Pneumonia

J Periselneris
J S Brown
RJ José

Jimstan N Periselneris BSc MB ChB MRCP PhD is a Consultant in respiratory medicine at King's College Hospital NHS Foundation Trust, London, UK. He has a specialist interest in respiratory infection in immunocompromised hosts and respiratory complications of haemato-oncological disease. Competing interests: none declared.

Jeremy S Brown MB BS PhD FRCP is a Professor in Respiratory Infection at University College London, London, UK, where he runs a research group investigating the molecular pathogenesis of lung infections. His main clinical interests are pneumonia, infections in the immunocompromised host, and bronchiectasis. Competing interests: none declared.

Ricardo J José MB ChB DA MRCP PhD FHEA is a Consultant in respiratory medicine at the Royal Brompton & Harefield NHS Foundation Trust, London, UK. His specialist interest is in respiratory infections and bronchiectasis in immunocompromised hosts, particularly immunodeficiency secondary to cancer and biological therapy. Competing interests: none declared.

Abstract

Pneumonia is a common lung infection that causes significant mortality and morbidity worldwide, particularly in children and elderly people. The microbiological aetiology varies by location, with a variety of viruses and bacteria causing disease. Bacterial causes are usually acquired by microaspiration of organisms colonizing the nasopharynx. Microbes reaching the distal airways and alveoli induce a local and sometimes systemic inflammatory response, as well as occasionally disseminating distal to the lung. Although most cases of pneumonia occur in the community, a significant subset develop in hospital, often caused by multidrug-resistant bacteria, which are associated with higher mortality. Pneumonia is diagnosed by chest radiology, identifying pulmonary infiltrates. Severity scoring systems can be used to predict outcome and identify patients who can be safely managed in an outpatient setting. Further investigations are sometimes required to identify the pathogenic organism. The mainstay of treatment is early antibiotics and, if appropriate, supportive therapies such as oxygen and intravenous fluids. Large vaccination programmes rolled out across much of the world have proven effective in reducing the incidence of some of the causative organisms; however, the overall incidence of pneumonia remains high, and further research is required to improve care in target groups such as the elderly.

Key points

- Community-acquired pneumonia is a common cause of morbidity and mortality, particularly affecting children and elderly individuals
- Hospital-acquired pneumonia is more likely to be caused by Gram-negative bacteria and organisms that are resistant to antibiotics
- Scoring systems such as CURB65 and the Pneumonia Severity Index can be used to stratify patients into those who can be treated as outpatients, those requiring inpatient monitoring and those requiring close monitoring in an intensive care setting
- Treatment should be empirical and based on local microbiology and antibiotic susceptibility data
- Vaccination strategies have been enormously successful in reducing target organism-related disease, but there have been increased rates of non-vaccine organisms causing pneumonia

Introduction

Pneumonia is a common acute respiratory infection, causing lung infiltrates visible on chest radiography. Pneumonia can be categorized in a number of ways; perhaps the most widely used is according to where infection is acquired, dividing into community-acquired (CAP) and hospital-acquired (HAP) pneumonia. CAP makes up by far the largest proportion of pneumonias, whilst HAP has a different range of pathogens are involved and are more likely to be resistant to antibiotics. The range of severity in clinical manifestations of pneumonia owing to differences in the biology of the causative pathogen and multiple host factors such as coexisting co-morbidities and immune status. Despite improvements in care over the last few decades, pneumonia still causes significant morbidity and mortality worldwide.

Epidemiology

In the UK, the incidence of CAP has increased from 1.5/1000 person–years in 2002 to 2.2/1000 in 2017.[1] This makes it the most common respiratory cause of hospital admission and the third most common respiratory cause of mortality. Global data suggest that the number of episodes of clinical pneumonia decreased from 178 million in 2000 to 138 million in 2015; at the same time, rates of hospitalization increased and mortality decreased from 1.7 million to 0.9 million. This suggests that there is better recognition and therefore timely treatment in an appropriate setting.

Pneumonia has a markedly increased incidence at the extremes of age. In children <5 years of age, CAP remains a common cause of death, causing >800,000 deaths a year, and accounting for >15% of deaths worldwide. A review of European studies indicates that increasing incidence is largely associated with increasing age (8/1000 person–years in those >65 years), as well as increasing rates of co-morbidity (Table 1) and coexisting immunocompromise.[2] Mortality rates for admitted patients vary from 5% to 30% depending on severity of illness at presentation. Recent national UK data indicate an overall inpatient mortality rate of 10% with a further 4% of patients dying within 30 days of discharge. As a result pneumonia imposes a significant healthcare burden, with annual expenditure of inpatient care throughout Europe of around €5.7 billion.

