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EDITED BY
John D. Firth
Christopher P. Conlon
Timothy M. Cox

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recommendations for empirical treatment of community-acquired pneumonia typically as follows (but local hospital protocols and policies may vary): (1) outpatients—amoxicillin, doxycycline, macrolide (erythromycin, clarithromycin, azithromycin), or fluoroquinolone (levofloxacin, moxifloxacin, or other fluoroquinolone with enhanced activity against *S. pneumoniae*); (2) hospital inpatients, moderate severity—β-lactam (amoxicillin) plus macrolide, or fluoroquinolone alone; (3) hospital inpatients high severity/intensive care unit—β-lactamase stable β-lactam (coamoxiclav, cefotaxime, ceftriaxone) plus macrolide, or β-lactam plus fluoroquinolone; (4) special circumstances: aspiration pneumonia—clindamycin, or β-lactamase stable β-lactam.

18.4.2 Pneumonia in the normal host

Wei Shen Lim

ESSENTIALS

Pneumonia is an acute or chronic infection involving the pulmonary parenchyma.

Aetiology—most cases are caused by microbial pathogens, the commonest being *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, legionella, anaerobic bacteria, and viruses (influenza, parainfluenza, and respiratory syncytial virus). *Staphylococcus aureus* is an important superinfecting pathogen in influenza, and the most common form of embolic pulmonary infection with injected drug use and tricuspid valve endocarditis.

Prevention—the main preventive measures are smoking cessation, and vaccination against influenza and *S. pneumoniae*.

Clinical features—classic presentation is with cough and fever, with variable sputum production, dyspnoea, and pleurisy. Most patients have constitutional symptoms and many also have gastrointestinal symptoms. Clinical examination may reveal features indicative of the severity of respiratory compromise and (in some cases) of consolidation. *The 'CURB-65' score*—based on compromised consciousness, elevated blood urea nitrogen, increased respiratory rate, reduced blood pressure, and age over 65 years—is a useful predictor of mortality from pneumonia.

Diagnosis—the key test is the chest radiograph, showing an infiltrate consistent with infection. The use of laboratory studies for identifying pulmonary pathogens in pneumonia is evolving: even with extensive use of current diagnostic resources a likely aetiological agent is only detected in 40–60% of cases. For outpatients, microbiological tests are not routinely performed; empirical therapy is generally advocated. For inpatients, blood cultures (preferably taken before the initiation of antibiotic treatment) and Gram stain and culture of expectorated sputum (if any) are recommended. Rapid urinary antigen tests for legionella (which detects *L. pneumophila* serogroup 1; responsible for 80% of cases) and *S. pneumoniae* are available. Pleural effusions should be sampled to exclude empyema.

Management—supportive treatment includes (as appropriate) intravenous fluids, supplementary oxygenation, and ventilatory support. Antibiotics are the mainstay of therapy, with

Introduction

History

Pneumonia has been recognized since Hippocrates described 'peripneumonia' in the fourth century BC. Up to the early nineteenth century, the nature of pneumonia was poorly understood, although it was regarded as some sort of inflammation of the lungs.

In 1834, Laennec described three stages of consolidation that are still recognized today. These are associated with classical auscultatory findings heard with the stethoscope which he invented in 1816 (Table 18.4.2.1).

Towards the end of the nineteenth century, infectious agents as the cause of pneumonia began to be recognized. Between 1881 and 1884, Friedlander first found bacteria in the lungs of fatal cases of pneumonia using the newly described staining methods of his colleague Gram. In 1884, Fraenkel isolated an organism which he called 'pneumoniemikroccus' (pneumococcus) from a 30-year-old man dying of pneumonia. In 1892, *Haemophilus influenzae* was discovered and initially thought to be the cause of influenza. The influenza virus was not identified as the causative agent of influenza until 1933 at the Medical Research Council laboratories in Mill Hill, England, many years after the 1918 pandemic.

Advances in microbiological techniques have since enabled a range of pathogens to be identified in association with pneumonia (Table 18.4.2.2). The importance of viruses is increasingly recognized.

Definition of pneumonia

Pneumonia may be defined as an acute inflammatory condition of the lung characterized by consolidation due to the presence of

Table 18.4.2.1 Laennec's three stages of consolidation in pneumonia

Stage	Pathological findings	Auscultatory findings
1st stage	Engorgement: the lung is wet, oedematous, and congested.	Crepitus rattle (crepitations)
2nd stage	Red hepatization: the lung is dry, red, friable, and solid like liver.	Bronchial breathing
3rd stage	Grey hepatization: the lung is softer and exudes yellow purulent material indicative of resolution.	Rhonchus crepitus redux (return of crepitations)

Table 18.4.2.2 Important events in the history of pneumonia

Date	Discovery/ event
1834	3 stages of lobar pneumonia described by Laennec
1881	Pneumococcus first isolated by Pasteur and Sternberg
1884	Pneumococcus in pneumonia described by Fraenkel
1892	*Haemophilus influenzae* discovered by Pfeiffer
1928	Penicillin discovered by Alexander Fleming
1933	Influenza virus discovered by Wilson Smith, Christopher Andrewes, and Patrick Laidlaw
1938	*Coxiella burnetii* (Q fever) named after discoverers Macfarlane Burnet and Herald Rea Cox
1944	*Mycoplasma pneumoniae* discovered by Monroe Eaton
1969	First report of penicillin-resistant pneumococcus
1974	Pneumococcus named *Streptococcus pneumoniae*
1976	Legionella pneumonia (legionnaires' disease) described following Philadelphia outbreak
1977	Emergence of multidrug resistant pneumococcus
1986	*Chlamydophila pneumoniae* identified
2003	Severe acute respiratory syndrome (SARS)-coronavirus identified following international outbreak
2012	Middle East respiratory syndrome (MERS)-coronavirus identified following first case in the Kingdom of Saudi Arabia

exudate in the alveolar spaces and caused by an infectious agent. In clinical practice, a definite diagnosis of pneumonia relies on a complex of symptoms and signs, together with relevant radiological findings. This may be summarized as the combination of:

- Symptoms of an acute lower respiratory tract infection (e.g. cough, sputum production, dyspnoea)
- Systemic features of infection (e.g. fever, chills)
- Signs of consolidation on clinical examination (e.g. focal lung crepitations)
- Radiological features consistent with pneumonia
- No other alternative explanation for the illness

In situations where access to radiological tests is not available, a presumptive clinical diagnosis of pneumonia may be made based on the presence of clinical features alone. This is generally the case for patients diagnosed outside a hospital setting.

Classification

Pneumonia may be classified according to:

- Source of infection (e.g. community acquired, hospital acquired)
- Radiographic features (e.g. bronchopneumonia, lobar pneumonia)
- Severity of infection (e.g. severe, nonsevere)
- Microbiology (e.g. pneumococcal pneumonia, legionella pneumonia)

These classifications are useful in identifying patient groups with common features that inform patient management. Rather confusingly, the term 'pneumonia' is also adopted in some conditions that are noninfectious in nature, such as eosinophilic pneumonia and usual interstitial pneumonia. Further discussion in this chapter is restricted to community-acquired pneumonia (CAP) in the adult immunocompetent host.

Aetiology

The relative frequencies of different pathogens causing community-acquired pneumonia differ according to geography and setting. Results from studies conducted in Europe and Asia are summarized in Table 18.4.2.3. Important limitations of these studies are that most were conducted in large urban hospitals; diagnostic tests performed after antibiotic treatment mask the relative frequency of antibiotic-susceptible pathogens; no pathogens were identified in 30–85% of cases, even with the use of multiple diagnostic tests; and there are seasonal variations in the frequency of infection by specific pathogens. These limitations make a direct comparison of studies conducted in different regions difficult.

Some important differences in the microbial aetiology of CAP in Asia, compared to the West are that *Mycobacterium tuberculosis* is a relatively common pathogen in some areas; *Burkholderia pseudomallei* is the commonest pathogen identified in northeast Thailand and is an important pathogen in neighbouring countries including Malaysia and Singapore; and *Klebsiella pneumoniae* (a Gram-negative enteric bacilli) is a common pathogen in Asia, particularly in patients with severe disease.

More sophisticated diagnostic tests are being developed that may fill the gaps in our current knowledge and provide more rapid pathogen-specific diagnoses at the time of clinical presentation.

