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CONTINUING PROFESSIONAL DEVELOPMENT

Pneumonia: CAP, HAP and other types

Pneumonia is one of the leading causes of mortality with four million deaths worldwide each year. This article consolidates your knowledge of symptoms, diagnosis and treatment

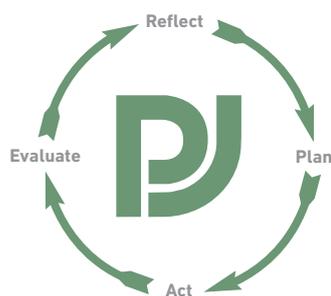
TOBY CAPSTICK LEAD RESPIRATORY PHARMACIST AT LEEDS TEACHING HOSPITALS NHS TRUST

THE term “respiratory tract infection” (RTI) describes any infection of the upper or lower airway. A quarter of the population visit a GP each year because of an RTI, and approximately 60 per cent of all antibiotics prescribed in general practice are to treat these types of infection,¹ despite the limited evidence for efficacy of antibiotics in many cases.

Pneumonia is an acute respiratory illness affecting the distal airways of the respiratory tract and lung parenchyma (ie, the lower respiratory tract). Unlike other lower respiratory tract infections (LRTIs), such as acute bronchitis, bronchiolitis and tracheitis, pneumonia is one of the leading causes of mortality, with four million deaths worldwide each year. Consequently it is important that pneumonia is accurately diagnosed and promptly treated. Definitions of different categories of pneumonia are given in Panel 1.

The incidence of community-acquired pneumonia (CAP) in the UK is estimated at 5–11 per 1,000 adults, and hospital admission is required for between 22 and 42 per cent of adults, of whom 5–10 per cent require admission to an intensive care unit. Most adults with CAP can be managed safely at home, where the mortality has been estimated at less than 1 per cent. However the mortality of adults with more severe CAP requiring hospital admission is reported to be between 5.7 and 14 per cent, and is higher — at over 30 per cent — in those admitted to intensive care.²

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection, increasing admission duration by seven to nine days, and has an



REFLECT

- 1 Can you list the common symptoms of pneumonia?
- 2 What are the most common bacterial pathogens implicated in pneumonia?
- 3 Do you know your local antibiotic guidelines for managing community-acquired pneumonia?

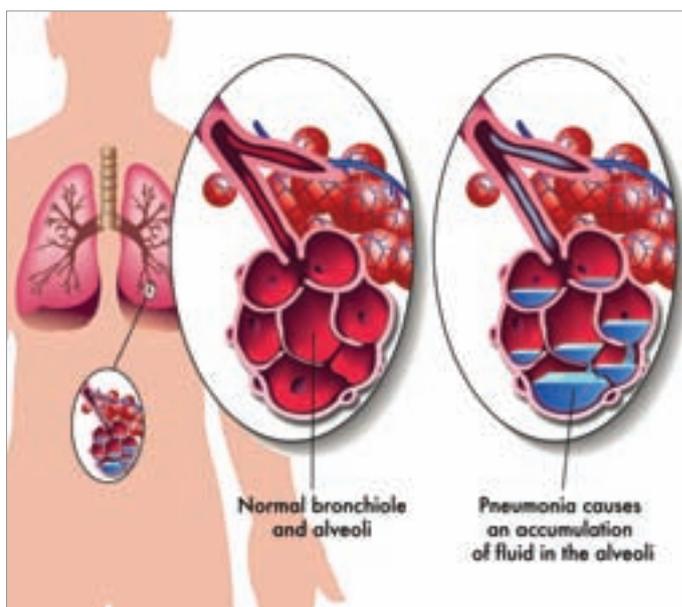
Before reading on, think about how this article may help you to do your job better.

estimated incidence of 0.5 to 2.0 per cent. HAP has a high mortality, with estimates varying from 30 per cent to over 70 per cent.⁴

Patients with HAP associated with mechanical ventilation are described as having ventilator-associated pneumonia (VAP), which is associated with a mortality rate of 24–50 per cent.⁵

