

Community-acquired pneumonia - a clinical approach to assessment and management

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Abstract

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality. The implementation of CAP guidelines can decrease patient mortality and limit antibiotic resistance. The South African Thoracic Society (SATS) has revised its guidelines for the management of CAP in adults. This article reviews the management of CAP and explores the rationale for the recommendations regarding point of care and antibiotic therapy.

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Introduction

Pneumonia is the result of infection and inflammation of the lung parenchyma distal to the terminal bronchioles. CAP specifically refers to pneumonia acquired within the general community. CAP remains a common and potentially fatal infectious disease despite advances in therapy. CAP is the fifth-largest killer in South Africa, accounting for 3.9% of all deaths in 2000.¹ A recent South African study reported a mortality of 20% for patients hospitalised with CAP.² The vast majority of patients with CAP can be safely managed as outpatients. In the United States of America only 20% of patients are hospitalised with 2% requiring management in an intensive care unit.³

A new group of pneumonia patients has been recognised – health care-associated pneumonia (HCAP). These patients are either resident in long-term care facilities or have frequent outpatient exposure to healthcare services. The bacteriology and management of patients with HCAP have more in common with nosocomial pneumonia and are a separate entity from CAP. Separate guidelines have been developed for the management of HCAP.⁴

Aetiology of community-acquired pneumonia

Several host defences need to be overcome in order for a pathogen to enter the host's alveoli and establish an infection. While recognised risk factors for pneumonia such as cardio-respiratory disease, immune compromise and smoking may be present, no obvious predisposing cause is apparent in the majority of cases of CAP. Although a large number of organisms cause CAP, only a few organisms are associated with the majority of cases.⁵ This allows for empiric antibiotic selection without the need for extensive investigation into the causative agent in an individual patient. Even with extensive investigation a causative agent is not identified in 98% of outpatients and 40–60% of inpatients.⁶

Most studies on the cause of CAP have been conducted in hospitalised patients, and although the exact proportions of each organism may vary, the relative frequency remains fairly constant

between countries. A review of published reports from North America found the following organisms responsible for CAP in hospitalised patients: *Streptococcus pneumoniae* (20–60%), *Haemophilus influenzae* (3–10%), *Mycoplasma pneumoniae* (1–6%), *Chlamydia pneumoniae* (4%), *Legionella sp* (2–8%), viruses (2%), aspiration (6–10%), *Staphylococcus aureus* (3%), Gram-negative bacilli (3–5%) and other identified organisms (10–20%).⁵ Since this review it has been recognised that a significant percentage of CAP may be polymicrobial.⁷

In the majority of studies *S pneumoniae* is the dominant organism across the spectrum of severity of CAP. The frequencies of the other pathogens vary in a predictable manner depending on age, co-morbidity and severity. *M pneumoniae* has an increased frequency in mild CAP while *Legionella sp*, *S aureus* and Gram-negative organisms such as *Klebsiella pneumoniae* show an increased frequency in severe CAP.⁶ *H influenzae* is more common in patients with chronic obstructive airways disease (COPD) and is the second most common cause of CAP in patients with HIV infection. In a recent local study *S. pneumoniae* was identified in 50% of isolates. It should be noted that atypical organisms were identified in 21% of this group of hospitalised patients.² The exact incidence of atypical pathogens as a cause of CAP in South Africa is uncertain, but it displays a cyclic variation over time and may be associated with outbreaks of CAP.⁸

Studies trying to determine the organisms responsible for mild CAP in persons treated as outpatients have been less congruent and demonstrate greater geographical variability. Viral pathogens, in particular Influenza A, may play a greater role in this group of patients with 10–50% of cases being viral. The most frequent bacteria identified in these outpatient studies were *H influenzae*, *M pneumoniae* and *S pneumoniae*.⁹

The high incidence of viruses in mild outpatient CAP makes this an attractive group to target for decreased antibiotic administration. Attempts have been made to identify patients with a viral pneumonia

who do not require antibiotic therapy.¹⁰ Clinical scores proposed to differentiate between viral and bacterial CAP are neither sensitive nor specific enough to use in clinical practice. There is a possibility that serum procalcitonin levels may be able to discriminate between those requiring and those not requiring an antibiotic; however, this is impractical on an outpatient basis and requires further investigation.¹¹

Diagnosis and investigation of CAP

A patient should be suspected of having pneumonia when presenting with an acute cough and one of the following: dyspnoea, tachypnoea, fever lasting more than four days or new focal chest signs. Elderly patients may present atypically with confusion or abdominal pain and few respiratory symptoms, thus a high index of suspicion is necessary in this group. The diagnosis of CAP should be confirmed with a chest radiograph.⁶

A chest radiograph is recommended for all patients with suspected pneumonia as history and examination alone have low sensitivity (47–69%) and specificity (50–75%).¹² The chest radiograph not only confirms the diagnosis but also identifies features of severity, complications and any underlying pulmonary pathology. The chest radiograph may be normal in early disease.