In severe pneumonia, the most frequently encountered pathogens are (Table 18.4.2.4):

- *Streptococcus pneumoniae*
- *Legionella* sp.
- *Staphylococcus aureus*
- Gram-negative enteric bacilli (such as *Klebsiella pneumoniae*)
- *Burkholderia pseudomallei*—in endemic countries (restricted to East Asia)

Table 18.4.2.3 Frequency of pathogens in patients with CAP: from one British study and summary figures from two large reviews of studies conducted in Europe (46 studies) and Asia (48 studies)

Pathogen	British study	Europe	Asia
	%	Range (%)	Unweighted average (range, %)
Streptococcus pneumonaie	48	12–68	13 (0–39)
Mycoplasma pneumoniae	13	0–32	8 (0–30)
Legionella sp.	3	0–13	3 (0–17)
Chlamydophila pneumoniae	2	0–27	7 (0–37)
Haemophilus influenzae	7	3–45	7 (9–19)
Staphylococcus aureus	1.5	0–12	4 (0–13)
Gram-negative enteric bacilli	1.4	0–41	9 (0–22)
Viruses	23	1–19	10 (1–22)
Mycobacterium tuberculosis	not reported	not reported	10 (0–21)

Table 18.4.2.4 Frequency of pathogens in CAP in Europe according to clinical setting (summary of 46 studies)

Pathogen	Outpatient	Hospital	Intensive care
S pneumonaie	38	27	28
M pneumoniae	8	5	2
Legionella sp	0	5	12
C pneumoniae	21	11	4
H influenzae	13	6	7
Staphylococcus aureus	1.5	3	9
Gram-negative enteric bacilli	0	4	9
Viruses	17	12	3

Figures are percentage means from 46 studies.

'Atypical' pathogens?

During the first half of the twentieth century, the concept of an 'atypical pneumonia syndrome' was described; this comprised fever without shaking chills, a nonproductive cough, headache, and myalgia. The 'atypical pneumonia syndrome' was thought to be associated with infections by pathogens such *Mycoplasma pneumoniae*. In contrast, 'typical pneumonia', which comprised an abrupt onset of high fever, shaking chills, pleuritic pain, and purulent sputum, was associated with *Streptococcus pneumoniae* infection. However, more recent studies have shown that specific pathogens are not associated with distinctive clinical presentations, hence the term 'atypical pneumonia' is now mostly abandoned.

The concept of an 'atypical pathogen' has been retained as useful in denoting those commonly encountered respiratory pathogens, which (a) replicate intracellularly, and (b) are therefore not susceptible to β-lactam antibiotics (such as penicillins and cephalosporins). While there is no global consensus as regards which pathogens fall into this group of atypical pathogens, this descriptive term is widely used in relation to *Mycoplasma pneumoniae, Legionella* sp., *Chlamydophila pneumoniae, Coxiella burnetti*, and *Chlamydophila psittaci*.

Specific pathogens

Streptococcus pneumoniae

Streptococcus pneumoniae is both a human commensal and pathogen, and widely recognized as the commonest pathogen associated with CAP. About 10–40% of children aged less than 7 years are asymptomatic carriers of *Streptococcus pneumoniae* in their nasopharynx. The carriage rate peaks around 2–3 years of age and diminishes thereafter to less than 10% in many adult populations. In adults, aerosol transmission of *S. pneumoniae* to the nasopharynx most commonly results in clearance. Clinical disease occurs when there is spread to the lungs or blood.

Epidemiological factors associated with an increased frequency of infection with this pathogen include close contact with children; winter months in temperate climates, rainy season in tropical climates; aged more than 65 years; and HIV infection (particularly bacteraemic pneumococcal infection)

There are at least 94 serologically distinct pneumococcal serotypes. In countries where the pneumococcal conjugate vaccine has been introduced into childhood immunization programmes, rates of pneumococcal pneumonia associated with vaccine serotypes have decreased in both children and adults.

Mycoplasma pneumoniae

Historically associated with atypical pneumonia, cold agglutinin pneumonia, and Eaton-agent pneumonia, this organism is one of the commonest causes of lower airways infection. It is more frequent in young adults and patients in a community setting with low severity pneumonia. *Mycoplasma pneumoniae* displays 4-yearly cycles of infection.

The typical patient is a young adult who experiences a respiratory tract infection accompanied by headache, myalgia, cough, and fever. The cough is often nonproductive, but when sputum is obtained it is mucoid, shows predominantly mononuclear cells, and no dominant organism. A characteristic feature is the relatively high frequency of extrapulmonary complications such as rash, neurological syndromes (aseptic meningitis, encephalitis, neuropathies), myocarditis, pericarditis, and haemolytic anaemia.

Legionella

Legionnaires' disease was originally described during the American Legion Convention in Philadelphia in 1976, with the putative agent reported the following year. Legionella causes two very different clinical syndromes: a self-limiting influenza-like illness—called 'Pontiac fever' in reference to an outbreak in 1967 in Pontiac, Michigan; and severe pneumonia—called legionnaires' disease.

Legionnaires' disease is defined as pneumonia caused by any species of the genera legionella, but most cases are caused by *Legionella pneumophila*. The disease may be epidemic or sporadic. Outbreaks are usually related to legionella contamination of potable water or the cooling systems of air conditioners, and have been recorded to occur at flower shows, in hotels, and on cruise ships. Patient-to-patient transmission does not occur.

Features of legionnaires' disease to consider at presentation:

- The incubation period from exposure to presentation is 10 days. In the United Kingdom, roughly half of cases of legionnaires' disease report travel outside the United Kingdom within the incubation period.
- There is a seasonal pattern with peak activity in late summer and autumn
- Most patients are severely ill and supportive management on a critical care unit may be required.
- Extrapulmonary features, such as diarrhoea and mental confusion, may predominate.
- A rapid diagnosis is possible using a urinary antigen assay for the detection of *L. pneumophila* serogroup 1 (which accounts for 70–80% of cases in Europe and the United States).

A negative legionella urinary antigen assay does not exclude a diagnosis of legionella pneumonia, which may be caused by another legionella species. In Australia, *Legionella longbeachae* causes half of all cases of legionella pneumonia and is related to exposure to potting compost. If legionella pneumonia is suspected, the microbiology laboratory should be alerted to set up legionella culture of respiratory secretions on selective media.

Chlamydophila pneumoniae

Although frequently identified in patients with pneumonia, the role of this pathogen in pneumonia has not been settled. It is often found in association with another pathogen (commonly *Streptococcus pneumoniae)* and resolution of pneumonia without appropriate antibiotic therapy is recognized. On the other hand, outbreaks of pneumonia due to this pathogen are well described. Consequently, its role in pneumonia may be as a primary pathogen, copathogen, or bystander. When implicated, it is generally associated with a non-severe pneumonia.

Haemophilus influenzae

When *Haemophilus influenzae* is identified in respiratory specimens, distinguishing between colonization and infection can be difficult. *H. influenzae* commonly colonizes the upper respiratory airways, leading to contamination of expectorated specimens, and in patients with chronic obstructive pulmonary disease (COPD) it is commonly found in the lower airways, even when patients are clinically stable.

H. influenzae strains causing pneumonia in adults are usually nontypable. In contrast, type B *H. influenzae* is a well-established pathogen, primarily in infants and young children, but is a relatively rare cause of disease in areas where there is widespread *H. influenzae* (Hib) immunization. Bacteraemia with *H. influenzae* in adults is very uncommon.

Staphylococcus aureus

Staphylococcus aureus is associated with different patterns of pneumonia:

- secondary pneumonia following influenza infection;
- bilateral (embolic) pneumonia in intravenous drugs users with tricuspid valve endocarditis; and
- cavitating pneumonia.

Staphylococcal pneumonia is often a fulminant infection. Cavitation occurs in up to 25% of cases and may be associated with Panton–Valentine Leukocidin (PVL)-producing strains. The PVL toxin creates pores on neutrophil membranes leading to neutrophil lysis. Overall, PVL-producing *Staphylococcus aureus* is relatively rare (about 10% of all staphylococcal pneumonias), but should be suspected in patients with frequent skin and soft tissue infections. When suspected, toxin gene profiling confirms the diagnosis, and antibiotic sensitivity testing is important because some PVL-producing strains are associated with methicillin resistance.

Klebsiella pneumoniae

Klebsiella pneumoniae was originally described in 1882 by Friedlander, who believed it was the cause of pneumococcal pneumonia. It has increasingly been implicated as a cause of severe community-acquired pneumonia, accounting for 5–10% of cases that require ICU support.

The classic description of 'Friedlander's pneumonia' was of:

- a severe pneumonia
- occurrence in men with chronic alcoholism
- sputum that resembled 'redcurrant jelly'
- involvement of the right upper lobe
- bulging interlobar fissures and cavitation on chest X-ray

Table 18.4.2.5 Viruses most commonly identified in hospitalized adults with CAP

Viral pathogen	Frequency (%)
Influenza virus	4–12
Respiratory syncytial virus	2–7
Rhinovirus (most as coinfections)	2–17
Parainfluenza	0–8
Human coronavirus	2–13
Human metapneumovirus	0–4
Adenovirus	0–4

Summary of six studies from *Review Inf Dis Clinic N Am*, 2013.

It is uncommon for patients with klebsiella pneumonia to have all these features at presentation.

Viral pathogens

With the use of advanced microbiological tests, a viral pathogen is identified in about 30% of adults with CAP (Table 18.4.2.5).

The role of viruses in the pathogenesis of pneumonia is complex and may differ for different viruses. In up to a third of cases, a bacterial copathogen is identified. In cases of coinfection, the viral infection usually predates the bacterial infection.

Influenza

Influenza virus usually causes a self-limiting respiratory tract infection. It is also associated with secondary bacterial pneumonia and, less commonly, a severe primary viral pneumonia. The latter is especially prominent during influenza pandemics when there is little host immunity to the new circulating strain of virus.