Causes and risk factors

Pneumonia may occur after inhalation or aspiration of bacterial, viral or fungal pathogens, and their subsequent invasion of the lower respiratory tract if respiratory defence mechanisms (eg, mucociliary clearance and cell-mediated immunity) fail. This results in the migration of inflammatory cells such as neutrophils into the alveoli and interstitium, and



PANEL 1: CATEGORIES OF PNEUMONIA

Community-acquired pneumonia (CAP) Pneumonia acquired in the community^{2,3}

Hospital-acquired pneumonia (HAP) Pneumonia that occurs 48 hours or more after hospital admission, which was not incubating at the time of admission.^{4,5} It is often further categorised into early onset (within four to five days of admission) and late onset HAP.⁴

Healthcare-associated pneumonia (HCAP) Pneumonia occurring in any patient who has been admitted to an acute care hospital for two or more days within 90 days of the infection; or has been a resident in a nursing home or long-term care facility; or has attended a hospital or haemodialysis clinic; or has received recent intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection.⁵

Aspiration pneumonia Includes both chemical or bacterial pneumonia resulting from inhalation of either oropharyngeal or gastric contents into the lungs. (Risk factors for aspiration pneumonia include altered level of consciousness, neurological disorders and dysphagia).²

Ventilator-associated pneumonia Pneumonia developing ≥ 48 hours after implementing endotracheal intubation or mechanical ventilation, or both, that was not present before intubation. Early onset VAP (occurring within the first four days of mechanical intubation) is often caused by typical community pathogens, while late onset VAP is often caused by antibiotic-resistant hospital opportunist pathogens.⁵

consolidation results as the alveoli fill with inflammatory exudate, bacteria and white blood cells.⁴

The most common cause of CAP in the UK is *Streptococcus pneumoniae*, but other common culprits include *Haemophilus influenzae*, *Legionella* spp, *Chlamydomphila pneumoniae*, and *Mycoplasma pneumoniae*. Viruses can also cause pneumonia or be a co-pathogen with bacteria, with influenza A and B being the most commonly reported respiratory viral infections. The time of year may influence the likely pathogen: *S pneumoniae* occurs most commonly in the winter, and legionella infection has been shown to peak in August and September. *Staphylococcus aureus* pneumonia is more common in winter months, and is often identified with coincident influenza infection.²

Certain pathogens are thought to be a more common cause of CAP in certain groups of patients. For example, *H influenzae* may be more common in elderly patients, while *M pneumoniae* and legionella infection are less common. *S pneumoniae*, Enterobacteriaceae, *Pseudomonas aeruginosa* and mixed infections tend to occur more commonly in chronic lung diseases such as chronic obstructive pulmonary disease.

Aspiration pneumonia with Gram-negative enteric bacilli and anaerobes may be more frequent in nursing home residents than in matched elderly patients.²

In patients diagnosed with HAP, *P aeruginosa*, *Acinetobacter* spp, *S aureus* and Enterobacteriaceae (such as klebsiella, *E coli* and *Enterobacter* spp) are commonly isolated from respiratory specimens. Since patients diagnosed with late-onset HAP are likely to have acquired bacterial infection during their hospital admission, or have already received antibiotic therapy, they are liable to have resistant organisms requiring broad-spectrum antibiotic treatment.^{4,5}

People at increased risk of pneumonia include smokers, those who are immunosuppressed due to immunodeficiency or drugs, and people with diabetes or a history of alcohol dependence. Medicines other than immunosuppressants that have been associated with an increased risk of pneumonia

include proton pump inhibitors, and inhaled corticosteroids when used to treat chronic obstructive pulmonary disease.

Symptoms and diagnosis

Diagnosis of pneumonia is complicated by the lack of clinical features that accurately distinguish pneumonia from other LRTIs. To aid differentiation between acute bronchitis and CAP, the British Thoracic Society (BTS) advises on their differing clinical features. Both types of LRTI are associated with the following symptoms:

- Sputum production
- Breathlessness and wheeze
- Chest pain
- Fever
- Sore throat
- Coryza (ie, catarrhal inflammation of nasal mucous membranes)

In pneumonia, however, there are also new focal chest signs or consolidation on chest X-ray for which there is no other explanation (ie, no pulmonary oedema or infarction).^{2,3}