HAP is the second most common healthcare-associated infection (HAI) and the most common cause of HAI-related mortality. Incidence is 5–20 cases per 1000 hospital admissions. Approximately a third are acquired in intensive care unit (ICU) settings, most of which can be classified as ventilator-acquired pneumonia (VAP). The estimated cost is £10,000 per episode of VAP. In the USA an additional type of pneumonia, termed healthcare-associated pneumonia (HCAP), has been described and is associated with infection by multidrug-resistant organisms. HCAP is defined as patients in the following groups: hospitalization for >2 days in the previous 90, nursing home residency, home infusions and chronic dialysis. However, European data suggest that the microbial aetiology of HCAP cases is not significantly different from those of CAP, and that the HCAP category is redundant.

Aetiology

Historically, *Streptococcus pneumoniae* was the most common identifiable cause of pneumonia, although before the era of genomic diagnostic tools, pathogens were not identified in most cases. The aetiology depends on the location and healthcare setting. In a recent meta-analysis of studies from Africa and Asia, 61% of cases were caused by viruses and 27% by bacteria; bacteria were over-represented in cases of severe pneumonia, and *Strep. pneumoniae* was the most common cause of blood culture-positive disease. Rhinovirus, human metapneumovirus, parainfluenza virus, *Mycobacterium tuberculosis*, *Haemophilus influenzae* and *S. pneumoniae* accounted for >5% of cases. A second meta-analysis agrees that viruses are the most common cause of pneumonia, with *Staphylococcus aureus* and *H. influenzae* non-type B the most common bacterial pathogens since the widespread use of pneumococcal and HiB vaccines.[3]

Importantly, co-infections of bacteria and atypical organisms (e.g. *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*) or viruses are frequent, with well-recognized associations between influenza in particular and secondary bacterial infections with *S. pneumoniae* and *S. aureus*. Interestingly, recent UK data suggest that *S. pneumoniae* remained the most common cause of hospitalization with pneumonia in one city, accounting for

36.6% of these cases. Additionally, rates of pneumococcal pneumonia in the UK increased over the 5-year period from 2013 to 2018.

HAP is associated with Gram-negative and multidrug-resistant organisms. In US studies the most common identified pathogens are *S. aureus* (often methicillin-resistant), *Pseudomonas aeruginosa*, *Klebsiella* spp. and *Enterobacteriaceae* spp. The emergence of carbapenemase-producing organisms is a major concern as this markedly restricts the potential effective antimicrobial therapies for these pathogens. HAP mortality rates are as high as 70%.

Pathophysiology

Pneumonia occurs as a result of pathogens accumulating in the lower airways and alveoli, leading to the influx of inflammatory exudative fluid. The most common source of these organisms is microaspiration from their usual ecological niche of the nasopharynx (*S. pneumoniae*, *H. influenzae*, *S. aureus*, *Enterobacteriaceae* spp.); occasionally, there is direct inhalation of airborne microorganisms (atypical bacterial pathogens, viruses).

Disease occurs when host local pulmonary immunity is overcome by large numbers of invading pathogens or by virulent organisms, resulting in a local inflammatory response and recruitment of immune cells including neutrophils to the alveoli. This impairs gas exchange, and can also be associated with a significant systemic inflammatory response. Pneumonia can also be complicated by septic shock, acute respiratory distress syndrome and distal spread of the infecting organisms to the pleura (to cause empyema), heart, joints or central nervous system. Less commonly, pneumonia is secondary to haematogenous spread from organisms in other parts of the body, for example from colonized indwelling catheters.

Clinical manifestations are a productive cough, breathlessness, fever, chest pain and haemoptysis. Classically, *S. pneumoniae* is described as causing rusty sputum and rigors, whereas atypical organisms cause more non-specific symptoms such as myalgia, headache and gastrointestinal symptoms. However, specific organisms cannot be reliably identified from clinical features. Examination findings include crackles, bronchial breathing, reduced air entry, fever, tachypnoea, tachycardia and altered mental status. Features of sepsis should be actively sought as specific sepsis-targeted supportive measures should be instituted as a matter of urgency.