Typical features of influenza-related secondary bacterial pneumonia are a biphasic illness, with a typical influenza-like illness which initially improves, followed by acute clinical deterioration; alveolar infiltrates on chest X-ray; and *Streptococcus pneumoniae* or *Staphylococcus aureus* infection.

Typical features of primary influenzal pneumonia are a rapidly progressive illness with severe pneumonia and bilateral consolidation on chest X-ray. During the 2009 H1N1 influenza pandemic, patients with influenza-related pneumonia were typically found to have a normal white cell count on hospital admission and only a marginally raised C-reactive protein level, even if severely unwell. Mental confusion was unusual. The median time from hospital presentation to intensive care admission was one day. Acute respiratory distress syndrome and multiorgan failure are recognized complications of primary influenzal pneumonia. Similar clinical presentations are described for human cases of avian influenza infection, such as with H5N1 and H7N9 influenza viruses.

Epidemiology

The incidence of CAP varies by country and increases with patient age. Estimates also vary according to clinical setting (Table 18.4.2.6).

The proportion of patients with CAP who are managed in hospital varies by country and depends on the structure of the healthcare system; estimates range from 10 to 50%. Of those

Table 18.4.2.6 Incidence of CAP in Europe

Clinical setting	Incidence per 1000 population
CAP diagnosed in the community	1.6 to 11
CAP requiring hospital admission	1.1 to 4

admitted to hospital, 5 to 15% receive treatment on an intensive care unit. The average length of hospital stay for an episode of CAP is 7 to 10 days.

Mortality from CAP treated in the community is generally low (<1%). For patients treated in hospital, studies report a range of mortality rates from 4% to over 20%. For critically ill patients treated in ICUs, mortality rates generally exceed 25%. Mortality increases sharply with increasing age (Fig. 18.4.2.1).

The economic burden associated with CAP is substantial. In the United States, it is estimated at over US$17 billion annually. Direct healthcare-associated costs related to CAP are mostly driven by the cost of hospital-based care (87–95% of total costs).

Future increases in population size together with relative increases in the proportion of older persons mean the overall number of episodes of pneumonia and hospitalizations for pneumonia are expected to increase. In a US model, total direct costs (in 2007 dollars) for pneumococcal pneumonia alone are predicted to double from US$2.5 billion in 2004 to US$5.0 billion in 2040, with the largest proportional increase in costs taking place between 2020 and 2030 (25% increase from US $3.3 billion to US$4.2 billion).

Table 18.4.2.7 Risk factors for the development of pneumonia

Risk factors for pneumonia	Crude odds ratios for pneumonia (based on case-control studies)
Patient factors	
Smoking	1.4–1.8
High alcohol intake (>41 g/day)	1.6–2.4
Being underweight (BMI <18.5 kg/m²)	1.04–2.2
Regular contact with children	1.5–3.4
Previous pneumonia	2.4–6.3
Hospitalization in the last 5 years	1.6
Comorbid diseases	
Chronic lung disease, including COPD	2.2–3.9
Chronic cardiovascular disease	1.4–3.2
Cerebrovascular disease/stroke	1.9–2.4
Dementia	2.1–2.4
Diabetes mellitus	1.4–1.5
Cancer	1.4–1.7
Chronic liver disease	1.7–2.2
Chronic renal disease	1.7–2.1
Rheumatoid arthritis	1.5–2.0
Asplenia	2.6[a]
HIV	2.5[a]–5.9[a]

[a] adjusted ORs

Pathogenesis

Risk factors for pneumonia

The common risk factors for pneumonia (Table 18.4.2.7) are broadly those that increase a person's vulnerability to pneumonia, either through affecting the risk of exposure to pathogens or the host immune response. In adults, increasing age is strongly associated with an increasing incidence of pneumonia and increasing rates of hospitalization for pneumonia.

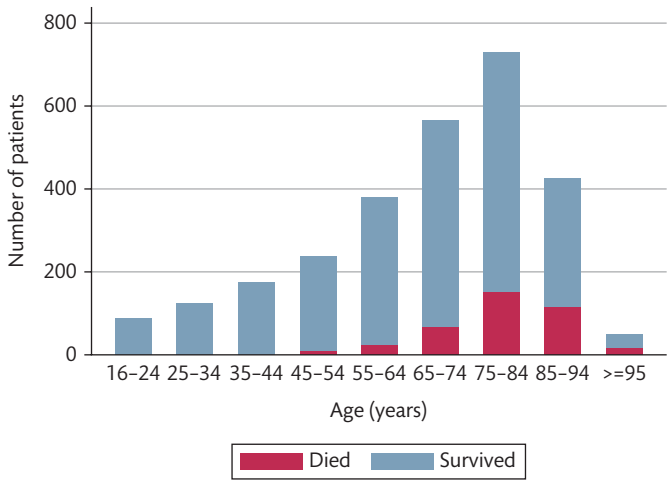

Fig. 18.4.2.1 Hospital admissions for CAP and 30-day mortality according to age: data from a single British centre (n = 2764).

Cigarette smoking is a strong modifiable risk factor for the development of pneumonia, including specifically invasive pneumococcal disease and legionella pneumonia. A dose-response relationship has been described, particularly for invasive pneumococcal disease; the greater the cigarette smoke exposure, the higher the risk. Possible mechanisms of action include suppression of the immune system, impairment of wound healing, disruption of the respiratory epithelium or impairment of mucociliary clearance. Sustained smoking cessation decreases the risk of pneumonia.

Impairment of the host's immune response may occur because of coexisting disease (e.g. HIV), or medication (e.g. immunosuppressive agents), including corticosteroids. Patients with chronic lung disease are particularly at risk of pneumonia, and in patients with COPD the use of inhaled corticosteroids further increases the risk of pneumonia.

Obesity (body mass index (BMI) 30 to 39 kg/m²) and morbid obesity (BMI ≥40 kg/m²) are both associated with an increased risk of influenza-related pneumonia but (surprisingly) the association with CAP is less strong.

Children are efficient carriers of the pneumococcus in their nasopharynx. In contrast, adults tend to either clear the pneumococcus or develop disease when challenged. Regular contact with children is associated with an increased risk of pneumonia, probably as a result of transmission of the pneumococcus or other pathogens from child to adult.

Clinical features

The medical history in a patient with suspected pneumonia is directed at establishing the diagnosis, risk factors for the development (and future prevention) of pneumonia, prognostic factors related to clinical outcome, and epidemiological factors associated with specific pathogens.

Clinical history

Symptoms

The average duration from symptom onset to presentation is 2–5 days. However, the timing of onset of illness can be difficult to determine, especially in older persons. There may be a preceding history of an upper respiratory tract illness, particularly with viral and mycoplasma infections.

Systemic symptoms common to any febrile illness are usually present—fever, malaise, anorexia, sweating, myalgia, and headache.

- Chills (the sensation of cold accompanied by shivering) are more frequently experienced in younger patients compared to older patients
- Rigors are reported in up to 62% of patients with pneumococcal pneumonia
- New onset confusion is a relatively common symptom in the older patient (*c.*10%) and in patients who are severely ill

Respiratory symptoms commonly experienced include:

- Cough *c.*75%
- Dyspnoea *c.*65%
- Sputum production *c.*50%—when produced, this is purulent in about 50%. Bloodstained sputum which is described as 'rust coloured' is classically associated with pneumococcal pneumonia, while in klebsiella pneumonia it is classically described as resembling redcurrent jelly
- Pleuritic chest pain *c.*30%—more commonly reported by younger patients

Extrapulmonary manifestations of pneumonia may be present (Table 18.4.2.8). Although an association of some of these symptoms with specific pathogens is recognized, they should not be considered diagnostic in the absence of microbiological confirmation. Other concomitant causes for these symptoms may be more likely and should also be sought, for instance, recent antibiotic therapy causing diarrhoea or a skin rash.

Unusual presentations

Approximately 10% of patients with CAP present to hospital with atypical, or extrapulmonary symptoms alone. Older patients may present with a fall, acute confusion, or simply with generalized weakness (commonly described as being 'off legs'). Occasionally, patients with lower lobe pneumonia present with features suggestive of an acute abdomen—acute abdominal pain, rigidity, and ileus.

In older patients presenting with nonspecific symptoms, a chest X-ray is usually necessitated, even if the chest examination is normal as clinical signs may be subtle. The diagnosis of pneumonia is frequently delayed in patients who present with atypical symptoms with consequent delay in the institution of appropriate therapy and a poorer outcome.