No additional investigations are required in previously healthy patients considered to have mild pneumonia; however, counselling and testing for HIV should be offered.

Sputum Gram stain and culture should be reserved for patients with co-morbid disease and severe pneumonia. Only specimens with a Bartlett score of +2 (> 25 neutrophils and < 10 epithelial cells per low power field) are representative of the lower respiratory tract. A limitation of sputum is that certain organisms can cause both colonisation and disease. Sputum should be submitted for acid-fast bacilli (auramine or Ziehl-Neelsen stain) if tuberculous infection is suspected. Induced sputum should be sent for *Pneumocystis jirovecii* immunofluorescence if *Pneumocystis jirovecii* pneumonia is suspected in HIV-infected individuals.

The routine collection of blood cultures has not been shown to improve patient outcome in CAP and seldom results in a change of the initial empiric antibiotic.¹³ However, it is wise to obtain two sets of blood cultures prior to the administration of antibiotics in patients with severe CAP.¹⁴

Clinical judgement underlying co-morbidity and severity of CAP should guide the necessity and frequency of haematological and biochemical investigations. White cell count, serum urea and serum albumin are important in the further assessment of the severity of CAP. Renal function needs to be monitored if nephrotoxic drugs such as the aminoglycosides are used. HIV testing should be offered to all patients as a positive diagnosis may broaden the list of likely pathogens and influence antibiotic selection. The routine use of serum activity markers such as CRP and procalcitonin is not recommended. Serological tests for atypical organisms are not routinely indicated.

Oxygenation and the need for supplemental oxygen may be assessed with pulse oximetry, but arterial blood gas analysis is required to assess Pa CO₂ in patients who are in respiratory distress and are tiring or where there is a concern of CO₂ retention in patients with COPD.

All patients with pleural effusion should undergo diagnostic thoracentesis to rule out an empyema. In addition to the routine

testing of pH, glucose, protein, LDH and MC&S, pleural fluid should also be sent for tuberculosis microscopy and culture.

Treatment of CAP

Numerous societies have developed guidelines for the management of CAP; the guidelines differ based on local conditions such as patient population, pattern of pathogen frequency and antibiotic resistance. Most guidelines divide patients with CAP into subgroups based on the need for hospitalisation, age, co-morbid disease and the severity of pneumonia. These subgroupings allow for recommendations on the most appropriate antibiotic choice, based on the frequency of likely pathogens in each group. Rational recommendations on the appropriate level of care can also be made.

It has been shown that implementation of CAP guidelines results in a significant decrease in morbidity and mortality.⁶ SATS has recently revised guidelines for the management of CAP in adults.¹⁵ Although these guidelines have not been validated, they are based on the latest evidence available from both local and international studies and on local antibiotic resistance profiles. Adherence to these guidelines should result in decreased mortality and prevent the ever-increasing antibiotic resistance problem in South Africa. Despite offering benefit to both the individual patient and the community, guidelines are seldom followed. Only 8% of the patients in a recent local study were treated according to the guidelines. Unfortunately the numbers in the study were too small to comment on the validity of the guidelines.² The revised SATS guidelines algorithm is shown in Figure 1.

