Pharmacological treatment of bacterial infections of the respiratory tract

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Abstract

Bacterial infection of the respiratory tract is amongst the commonest presentations to primary and secondary care. In addition to supportive care the mainstay of pharmacotherapy is antibiotics. Antibiotic treatment of bacterial infections of the respiratory tract needs to consider patient factors such as age, co-morbidities, location, previous antibiotic use, microbiological results and allergy. The emergence of multi-drug-resistant bacteria, partly a consequence of inappropriate antibiotic use, has both focussed the need for careful management of bacterial infection and presented a new therapeutic challenge. The choice of antibiotic for respiratory infections needs to be within national guidelines modified by local susceptibility profiles. Bacterial infections of the respiratory tract affect all levels of the airway tree and can be simply classified by their anatomical location for example: epiglottitis, exacerbations of chronic obstructive pulmonary disease and bronchiectasis and pneumonia. As with all pharmacotherapy alongside the benefit the potential side effects of the treatment needs to be considered. This is particularly important for the 6-month treatment of tuberculosis, which should only be managed by a specialist. The majority of bacterial infections of the respiratory tract respond well to therapy, but it is important to recognize that this remains a major cause of mortality.

Keywords Antibiotics; bronchiectasis; COPD; epiglottitis; pneumonia; tuberculosis

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Learning objectives

After reading this article you should be able to:

- describe the management of exacerbations of chronic obstructive pulmonary disease and bronchiectasis
- describe the antibiotic regimen for tuberculosis and the potential side effects of treatment
- define the severity of pneumonia

Epiglottitis

Occurrence has decreased following introduction of the *Haemophilus influenzae* type b vaccine. Causes include *H. influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae* and group A streptococci. A third-generation cephalosporin or co-amoxiclav is preferred due to increasing amoxicillin resistance. Second-line treatment is chloramphenicol.

Chronic obstructive pulmonary disease (COPD) exacerbations

Exacerbations can be caused by viruses, bacteria and non-infectious agents. Sputum cultures often show *H. influenzae*, *Strep. pneumoniae* or *Moraxella catarrhalis*, but the extent to which this explains exacerbations is difficult to determine as the respiratory tract is often colonized. Antibiotics are recommended for increasingly purulent sputum, increased quantities of sputum and increased breathlessness. Amoxicillin, a macrolide or a tetracycline is recommended.

Bronchiectasis exacerbations

Patients often produce purulent sputum when stable, so purulent sputum alone is not an indication for antibiotics. Common organisms causing exacerbations are *Strep. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *Staphylococcus aureus* (meticillin-sensitive (MSSA) or meticillin-resistant (MRSA)), and *Pseudomonas aeruginosa*. Antibiotic choice is usually empirical although may be influenced by previous sputum cultures, with antibiotic duration 14 days. *H. influenzae* is responsible in the majority of cases and a β-lactam is appropriate (e.g. amoxicillin or clarithromycin if penicillin allergy). *P. aeruginosa* exacerbations should be treated with oral quinolones, cautiously acknowledging the association between quinolones and *Clostridium difficile* colitis. Intravenous monotherapy with an anti-pseudomonal β-lactam antibiotic (e.g. ceftazidime, tazocin) should be considered if patients have not responded to ciprofloxacin. Combination antibiotics should be used for resistant strains of *P. aeruginosa*, (e.g. third-generation cephalosporin and aminoglycoside). Exacerbations where sputum cultures are positive for MRSA should be treated with two oral antibiotics (e.g. rifampicin and trimethoprim or doxycycline) or a single intravenous agent (e.g. vancomycin or teicoplanin).

Community-acquired pneumonia (CAP)

The British Thoracic Society (BTS) advocates using CURB65 scores (Table 1), combined with clinical judgement, to identify patients at high risk of pneumonia-related mortality. Those with low CURB65 scores (0–1) can be considered for outpatient treatment, whereas those with moderate (CURB65 = 2) and high-severity scores (CURB65 = 3–5) – reflecting a higher mortality risk (Table 2) — should be considered for inpatient management, with antibiotic regimens altered accordingly.

In the outpatient setting, bacterial causes of CAP in descending order of frequency are *Strep. pneumoniae*, *Mycoplasma pneumoniae*, *H. influenzae*, *Chlamydia pneumoniae*, with inpatient bacterial aetiologies including *M. pneumoniae*, *C. pneumoniae*, *H. influenzae*, and *Legionella* species. Prompt antibiotic administration reduces illness duration, complications, and lowers mortality. Few infections are defined microbiologically at initial assessment and hence most prescribing is empirical. All empirical regimens

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CURB65 is a five-point scoring system, with one point scored for each of the following components

C	**C**onfusion	Abbreviated mental test score of 8 or less
U	**U**rea	≥7 mmol/litre
R	**R**espiratory rate	≥30/minute
B	**B**lood pressure	Systolic blood pressure ≤90 mmHg, or diastolic blood pressure ≤60 mmHg
65	**A**ge	Age ≥65 years

Table 1

should include a β-lactam to target *Strep. pneumoniae*. Current UK rates of penicillin resistance remain below 4%, so this does not currently influence empirical antibiotic choice.