Table 18.4.2.8 Extrapulmonary symptoms of pneumonia and associated pathogens

Presentation	Possible pathogen
Myringitis	*Mycoplasma pneumoniae*
Cerebellar dysfunction	*Legionella* sp., *Mycoplasma pneumoniae*
Meningitis	*Legionella* sp., *Mycoplasma pneumoniae, Streptococcus pneumoniae*
Encephalitis	*Coxiella burnetii, Mycoplasma pneumoniae, Legionella* sp.
Acute flaccid paralysis (in children)	Enterovirus-D68
Diarrhoea	*Legionella* sp., *severe pneumococcal pneumonia*
Polyarthropathy	*Legionella* sp., *Mycoplasma pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae*
Skin rash	*Chlamydophila pneumoniae, Chlamydophila psittacii, Mycoplasma pneumonaie, Pseudomonas aeruginosa*
Herpes labialis	*Streptococcus pneumoniae*

Social, travel, and immunization history

Relevant factors to consider in the history are:

- occupation
- recent travel
- recent contact with other persons with pneumonia
- recent contact with animals, wild, and domestic
- smoking habits
- alcohol consumption
- recreational drug use
- pneumococcal immunization
- influenza immunization

Occupational, travel, and contact histories are helpful in determining likely causative pathogens and for the early identification of disease outbreaks (Table 18.4.2.9).

Table 18.4.2.9 Social, travel, and occupational features associated with specific pathogens

History/exposure to	Possible pathogen
Contaminated water source (hotel shower, sauna, jacuzzi, water fountain)	*Legionella* sp.
Farm animal around birthing time (cattle, sheep, goats, rabbits)	*Coxiella burnetii*
Poultry and birds	*Chlamydophila psittaci*
Bat droppings in endemic area (e.g. Midwest, United States)	*Histoplama capsulatum*
Rabbits in endemic area (e.g. Finland)	*Francisella tularensis*
Camels in endemic area (e.g. Middle East)	MERS-CoV
Recent influenza infection	*Staphylococcus aureus*
Intravenous drug use	*Staphylococcus aureus, anaerobes*
Travel to:	
South Mediterranean countries	*Legionella* sp.
Southeast Asia, Thailand, northern Australia	*Burkholderia pseudomallei*
Desert areas in south-western United States	*Coccidioides immitis*

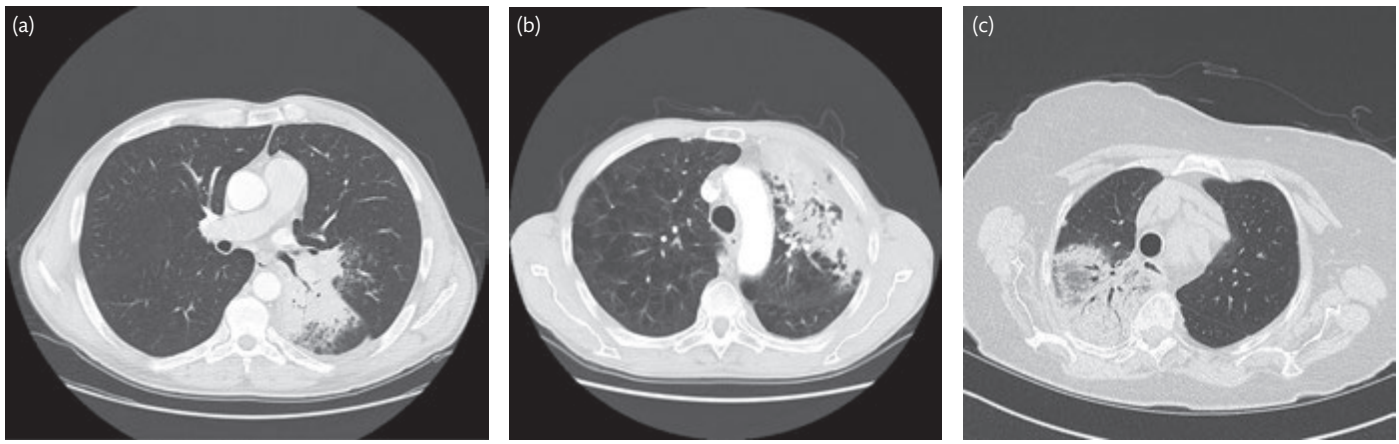

Fig. 18.4.2.2 CT appearances of (a) cryptogenic organizing pneumonia, (b) lung adenocarcinoma, (c) lobar pneumonia.

Physical signs

The patient usually looks flushed and unwell. Fever is present in about 85% of cases. The absence of fever is commoner in older patients and may detract from an early diagnosis. Tachycardia and a raised respiratory rate may be the only signs indicating a pneumonia. A low blood pressure is usually associated with severe illness and raises concerns of septic shock.

Examination of the chest will reveal reduced movement on the affected side, particularly if pleuritic pain is prominent. A pleural rub may be heard even in the absence of pleural pain. The classic signs of lobar consolidation are dullness to percussion, bronchial breathing, and egophony, but these are uncommon, occurring in only 10–30% of patients. More commonly, in 60–80% of patients, focal crepitations or coarse crackles are heard. Occasionally, the chest examination appears normal and consolidation is only evident on radiological imaging.

Clinical signs outside the chest may be present even if the patient does not report any extrapulmonary symptoms. Tenderness in the upper abdomen may be a feature of lower lobe pneumonia.

Differential diagnosis

In the absence of a chest X-ray, the main alternative diagnoses to consider in a patient presenting with symptoms suggestive of a respiratory infection are acute bronchitis and nonpneumonic exacerbation of underlying lung disease (asthma, COPD). A bacterial pathogen is implicated in only about 50% of exacerbations of COPD and up to 20% of exacerbations of asthma and acute bronchitis.

Some noninfectious conditions may mimic the radiographic features of pneumonia and lead to diagnostic confusion (Fig. 18.4.2.2a and b). Patient and clinical factors are important in arriving at the correct diagnosis (Table 18.4.2.10). In patients with multiple comorbid illnesses, it can sometimes be very difficult to differentiate between cardiac failure, pulmonary infarction, and pneumonia. Immediate treatment for more than one condition may be appropriate until the diagnosis becomes clearer.

Table 18.4.2.10 Noninfectious conditions mimicking pneumonia radiologically

Condition	Distinguishing features from pneumonia
Pulmonary infarction	Sudden onset dyspnoea Risk factors for pulmonary emboli
Pulmonary oedema	Other features of cardiac failure
Cryptogenic organizing pneumonia	Subacute clinical course
Adenocarcinoma of the lung, lepidic pattern	Not acutely unwell with relative lack of systemic inflammatory response
Eosinophilic pneumonia	Blood eosinophilia
Allergic bronchopulmonary aspergillosis	Flitting shadows over time Background of asthma
Pulmonary haemorrhage	Haemoptysis, usually fresh blood

Clinical investigations

Radiology

Chest X-ray is considered the 'gold standard' investigation for the diagnosis of pneumonia. The three commonest radiographic patterns associated with a diagnosis of pneumonia are:

a) Lobar or segmental alveolar consolidation (lobar pneumonia)
b) Patchy alveolar consolidation (bronchopneumonia)
c) Interstitial shadowing (nodular and reticular patterns)

Although some earlier studies suggested that certain radiographic patterns are associated with specific pathogens, it is now widely accepted that these radiographic patterns do not reliably discriminate the causative pathogen. For instance, although an interstitial pattern has been more frequently described in association with *Mycoplasma pneumoniae* infection, all three radiographic patterns can be caused by *S. pneumoniae, Legionella* sp., *Mycoplasma pneumoniae, and* influenza virus infections. Pleural effusions are noted in 20–40% of cases at presentation. They are usually small to

moderate in size and are commonly associated with pneumococcal pneumonia.

Less common radiographic abnormalities noted on the chest X-ray in pneumonia include lung cavitation and lymphadenopathy. The range of pathogens associated with these abnormalities is different. The commonest pathogens associated with lung cavities are:

- *Staphylococcus aureus*
- *Mycobacterium tuberculosis*
- Gram-negative bacteria (e.g. *Klebsiella pneumoniae*)
- Anaerobes (e.g. *Peptostreptococcus)*

The presence of prominent lymphadenopathy in pneumonia is associated with infection with:

- *Mycoplasma pneumoniae*
- *Coxiella burnetti*
- *Mycobacterium tuberculosis*

Greater detail can be obtained with CT scanning, which has a higher sensitivity than the chest X-ray for the diagnosis of pneumonia. Ground-glass opacities are best appreciated on CT scanning and are another pattern associated with pneumonia (see Fig. 18.4.2.3). The pathogens most commonly associated with this finding are *Mycoplasma pneumoniae, Pneumocystis jirovecii*, and viruses. However, even with CT scanning, the pattern of radiographic abnormality cannot reliably discriminate between viral and bacterial pathogens, nor between specific pathogens.

General investigations

General investigations are performed to establish the diagnosis, assess the severity of illness, evaluate the impact on comorbid diseases, and to identify complications (Table 18.4.2.11). For many patients with mild pneumonia, blood investigations do not contribute to clinical management and are not necessary.

Fig. 18.4.2.3 CT appearance of acute TB pneumonia demonstrating ground-glass opacities.

