Severe community-acquired pneumonia

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Severe community-acquired pneumonia (CAP) is an increasingly common reason for admission to the intensive care unit (ICU). It is associated with significant morbidity, mortality, and utilization of health service resources. Inability to differentiate between CAP and non-pneumonic lower respiratory tract infections such as acute exacerbation of chronic obstructive pulmonary disease (COPD) has led to overtreatment, with a dramatic increase in the use of broad-spectrum antibiotics. This is associated with an increase in costs and side-effects, particularly Clostridium difficile-associated diarrhoea. A reduction in the frequency of Streptococcus pneumoniae infection has been associated with a simultaneous increase in the frequency of new pathogens such as Legionella, Chlamydia pneumoniae, and gram-negative bacilli such as Pseudomonas.

Definition

CAP is defined as an acute lower respiratory tract infection acquired by an immunocompetent individual in the community. It is associated with new focal signs on clinical and radiological chest examination and with at least one systemic feature such as temp. >38°C or symptom complex of fever, sweating, myalgia, and chest pain. It is important to differentiate from health-care-associated pneumonia, which is defined as pneumonia occurring in a patient within 90 days of previous acute care hospital admission, in patients admitted from nursing homes or long-term care institutions, or those who have received i.v. antibiotics, chemotherapy, or wound care within 30 days of the infection.

Epidemiology

The annual incidence of CAP in the UK is 5–11/1000 adult population. Twenty-two percent of adults with CAP require hospitalization and about 10% of these require ICU admission. Severe CAP accounts for about 6% of all ICU admissions, with an ICU mortality of 35%, and overall hospital mortality of 50%.

Aetiology

Streptococcus pneumoniae, Legionella pneumophila, and Staphylococcus aureus are the most common pathogens causing severe CAP, followed by Haemophilus influenzae (more common in patients with COPD), enteric bacilli, atypical pathogens, and viruses.

Streptococcus pneumoniae

Streptococcus pneumoniae is a gram-positive, capsule, lancet-shaped diplococcus found in the nasopharynx of 5–10% of healthy adults. It has a polysaccharide capsule which is the prime determinant of virulence. Antibodies against the capsular polysaccharide promotes killing of the bacterium. Risk of infection is highest in the elderly, immunocompromised, and asplenic or hyposplenic patients. Typically, the onset is acute, with high fever, cough, and pleuritic chest pain. The bacterium is usually penicillin-sensitive and the incidence of resistance appears to be decreasing in the UK. Penicillin-resistant strains are sensitive to macrolides, vancomycin, tazobactam–piperacillin (tazocin), and fluoroquinolones.

Legionella pneumophila

Legionella pneumophila is an aerobic gram-negative bacillus. It is motile, non-acid-fast, and produces beta-lactamase. It is present in natural habitats such as fresh water ponds, lakes, and reservoirs and artificial sources such as cooling towers, air conditioning systems, fountains, and respiratory therapy equipment. It is a facultative intracellular parasite replicating in amoebae in its aquatic habitat and in humans within macrophages. It is most commonly seen

Key points

Severe community-acquired pneumonia is associated with a very high mortality. Streptococcus pneumoniae remains the most common aetiological agent. Patients present with respiratory and systemic illness and typical radiological abnormalities. Pneumonia severity index and CURB-65 scores are helpful in assessing illness severity. Early identification of the high-risk patient and intensive goal-oriented therapy may reduce mortality.
in younger patients and smokers. Severe infection may occur particularly in the elderly and immunocompromised. Multisystem involvement is not uncommon with presentation of altered mental status, elevated liver enzymes, and diarrhea in addition to multilobar pneumonia. History of travel is usually but not always present. *Legionella pneumophila* is sensitive to macrolides, fluoroquinolones, and rifampicin.

**Staphylococcus aureus**

*Staphylococcus aureus*, a normal commensal of the skin and nasopharynx, is a gram-positive aerobic diplococcus that appears as grape-like clusters under the microscope. It is coagulase positive which differentiates it from other staphylococci which are usually coagulase negative. Most strains produce penicillinase (beta-lactamase) which confers resistance to penicillins. Beta-lactamase-producing strains were sensitive to beta-lactamase-resistant antibiotics such as methicillin and fluoroquinoloxin, but methicillin resistance has become widespread. Methicillin-resistant *Staphylococcus aureus* (MRSA) is treated with antibiotics such as vancomycin, linezolid, teicoplanin, tetracycline, and rifampicin. Vancomycin-resistant *Staphylococcus aureus* strains have now started emerging. *Staphylococcus aureus* pneumonia can be very severe and may occur as a complication of influenza. To date, the incidence of community-acquired MRSA pneumonia remains low in the UK. Panton-valentine leukocidin (PVL) toxin producing MRSA resulting in cutaneous lesions and severe necrotizing pneumonia has been reported in the community.