Investigations

Initial investigations should include a chest radiograph (National Institute for Health and Care Excellence (NICE) guidelines recommend that a chest X-ray take place within 4 hours of presentation to secondary care), to identify consolidation and look for complications such as pleural effusions, and blood tests including a full blood count and renal function. Arterial blood gases should be performed in patients with hypoxaemia or hypotension.

The use of specific microbiological investigations is not recommended in non-severe pneumonia as they do not affect outcome. However, microbiological identification is important in severe pneumonia and in patients at high risk of HAI (including methicillin-resistant *S. aureus* (MRSA) and *P. aeruginosa*); recommendations include sputum and blood culture, and pneumococcal and *Legionella* urinary antigen. Additional microbiological investigations are also useful in cavitary disease and in patients with associated pleural effusions. With VAP, endotracheal aspirates should always be performed, given the risk of multidrug-resistant organisms. Molecular diagnostic techniques such as mass spectrometry and polymerase chain reaction have increased detection rates of CAP to 87%, from 39% with culture-based only methods.

The use of procalcitonin to differentiate viral from bacterial infections has not proved effective. Although testing for influenza has a well-established role in identifying patients who need isolation, there are currently no data on its role in affecting outcomes of pneumonia.

Risk stratification

Various clinical prediction rules have been validated to predict outcomes for CAP. The CURB65 score (Table 2) is an easy to use prognostic score that has been incorporated into British Thoracic Society (BTS) and NICE guidelines for use at the initial clinical assessment to identify individuals who can be safely treated as outpatients and those who should be admitted to a high-dependency setting.

Other scores are better at predicting outcome but more cumbersome to use. The American Thoracic Society (ATS) recommends the Pneumonia Severity Index (Table 3), which is perhaps most useful for patients admitted to a critical care environment. The Sequential

Organ Failure (SOFA) score (Table 4) was initially designed to predict organ dysfunction and complications in critically unwell patients, but has also been shown to predict outcome in this cohort. Analysis of the PROGRESS study has shown that SOFA is a better predictor of 28-day mortality or admission to ICU in comparison to other pneumonia scoring systems.

Treatment

The mainstay of treatment remains the early administration of antibiotics, with NICE guidance suggesting that antibiotics should be administered within 4 hours of diagnosis of pneumonia. As clinical manifestations are not reliable indicators of the infective pathogen, treatment is empirical and depends on which organisms are the locally dominant causes of CAP or HAP. Signs of sepsis should be actively sought, and in these cases intravenous antibiotics should be administered within an hour of admission and accompanied by adequate fluid resuscitation and supplementary oxygen if the patient is hypoxaemic.

BTS and recent ATS guidelines suggest a combination of a β-lactam and a macrolide antibiotic for severe pneumonia. Patients considered well enough for outpatient management are recommended amoxicillin, doxycycline or a macrolide. Aspiration pneumonia does not require the addition of extra anaerobic cover. Patients with previously isolated resistant organisms or who present with an HAP need specific additional coverage. There should be consideration of an anti-pseudomonal β-lactam with the addition of gentamicin or a fluoroquinolone. If MRSA is a concern, vancomycin or linezolid should also be added.

In a recent US study, the use of broad-spectrum antibiotics (used in 39.7% patients) for CAP was associated with longer hospital stay, greater healthcare costs and increased rates of *Clostridium difficile* infection, although rates of resistant organisms causing pneumonia were low (3%). This suggests that, where possible, local data should inform antibiotic treatment with as narrow a range of coverage as possible.

There has been significant interest in adjunctive treatment of pneumonia, mainly targeted against the excess inflammatory response thought to contribute to pathology. There have been discordant results in studies and meta-analyses of the addition of corticosteroids in terms of the outcome of both non-severe and severe pneumonia. A bundled intervention including corticosteroids, early mobilization and dietary interventions had no impact on mortality, length of stay or readmission rates, although there was some evidence of increased bleeding from the gastrointestinal tract.[4]

A recent trial of a novel antitoxin in patients in ICU that targets pneumolysin, a toxin thought to modulate the immune response during pneumococcal pneumonia, has shown promise, with treated patients having a better response in terms of SOFA score compared with conventional treatment.[5]

Prevention

Vaccination to reduce the incidence of pneumonia has largely been targeted against *S. pneumoniae* because of its historical position as the most common cause of pneumonia. The latest iteration of the conjugate vaccine generates immunity against 13 capsular serotypes of *S. pneumoniae*. Epidemiological studies have shown that a roll-out of this vaccination to children has resulted in a reduced incidence of childhood colonization by vaccination serotypes and childhood pneumonia. As children are the main reservoir of *S. pneumoniae* infections, vaccination of children has also had significant herd immunity effects and reduced invasive pneumococcal disease in adults, as well as hospitalization of adults because of pneumonia.

