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Management of community-acquired pneumonia – essential tips for the physician on call

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Management of community-acquired pneumonia – essential tips for the physician on call

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Abstract

Community-acquired pneumonia (CAP) is a common clinical problem requiring admission to hospital, with a particularly high incidence in the elderly population and those with significant comorbidities. Diagnosis is made on the combination of a short history of respiratory symptoms and systemic ill-health with new examination and / or radiological features of consolidation. Multiple other infective and non-infective conditions can mimic CAP, leading to misdiagnosis in 5-17% of cases. The CURB-65 scoring can identify high-risk CAP patients, but is insensitive at identifying patients requiring intensive care support and needs to be combined with clinical markers of potential severity. Both high admission levels of C-reactive protein and its failure to decline by >50% by day 4 after admission are associated with higher risk of complications, need for ventilation or inotropic support, and mortality. Empirical antibiotic therapy for most patients admitted to hospital is combination of a ß-lactam and a macrolide. Short-courses of antibiotics do not result in significantly different outcomes to longer courses unless the patient has developed complications such as a complex parapneumonic effusion. Implementation of a CAP care bundle into clinical practice has been demonstrated to improve mortality, and should be a high priority for all acute hospitals.

Key points:

- Accurate interpretation of the chest radiograph is key to identifying potential differential diagnoses and complications of CAP.
- The CURB-65 scoring system is an essential management tool for CAP but is insensitive at identifying severe cases requiring intensive care treatment, and needs to be combined with a clinical assessment of physiological markers of severity.
- Failure of the admission C-reactive protein level to fall by <50% at day 4 is associated with higher risk of mortality, complications and invasive ventilation / inotrope use.
- The outcomes of short-course and long-course antibiotic treatments for CAP patients are similar.

- CAP mortality can be reduced by establishing appropriate systems of care to ensure care bundles are adhered to.

Introduction and background on pneumonia

Pneumonia occurs when the alveoli become infected with microorganisms, causing a local and systemic inflammatory response that results in the alveoli filling with exudative fluid and inflammatory cells. It is this local alveolar inflammatory reaction to the infection which leads to consolidation, the clinical hallmark of pneumonia. Extensive consolidation compromises gas exchange and can lead to life-threatening hypoxia (Quinton et al. 2018). Pneumonia is classified according to the patient's location when they acquired the infection. Community-acquired pneumonia (CAP) occurs when infection is acquired outside the hospital and is by far the commonest type of pneumonia. CAP has an overall incidence estimated between 1.5 and 14 cases per 1000 person-years depending on geographical location, the season (with a distinct increase in winter in the UK) and characteristics of the population (Prina et al. 2015). Hospital acquired pneumonia (HAP) is pneumonia acquired 48 hours after admission to hospital or within 14 days after discharge from hospital. Ventilator acquired pneumonia (VAP) is a subset of HAP affecting patients 48 hours after endotracheal intubation (Jean et al. 2020). This classification allows clear communication between clinicians about the patient's condition, but importantly also ensures the correct empirical antibiotic therapy is chosen as the potential infecting microorganisms vary between CAP, HAP and VAP. Pneumonia developing in patients with a severe degree of immunosuppression such as chemotherapy-induced neutropenia, after organ transplantation, or in patients with advanced Human Immunodeficiency Virus (HIV) infection are considered separately due to the extensive range of potential causative microorganisms (Di Pasquale et al. 2019).

Pneumonia is one of the most commonly encountered respiratory infection accounting for approximately 230,000 deaths in Europe (29,000 in the UK) per year, and in the UK is responsible for more hospital admissions than any other lung disease (Chalmers et al. 2017;