**Atypical pathogens**

The term atypical pneumonia is no longer recommended. ‘Atypical pathogens’ include organisms such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia psittaci*, and *Coxiella burnetii*, which are uncommon causes of severe CAP. These pathogens are difficult to diagnose early in the illness and are only sensitive to antibiotics other than beta-lactams, such as macrolides, tetracyclines, or fluoroquinolones. They are concentrated intracellularly, where they replicate. *Legionella* species, although sharing some of these characteristics, are not considered to be an ‘atypical pathogen’ as there are different species and these can be acquired both in the community and in the hospital environment.²

**Clinical features**

Patients with severe CAP usually present with generalized malaise, high-grade fever, productive cough, shortness of breath, and pleuritic chest pain. They may develop systemic features of sepsis such as hypotension, respiratory failure, and renal dysfunction. Fever is less likely in the elderly while chest pain is less frequently reported with *Legionella* infection.

**Investigations**

**General**

General investigations are performed to assess severity, to assess the impact on or detect the presence of any co-morbid disease, to identify complications, and to monitor progress.

White cell count of $>15 \times 10^9 \text{ litre}^{-1}$ strongly suggests a bacterial aetiology, and a count of $>20 \times 10^9$ or $<4 \times 10^9 \text{ litre}^{-1}$ indicates severe disease. Urea, electrolytes, and liver function tests are performed to assess severity and for the identification of underlying or associated renal or hepatic disease. Plasma C-reactive protein (CRP) level $>100 \text{ mg litre}^{-1}$ on admission has been shown to be a more sensitive and highly specific marker of pneumonia than pyrexia or raised white cell count. Serial measurements of CRP may be useful for monitoring treatment response. A CRP level that does not decrease by 50% within 4 days suggests treatment failure or the development of complications such as empyema or antibiotic-associated diarrhoea.⁴

**Microbiology**

Gram stain, culture, and sensitivity of sputum or bronchoalveolar lavage may aid the identification of the causative agent. Blood culture is recommended for all patients with severe CAP, preferably before commencement of antibiotic treatment. Isolation of bacteria from blood cultures is highly specific and is also a marker of illness severity. Antigen detection in the urine is useful for the diagnosis of pneumococcal and *Legionella* infection. Serological testing may aid the diagnosis of atypical pathogens and *Legionella* infection. The detection of antibodies to the pneumococcal toxin pneumolysin is highly sensitive and specific in the diagnosis of pneumococcal infection.

**Radiology**

Chest radiography is the first choice imaging investigation in severe CAP. Unilobar consolidation, especially of the lower lobe, is common, except for *Klebsiella* where the right upper lobe is more commonly involved. Multilobar involvement is seen in *Legionella*, severe pneumococcal, and staphylococcal pneumonia. Bacteraemic pneumococcal pneumonia also shows pleural effusions, whereas staphylococcal pneumonia can present with cavitary and spontaneous pneumothorax. Radiological resolution usually lags behind clinical improvement, especially in the elderly and in multilobar involvement.

Ultrasound is useful in confirming the presence of effusion and empyema, and to localize them for drainage. Computed tomography of the chest is helpful, especially in severe infection with uncommon radiological features or those failing to respond to treatment.
**Severity assessment**

Assessment of disease severity and monitoring response to therapy is very important in risk stratification as severe CAP has a very high mortality. Early identification of high-risk patients allows prompt initiation of appropriate antibiotic treatment and admission to a critical care area for an enhanced level of monitoring and support. Predictors of illness severity specific to CAP such as the pneumonia severity index (PSI) and CURB-65 are reviewed below. These may be used alongside ‘track and trigger’ systems such as the Modified Early Warning Score.

**Pneumonia severity index**

PSI is one of the earlier and well-validated severity indices. Patients with CAP are categorized into five groups based on 21 variables and risk stratified as described in Tables 1 and 2.

**CURB-65 score**

CURB-65 score (Tables 3 and 4) provides a simple, numeric means of assessing illness severity. Each of five core adverse prognostic factors present is allocated a score of 1, thereby yielding a maximum possible score of 5. Advantages of CURB-65 include its simplicity, and focus on illness severity and pathophysiological findings requiring immediate intervention.

**Management**

**Immediate ABCD approach**

(i) Ensure patent airway.