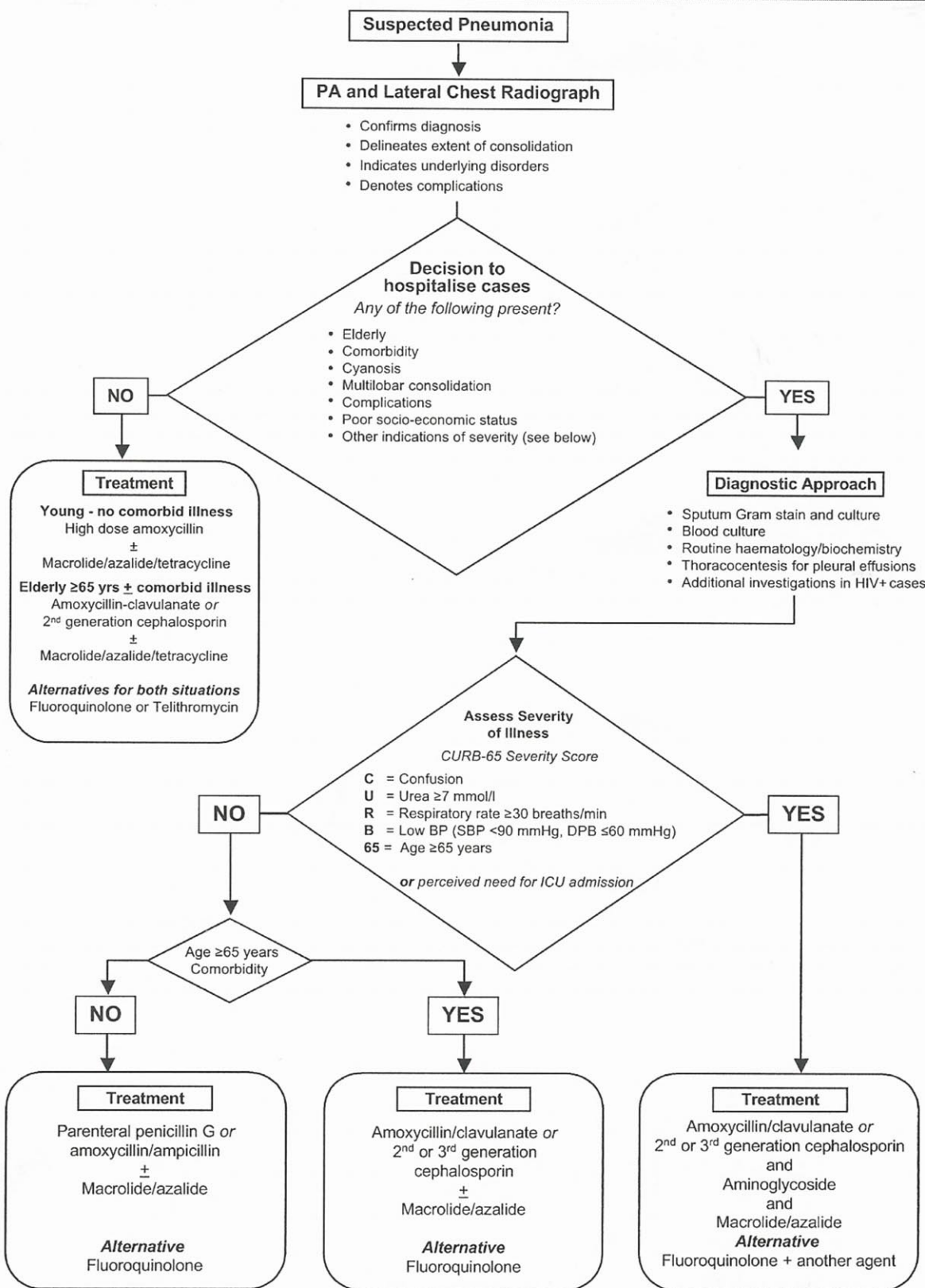
One of the most important aspects in the management of a patient with CAP is the decision of whether the patient can be safely treated as an outpatient or whether hospitalisation is required. Once a decision to hospitalise a patient is reached the appropriate level of care, ranging from a general ward to an intensive care unit, must be determined.

The need for hospitalisation is multi-factorial. Advanced age, preexisting conditions, complications of pneumonia, the need for supplemental oxygen and the ability to tolerate oral medication must be considered. In addition to the clinical assessment, psychosocial circumstances, such as the patient's wishes, home support system, and factors such as substance abuse or homelessness need to be explored if outpatient therapy is being considered. If the patient is considered suitable for outpatient management after the above considerations have been taken into account, a prognostic score should be determined. Patients with a low predicted mortality are suitable for outpatient management.¹⁶

The SATS guidelines make use of the Modified British Thoracic Society Rule/CURB65 score. The CURB65 score is derived from five variables: **C**onfusion, **U**rea > 7 mmol/l, **R**espiratory rate > 30 breaths per minute (bpm), **B**lood pressure (systolic < 90 mm Hg, diastolic < 60 mm Hg) and **A**ge > 65 years. A point is given to each variable present and added up to reach a score between zero and five for the patient. The higher the score, the greater the predicted mortality.¹⁷