Marshall et al. 2018). For CAP patients admitted to hospital the 30-day mortality rate is between 5-15% (Chalmers et al. 2017). The incidence of pneumonia is increasing over time, and at present Europe spends €5.7 billion per year on inpatient care and half a billion on outpatient care for patients with pneumonia (Chalmers et al. 2017). The incidence of CAP and risk of death are related to age, sex and the presence of comorbidities (Prina et al. 2015; Luna et al. 2016). CAP is commoner in older adults with approximately 45% of cases in the over 65 years age group (Cillóniz et al. 2018), and the incidence is also higher in males than in females (Prina et al. 2015). The exponential increase in CAP incidence after 65 years of age is partially due to the presence of comorbidities associated with CAP, but is also probably related to immunosenescence – the decreased efficacy of the adaptive and innate immune systems with increasing age (Cillóniz et al. 2018). The mortality of CAP is also higher in patients with more than one comorbidity and some specific comorbidities eg cardiac failure (20.5%) compared to patients with chronic obstructive pulmonary disease (COPD) (8.1%) (Luna et al. 2016).

This article will explore the diagnostic features of CAP, some of the potential traps for misdiagnosis, the recognition of possible complications and patients with severe disease, and discuss some of the important issues when selecting appropriate antibiotic treatment.

Diagnosis of CAP and diagnostic pitfalls

To make a diagnosis of CAP requires evidence of new lung consolidation (eg dyspnoea, pleuritic chest pain, signs of consolidation, and / or air space shadowing on the chest radiograph) associated with evidence of a significant inflammatory response (eg a fever, tachycardia, and raised C-reactive protein or erythrocyte sedimentation rate) (Lim et al. 2009). However, these features also occur in many other less common conditions. Although a pyrexia and raised biomarkers such as C-reactive protein may suggest an infective aetiology, they are not specific for infectious causes of inflammation (Black 2016) and are often abnormal in non-infective causes of lung inflammation. Perhaps 5-17% of patients admitted to hospital with a diagnosis of CAP actually have non-infectious mimics of CAP (Black 2016), the correct

diagnosis of which will enable the patient to receive appropriate treatment. An important clinical point is that CAP will usually present with a short history of days rather than weeks - if a patient has a prolonged history of illness then other diagnoses need to be considered such as subacute lung infection (eg tuberculosis, actinomycosis) or non-infective causes of lung shadowing and inflammation (Figure 1). A particularly cautious approach to making a diagnosis of CAP is required when there is a background history of previous immunosuppression, lung diseases such as interstitial lung disease, bronchiectasis or allergic bronchopulmonary aspergillosis (ABPA), and in patients on certain drugs like amiodarone. These are all associated with non-CAP lung infections (eg an infective exacerbation of bronchiectasis) and / or non-infective mimics of CAP. Table 1 lists some of the common and less common conditions that are often misdiagnosed as CAP and the clinical clues which can be used to differentiate them from CAP. Often the accurate interpretation of the chest radiograph would suggest the cause of the patients presentation is a diagnosis other than CAP (Figure 1, Table 1).

Severity assessment and recognition of complications of CAP

CAP can lead to several different serious complications, including severe physiological disturbance with acute respiratory failure due to extensive consolidation or the development of the acute respiratory distress syndrome (ARDS), and / or septic shock and organ dysfunction (Ferrer et al. 2018). Other complications reflect evolution of the infection such as infected parapneumonic effusions, empyema, and lung abscess. These complications of CAP will usually the length of stay in hospital, possibly require admission to intensive care for non-invasive (CPAP, optiflow) or invasive ventilatory support, or need interventions such as tube drainage or surgery. The development of a complication results in a substantial increase in mortality (Chalmers et al. 2009; Morgan and Glossop 2016; Lee 2017); for example, ventilated patients with CAP have a 38% 30-day mortality (Ferrer et al. 2018). Early clinical recognition of CAP patients at risk of complications is essential to ensure rapid instigation of appropriate management that might avoid the development of complications or mitigate their impact.