(ii) Breathing: assess oxygenation with pulse oximetry and blood gas analysis, if $P_{aO_2} < 92%$. Administer continuous oxygen for those with $P_{aO_2} < 8 kPa$, hypotension (systolic arterial pressure of < 100 mm Hg), metabolic acidosis with bicarbonate of < 18 mmol litre$^{-1}$, or ventilatory frequency > 24 bpm. The aim of oxygen therapy is to keep $P_{aO_2} > 8 kPa$ or $S_{aO_2} > 92%$. Persistent hypoxaemia, despite maximal oxygen administration, progressive hypercapnia, or severe acidosis ($pH < 7.26$), shock, or depressed consciousness, indicates transfer to the ICU for airway management, ventilatory, and cardiovascular support.

(iii) Circulation: assess volume status and administer fluids and vasoactive drugs as required. Assess for severity of sepsis and resuscitate as per the Surviving Sepsis guidelines. Initiation of invasive monitoring and early goal-directed therapy aiming to achieve a central venous pressure of ≥ 8, mean arterial

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**Table 1** Predictor variables for calculating the PSI

<table>
<thead>
<tr>
<th>Type of variable</th>
<th>Specific variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristic</td>
<td>Age ≥ 50 yr</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Nursing home residence</td>
<td>10</td>
</tr>
<tr>
<td>Coexisting illness</td>
<td>Congestive cardiac failure</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Neoplasia</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Liver failure</td>
<td>10</td>
</tr>
<tr>
<td>Physical examination findings</td>
<td>Ventilatory frequency &gt; 30 bpm</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Systolic arterial pressure ≤ 90 mm Hg</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Altered mental status</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Temperature &lt; 35°C or &gt; 40°C</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Heart rate ≥ 125 beats min$^{-1}$</td>
<td>10</td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>Arterial pH &lt; 7.35</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Plasma sodium &lt; 130 mmol litre$^{-1}$</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Blood urea nitrogen &gt; 11 mmol litre$^{-1}$</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Haematocrit &lt; 30%</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Blood glucose &gt; 14 mmol litre$^{-1}$</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>$P_{aO_2} &lt; 8 kPa$</td>
<td>10</td>
</tr>
<tr>
<td>Radiological findings</td>
<td>Pleural effusion</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 2** Risk stratification based on PSI

<table>
<thead>
<tr>
<th>Class</th>
<th>PSI score</th>
<th>Risk</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0–10</td>
<td>Low</td>
<td>Suitable for outpatient treatment</td>
</tr>
<tr>
<td>II</td>
<td>11–70</td>
<td>Low</td>
<td>Consider inpatient treatment</td>
</tr>
<tr>
<td>III</td>
<td>71–90</td>
<td>Intermediate</td>
<td>Need aggressive treatment</td>
</tr>
<tr>
<td>IV</td>
<td>91–130</td>
<td>High</td>
<td>preferably in an ICU setting</td>
</tr>
<tr>
<td>V</td>
<td>&gt; 130</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>
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pressure of $\geq 65$ mm Hg, and central venous oxygen saturations of $\geq 70\%$ with the use of i.v. fluids, vasopressors, or both has been shown to improve the outcome in severe sepsis and septic shock when used in the first 6 h of resuscitation.\(^8\) There has been a failure to demonstrate improved outcomes utilizing the pulmonary artery flotation catheter (PAFC) for complex haemodynamic assessment. Other less invasive means of haemodynamic monitoring such as transoesophageal Doppler or pulse contour analysis devices (LiDCO\textsuperscript{TM}, PiCCO\textsuperscript{TM}) have not been subjected to the same degree of scrutiny as the PAFC, although in common use. Evidence for choice of resuscitation fluid is also limited. Isotonic crystalloid or albumin may be used.

(iv) Administer appropriate antibiotics preferably after taking blood cultures (as soon as practically possible).

**General**

(i) Perform chest radiograph and routine haematological and biochemical investigations including CRP.

(ii) Start early feeding (enteral unless contraindicated), especially in patients who are receiving mechanical ventilation.

(iii) Administer stress ulcer prophylaxis and venous thromboembolism-prophylaxis (see ventilator bundle below).

**Respiratory**

(i) Respiratory support: Invasive ventilation may be avoided in some patients with hypoxaemic respiratory failure by the use of non-invasive ventilatory strategies (CPAP or BiPAP). The use of non-invasive ventilation in severe CAP, particularly in the presence of hypercapnia and acidosis, however, carries a high risk of failure. Invasive positive pressure ventilation reduces oxygen demand and improves oxygenation and CO\textsubscript{2} elimination. Utilizing a lung protective ventilatory strategy with low tidal volumes ($5–7$ ml kg\textsuperscript{-1}), and limited plateau inspiratory pressures has been shown to reduce volutrauma and improve the patient outcome. Strategies using higher levels of PEEP may not confer additional benefit. Optimal timing of tracheostomy in patients expected to require a prolonged period of ventilatory support is uncertain. Decision as to timing with current knowledge is individualized according to illness severity, pre-morbid state, and clinician preference. Bronchoscopy and tracheo-bronchial toilet may aid in the removal of secretions, to obtain samples for microbiological analysis and to exclude endobronchial abnormalities such as carcinoma.