Table 18.4.2.11 Purpose of general investigations in patients with pneumonia

Investigation	Purpose and interpretation
Chest X-ray	To establish the diagnosis.
Oxygen saturation or arterial blood gases	To inform severity assessment and identify respiratory failure.
Full blood count	High white cell count (WCC) supports a diagnosis of pneumonia. WCC of >15 × 10^9/litre is associated with pneumococcal pneumonia. Very high (>20 × 10^9/litre) and low (<4 × 10^9/litre) WCCs indicate a poorer prognosis. Haemolytic anaemia is associated with infection by *Mycoplasma pneumoniae*[a] and (more rarely) *Coxiella burnetii*.
Urea and electrolytes	Raised urea (>7 mmol/litre) is a poor prognostic factor. Low sodium (<130 mmol/litre) is associated with legionella pneumonia and severe pneumococcal pneumonia.
Liver function tests	Commonly deranged in one-third of pneumococcal pneumonia and half of legionella pneumonia. Hepatitis seen in infection with atypical pathogens. Low albumin (<30 g/litre) is a poor prognostic factor.
C-reactive protein (CRP)	Aids diagnosis of pneumonia. Most patients with pneumonia have a CRP >50 mg/litre at presentation. A bacterial infection is unlikely if CRP <20 mg/litre. A fall of less than 50% in the level of CRP after 3 days of treatment is associated with a poorer prognosis.
Procalcitonin	A bacterial infection is unlikely if procalcitonin <0.1 ug/litre.
HIV serology (in at-risk patients)	Identify altered host immune status.

[a] This is due to the presence of cold agglutinins which are present in up to 50% of cases of mycoplasma pneumonias. A bedside test for cold agglutinins involves mixing a few drops of fresh blood with the same volume of sodium citrate (as found in a prothrombin tube) and leaving this in a refrigerator for 2–3 minutes to reach about 4°C. Coarse agglutination of the blood, seen as the cooled tube is rotated, is usually associated with cold agglutinin titres greater than 1:64.

C-reactive protein (CRP) is an acute phase protein synthesized by the liver in response to infection and inflammation. CRP levels are almost always raised (>50 mg/litre) in immunocompetent patients with pneumonia, and levels of CRP are higher in bacterial compared to viral infections. In the primary care setting, when the diagnosis of pneumonia is uncertain on clinical grounds alone, a very low CRP level (<20 mg/litre) may be used to exclude the need for antibiotic therapy. A CRP level of more than 100 mg/litre usually indicates that antibiotic therapy is warranted. Intermediate levels of CRP are less helpful in guiding treatment decisions.

Microbiological investigations

Microbiological investigations are used to identify the aetiological agent and hence direct antimicrobial therapy. However, results from microbiological tests are not usually available immediately, hence their use in the community setting is limited.

For hospitalized patients, the recommended depth of microbiological investigations is partly dependent on the severity of illness.

Table 18.4.2.12 Recommended microbiological tests in hospitalized patients with moderate and high severity CAP

Sample	Microbiological test
Blood (minimum 20 ml)	Bacterial culture and sensitivities
Sputum	Gram stain, bacterial culture and sensitivities PCR for respiratory viruses and atypical pathogens
Urine	Pneumococcal urinary antigen Legionella urinary antigen

In patients with low severity illness, the diagnostic rate from microbiological tests is lower and a positive test result leads to an alternation in antimicrobial management in only a small proportion of patients. Considerations of cost-effectiveness mean that microbiological tests are most warranted in patients with moderate and severe disease (Table 18.4.2.12); patients where there is clinical suspicion of less common pathogens that may not be covered by standard empirical therapy; and in outbreaks of pneumonia. In areas where *Mycobacterium tuberculosis* is a relatively frequent cause of CAP, microbiological investigations for *M. tuberculosis* should always be considered.

Specific investigations

Viral pathogens, including influenza virus

Viral polymerase chain reaction (PCR) is increasingly the diagnostic test of choice for the detection of respiratory viral pathogens. Respiratory samples for viral PCR are ideally lower respiratory tract samples such as an induced sputum, bronchoalveolar lavage, or endotracheal aspirate. Where this is not possible, a nose or throat swab is acceptable. Multiplex viral PCR assays enable the detection of:

- respiratory syncytial virus
- influenza A and B viruses
- parainfluenza virus
- adenovirus
- rhinovirus
- human metapneumovirus
- coronaviruses

Mycoplasma pnemoniae and *Chlamydophila* species

The serological investigation of *M. pneumoniae and Chlamydophila* species is increasingly being replaced by PCR detection in respiratory samples. Serological tests may be unreliable in patients who are immunocompromised and may not provide a definitive result until the convalescent phase of the illness. Lower respiratory tract samples or throat swabs are the preferred samples for PCR of *M. pneumoniae* and *Chlamydophila* species.

Legionella species

The use of serological tests to diagnose *Legionella pneumophila* infection is unreliable and is no longer offered in many places. Urinary antigen detection is the main method of diagnosis: this has a sensitivity of 80–90% for the diagnosis of community-acquired legionella pneumonia caused by *L pneumophila* serogroup 1, but less than 50% sensitivity for other *L. pneumophila* strains.

Culture and isolation of legionellae from clinical specimens (blood, respiratory samples) is the diagnostic gold standard, allows detection of non-*L. pneumophila* strains, and has a sensitivity of 50–80%. However, reliable isolation of legionellae is not simple and requires the use of selective agars and pretreatments with heat or acid. These microbiology cultural techniques are not routinely performed in most laboratories and may need to be specifically requested when clinically indicated. Crucially, isolation of the infecting strain allows epidemiological typing to be done, which is important for the control and prevention of further cases, hence culture from appropriate specimens should always be pursued in patients where urinary antigen detection was the initial means of diagnosis.

PCR allows detection of any *L. pneumophila* serogroup with a higher sensitivity than culture (around 15% increased yield). However, the specificity of PCR remains unclear and respiratory samples for PCR are not always available as (typically) patients with legionella pneumonia have a dry cough.

Pleural fluid

In patients with para-pneumonic effusions, a sample of pleural fluid should be sent for Gram stain and bacterial culture. Inoculating pleural fluid into a blood culture bottle, in addition to standard culture of pleural fluid, increases the microbiological yield by about 20% (from 38% to 58% in one study). Pneumococcal urinary antigen detection from pleural fluid is not a licensed indication for most commercial assays but has a sensitivity and specificity of about 88% and 70%, respectively.

Treatment

Severity assessment at presentation

Patients with CAP present with a wild spectrum of illness ranging from mild and self-limiting to fulminant and life-threatening. An accurate assessment of disease severity at the outset informs decisions regarding site of care (community, hospital), extent of microbiological testing, choice of empirical antimicrobial therapy, route of administration, and duration of treatment.

Prognostic studies using mortality as the main outcome measure have been the most widely studied. A number of clinical features, investigations, and radiographic features are independently associated with mortality at 30 days. Many of these factors have been combined in the form of a prediction tool called the pneumonia severity index (PSI) (Fig. 18.4.2.4), which enables patients to be stratified on admission to hospital into five categories based on the risk of mortality at 30 days. In clinical practice, a limitation of the PSI is the requirement for numerous test results and complex calculations.

An alternative mortality prediction tool is the CURB65 score which relies on five factors and enables patients to be stratified into three groups (Fig. 18.4.2.5).

Both PSI and CURB65 prediction tools have been internationally validated and are the two most widely recommended tools for severity assessment in national CAP guidelines. In comparative studies, both tools perform equally well. However, and most importantly, when using any prediction tool, it must be acknowledged