The clinical prediction rule developed in the United Kingdom to classify severity for CAP patients is the CURB-65 score. With the CURB-65 score the patient is attributed a score of 0 or 1 for five factors: confusion (new onset confusion or abbreviated mental test score ≤8); urea >7; respiratory rate ≥30; blood pressure diastolic <60 or systolic <90 mmHg; and age ≥65 (Lim et al. 2009; NICE 2019). CAP mortality increases with the score, with a score of 0-1 having a <3% mortality, a score of 2 a 9% mortality, a score of 3 a 15% mortality, and scores of 4 or 5 a 40+% mortality (Lim et al. 2009; NICE 2019). The score is also used to assess patient placement (0-1, treat at home, 2+ admit to hospital, 3+ consider referral to intensive care), and dictates which antibiotic regimen should be used. The CURB-65 is a very useful management tool for patients with CAP, and does identify patients at high risk of death. However, the CURB-65 and other more complex pneumonia severity scores like the Pneumonia Severity Index are insensitive for predicting which CAP patients are at risk of developing complications or will need treatment in intensive care (Chalmers et al. 2009; Liu et al. 2016). For example, Ilg et al. (2019) found that 16% of admitted CAP patients with a CURB-65 score of of 0-1 will require admission to intensive care, and conversely Charles et al. (2008) found a CURB-65 score of 3+ only identified 39% patients needing admission to intensive care.

This gap in the utility of the CURB-65 score has led to several attempts to develop new clinical scoring systems that are able to accurately identify CAP patients at risk of complications or who might need intensive care treatment (Charles et al. 2008; Chalmers et al. 2009; Liu et al. 2016). These scoring systems tend to have increased sensitivity and specificity for identifying severe cases of CAP. However, they are more complex than the CURB-65 score making them much less easy to use and they still fail to identify a substantial minority of CAP patients who develop severe disease. Several of the criteria identified by these severity scoring systems (box 1) are physiological markers for patients who are unwell eg a significant alveolar / arterial oxygen gradient or thrombocytopaenia (Morgan and Glossop 2016; Ferrer et al. 2018). As

such, they are readily identified by the clinician. Overall these data suggest that combining recognition of these markers of physiological disturbance with the CURB-65 score will help ensure patients at risk of developing severe CAP are better recognised.

One biomarker that can also help with severity assessment is measurement of serum levels of the acute phase protein C-reactive protein (CRP). CRP is released by the liver in response to raised interleukin 6 levels and has a very large dynamic range, from a normal level of <5 mg/L to levels that can reach 500+ mg/L in acute severe infections such as CAP (Chalmers et al. 2008). An admission CRP level >250 mg/L is an independent marker for raised mortality, associated with a 15% higher mortality in patients with a CURB-65 score of 3+ (Chalmers et al. 2008). If the admission CRP is >100 mg/L then there is a 16-fold increase in the risk of complications for patients with CAP, and a specific increased risk in developing a complex parapneumonic effusion (the commonest infective complication) (Chalmers et al. 2008, 2009). CRP can be used to provide information to aid diagnosis, and serial measurements can ascertain whether there has been a response to treatment (Chalmers et al. 2008, 2009; Lim et al. 2009). Box 2 summaries the usefulness of CRP measurements in the management of CAP.

Antibiotic selection

Patients with CAP are initially given antibiotics empirically as a microbiological diagnosis is usually not available for over 24 hours, and in fact is not achieved in the majority of patients outside of research studies (Prina et al. 2015; Bianchini et al. 2019). Treatment is commenced as recommended by the British Thoracic Society (BTS) (Lim et al. 2009) and National Institute for Health and Care Excellence (NICE 2019) guidelines and involves a broad-spectrum ß-lactam and a macrolide (box 3). This combination covers the main bacterial pathogens *S. pneumoniae* (up to 50% of cases) (Cillóniz et al. 2018), and the atypical bacteria *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* (10-15% of cases) (NICE 2019). In addition, the empirical regimen for CAP usually has good activity against the less common causative