A CURB65 score of zero to one has a predicted mortality of 1.7% and these patients may be treated as outpatients.¹⁴ Patients with a CURB65 score of three or more have a high rate of mortality and would be suitable for ICU admission. The CURB65 score does not take co-morbid conditions into account and may underestimate the severity of CAP in patients with pre-existing disease. The CURB65 score does not require estimation of serum urea and is equivalent to the CURB65 score for predicting mortality. It is useful for outpatient assessment.¹⁸

Figure 1: Algorithm for the management of community-acquired pneumonia in adults



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The overriding factor in the final decision of whether or not to admit a patient should remain the attending doctor's clinical judgement. In cases where uncertainty exists one should err on the side of admission even if it is only for a short observation period.¹⁹ Patients who are treated as outpatients should be reassessed at 24–48 hours as this is the time period in which patients are most likely to deteriorate.¹⁹

If a patient is hospitalised the level of care is based on clinical judgement and guided by further assessment of severity, using clinical and laboratory parameters. Parameters suggesting severe infection are the following:

- Confusion or decreased level of consciousness
- Respiratory rate > 30 bpm
- Hypotension (systolic < 90 mm Hg or diastolic < 60 mm Hg)
- Hypoxaemia (PaO₂ < 7.5 KPa)
- White cell count < 4 or > 30 × 10⁹
- Urea > 7 mm ol/l

The presence of two of these features suggests severe pneumonia that may require transfer to a high care facility. Three or more of these features suggest a need for management in an ICU.²⁰ Again it is imperative that the attending doctor makes the final placement decision based on clinical judgement and common sense.

Early administration of appropriate antibiotics has been shown to decrease mortality in patients hospitalised for CAP.¹⁴ Investigations for an aetiological agent in CAP are time consuming and often inconclusive, thus therapy for CAP is empiric with antibiotic choice directed at the most likely organism for the patient and clinical scenario (see Figure 1).

Resistance patterns of common pathogens and the therapeutic implications

S pneumoniae is the most common pathogen isolated in all the subgroups, thus any antibiotic chosen must have reliable anti-pneumococcal cover.

β-lactams

The class of β-lactam antibiotics consists of the penicillins, aminopenicillins and cephalosporins. Pneumococcal resistance to this class of antibiotics is related to alterations of the penicillin binding chains (PBC) of the organism. This results in a decreased affinity of the antibiotic for the organism, which can be overcome with higher concentrations of β-lactam antibiotics.³ The pharmacokinetic and pharmacodynamic (PK/PD) indices of the β-lactams as well as their ability to reach high concentrations in the respiratory tract allow them to readily overcome *in vitro* reduced-penicillin-susceptible strains (penicillin-intermediate and -resistant strains) of pneumococci causing CAP. No difference in clinical outcome has been demonstrated between penicillin-susceptible and reduced-penicillin-susceptible strains when adequate doses of the penicillins have been used.²¹ Clinical studies support the efficacy of the penicillin antibiotics in the treatment of reduced-penicillin-susceptible pneumococcal CAP.²² It is possible that as pneumococcus develops higher minimum inhibitory concentration (MIC) to penicillin, negative clinical outcomes may occur. Continued surveillance is essential to allow early detection of this potential problem.

The second-generation cephalosporin cefuroxime has borderline PK/PD indices,²¹ and clinically adverse outcomes have been observed

when low doses (750 mg eight hourly IVI) are used, thus cefuroxime should only be given at a higher dosage for CAP (1 500 mg eight hourly).²² The third-generation cephalosporins continue to have good activity against reduced-penicillin-susceptible pneumococci.

H influenzae may produce β-lactamase, which renders it resistant to the aminopenicillins; the addition of clavulanate, a β-lactamase inhibitor, overcomes this resistance. The overall rate (7%) of β-lactamase producing *H influenzae* is low in South Africa.²³ However, patients with conditions that predispose them to infection with resistant *H influenzae*, such as COPD, should receive antibiotic treatment accordingly. β-lactams offer no cover against atypical organisms and an additional agent with atypical bacteria cover, usually a macro/azalide, should be added in cases where infection with an atypical organism is suspected. Taking all the current evidence into account the β-lactams are still the recommended first-line antibiotics for CAP of all severities.