Broad-spectrum antibiotics (e.g. cephalosporins and fluoroquinolones) have recently been associated with an increase in healthcare-associated infections (HCAIs), such as MRSA and *C. difficile*. These HCAIs are associated with volume of antibiotic use, and there has been pressure to limit use of these antibiotic groups.

Moderate-severity CAP

Strep. pneumoniae is the most likely organism, although 'atypical' pathogens and *Legionella* species account for up to 20%. A combination of a β-lactam antibiotic (e.g. amoxicillin) with macrolide is recommended. For patients with penicillin allergies, levofloxacin or combination of cephalosporin with clarithromycin are appropriate. Macrolide monotherapy is not recommended as 9% of pneumococci are erythromycin resistant.

High-severity CAP

Strep. pneumoniae remains the most common pathogen. *Staph. aureus* and Gram-negative enteric bacilli have high associated mortality, so the regimen should cover these, and *L. pneumophila*. The BTS recommends combination therapy with broad spectrum β-lactam antibiotics and macrolides. Initial therapy should be intravenous to ensure high blood and lung concentrations. Legionella urinary antigen testing can allow a positive diagnosis of legionella infection early.

Legionella pneumonia

Quinolones, macrolides, rifampicin and fluoroquinolones are effective agents. A recent review concluded that fluoroquinolones have significant advantages over macrolides, although the mortality rate is similar.

CURB65 scores can be used to stratify pneumonia severity in terms of mortality risk

CURB65 score	Pneumonia severity	Mortality risk
0–1	Low	0.7–2.1%
2	Moderate	9.2%
3–5	Severe	15–40%

Table 2

Post-influenza pneumonia

Secondary bacterial pneumonia is more common than primary viral pneumonia. Pathogens are similar to those causing CAP (e.g. *Strep. pneumoniae*, *H. influenzae* and *Staph. aureus*). Secondary staphylococcal pneumonia is associated with a poor prognosis. For high-severity cases (classified by CURB65 score), a broad-spectrum β-lactamase stable antibiotic (e.g. co-amoxiclav, cefuroxime) with macrolide is preferred. For patients known to be colonized with MRSA, or recently hospitalized, antibiotic choice should provide MRSA cover and include vancomycin (±rifampicin).

Panton-valentine leukocidin (PVL) – *Staph. aureus* pneumonia

The PVL-producing strain of *Staph. aureus* (PVL-SA), which can be either MSSA or MRSA, is a rare cause of high-severity pneumonia. It is characterized by rapid lung cavitation, lung necrosis and multi-organ failure. If suspected, blood and respiratory cultures should be cultured on non-selective media to aid pathogen identification. Current recommendations for suspected necrotizing pneumonia include the addition of intravenous linezolid, clindamycin and rifampicin to the initial antibiotic regime. As soon as PVL-SA infection is either confirmed or excluded, the antibiotic regime can be narrowed accordingly.

Hospital-acquired pneumonia (HAP)

HAP is pneumonia developing more than 48 hours after hospital admission. Early-onset disease (within 4–5 days of admission) is often caused by community pathogens (e.g. *Strep. pneumoniae*, *H. influenzae*), with late-onset infections often caused by antibiotic-resistant hospital pathogens (e.g. *P. aeruginosa*, resistant Gram-negative bacteria or MRSA).

The 2008 UK guidelines recommend that antibiotic regimens should include antibiotics active against Gram-negative bacilli, but states that no one antibiotic is superior to another. Thus treatment choice should depend on local antimicrobial susceptibility profiles with possible agents including ceftazidime, tazocin and meropenem. Empirical therapy should take account of inpatient duration, recent antibiotic administration and co-morbidities. Definitive therapy should be determined by culture and sensitivity results. If patients are known to be colonized or infected with MRSA, antibiotic regimes should include vancomycin, linezolid or teicoplanin.

Pulmonary tuberculosis (TB)

Treatment should be supervised by a specialist. Treatment involves a combination of four antibiotics (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months, followed by 4 months of two antibiotics (isoniazid and rifampicin). Multi-drug-resistant tuberculosis (MDR-TB) is defined as resistance to the two most effective drugs: isoniazid and rifampicin.

Antibiotics

β-lactam antibiotics

Characterized by three structural components: a β-lactam ring, a free carboxyl-acid group and substituted amino acid side chains. All β-lactam antibiotics are bactericidal by inhibiting bacterial