bacterial pathogens such as *Haemophilus influenzae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. However, this empirical regimen is only appropriate for cases of CAP; a much higher proportion of HAP is caused by Gram negative bacteria that are potentially antimicrobial resistant (Jean et al. 2020), and pneumonia in the immunosuppressed can also be caused by fungi and viruses (Di Pasquale et al. 2019). Hence it is important to ensure the patient presenting with pneumonia has not recently been in hospital, and does not have significant immunosuppression such as undiagnosed HIV infection with a low CD4 cells counts. The risk that CAP is caused by an antimicrobial resistant organism such as *Pseudomonas aeruginosa* (a frequent pneumonia pathogen in HAP and in immunocompromised patients) (Di Pasquale et al. 2019; Jean et al. 2020) remains low in the UK, but is probaby rising due to the increasing age and presence of comorbidities in patients presenting with CAP (Shindo et al. 2013). Ensuring infection with resistant organism is not missed is important as (perhaps not surprisingly) antibiotic treatment with lack of activity against the microbial cause of CAP is associated with treatment failure. Risk factors for infection with a resistant organism are listed in box 4, and are largely related to a poor overall health status of the patient; in the absence of any risk factors 3.7% of patients have infection with a resistant organism (Shindo et al. 2013). An additional potential risk factor for infection with a resistant organism is a recent travel history, as high levels of macrolide and penicillin resistance are common amongst *S. pneumoniae* isolates in some parts of the world (Schroeder and Stephens 2016). Travel is also a risk factor for infection with contagious respiratory viruses such as Middle Eastern Respiratory Syndrome (MERS) or Covid-19, and a history of travel to affected areas means a patient with CAP should be isolated until a coronavirus infection has been excluded. Studies on the duration of antibiotics for CAP have shown that a short-course (≤7 days) of antibiotics does not result in significantly poorer outcomes to a long-course (>7 days) (Li et al. 2007). Reduction in exposure to antibiotics will reduce cost, antibiotic resistance and improve patient adherence (Li et al. 2007). A 5-day course of antibiotics should suffice in most cases of low-severity CAP except if there are infective complications such as lung abscess or complex parapneumonc effusion, or infection with microrganisms such as Gram negative pathogens

that are thought to require more prolonged therapy (Lim et al. 2009; Prina et al. 2015; NICE 2019).

Improving outcomes

Is there any evidence that the high risk of morbidity and mortality associated with CAP can be improved? The answer to this question is yes. Administration of the pneumococcal and the annual influenza vaccination to the elderly population is an important preventative approach, and pneumococcal vaccination of children has also resulted in significant herd immunity protection of adults (Cillóniz et al. 2018). The BTS have developed a CAP care bundle (box 5), implementation of which in 16 UK hospital trusts was associated with improvements in oxygen assessment, early antibiotic administration (odds ratio (OR) 1.26 and 1.52 respectively), and most importantly in 30-day mortality (8.8% vs 13.6%, OR 0.59). Wider implementation of the care bundle on a regional scale using pay for performance as an incentive reduced 30 day CAP mortality by 1.9% (Sutton et al. 2012). Bianchini et al. (2019) reported that using an innovative pharmacist-directed pneumonia diagnostic care bundle also improved management, increasing antimicrobial de-escalation by two-fold as well as reducing antimicrobial adverse drug events, *Clostridium difficile* infection and 30-day readmission. These data show that implementation of focussed attempts to improve CAP management can be successful and lead to significant improvements in patient care.

Conclusion

In the UK CAP is the commonest serious infectious disease and is increasing in incidence. The clinical syndrome of CAP usually presents with a relatively short duration of symptoms over days rather than weeks, and a combination of new consolidation and evidence of systemic inflammation. Many rarer inflammatory lung conditions mimic CAP although these often have a longer disease course measured in weeks rather than days and distinctive radiological features; accurate interpretation of chest x-ray is key to making the correct diagnosis. The CURB-65 score is an essential management tool for patients with CAP, but

needs to be used in conjunction with other clinical markers of severity to identify patients at high risk of developing complications or requiring intensive care treatment. Establishing appropriate systems of care that can ensure delivery of care bundles has been shown to improve outcomes of CAP, and should be a high priority for all acute hospitals.

Conflict of interest

The authors have no conflicts of interest to declare.