Nevertheless, a pragmatic approach to diagnosis in primary care means that general investigations such as chest X-ray and microbiological testing may not be required unless the patient is unwell, diagnosis is unclear, or clinical improvement does not occur.^{2,4} In secondary care, however, all patients admitted to hospital with suspected pneumonia should have a chest X-ray to confirm consolidation. In addition, all patients admitted to hospital should have their oxygen saturations checked (and arterial blood gases if <94 per cent) to assess their need for emergency oxygen therapy, urea and electrolyte levels measured (to assist in assessment of severity of CAP), C-reactive protein measured, and full blood count and liver function tests done. Microbiological tests (including sputum and blood cultures, urine legionella and pneumococcal antigen testing) are recommended to guide antibiotic therapy in all patients admitted with moderate to severe CAP.

Biomarkers

A number of biomarkers have been proposed as having the potential to guide the appropriate prescribing of antibiotics. The

KEY POINTS

- In pneumonia alveoli fill with inflammatory exudate, bacteria and white blood cells and there is pulmonary consolidation.
- Pneumonia can be caused by bacterial (commonly *Streptococcus pneumoniae*), viral or fungal infection and categories include community-acquired and hospital-acquired.
- Tools to assess the severity of pneumonia include CURB-65.
- Treatment of pneumonia depends on the likely pathogen. For mild community-acquired pneumonia, amoxicillin is the first-line antibiotic.
- Pharmacists can advise on lifestyle issues related to pneumonia risk, and on vaccination.

strongest of these is perhaps procalcitonin — a precursor peptide for the hormone calcitonin, which has been shown to be raised in infection as well as in trauma, burns, and neuroendocrine tumours, and may be used to facilitate antibiotic prescribing decisions. Some studies have suggested that procalcitonin may allow shorter durations in antibiotic treatment for CAP, but others have suggested that it may be less sensitive for severe or bacteraemic CAP where levels may continue to be raised after appropriate courses of antibiotic treatment. Other potential biomarkers include proadrenomedullin and B-natriuretic peptide, which are associated with increasing severity of CAP.⁶

Severity assessment

A number of predictive models have been developed to assess the severity of CAP. The most commonly used are the Pneumonia Severity Index (PSI) and the CURB-65 score.

PSI

The PSI uses 20 variables that stratify patients into one of five risk categories based on their 30-day mortality risk. Those in PSI category IV or V are generally thought to have moderate-to-severe CAP with case fatality rates of 9 and 30 per cent, respectively.^{2,7}

CURB-65

More commonly used is the CURB-65 score, a five-point tool that scores one point for each of the following risk factors based on initial pre-treatment tests on admission to hospital:

- Confusion (new confusion defined as an Abbreviated Mental Test Score of 8 or less)
- Urea >7 mmol/L
- Respiratory rate ≥30/min
- Blood pressure, low systolic (<90 mm Hg) and/or diastolic (<60 mm Hg)
- Age >65 years

The CURB-65 score stratifies patients into five risk categories with a mortality risk as follows: score 0 = 0.7 per cent; score 1 = 2.1 per cent; score 2 = 9.2 per cent; scores 3–5 = 15–40 per cent. Patients admitted to hospital with a CURB-65 score of 3–5 are considered to have a severe CAP, and those with a score of 4–5

PANEL 2: EMPIRICAL ANTIBIOTIC TREATMENT OF CAP^{2,8}

Low severity CAP Oral

amoxicillin 500mg *tds* or oral doxycycline, 200mg loading dose, then 100mg *od*

Moderate severity CAP Oral

amoxicillin 500mg *tds* plus clarithromycin 500mg *bd*; or oral doxycycline, 200mg loading dose, then 100mg *od*

Severe CAP Intravenous

co-amoxiclav 1.2g *tds* plus clarithromycin 500mg *bd*; or IV benzylpenicillin 1.2g *qds* plus clarithromycin 500mg *bd*; or IV benzylpenicillin 1.2g *qds* plus oral doxycycline 100mg *bd*

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should be considered for admission to a critical care unit. Patients with a moderate severity CAP (score 2) are at a moderate risk of death from CAP and should be admitted to hospital for inpatient treatment. Those with a score of 0–1 are at low risk of death and are considered suitable for discharge with a course of oral antibiotics.²