Modelling suggests that pneumococcal vaccination has avoided >43,000 admissions with pneumococcal disease in the UK, primarily by preventing pneumonia. Despite the success of vaccination, there are concerns about serotype replacement within *S. pneumoniae* strains, with a recent UK study showing increased rates of disease caused by non-vaccine serotypes. As many cases of pneumonia are related to influenza, either as a direct cause of pneumonia or indirectly by allowing bacterial pneumonia to develop, influenza vaccination is an important preventive strategy.

Table 1

Risk factors for CAP and drug-resistant organisms		
Risk factors for CAP		**Risk factors for multidrug-resistant organisms**
Co-morbidities	**Lifestyle factors**	
Chronic respiratory disease •COPD •Asthma	Smoking	Age >65 years
Chronic heart failure	Chronic alcohol abuse	Antimicrobial therapy or hospitalization (≥2 days) within the previous 90 days
Diabetes mellitus	Underweight	Chronic dialysis
Stroke	Multiple occupancy housing	Congestive heart failure
Dementia	Not visiting the dentist	Gastric acid suppressive therapy
Cancer	Low socioeconomic class	Tube feeding
Chronic liver disease		
Chronic kidney disease		

Table 2 CURB 65 severity score

CURB65 scoring system – 1 point each for the following
•Abbreviated Mental Test Score ≤ 8
•Urea >7 mmol/litre
•Respiratory rate > 30/minute
•Systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg
•Age ≥65 years

Score	Mortality
0	0.6% – outpatient
1	2.7%
2	6.8%
3	14%
4 or 5	27.8%

Table 3

Pneumonia Severity Index scoring system	
Age •Men •Women •Nursing home resident	Age in years Age in years −10 Age in years +10
Co-morbidities •Neoplastic disease •Liver disease •Heart failure •Stroke •Renal failure	+30 +20 +10 +10 +10
Physical examination •Altered mental status •Respiratory rate > 30/minute •Systolic blood pressure <90 mmHg •Temperature <35°C or >40°C •Pulse >125/minute	+20 +15 +10 +10 +10
Laboratory and radiological findings •Arterial pH <7.35 •Urea ≥11 mmol/litre •Sodium <130mmol/litre •Glucose ≥14 mmol/litre •Haematocrit <30% •PaO_2 <8 kPa or saturations ≤90% •Pleural effusion	+30 +20 +20 +10 +10 +10 +10

Score	Category	Mortality
<51	I	0.2%
51–70	II	0.5%
71–90	III	2.6%
91–130	IV	9.3%
>130	V	24.9%

Table 4

SOFA score	PaO$_2$/FiO$_2$ (mmHg)	GCS score	Cardiovascular system	Bilirubin (micromol/litre)	Platelets (×10^9/litre)	Creatinine (micromol/litre)
SOFA severity scoring system						
0	≥400	15	MAP ≥70 mmHg	<20	≥150	<110
+1	<400	13–14	MAP <70 mmHg	20–32	100–150	110–170
+2	<300	10–12	Dopamine <5 microgram/kg/ml or dobutamine	33–101	50–99	171–299
+3	<200 and mechanically ventilated	6–9	Dopamine >5 microgram/kg/ml or epinephrine/norepinephrine ≤0.1 microgram/kg/ml	102–204	20–49	300–440
+4	<100 and mechanically ventilated	<6	Dopamine >15 microgram/kg/ml or epinephrine/norepinephrine >0.1 microgram/kg/ml	>204	<20	>440

FiO$_2$, fraction of inspired oxygen; GCS, Glasgow Coma Scale; MAP, mean arterial pressure.