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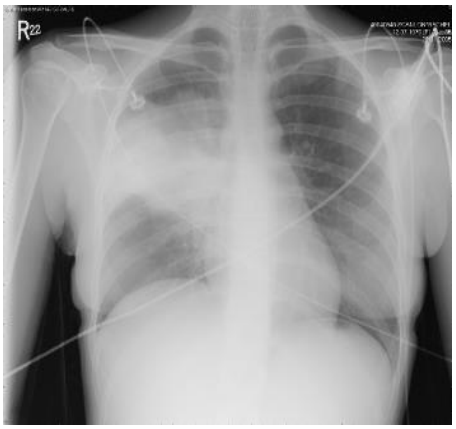
Boxes, Figures and Tables

Table 1: Conditions misdiagnosed as CAP and clinical clues to the diagnosis	
Respiratory	
Infective exacerbations of COPD	No consolidation on chest radiograph, CRP <40 mg/L
Influenza	High fever, rigor, coryzal / nasal symptoms, absence of lobar consolidation
Bronchiectasis	Chronic daily sputum production / recurrent chest infections, normal or mildly raised CRP, ring shadows and tramlines on chest radiograph
Acute respiratory distress syndrome	Rapid development of bilateral shadowing, severe hypoxia, PaO_2/FiO_2 ratios (mild <300mmHg, moderate <200mmHg, severe ≤100mmHg)
ABPA	Pre-existing asthma, central bronchiectasis, elevated total IgE, eosinophilia, expectorating sputum plugs, peribronchial shadowing
Cardiovascular	
Pulmonary oedema	Bilateral fine crepitations, bilateral alveolar shadowing, small pleural effusions, history of cardiac impairment
Pulmonary embolism (PE)	Pleuritic chest pain, peripheral deep vein thrombosis, risk factors for PE, wedge shaped infarct on chest radiograph, CRP <40 mg/L
Neoplastic	
Lung malignancy	Large intrapulmonary mass, bronchial obstruction leading to distal infection and / or collapse
Lymphoma	Intrapulmonary masses in a non-lobar distribution
Immunological disorders	
Organising pneumonia	Bilateral often subpleural patchy consolidation (non-lobar distribution)
Eosinophilic pneumonia	Bilateral often subpleural patchy consolidation ('reverse batswing'), BAL eosinophilia (systemic eosinophila not essential)
Hypersensitivity pneumonitis	Ground-glass infiltrates mainly in upper zones, history of a risk occupation or hobby (eg owning pet birds)
Granulomatosis with polyangiitis	Haemoptysis, renal impairment, upper respiratory tract symptoms, cavitation on chest imaging
Diffuse alveolar haemorrhage	Haemoptysis, diffuse bilateral infiltrations / alveolar airspace shadowing, known vasculitis / autimmune disease
Drug induced toxicity	Drug history, subacute onset, bilateral crepitations and radiological infiltrates
Radiation pneumonitis	Shadowing in the radiation field of recent radiotherapy treatment

ABPA, allergic bronchopulmonary aspergillosis; BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein (Black 2016; Lee 2017; Quinton et al. 2018).

Figure 1: Chest radiographs of CAP and clinical conditions that are often misdiagnosed as CAP

Community acquired pneumonia

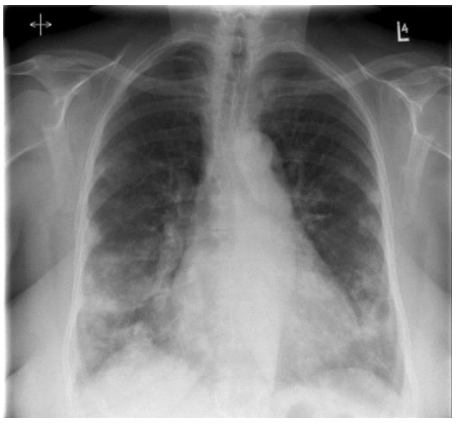


3 days fever, cough, dyspnoea, CRP 278
CXR: dense unilateral consolidation in lobar pattern