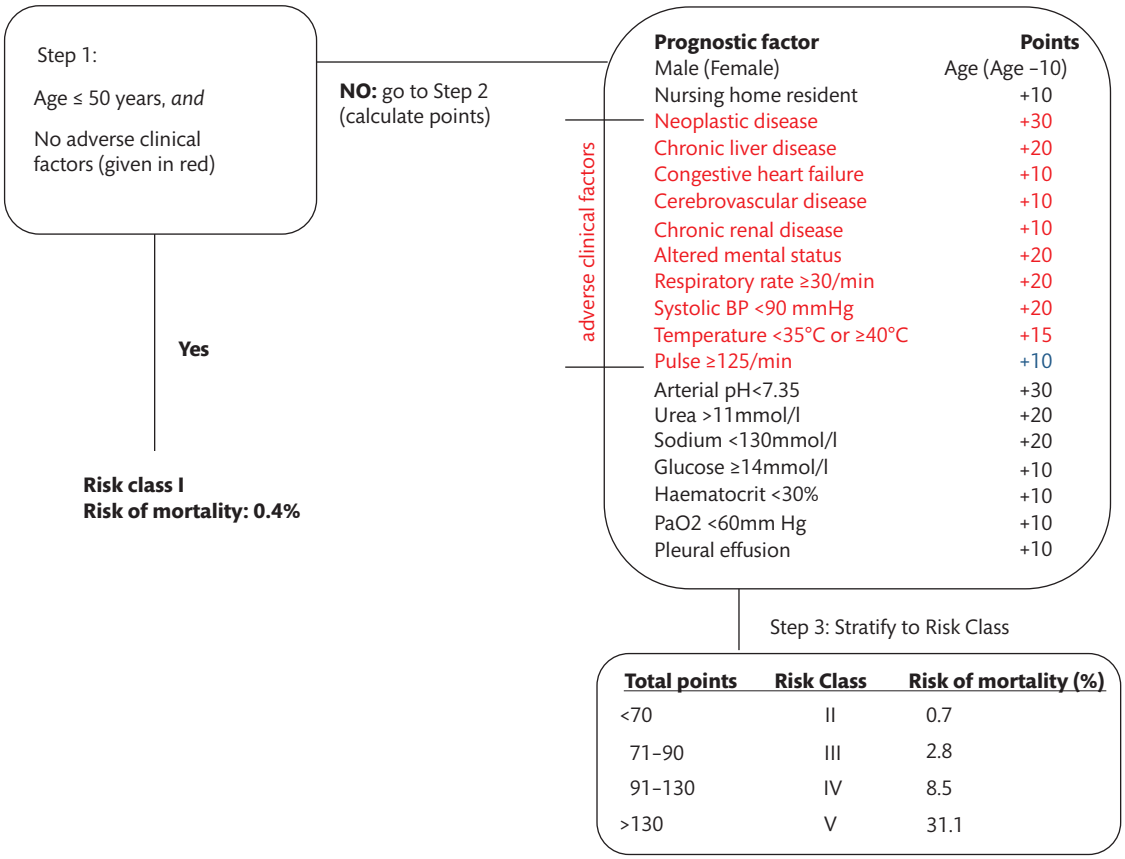

Fig. 18.4.2.4 Pneumonia severity index: calculation and interpretation. Step 1: Determine if risk class I or risk classes II–V. Step 2: If not risk class I, calculate total points. Step 3: Stratify to risk classes II–V.
After Fine MJ, *et al.* (1997). A prediction rule to identify low-risk patients with community-acquired pneumonia. *New Engl J Med*, 336, 243–50.

that no prediction tool is perfect (miscategorization does occur); prediction tools are adjuncts to, not replacements for, clinical judgement; and regular reassessment during the course of treatment is required.

A variation of the CURB65 score is the CRB65 score, which does not require any test result for its calculation. It can therefore be applied in the community where access to tests is limited. Interpretation of the CRB65 score:

- Score 0: less than 1% mortality risk
- Score 1 or 2: 1–10% mortality risk
- Score 3 or 4: more than 10% mortality risk

The 2014 UK National Institute for Clinical Effectiveness (NICE) Pneumonia Guideline recommends the following for patients with CAP assessed in a:

Community setting—clinical judgement in conjunction with the CRB65 score is used to inform decisions about whether patients need hospital assessment as follows: consider home-based care for patients with a CRB65 score of 0; consider hospital assessment for all other patients, particularly those with a CRB65 score of 2 or more.

Hospital setting—clinical judgement in conjunction with the CURB65 score is used to guide the management of community-acquired pneumonia, as follows: consider home-based care for patients with a CURB65 score of 0 or 1; consider hospital-based care for patients with a CURB65 score of 2; consider intensive care assessment for patients with a CURB65 score of 3 or mores.

Aside from disease severity assessment, other factors that should be taken into account when considering management decisions are stability of comorbid illnesses; the social circumstances of the patient, especially for community treatment; and the patient's wishes. Up to 40% of patients who are hospitalized with CAP have low

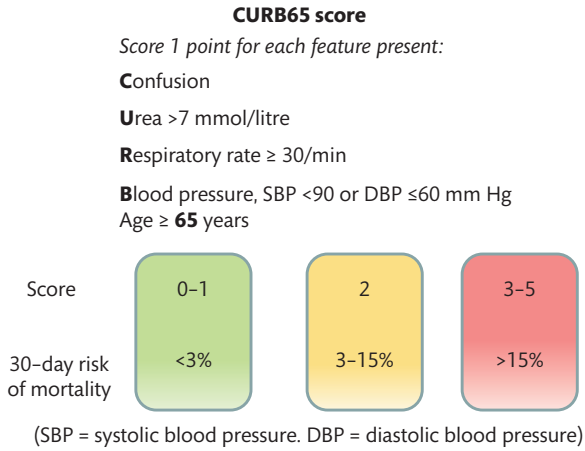

Fig. 18.4.2.5 CURB65 score: calculation and interpretation.

severity pneumonia reflecting the importance of other factors in determining their need for hospital care.

Biomarkers

Biomarkers that can characterize underlying mechanisms of disease in CAP may, theoretically, provide additional prognostic information. Inflammatory biomarkers such as CRP, procalcitonin, and cytokines (e.g. interleukin-6, tumour necrosis factor-α) are associated with disease severity and mortality. Cardiovascular biomarkers include N-terminal B-type natriuretic peptide (NT-proBNP), proendothelin-1 (proET-1), midregional proatrial natriuretic peptide (MR-proANP), proarginin-vasopressin (copeptin), and midregional proadrenomedullin (MR-proADM). Coagulation biomarkers such as D-dimers have been studied in CAP but the overlap with its established use in venous thromboembolic disease is troublesome clinically. Stress response biomarkers such as cortisol and copeptin are associated with disease severity and early clinical instability. Cortisol levels may be affected by the timing of sampling and concurrent use of corticosteroids. Overall, biomarkers are best considered as complementary to clinical prognostic tools, but in the future they may be employed selectively to assess different aspects of patient management at different phases of illness.

General management

The components of initial management include appropriate:

- fluid administration
- oxygen supplementation
- antipyretics (e.g. paracetamol)
- prophylaxis for venous thromboembolism

Mechanical ventilatory support may be indicated in critically ill patients. Expectorants and cough suppressants have not been shown to be of proven value and chest physiotherapy is not routinely advised. In patients with large pleural effusions, drainage may be beneficial.

Antimicrobial therapy

Antimicrobial agents are the mainstay of therapy. A definitive microbiological diagnosis is rarely established at the point of initial diagnosis, hence most initial prescribing is empirical and based around the most likely pathogens expected in the clinical context. Invariably, a tension arises between providing sufficiently broad antimicrobial cover for a range of pathogens versus inappropriate overuse of antimicrobials with associated risks of adverse effects in both the short and long terms.

There are no robust placebo-controlled trials of antimicrobial therapy in CAP. Drug-drug comparative trials have been mainly designed to demonstrate noninferiority and most compare new agents against older agents which are commonly used as the standard of care, meaning that considerable debate continues regarding the most appropriate treatment regimens for patients.

Most studies indicate that in low severity CAP, most patients can be adequately treated with a single antibiotic. In moderate and high severity CAP, most data suggest that a combination of a β-lactam plus a macrolide is superior to a β-lactam alone in terms of mortality and treatment failure, although newer studies are challenging this view.

In general, most guideline recommendations for empirical antimicrobial therapy in CAP reflect the following principles:

- *Streptococcus pneumoniae* should always be covered initially.
- Broader coverage is offered for patients who are severely ill, in whom the consequences of treatment failure can be life-threatening.
- Therapy should be directed by microbiological test results as soon as possible.
- The oral route of administration should be used as soon as appropriate.

The 2014 UK NICE Pneumonia Guideline recommendations are based around β-lactams and macrolides (**Table 18.4.2.13**). Other guidelines offer alternative recommendations that include respiratory fluoroquinolones (mostly in place of macrolides).

Antibiotic therapy should be given as soon as possible once a diagnosis is made. For patients referred to hospital, delay in antibiotic therapy beyond 4 to 6 hours from presentation has been associated with a poorer prognosis. However, efforts to achieve early antibiotic therapy should not disregard the need to also establish a diagnosis of pneumonia.

Suggestions for specific agents according to microbial pathogen are summarized in **Table 18.4.2.14**; these suggestions do not represent an exhaustive list of all possible antimicrobial agents.

Antimicrobial resistance

Streptococcus pneumoniae

Antimicrobial resistance in relation to the leading pathogen in CAP, *Streptococcus pneumoniae*, is of greatest concern. Rates of pneumococcal drug-resistance vary greatly across the world. In the United States, resistance to one or more antibiotics is found in about 30% of invasive pneumococcal infections.

Resistance to penicillin and other β-lactams in *Streptococcus pneumoniae* is mediated by modifications in penicillin binding proteins, and most β-lactam resistance arises from mutations in three of six such proteins. Fortunately, high-doses of β-lactams can often still be used to successfully treat infections caused by penicillin nonsusceptible *S pneumoniae*.