A modified version of CURB-65 is available for use in primary care and omits the need for blood tests to determine urea levels. Using this CRB-65 model, mortality risk is estimated as follows: score 0 = 1.2 per cent; score 1 = 5.3 per cent; score 2 = 12.2 per cent; scores 3–4 = up to 33 per cent. Patients with a score of 3–4 are considered to be at high risk of death and require urgent hospital admission. Those with a score of 1 or 2 are also at increased risk of death and hospital assessment is advised, while those with a score of 0 can usually be treated in the community.²

Other adverse prognostic signs include severe hypoxaemia, multilobar pneumonia (confirmed by X-ray) and comorbidities such as COPD, cardiac disease, stroke and diabetes.

Treatment

The treatment of pneumonia is guided by its likely causative pathogens, which, in turn, will be linked to the source of the infection (eg, community-, hospital- or ventilator-associated), as well as local antibiotic resistance patterns.

CAP

For patients with mild CAP, empirical therapy is directed towards the most likely bacterial pathogen, *S pneumoniae*. Amoxicillin is the preferred choice in the UK due to its low cost and low level of resistance in this country. Alternatives in the case of allergy or intolerance include macrolides and tetracyclines, for which resistance rates are similarly low.²

In moderate severity CAP, *S pneumoniae* continues to be the most likely causative pathogen, but atypical pathogens, such as *Legionella* spp, may also be common, and consequently combined oral therapy with a beta-lactam and macrolide is recommended.² (See Panel 2.)

For patients with high severity CAP intravenous antibiotics are recommended to achieve high blood and lung concentrations rapidly. These patients should be switched to oral therapy as soon as clinically appropriate. Panel 3 lists the features indicating response to initial empirical parenteral therapy and so permitting consideration of oral antibiotic substitution. The BTS recommends combination treatment with a broad-spectrum beta-lactam (such as co-amoxiclav) plus a macrolide in these patients to cover pneumococcus, *H influenzae*, *S aureus* and *Legionella* spp. They also advise that cephalosporins and fluoroquinolones may be effective alternatives, but due to the associated risks of hospital-acquired infections such as *Clostridium difficile*, they are not the preferred first-line choices.² However the British Society for Antimicrobial Chemotherapy (BSAC) advises against using co-amoxiclav due to the risk of predisposing patients to *C difficile*-associated diarrhoea, and instead recommends benzylpenicillin plus a macrolide or doxycycline as the first-line therapy for moderate to severe CAP.⁸

A retrospective review of patients with septic shock (of whom 37.3 per cent had CAP or HAP) found that if antibiotics were given within one hour, the survival rate was 79.9 per cent, but for every hour of delay, the probability of survival fell by 12 per cent.⁹ Studies have also demonstrated that starting antibiotics within four hours of diagnosis of pneumonia is associated with a significantly improved survival.^{2–4,10,11}

The duration of treatment for CAP should be seven days for

PANEL 3: CRITERIA FOR SWITCHING TO ORAL ANTIBIOTICS²

- Resolution of fever for >24h
- Pulse rate <100bpm
- Resolution of tachypnoea
- Patient is clinically hydrated and taking oral fluids
- Resolution of hypotension
- Absence of hypoxia
- Improving white cell count
- Non-bacteraemic infection
- No microbiological evidence of legionella, staphylococci or Gram-negative enteric bacilli infection
- No concerns over gastrointestinal absorption

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Glossary

Lung abscess Occurs when the lung infection results in necrosis of the pulmonary tissue and formation of cavities.

Empyema Defined as pus in the pleural space. May occur in association with pneumonia.

mild to moderate CAP, and seven to 10 days for high severity CAP. Longer durations are not necessary, except for *S aureus* or Gram-negative enteric bacilli pneumonia where a treatment for 14 to 21 days may be required. Prolonged courses may be required for complications such as abscess formation, empyema or systemic embolic phenomena.² Where microbiological testing, identifies a specific pathogen, antibiotic therapy directed at the causative agent should be prescribed (see Panel 4).