Macrolides and azalides

South Africa's rates of macro/azalide-resistant pneumococcus are amongst the highest in the world. A surveillance study of private laboratories conducted in 2000–2001 found 61% of pneumococcal isolates to be resistant to macro/azalides with 47% showing high-level resistance.²³ This high-level macrolide resistance cannot be overcome with increased dosing and the macro/azalides should not be used as monotherapy in CAP.²⁴ The major role for the macro/azalides is as add-on therapy for atypical bacteria cover and as part of combination therapy in the treatment of severe pneumonia.

Ketolides

Telithromycin has broad-spectrum antibacterial cover with activity against atypical pathogens and excellent activity against *S pneumoniae* including penicillin-resistant and erythromycin-resistant strains. It may not offer optimal activity against *H influenzae*.¹⁶ Its association with severe adverse events requires that it be used with caution.²⁴ It is recommended that telithromycin be reserved for patients with severe allergy to β-lactams and cases of highly resistant pneumococcal CAP. Pneumococcal resistance to telithromycin is low.²⁵

Respiratory fluoroquinolones

Levofloxacin, gemifloxacin and moxifloxacin have excellent activity against *S pneumoniae* (including penicillin-resistant and erythromycin-resistant strains) and the other common pathogens causing CAP, including the atypical bacteria. Pneumococcal resistance to and treatment failure of this class have been described and are on the rise with the increasing use of these agents.²⁶ Exposure to fluoroquinolones in the previous three months increases the risk of resistance. The safety profile of the fluoroquinolones renders them unsuitable for routine use.²⁴ As they are also effective second-line antituberculosis agents, patients with tuberculosis may show an initial clinical response if treated with fluoroquinolones. TB rapidly develops resistance when exposed to monotherapy, and these agents should be avoided if TB is suspected.

Fluoroquinolones should be reserved for patients with severe penicillin allergy, failed first-line therapy, known infection with high-level penicillin-resistant pneumococci or who have received a β-lactam in the past three months. Combination therapy, usually a β-lactam and a macrolide, is superior to a fluoroquinolone alone in severe pneumonia. An additional agent should be added to the fluoroquinolones when treating severe CAP.²⁷

Aminoglycosides

Aminoglycosides are a poor choice for respiratory tract infections as they have limited penetration into the lung. In South Africa *K pneumoniae* is a common cause of severe CAP with a high mortality rate.²⁸ The addition of an aminoglycoside to the initial therapy of severe CAP has been shown to significantly improve the mortality of patients with *K pneumoniae*,²⁸ probably by controlling bacteraemia. As these patients cannot be separated clinically from patients with other causes of severe pneumonia, the addition of an aminoglycoside to the initial empiric therapy is recommended in patients with severe pneumonia. The aminoglycosides act synergistically with the β -lactams but not the fluoroquinolones. It is not known whether the addition of an aminoglycoside to a fluoroquinolone will confer the same benefit as demonstrated with the β -lactam-aminoglycoside combination.

Doxycycline

The high prevalence of *S pneumoniae* resistance to doxycycline limits its use for CAP to add-on therapy to β -lactams for the cover of atypical organisms.

General principles of antibiotic therapy

An antibiotic should only be prescribed if a bacterial infection is suspected and not as prophylaxis against possible secondary bacterial infections. All antibiotics should be given in the correct dose at the correct interval. (See Table I.) If an antibiotic has been received in the preceding three months an antibiotic of a different class should be used. Combination therapy with a β -lactam and either a macrolide or a fluoroquinolone has been shown to offer a survival benefit over monotherapy in patients with severe CAP and hypotension.²⁷ It is advised that combination therapy be used in patients with severe CAP.

Duration of therapy

The exact duration of therapy for CAP remains uncertain. The current guidelines recommend five to seven days therapy for CAP and 14 days for severe *Legionella* infection.¹⁵ A recent trial has shown three-day therapy to be safe and efficacious in patients admitted to hospital with mild to moderate CAP.²⁹ Further trials are required to determine the optimal duration of therapy. At present, continuation of therapy for 48–72 hours after vital signs normalise is a safe option. Patients on parenteral therapy may be converted to the same oral formulation once vital signs return to normality.