Macrolide resistance is mediated by two different mechanisms: the efflux mechanism (*mef* gene), which confers low level resistance and is common in the United States; and ribosomal target site mutations (*erm* gene), which confer high level resistance

Table 18.4.2.13 Summary of the 2014 UK NICE Pneumonia Guideline antimicrobial recommendations for adults presenting with CAP

Severity of pneumonia	Antimicrobial choice	Duration of therapy
Low severity	Amoxicillin *Alternatives:* macrolide, or a tetracycline	5 days
Moderate severity	Amoxicillin plus a macrolide	7–10 days
High severity	β-lactamase stable β-lactam plus a macrolide	7–10 days

Examples (nonexhaustive list) of:
- *macrolides: clarithromycin, erythromycin, azithromycin.*
- *β-lactamase stable β-lactams: coamoxiclav, 2nd or 3rd generation cephalosporins.*

Table 18.4.2.14 Antimicrobial therapy of pneumonia by specific pathogens

Pathogen	Preferred	Alternative
S *pneumoniae*	Amoxicillin	Macrolide, respiratory fluoroquinolone, doxycycline, cephalosporins
M *pneumoniae*	Doxycycline Macrolide	Fluoroquinolone
C *pneumoniae*	Doxycycline Macrolide	Fluoroquinolone
Legionella sp.	Fluoroquinolone	Macrolide
C *psittaci*	Doxycycline	Macrolide, fluoroquinolone
C *burnetii*	Doxycycline	Macrolide, fluoroquinolone
H *influenza*	Amoxicillin (if non-β-lactamase producing) β-lactamase stable β-lactam	Macrolide, fluoroquinolone
Staphylococcus aureus i) non-MRSA	Flucloxacillin +/– rifampicin	Cefazolin, cefuroxime, Teicoplanin, Vancomycin, clindamycin, TMP–SMX, fluoroquinolone
ii) MRSA	Vancomycin Linezolid Teicoplanin +\– rifampicin	Requires *in vitro* testing
P *aeruginosa*	Aminoglycoside + antipseudomonal β-lactam: ceftazidime, imipenem, meropenem, doripenem, piperacillin/ticarcillin, cefepime or aztreonam	Aminoglycoside + ciprofloxacin Ciprofloxacin + antipseudomonal β-lactam
GNEB	Cephalosporin—3rd generation ± aminoglycoside Carbapenem	Aztreonam, β-lactamase stable β-lactam, Fluoroquinolone
Influenza	Neuraminidase inhibitor	-
Examples of: *macrolides*: erythromycin, clarithromycin, azithromycin, dirithromycin *respiratory fluoroquinolones*: levofloxacin, moxifloxacin—has enhanced activity against *S. pneumoniae* *nonrespiratory fluoroquinolone*: ciprofloxacin—has activity against *legionella spp.*, *C. pneumoniae, M. pneumoniae*, fluoroquinolone-sensitive *Staphylococcus aureus*, and most Gram-negative bacilli neuramidase inhibitors: oseltamivir, zanamivir, peramivir		

and are common worldwide, and increasingly common in the United States.

Fluoroquinolone resistance arises from the alteration of the fluoroquinolone binding site through the gradual accumulation of spontaneous mutations in the quinolone resistance determinant region of *gyrA* and/or *parC*. Monotherapy of pneumococcal CAP with macrolides or fluoroquinolones in the presence of corresponding drug-resistance is usually associated with treatment failure.

Haemophilus influenzae

Resistance of *H. influenzae* to penicillin is mediated predominantly by β-lactamase resistance. β-lactamase-positive nontypeable *H influenzae* strains account for 10–25% of strains in most regions (South Africa, Europe, United States, Canada, Central America, South America), but up to 55% of strains in other regions (Taiwan, Vietnam, Japan, South Korea). Of some concern is the emergence of *H. influenzae* strains with higher levels of β-lactam resistance, including new mechanisms of resistance.

Adjuvant therapy

The goal of adjuvant therapy (given alongside antimicrobial therapy) is to suppress overexuberant pathogen-activated inflammation, thereby attenuating unwanted pulmonary damage.

Macrolides have anti-inflammatory properties as well as antimicrobial properties. This may partly explain the benefits of combination therapy with a β-lactam plus macrolide over β-lactam therapy alone observed in some studies of patients with severe pneumonia, and also in penicillin-sensitive pneumococcal pneumonia. Further studies are required to better define the role of macrolides as adjuvant therapy in CAP.

Corticosteroids are currently the most promising anti-inflammatory agents in pneumonia. Placebo-controlled randomized trials in hospitalized patients, excluding those with severe pneumonia, suggest corticosteroids reduce the time to clinical stability and length of hospital stay, but have no impact on mortality. At the same time, other trials conducted in patients with severe pneumonia, including those admitted to the intensive care, suggest corticosteroids reduce treatment failure and mortality. Further results from larger trials of corticosteroids in pneumonia are awaited.

Several other candidates have been tested over the years but have not been found to be beneficial; this list includes granulocyte colony stimulating factor (G-CSF), recombinant human activated protein C (drotrecogin alfa) and recombinant tissue factor pathway inhibitor (tifacogin).

Critical care support

Patients with high severity CAP who are at high risk of mortality should be considered for supportive care in a critical care setting. Indications for such transfer include:

- persisting hypoxia (PaO_2 <8 kPa) despite oxygen supplementation
- progressive hypercapnia

- severe acidosis (pH <7.26)
- depressed consciousness

The use of continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) for the treatment of respiratory failure in CAP has not been adequately tested in clinical trials. Neither mode of treatment is routinely indicated. If the use of CPAP or NIV is attempted, this should ideally be conducted in a setting that permits a rapid transition to invasive mechanical ventilation as soon as it becomes evident that the patient is failing to respond to CPAP or NIV.

The value of extracorporeal membrane oxygenation (ECMO) in the management of acute respiratory failure due to CAP is also unclear. During the 2009 H1N1 pandemic, ECMO was used with some reported success.

Prognosis/outcome

Response to treatment

Following appropriate initial treatment, including antibiotics, most patients with pneumonia will begin to improve. The median time to return to normal levels for heart rate and blood pressure is 2 days; and for temperature, respiratory rate, and oxygen saturation is 3 days. In up to 30% of patients, a lack of response is evident after 3 days.

Blood cultures in bacteraemic patients are usually negative within 24–48 hours. Cultures of sputum will usually show eradication of bacterial pathogens within 24 to 48 hours.

Patients with nonbacteraemic infection who are initially treated with intravenous antibiotics can usually be switched to receive oral agents after 2–3 days when the following features are met: evidence of clinical improvement; there is resolution of fever for more than 24 hours; the patient can take oral fluids and there are no concerns over gastrointestinal absorption. Following a switch to oral antibiotics, no benefit has been found with keeping a patient in hospital for a further 24 hours of observation if otherwise clinically fit for hospital discharge

Chest X-ray response

Radiographic improvement lags behind clinical improvement. In patients who are clinically improving, repeat chest radiographs are generally unnecessary except for patients in whom there are concerns that the pneumonia was a complication of an underlying condition such as lung cancer. The recommended time to arrange such chest X-rays is about 6 weeks after treatment.

Failure to respond

It is important to differentiate between a true failure to respond and an adequate response that is slower than expected. The CRP level is useful as a prognostic marker in this respect. A fall in CRP level from day 1 to day 4 of less than 50% is associated with a poorer clinical outcome and suggests an inadequate response. Careful clinical evaluation for the cause of an inadequate response is necessary (Table 18.4.2.15). Investigations to consider include repeat blood and sputum cultures, chest imaging and bronchoscopy.

A more protracted clinical course of recovery is often seen in older people and in severe legionella pneumonia. In such instances, no alteration to therapy may be required, but close observation is mandatory.

Table 18.4.2.15 Causes of failure to respond to treatment (acronym CHAOS)

Cause	Example
Complication of pneumonia	Parapneumonic effusion or empyema Lung abscess Metastatic infection Septicaemia
Host susceptibility	Immunocompromised state (e.g. HIV, corticosteroid use) Impaired local defences (e.g. endobronchial obstruction, bronchiectasis)
Antibiotic	Inappropriate antibiotic Inadequate dose Inappropriate route of administration (e.g. oral route in patient with gastrectomy) Antibiotic hypersensitivity
Organism	Antibiotic-resistant organism Unexpected organism More than one organism
Second diagnosis	Antibiotic-associated diarrhoea Phlebitis at intravenous cannula site Pulmonary embolism Incorrect diagnosis in the first instance (not pneumonia!)

Special circumstances/complications

Parapneumonic effusion

A pleural effusion is found in 20–40% of patients hospitalized with CAP. Many of these are small parapneumonic effusions that resolve with appropriate antibiotic therapy alone. In some patients, a parapneumonic effusion may be the cause of a persisting fever despite appropriate antibiotic therapy. Drainage of the pleural space is usually indicated if the pleural fluid pH is less than 7.2 (even if the fluid looks clear) or there is pus or microbiologically confirmed infection in the pleural space (an empyema). Further details on the management of complicated parapneumonic effusions are given in Chapter 18.17.

Lung abscess and cavitating pneumonia

The development of a lung abscess during the course of pneumonia is uncommon. Patients may appear surprisingly well despite the presence of a lung abscess; a persistence of fever or high inflammatory markers may be the only manifestations. The diagnosis is usually evident on chest X-ray.

Presence of a lung abscess should prompt consideration of less common bacterial pathogens such as *Staphylococcus aureus*, anaerobes (including *Streptococcus milleri*), and Gram-negative bacilli (e.g. *Klebsiella pneumoniae*). Poor dentition and aspiration are risk factors associated with anaerobic and Gram-negative infections.

Prolonged antibiotic therapy (2–6 weeks), initially with intravenous antibiotics, is typically given in patients with lung abscesses. Response to treatment is the best guide to the total duration of therapy. Complete resolution of even large abscesses (>4 cm size) is possible with antibiotic therapy alone. In the uncommon instance when drainage of a lung abscess may be considered, an individualized assessment is required, taking into account the size, location, and number of abscesses, response to antibiotics, host fitness, and pathogen involved.