Antibiotic resistance

Antibiotic resistance is a rising concern and susceptibility of *S pneumoniae*, the most common cause of CAP, to penicillins and macrolides is variable across Europe. Data from the European Antimicrobial Resistance Surveillance Network show that in Europe in 2012, 11.6 per cent of *S pneumoniae* strains were non-susceptible to penicillin and 16.9 per cent to macrolide antibiotics. Four countries (Malta, Romania, Bulgaria and Spain) reported non-susceptibility rates above 25 per cent. However in the UK, non-susceptibility to penicillin and macrolides was lower than in many EU countries, being detected in only 4.9 and 6.8 per cent of isolates, respectively.¹⁰

HAP

The recommended empirical antibiotic regimens for treating HAP should be based on local pathogens and resistance profiles within individual hospitals, and should be adjusted according to microbiological culture and susceptibility testing.

The BSAC recommends that patients with early-onset HAP who have not received any antibiotics during the hospital admission should receive

PANEL 4: RECOMMENDED TREATMENT OF MICROBIOLOGICALLY DOCUMENTED PNEUMONIA²

Pathogen	First-line antibiotic	Alternative
<i>S pneumoniae</i>	Amoxicillin (oral) or benzylpenicillin (IV)	Clarithromycin (oral) or cephalosporin (IV)
<i>M pneumoniae</i> or <i>C pneumoniae</i>	Clarithromycin (oral or IV)	Doxycycline (oral) or fluoroquinolone (oral or IV)
<i>H influenzae</i>	Amoxicillin or co-amoxiclav (oral or IV)	Cephalosporin (IV) or fluoroquinolone (oral or IV)
<i>Legionella</i> spp	Fluoroquinolone (oral or IV)	Clarithromycin (oral or IV)
<i>C psittaci</i>	Doxycycline oral	Clarithromycin (oral or IV)
<i>P aeruginosa</i>	Ceftazidime ± aminoglycoside	Ciprofloxacin (oral or IV) or piperacillin/tazobactam (IV) or meropenem (IV) ± aminoglycoside
<i>S aureus</i>	Flucloxacillin (IV) ± rifampicin (oral or IV)	Seek local microbiology advice
MRSA	Vancomycin (IV) or linezolid (IV)	Seek local microbiology advice

empirical treatment with either co-amoxiclav or cefuroxime. However those with late-onset HAP, or who have recently been treated with antibiotics should receive broad-spectrum antibiotics such as a third-generation cephalosporin, a fluoroquinolone or piperacillin/tazobactam.⁵ There is no evidence that treatment outcomes are improved with combination therapy (eg, by addition of an aminoglycoside). Where patients respond to antibiotic treatment, the duration of therapy should be no more than eight days.

In patients with HAP caused by *P aeruginosa*, treatment options include ceftazidime, ciprofloxacin, meropenem and piperacillin/tazobactam, although recommended treatment for MRSA is either linezolid or a glycopeptide.^{5,12,13}

Aspiration pneumonia

The treatment of aspiration pneumonia requires antibiotics that are effective against anaerobic bacteria, such as co-amoxiclav or piperacillin/tazobactam. Alternatives in the case of intolerance include clindamycin, or a combination of cephalosporin plus metronidazole.¹²

Other treatment and support

Hypoxia may occur in pneumonia due to pulmonary blood flow through unventilated lung tissue, resulting in non-specific symptoms of altered mental state, dyspnoea and tachypnoea. Supplemental oxygen therapy is required for patients with arterial oxygen tension (PaO₂) <8kPa, in order to achieve a target PaO₂>8 kPa or oxygen saturation in the range of 94–98 per cent in patients who are not at risk of hypercapnic respiratory failure.¹⁴

Patients admitted to hospital with pneumonia should be assessed for volume depletion and treated with intravenous fluids if needed. In patients who are not fully mobile, prophylaxis against venous thromboembolism should be started.²

Patients diagnosed with pneumonia should be advised to rest and, especially when febrile, be encouraged to drink plenty of fluids. Simple analgesia is recommended for symptomatic relief of pleuritic chest pain.^{2,12}