(ii) In patients receiving mechanical ventilation, the components of the ventilator bundle should be applied: elevation of the head end of the bed to $\geq 30^\circ$, daily sedation hold for assessing readiness for tracheal extubation, peptic ulcer prophylaxis with histamine H\textsubscript{2}-receptor antagonists, and thromboprophylaxis with thromboembolic stockings and low-molecular-weight heparin.

**Antibiotic therapy**

Severe CAP requires prompt (within 1 h of consideration of diagnosis) administration of appropriate antibiotics. Initial treatment is empirical and broad spectrum, and is aimed to cover *S. pneumoniae* (the most common organism), *S. aureus*, and gram-negative enteric bacilli (associated with high mortality). The drugs commonly used are co-amoxiclav or cephalosporin in combination with a macrolide. Alternatively, a quinolone with enhanced pneumococcal activity (levofloxacin or moxifloxacin) may be used in combination with penicillin. Rifampicin can be added if required, especially if *Legionella* or MRSA is suspected. The use of cephalosporins and quinolones may impact negatively on subsequent risks of acquiring MRSA or *C. difficile*-associated diarrhoea. The i.v. route is chosen initially to maximize blood and tissue concentrations. The duration of treatment is generally 7–10 days, if no organisms are isolated and *S. pneumoniae* is the most likely cause. This should be extended to 14–21 days, if *Legionella*, staphylococcal, or gram-negative enteric bacilli are suspected or confirmed.

**Complications**

**Pulmonary**

(i) *Parapneumonic effusion and empyema* is seen in up to 57% of patients with pneumonia. Empyema is a common cause of persistent pyrexia and failure to improve. The presence of bilateral effusions is associated with increased mortality.\(^9\) All empyema, large effusions, and effusions not resolving with antibiotics should be effectively drained.

(ii) *Lung abscess* is commonly seen in debilitated or alcoholic patients and after aspiration of gastric contents. *Staphylococcus aureus*, gram-negative enteric bacilli, and tuberculosis should be considered. These patients may need a prolonged course of antibiotics and sometimes surgical chest drainage.

(iii) *ALI and ARDS*. Pulmonary sepsis is the most common cause. Treatment is supportive and a lung protective ventilation strategy should be used. Rescue therapies of unproven benefit for those with severe disease may include inhaled nitric oxide, high-frequency oscillatory ventilation, or extracorporeal membrane oxygenation.

**Other**

(i) Metastatic infection: meningitis, pericarditis, peritonitis, and septic arthritis have all been reported.

(ii) Severe sepsis or septic shock with multiple organ failure: acute kidney injury, hepatic dysfunction, gut dysfunction, coagulopathy, thrombocytopenia, and encephalopathy.

(iii) Antibiotic resistance.
Role of vaccination

Influenza vaccine

Patients with underlying cardiac, respiratory, renal or hepatic disease, diabetes mellitus, immunosuppression, and those aged >65 yr have high mortality due to secondary bacterial pneumonia associated with influenza. Influenza vaccination in these patients can significantly reduce the incidence of pneumonia, but evidence regarding reduction in hospital admission and mortality is insufficient.10

Pneumococcal vaccine

Patients in the above-mentioned high-risk category and those with asplenia or severe splenic dysfunction such as sickle cell disease are at increased risk of developing pneumococcal infection. The Department of Health recommends administering the vaccine in these circumstances, although evidence of effectiveness is lacking.

Recent advances: role of activated protein C

Protein C is a naturally occurring anticoagulant which when activated has significant anti-inflammatory activity. Activated protein C (APC) levels are reduced in sepsis and may contribute to the severe inflammatory response. Subgroup analysis of the PROWESS study (which used recombinant APC in patients with severe sepsis or septic shock) revealed that of the patients in the study group with single organ failure, more than half of them had sepsis of pulmonary origin and more than 75% required mechanical ventilation.11 As there was a significant reduction in the 28 day mortality in the APC-treated group, APC may have a role to play in the management of severe CAP with single or multiorgan failure.

Summary

Severe CAP accounts for a significant and increasing proportion of adult ICU admissions. The mortality remains high, especially in those admitted later in their hospital stay. Appropriate hospital care, particularly timely initiation of empiric antibiotic therapy, and early identification and prompt resuscitation of the high-risk patient may improve the outcome.

References


Please see multiple choice questions 13–17