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Question 1
A 43-year-old man presented with cough productive of green sputum, breathlessness, some left-sided chest pain and mild confusion. He had no known drug allergies.
On clinical examination, he was not orientated in place and time. His temperature was 38.2°C, heart rate 112 beats/minute, blood pressure 102/54 mmHg, respiratory rate 28/minute, and oxygen saturations 91% on air. On auscultation of his chest, he had bronchial breathing at the left base

Investigations
•Haemoglobin 125 g/litre (130–180)
•Platelets 450 × 10⁹/litre (150–400)
•White cell count 14.8 × 10⁹/litre (4.0–11.0)
•Neutrophils 11.3 × 10⁹/litre (1.5–7.0)
•Sodium 129 mmol/litre (137–144)
•Potassium 3.9 mmol/litre (3.5–4.9)
•Urea 11.2 mmol/litre (2.5–7.0)
•Creatinine 96 micromol/litre (60–110)
•C-reactive protein 183 mg/litre (<10)
•Arterial blood gases
 – pH 7.32 (7.35–7.45)
 – PaO_2 7.9 kPa (11.3–12.6)
 – $PaCO_2$ 4.1 kPa (4.7–6.0)
 – Base excess −4 mmol/litre (±2)
 – Lactate 1.1 mmol/litre (0.5–1.6)

What is the best treatment to give him?

> A – Ciprofloxacin intravenously and gentamicin intravenously
> B – Co-amoxiclav intravenously and oral clarithromycin intravenously
> C – Levofloxacin orally
> D – Vancomycin intravenously and gentamicin intravenously
> E – Non-invasive ventilation

Correct answer: B. British Thoracic Society, National Institute for Health and Care Excellence and American Thoracic Society guidelines agree that severe community-acquired pneumonia should be treated with an intravenous penicillin and an oral macrolide or doxycycline. Vancomycin (D) should be used when methicillin-resistant *Staphylococcus aureus* is suspected. Non-invasive ventilation (E) should be used when there is respiratory, rather than metabolic, acidosis.

Question 2
A 73-year-old woman presented with symptoms and signs of a community-acquired pneumonia. She had had a 1-week prodrome of viral upper respiratory tract infection symptoms and had been treated with oral amoxicillin, without effect. She had no known drug allergies.

Investigations
•Chest X-ray showed cavitating left middle zone consolidation
•A nasopharyngeal swab was positive for influenza B

What is the best treatment to add in at this stage?
> A – Amantadine orally
> B – Hydrocortisone 100 mg 6-hourly, intravenously
> C – Ribavirin via a nebulizer
> D – Piperacillin/tazobactam intravenously
> E – Oseltamivir orally and vancomycin intravenously

Correct answer: E. The most likely infections after influenza are *Staphylococcus aureus* and *Streptococcus pneumoniae*, so vancomycin should be added to cover methicillin-resistant

Staph. aureus. It is reasonable to treat influenza when found, even though there are no studies on treatment outcome in pneumonia. Amantadine (A) is effective only against influenza A. No current guidelines endorse corticosteroids (B). Ribavirin (C) has been used in parainfluenza, respiratory syncytial virus and adenovirus infections. Piperacillin/tazobactam (D) would be added to cover Gram-negative organisms if isolated.

Question 3
A 77-year-old woman presented for admission from her nursing home with a 3-day history of fevers and dyspnoea. Her CURB65 score was 3, and a Pneumonia Severity Index score was 97. She had a previous history of stroke with right-sided hemiplegia and dysphagia requiring thickened fluids. She had had an admission for seizures 6 months previously, requiring a 48-hour admission to optimize epileptic medication. She had no known drug allergies.

What is the best treatment?
        A – Clindamycin orally
        B – Ceftazidime intravenously and metronidazole intravenously
        C – Moxifloxacin orally
        D – Co-amoxiclav intravenously and clarithromycin orally
        E – Vancomycin intravenously and gentamicin intravenously

Correct answer: D. This patient should be treated as having severe community-acquired pneumonia (CAP) despite coming from a nursing home as, although she has risk factors for healthcare associate pneumonia (HCAP), she has no risk factors for hospital-acquired pneumonia (HAP). In the UK and Europe, HCAP should be treated as for CAP. Clindamycin (A) is not recommended in any guidelines. Ceftazidime plus metronidazole (B) is recommended treatment for HAP. Moxifloxacin (C) is no longer first-line treatment. Vancomycin and gentamicin (E) can be recommended in the setting of penicillin allergy.