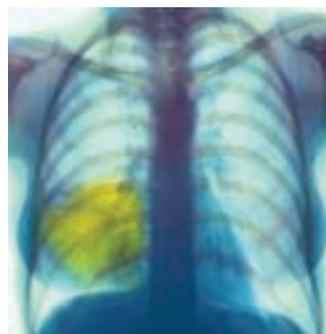
All smokers with pneumonia should be advised about the

PANEL 5: CHECKLIST FOR PROMPT REFERRAL

The following signs and symptoms indicate the need for prompt referral:

- Dyspnoea, difficulty in breathing or wheezing
- No improvement in condition after two to three weeks
- Persistent cough for longer than three weeks
- Recurrent cough
- Dry night-time cough in children
- Haemoptysis
- Chest pain
- Weight loss
- General malaise, feeling systemically unwell, persisting sweats or fever
- Painful or swollen, inflamed calf

In addition, patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression or cystic fibrosis, and young children who were born prematurely should be referred, as should patients with a potential adverse drug reaction (eg, a cough in a patient taking an angiotensin-converting enzyme inhibitor).



In pneumonia, consolidation can be seen on chest X-rays (SCIENCE PHOTO LIBRARY)

benefits of giving up and offered referral to local stop smoking services.

Acute cough is a common symptom of pneumonia and is a useful defence mechanism for clearing sputum, so cough suppression is not appropriate. There is also a lack of evidence to demonstrate a beneficial effect for treatment with expectorant or mucolytic agents in patients with productive coughs, despite their widespread use in the general population.

Warning symptoms

Although it may be appropriate for pharmacists to advise on the management of simple symptoms such as cough, it is important that they are aware of warning symptoms that may be suggestive of more serious illness and consequently when to refer to a GP. Such conditions may include exacerbations of asthma, pulmonary embolism, adverse drug reactions or lung cancer. For example, patients reporting symptoms of cough persisting for more than three weeks should be referred to their GP, particularly if there are other associated symptoms such as haemoptysis, weight loss and breathlessness — these symptoms may be suggestive of lung cancer and urgent chest X-ray may be required.

Panel 5 contains a checklist of symptoms that require prompt referral to a doctor.

Follow-up

Patients with uncomplicated pneumonia usually start to improve in the first few days of treatment, however radiographic images change relatively slowly and lag behind clinical recovery. Consequently repeat chest X-rays are recommended after about six weeks for patients with persistent signs or symptoms and those who are at higher risk of underlying malignancy (eg, smokers and those aged >50 years).^{2,4}

Patients with an unsatisfactory response to treatment require further clinical review. Potential reasons include inappropriate use of antibiotics (eg, wrong route or dose), antibiotic resistance, and inadequate coverage (eg, in patients who may be at high risk of *P aeruginosa* or MRSA).⁷ Alternatively, complications such as parapneumonic effusions and empyemas may have occurred, requiring chest tube drainage and prolonged antibiotic therapy. Lung abscess is another rare complication, requiring prolonged courses of antibiotic therapy or surgical drainage.⁴

Prevention

Pharmacists are in a good position to advise on pneumonia prevention measures. For example, they can advise on lifestyle issues such as smoking and alcohol consumption as well as good hygiene. They can also give advice on vaccination.

Pneumococcal vaccination is recommended for infants as part of routine childhood immunisation, adults aged over 65 years, and people considered at-risk (eg, those with asplenia, diabetes or chronic respiratory, heart, kidney or liver disease, and those who are immunosuppressed).¹⁵ The current influenza immunisation programme recommends vaccination for people aged over 65 years, children aged two or three years, and all those aged six months or older in at risk groups, and pregnant women.¹⁵

References available online. <http://bit.ly/L2tWbX>

The author will be available to answer questions on this topic until 3 February 2014

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PRACTICE POINTS

Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist's CPD portfolio.

1. Use the information in this article to improve your antimicrobial stewardship to advise local practitioners on the appropriate use of antibiotics.
2. Find out more about pneumococcal vaccination (eg, visit www.nhs.uk/Conditions/vaccinations/Pages/pneumococcal-vaccination.aspx) and discuss this and influenza vaccination as part of medicines use reviews for those at risk.
3. Consider the general healthy lifestyle advice you give and how it links with respiratory tract infections such as pneumonia. Could it be improved?

Consider making this activity one of your nine CPD entries this year.