacts of high-risk persons, High-risk persons 2–64 years of age and Current smokers should be given (intramuscular) pneumococcal polysaccharide vaccine
- All persons > 50 years of age, Household contacts of high-risk persons High-risk persons of 6 months–49, Health care providers, Children 6–23 months of age should receive (intramuscular) inactivated Influenza vaccine.
- Live Influenza (intranasal spray) vaccine recommended for healthy persons 5–49 years of age including health care workers and household contact is not yet available in Pakistan.

High-risk Groups for Vaccination:

Pneumococcal Vaccine:

Vaccination Schedule:
One-time revaccination after 5 years for (1) adults >65 years of age, if the first dose is received before age 65 years; (2) persons with asplenia; and (3) immuno- compromised persons

Haemophilus Influenza Vaccine (given annually / inactivated)
Chronic cardiovascular or pulmonary disease (including asthma) Chronic metabolic disease (including diabetes mellitus) Renal dysfunction Hemoglobinopathies Immuno-compromising conditions/medications Compromised respiratory function or increased aspiration risk Pregnancy. Residence in a long-term care facility Aspirin therapy in persons <18 years of age Healthy persons 5–49 years of age, including health care providers and household contacts of high-risk persons

**NOTE:**
Avoid using live influenza vaccine in persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including diabetes, renal dysfunction, and hemoglobinopathies; persons with immunodeficiencies or who receive immunosuppressive therapy; children or adolescents receiving salicylates; persons with a history of Guillain-Barre` syndrome; and pregnant women.

Vaccinating current smokers with pneumococcal vaccine is recommended and is the mainstay for preventing CAP. Health care workers in inpatient and outpatient settings and long-term care facilities should receive annual influenza immunization. Pneumococcal polysaccharide vaccine and inactivated influenza vaccine are recommended for all older adults and for younger persons with high-risk concurrent disease. Influenza vaccine should be offered to persons at hospital discharge or during outpatient treatment during the autumn and winter. Patients with an acute fever should not be vaccinated until their fever has resolved.

**KEY POINTS**

<table>
<thead>
<tr>
<th>SHOULD PNEUMOCOCCAL VACCINE BE USED TO PREVENT LRTI?</th>
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<tr>
<td>For pneumococcal vaccination the following are recommended.</td>
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<tr>
<td>The evidence for vaccination with the 23-valent polysaccharide pneumococcal vaccine is less strong than that for influenza vaccination, but we recommend the vaccine to be given to all adult persons at risk for pneumococcal disease.</td>
</tr>
<tr>
<td>Risk factors for pneumococcal disease are age ≥ 65 years, institutionalisation, dementia, seizure disorders, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, history of a previous pneumonia, chronic liver disease, diabetes mellitus, functional or anatomic asplenia, and chronic cerebrospinal fluid leakage. Although smoking seems to be a significant risk factor in otherwise healthy younger adults measures aimed at reducing smoking and exposure to environmental tobacco smoke should be preferred in this group.</td>
</tr>
<tr>
<td>Revaccination, once, can be considered in the elderly, 5-10 years after primary vaccination</td>
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**KEY POINTS**

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<tr>
<th>SHOULD INFLUENZA VACCINE BE USED TO PREVENT LRTI?</th>
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<tr>
<td>For influenza vaccination the following are recommended:</td>
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Influenza vaccine should be given yearly to persons at increased risk for complications due to influenza. Vaccination is recommended for immunocompetent adults belonging to one, or more, of the following categories; age ≥ 65 years, institutionalisation, chronic cardiac diseases, chronic pulmonary diseases, diabetes mellitus, chronic renal diseases, hemoglobinopathies, and women who will be in the second or third trimester of pregnancy during the influenza season.

Repeated vaccinations are safe and do not lead to a decreased immune response. In adults inactivated, rather than live attenuated, vaccine is recommended.

In health care personnel we recommend yearly vaccination, especially in settings where elderly persons or other high risk groups are treated.

Chemoprophylaxis can be used as an adjunct to vaccination for prevention and control of influenza. Oseltamivir and zanamivir are both approved for prophylaxis; amantadine and rimantadine have FDA indications for chemoprophylaxis against influenza A infection.

Developing an adequate immune response to the inactivated influenza vaccine takes ~2 weeks in adults; chemoprophylaxis may be useful during this period for those with household exposure to influenza, those who live or work in institutions with an influenza outbreak, or those who are at high risk for influenza complications in the setting of a community outbreak. Chemoprophylaxis also may be useful for persons with contraindications to influenza vaccine or as an adjunct to vaccination for those who may not respond well to influenza vaccine (e.g., persons with HIV infection).

Smoking cessation should be a goal for persons hospitalized with CAP who smoke. Smokers who will not quit should also be vaccinated for both pneumococcus and influenza. Smoking is associated with a substantial risk of pneumococcal bacteremia. Smoking has also been identified as a risk for Legionella infection. The most successful approaches to quitting include some combination of nicotine replacement and/or bupropion / varenicline, a method to change habits, and emotional support.

Respiratory hygiene measures, including the use of hand hygiene and masks or tissues for patients with cough, should be used in outpatient settings and A&Es as a means to reduce the spread of respiratory infections. Key components of respiratory hygiene include encouraging patients to alert providers when they present for a visit and have symptoms of a respiratory infection; the use of hand hygiene measures, such as alcohol-based hand gels; and the use of masks or tissues to cover the mouth for patients with respiratory illnesses.
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