Aspiration pneumonia

Aspiration pneumonia generally refers to the development of pneumonia following the inhalation of material into the lower airways. It is typically associated with a defect in swallow or protective airways defences. However, not all patients with pneumonia and a defective swallow necessarily have aspiration pneumonia. Conversely, silent aspiration is well-recognized in older patients and aspiration events may be unwitnessed.

The lower lobes are usually affected, more commonly on the right. In patients who are recumbent at the time of aspiration, the posterior segment of the upper lobes may be affected.

Clinical presentations that increase the suspicion for aspiration pneumonia include recurrent pneumonias, anaerobic pneumonias, and lung abscesses. The microbiology reflects the organisms usually found in the oropharynx, including Gram-negative bacteria and anaerobes. Often, more than one pathogen is involved.

Prevention

Lifestyle factors, such as smoking and high alcohol intake, are important modifiable risk factors for the development of pneumonia. Exposure to drugs that modulate host immune responses is usually determined by the need for such medication. Whenever appropriate, the use of such drugs, including oral and inhaled corticosteroids, should be kept to the minimum.

Pneumococcal vaccines

Two types of pneumococcal vaccines are available. The most commonly used of these are:

- the pneumococcal polysaccharide vaccine containing polysaccharide from 23 serotypes (PPV23)l;
- the pneumococcal conjugate vaccine (PCV), generally containing polysaccharide from 10, 13 or 15 serotypes (PCV10, PCV13, or PCV15).

Recommendations for the use of PPV23 in adults have been in place in various countries since the mid-1980s. The efficacy of PPV23 in preventing invasive pneumococcal disease is still debated; some meta-analyses report efficacy estimates of 50–70%, while other studies have found no benefit. The value of PPV23 in preventing noninvasive pneumococcal pneumonia is also contested.

The poor immunogenicity of polysaccharides in infants less than 2 years of age led to the development of PCVs, which involves conjugation of pneumococcal capsular polysaccharides to a carrier protein that is nontoxic and nearly identical to diphtheria toxin (CRM197). A key advantage of PCVs is the activation of a T-cell dependent antibody response in the setting of mucosal immunity. Hence, PCV use in children is associated with decreased nasopharyngeal carriage of *S. pneumoniae* which in turn is associated with reductions in *adult* pneumococcal infections through decreased transmission (an effect know as herd protection).

A randomized-controlled trial of PCV13 involving roughly 85 000 adults aged 65 years and older found that PCV13 was associated with 45% fewer episodes of vaccine-type CAP; 45% fewer episodes of nonbacteraemic vaccine-type CAP; and 75% fewer episodes of vaccine-type invasive pneumococcal disease.

Following the introduction of PCV13 into the US infant immunization programme in 2010, a 12–32% decline in the incidence of total adult invasive pneumococcal disease by June 2013 was observed. Recommendations relating to the use of pneumococcal vaccines in adults issued by the US Advisory Committee on Immunization Practices (ACIP) are:

- Adults aged 19 years or over with immunocompromising conditions should receive PCV13 and PPV23 (issued 2012)
- All adults aged 65 years or over should receive both PCV13 and PPV23 (issued 2014)

New protein-based vaccines and live, attenuated whole cell vaccines are under development. If successful, these vaccines should offer broad serotype-independent protection from pneumococcal infections.

Influenza vaccine

The benefit of influenza vaccination in the general elderly population (65 years and older), many of whom have chronic health conditions, has not been adequately assessed in randomized trials. Early cohort studies suggested up to 43% effectiveness in preventing influenza-related pneumonia. However, more recent analyses suggest the true size of these estimates may not be as large. In the United Kingdom, adult influenza vaccination was recommended in 2017/18 for:

- everyone aged 65 and over
- everyone aged from 6 months to less than 65 years of age with a serious medical condition
- pregnant women, at any stage of pregnancy
- all those aged two and three (on 31 August 2017)
- all children in reception class and school years 1–4 (aged 4–9 years)
- everyone living in a residential or nursing home
- everyone who cares for an older or disabled person
- household contacts of anyone who is immunocompromised
- all frontline health and social care workers

Controversies/future developments

Research investment in pneumonia is disproportionately low compared to the global burden of disease. The lack of robust evidence to support many currently recommended therapies fuels ongoing controversy in these areas: use of macrolides in combination with β-lactams in empirical antibiotic regimens; use of corticosteroids as adjunctive therapy; optimal duration of antibiotic therapy; role of biomarkers in guiding management decisions; and use of CPAP or NIV in acute respiratory failure secondary to pneumonia.

Increased translational research into rapid microbiological diagnostics and novel antimicrobial agents (not just new antibiotics) is required. The future goal should be to provide individualized therapy which is pathogen-specific as soon as a diagnosis of pneumonia is made.

FURTHER READING

Briel M, *et al.* (2018). Corticosteroids in patients hospitalized with community-acquired pneumonia: Systematic review and individual patient data meta analysis. *Clin Infect Dis*, **66**(3), 346–54. doi: 10.1093/cid/cix801.

Kolditz M, Ewig S, Hoffken G (2013). Management-based risk prediction in community-acquired pneumonia by scores and biomarkers. *Eur Respir J*, **41**, 974–84.

Lee JS, Giesler DL, Gellad WF, Fine MJ. (2016). Antibiotic therapy for adults hospitalized with community-acquired pneumonia: A systematic review. *JAMA*, **315**(6), 593–602. doi: 10.1001/jama.2016.0115.

Lim WS, *et al.* (2009). BTS guidelines for the management of community-acquired pneumonia in adults: update 2009. *Thorax*, **64** Suppl, iii1–55.

Mandell LA, *et al.* (2007). Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*, **44** Suppl 2, S27–72.

National Institute for Health and Care Excellence (2014). Pneumonia in adults: diagnosis and management (CG191). https://www.nice.org.uk/guidance/cg191

Tomczyk S, *et al.* (2014). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*, **63**, 822–5.

Welte T, Torres A, Nathwani D (2012). Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax*, **67**, 71–9.

Wunderink RG, Waterer G (2017). Advances in the causes and management of community acquired pneumonia in adults. *BMJ*, **358**, j2471. doi: 10.1136/bmj.j2471.

18.4.3 Nosocomial pneumonia

Wei Shen Lim

ESSENTIALS

Nosocomial pneumonia is generally defined as a new pulmonary infiltrate on chest radiography, combined with evidence of infection expressed as fever, purulent respiratory secretions, and/or leucocytosis, with onset 48 hours or more after admission. It is the most frequent lethal nosocomial infection (overall mortality 7% in general ward inpatients to over 50% in critically ill patients).

Aetiology—most cases are caused by Gram-negative bacteria (50–70%) or *Staphylococcus aureus* (15–30%). Gram-negative bacteria reach the lung by aspiration of gastric contents or by microaspiration of upper airway secretions; throat cultures reveal that 60–75% of patients on intensive care units are colonized by these organisms (compared to 2–6% of healthy people).

Prevention—simple methods of prevention are by nursing the patient in the semi-upright position to reduce the risk of aspiration, and hand-washing between patients to prevent transmission of nosocomial pathogens.

Diagnosis—this can be difficult, especially on intensive care units, when pulmonary infection is confirmed in only about 30% of cases of suspected ventilator-acquired pneumonia.

Management—when empirical decisions are necessary in seriously ill patients, the favoured drugs directed against Gram-negative bacteria are ceftazidime, cefepime, imipenem/meropenem, piperacillin/piperacillin–tazobactam, ticarcillin/ticarcillin–sulbactam, or ciprofloxacin. For methicillin-resistant *S. aureus*, vancomycin or linezolid is added.

Introduction

Definition

Hospital-acquired pneumonia

Hospital-acquired pneumonia (HAP) is defined as an inflammatory condition of the lung parenchyma caused by infectious agents not present or incubating at the time of hospital admission (i.e. pneumonia that occurs 48 hours or more after hospital admission).

Hospital-acquired pneumonia is further classified into pneumonias that occur on the intensive care unit (ICU HAP) and those that occur on the ward (non-ICU HAP) (Fig. 18.4.3.1). Ventilator-acquired pneumonia (VAP) is a subset of HAP that includes all patients receiving mechanical ventilation at the time of infection. It is defined as HAP that develops more than 48 hours after endotracheal intubation.

Aetiology

Although most HAP occurs outside the ICU, knowledge about the microbiology of HAP is dominated by studies conducted

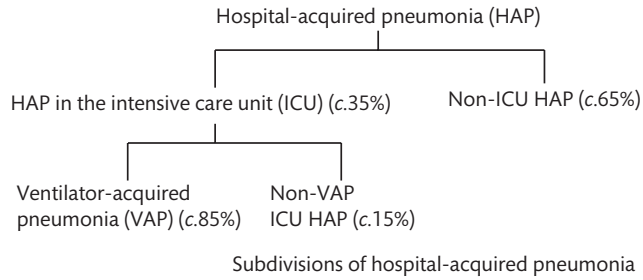

Fig. 18.4.3.1 Subdivisions of hospital-acquired pneumonia. HAP = hospital-acquired pneumonia. ICU = intensive care unit. VAP = ventilator-acquired pneumonia.