Response to therapy

Most patients with CAP should show an improvement and stabilisation of vital signs within 48–72 hours.³⁰ Cough and dyspnoea usually resolve within 14 days but non-respiratory symptoms such as fatigue may persist for longer, particularly in patients with co-morbid disease and in the elderly.³¹ While patients should return to their pre-pneumonia condition within six months, evidence suggests a lower long-term survival rate in elderly patients who have had pneumonia than in matched controls who have not.³¹

Failure of response

Severe pneumonia, old age, co-morbid disease and immunosuppression may cause a delay in clinical stabilisation. Failure to show stabilisation at 72 hours in the absence of risk factors for a protracted course or deterioration in the patient's clinical condition suggests treatment failure.³⁰ Causes for treatment failure may be

Table I: Recommended dosages of antibiotics for CAP

Penicillins	Fluoroquinolones
Oral Amoxicillin: 1 g eight hourly Amoxicillin-clavulanate: minimum of 500 mg amoxicillin with 125 mg clavulanate eight hourly. Sustained release preparations allow for 1 g 12-hourly dosing.	Oral Gemifloxacin: 320 mg daily Levofloxacin: 500 mg 12 hourly or 750 mg daily Moxifloxacin: 400 mg daily
Parenteral Penicillin G: 2-4 million units six hourly Ampicillin or Amoxicillin: 1-2 g six hourly Amoxicillin-clavulanate: 1,2 g eight hourly	Parenteral Levofloxacin: 500 mg 12 hourly or 750 mg daily Moxifloxacin: 400 mg daily
Cephalosporins	Aminoglycosides
Oral Second generation Cefuroxime axetil: 750 mg – 1 gm 12 hourly Cefpodoxime: 400 mg 12 hourly	Parenteral Amikacin: 15 mg/kg/day (maximum 1,5 g daily) gentamicin: 5–7 mg/kg/day (usual 320 mg daily) Tobramycin: 5–7 mg/kg/day (usual 320 mg daily)
Parenteral Second generation Cefuroxime: 1,5 g eight hourly	
Third generation Ceftriaxone: 2 g daily (can increase to 2 g 12 hourly) Cefotaxime: 3–4 g daily in two–four divided doses	
Macrolide/azalides	Tetracyclines
Oral Erythromycin: 500 mg six hourly Clarithromycin: 500 mg 12 hourly Clarithromycin XL: 1g daily Azithromycin: 500 mg daily	Oral Doxycycline: 200 mg stat followed by 100 mg 12 hourly
Parenteral Erythromycin: 4–5 mg/kg six hourly given into a large vein Clarithromycin: 500 mg 12 hourly Azithromycin: 500 mg daily	
Ketolides	
Oral Telithromycin: 800 mg daily	

either infectious or non-infectious. Infectious causes to be considered are complications of pneumonia (empyema or cavitation), resistance of usual organisms and infection with organisms not covered by the recommended initial empirical therapy such as tuberculosis or *P jirovecii* or a superadded nosocomial infection.

Non-infectious causes to be considered are neoplasia, pulmonary embolism, pulmonary oedema and vasculitis with pulmonary haemorrhage. Treatment failure is usually due to an infectious agent,³⁰ and all microbiological specimens should be reviewed and new specimens obtained. A change in antibiotics to cover resistant pneumococci, *S aureus* and *Pseudomonas aeruginosa* is required. Patients with treatment failure have a high mortality and should be referred to a specialist for further management.

Adjuvant therapy


Supplemental oxygen should be administered when required. Attention must be paid to the patient's state of hydration and nutritional requirements. Systemic corticosteroids have been shown to decrease both morbidity and mortality in patients with severe CAP and may be

of value in this subgroup of patients. Prophylaxis against deep vein thrombosis with unfractionated heparin is recommended for all non-ambulant patients.

Prevention of CAP

Vaccination against pneumococcus decreases the incidence of invasive pneumococcal disease³² and results in a lower morbidity and mortality in patients who later develop CAP.³³ Pneumococcal vaccine is recommended for all persons who meet the recommended vaccination criteria. Influenza vaccination in at-risk persons decreases the incidence and severity of CAP. All persons with an indication for the influenza vaccine should be encouraged to receive it annually. Smoking is a risk factor for CAP and the development of invasive pneumococcal disease. All smokers should be encouraged to stop smoking.

Conclusion

CAP remains a common and potentially fatal condition. CAP is usually caused by a few pathogens and evidence is available to predict the most likely causative pathogen depending on patient age, co-morbidity and severity of the pneumonia. The resistance mechanisms and patterns are also known for the pathogens causing CAP. This allows for a rational choice of antibiotics for patients with CAP. SATS has released its revised guidelines for the management of CAP in adults, which, if adhered to, should result in improved survival for patients as well as limiting inappropriate antibiotic use and preventing antibiotic resistance. 

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