Subacute lung infection: actinomycosis

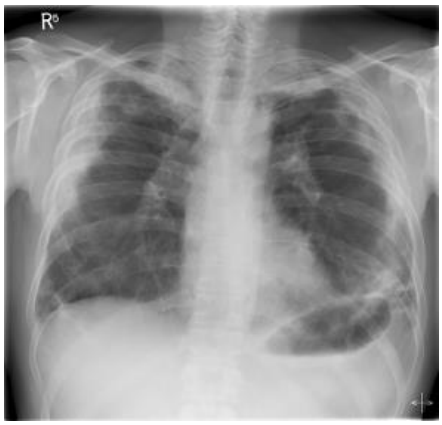
3 months fever, cough, poor response to amoxicillin
CXR: right lower lobe consolidation

Organising pneumonia due to amiodarone



3 weeks mild fever, cough, dyspnoea, CRP 67
On amiodarone for atrial fibrillation
CXR: peripheral patchy basal consolidation

Pulmonary eosinophilia



2 weeks fevers, cough, dyspnoea, CRP 222
CXR: ‘reverse batswing’ peripheral symmetrical subpleural consolidation

CXR, chest-x-ray

Box 1: Clinical parameters associated with severe CAP **(% = proportion of severe CAP patients with that parameter)**	
White cell count $<4\times10^9$/L	7%
PaO_2/FiO_2 ratio ≤250 mmHg	59%
Urea ≥7.14 mmol/L	54%
Respiratory rate ≥30 breaths per minute	56%
Confusion/disorientation	48%
Thrombocytopenia $<100\times10^9$/L	4%
Multilobar infiltrates	45%
Hypothermia ($<36^0$C)	11%
Hypotension	15%

Gathered from Morgan and Glossop (2016) and Ferrer et al. (2018).

Box 2: Utility of CRP when managing CAP
1. Admission CRP and rate of complications:
- <100 mg/L 4% rate of complications and reduced 30-day mortality (OR 0.18)
- >400 mg/L 71% rate of complications
- >250 mg /L 15% increase in mortality in patients with a CURB-65 score of 3+
- >200 mg/L associated with slower radiographic resolution.
2. Failure of admission CRP to fall by <50% at day 4 is associated with:
- higher risk of mortality (OR 24.5)
- empyema or complicated parapneumonic effusion (OR 15.4)
- requirement for invasive ventilation and / or inotropic support (OR 7.1)

CRP, C-reactive protein; OR, odds ratio (Chalmers et al. 2008; Lim et al. 2009).

Box 3: Preferred antibiotics treatment for CAP
Mild (CURB-65: 0-1): amoxicillin 500 mg TDS **or** clarithromycin 500 mg BD
Moderate (CURB-65: 2): amoxicillin 500 mg TDS **and** clarithromycin 500 mg BD
Severe (CURB-65: 3+): co-amoxiclav 1.2 g TDS **and** clarithromycin 500 mg BD

CURB-65, confusion, urea, respiratory rate, blood pressure, age ≥65 years; BD, twice daily; TDS, three times per day (Lim et al. 2009).

Box 4: Risk factors for resistant organisms (univariate analysis)
Home intravenous therapy (OR 1.17)
Chronic lung disease (OR 1.23)
Nursing home resident (OR 2.58)
Immunosuppression (OR 2.68)
Use of gastric acid suppressive agents (OR 2.78)
Non-ambulant patients (OR 2.89)
Home wound care in previous 90 days (OR 2.95)
Use of antibiotics in the previous 90 days (OR 3.6)
Hospitalization for ≥2 days in the preceding 90 days (OR 4.63)
Feeding tube present (OR 6.15)
MRSA history in the previous 90 days (OR 6.3)

MSRA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio (Shindo et al. 2013).

Box 5:Care bundle
Chest x-ray within 4 hours of hospital admission
Oxygen assessment and prescription
Severity assessment (using CURB-65 as part of the assessment)
Antibiotic administration within 4 hours

Information gathered from Lim et al. (2016).

Management of community-acquired pneumonia – essential tips for the physician on call

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