March 2025

Therapeutic Guidelines: Antibiotic is published by Therapeutic Guidelines, an independent not-for-profit organisation that aims to promote quality use of medicines. *Therapeutic Guidelines* is a leading source of independent, evidence-based, practical treatment advice to assist Australian healthcare professionals with decision making at the point-of-care.

Therapeutic Guidelines: Antibiotic provides guidance on the management of a wide range of infectious diseases. The guidelines are based on a review of the latest literature, discussed and interpreted by several multidisciplinary expert groups, with input from an extensive network of other healthcare professionals. During the review process, the Antibiotic 17 Hospital, Primary care and Drug information Expert Groups identified areas where evidence was lacking, insufficient or conflicting, warranting further research. To support the research community, these evidence gaps have been collated and published below.

The gap that was raised most often was the optimal duration of antimicrobial therapy for various infections in both adults and children, followed by the optimal duration of intravenous therapy (if it is required) before switching to oral therapy. Despite recent publications addressing these questions, additional data are required for both the implementation of the existing evidence and infections for which these questions have not been answered, including:

- endocarditis after transcatheter aortic valve replacement or implantation
- cardiac implantable electronic device infections (pocket infection or endocarditis) after device removal
- infected vascular stents customised to stent location and pathogen
- septic jugular thrombophlebitis
- mediastinitis
- exacerbations of bronchiectasis
- prophylaxis of chronic obstructive pulmonary disease exacerbations
- lung abscess when the pathogen is not identified
- complicated parapneumonic effusion or empyema after source control is achieved.

The remaining evidence gaps are grouped according to the order of topics in *Therapeutic Guidelines: Antibiotic*, rather than being listed in order of research priority. They may not represent all areas in which research is needed.

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Gaps that impact multiple topics

- Optimal dosage of intravenous amoxicillin+clavulanate for children.
- Randomised controlled trial evidence of clinical efficacy of 12-hourly versus 8-hourly intravenous and/or oral metronidazole for empirical treatment of anaerobic bacterial infections.
- Optimal dosage of trimethoprim+sulfamethoxazole for people with obesity.

Cardiovascular infections

Infective endocarditis

- Clinical outcomes of partial oral therapy compared to ambulatory parenteral therapy (eg Hospital-in-the-home) for infective endocarditis, and the efficacy of individual oral antibiotics, and combinations, for directed therapy of infective endocarditis.

Cardiac implantable electronic device infections

- Pathophysiology of cardiac implantable electronic device infection after upgrade or replacement, including why the risk of infection is greater than the risk of infection after a new implant.
- Optimal timing for reimplantation of a new cardiac implantable electronic device after removal of the device because of a pocket infection.

Septic jugular thrombophlebitis

- Prospective data demonstrating the outcomes of anticoagulation versus no anticoagulation for septic jugular thrombophlebitis, with consideration of the duration of anticoagulant therapy, and resolution of thrombus or metastatic foci.

Clostridioides difficile infection

- Cost-effectiveness of fidaxomicin for a first episode or first recurrence of *C. difficile* infection.
- Optimal formulations, route and dose of faecal microbiota transplantation for *C. difficile* infection (second or subsequent recurrences; ongoing refractory infection unresponsive to fidaxomicin; severe, complicated or fulminant infection).
- Cost-effectiveness of bezlotoxumab for preventing recurrence of *C. difficile* infection in the Australian healthcare setting.

Ear, nose and throat infections

Otitis externa

- Efficacy of nonantibiotic management strategies (eg aural toilet, tissue spears) to reduce the use of antibiotics for otitis externa.
- Prevalence of ototoxicity associated with the use of aminoglycoside-containing eardrops, particularly in cases of tympanic membrane perforation.

Otitis media

- Randomised controlled trial evidence of the safety and efficacy of antimicrobial eardrops for acute otitis media with perforation.

Peritonsillar abscess (quinsy) and peritonsillar cellulitis

- Optimal dose and duration of corticosteroid therapy in the treatment of peritonsillar abscess and cellulitis.

Retropharyngeal abscess

- Optimal dose and duration of corticosteroid therapy in the treatment retropharyngeal abscess.

Genital and sexually transmissible infections

Syphilis in pregnancy and congenital syphilis

- Effectiveness of non-penicillin antibiotics for both treating syphilis in pregnant patients with severe penicillin allergies and preventing congenital syphilis.

Intra-abdominal infections

- Clinical efficacy of intravenous amoxicillin+clavulanate compared to other non-aminoglycoside antibiotics (eg ceftriaxone) for intra-abdominal infections.
- Efficacy of extended infusions of beta lactams for non–critically-ill patients with sepsis from a biliary or gastrointestinal source.

Acute appendicitis

- Optimal antibiotic regimen for nonoperative treatment of acute uncomplicated appendicitis.
- Long-term effects on microbiota and risk of multidrug-resistant (MDR) organisms with non-operative treatment of acute uncomplicated appendicitis.

Diverticulitis

- Need for any antibiotics in uncomplicated diverticulitis. (This gap is likely to be addressed; 2 large pragmatic placebo-controlled randomised controlled trials are pending.)

Necrotising enterocolitis in neonates

- Optimal antibiotic regimen for empirical treatment of necrotising enterocolitis in neonates.

Mediastinitis

- The prevalence of oesophageal colonisation with gram-negative bacteria in aged-care facility residents, to help determine the optimal antibiotic regimen for mediastinitis following oesophageal rupture in this group.

Prevention of infection

Prevention of infection in patients with asplenia or hyposplenism

- Optimal antibiotic for prophylaxis against encapsulated bacteria (especially pneumococcus) in patients with asplenia or hyposplenism who have hypersensitivity to penicillins.

Pneumonia

- Microbiological aetiology of pneumonia in Australia.
- Whether biomarkers can help determine the need for, and optimal duration of, antibiotic therapy.
- Optimal antibiotic regimen for children with hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) or severe pneumonia.
- Whether rapid diagnostics and upper airway viral studies can identify community-acquired pneumonia (CAP) in children and the need for antibiotic therapy.
- Efficacy of linezolid compared with adequately dosed vancomycin for pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) without intermediate resistance to vancomycin.
- Optimal antibiotic regimens for gram-negative pneumonia, considering clinical outcomes and adverse effects (including impact on microbiome and potential for resistance). Pathogens of interest include:
  - non-MDR Enterobacterales
  - non-MDR *Pseudomonas aeruginosa*
  - community-acquired *Acinetobacter baumannii*
  - hospital-acquired *Acinetobacter baumannii*.
- Optimal dosing of antibiotics for pneumonia in patients requiring intensive care support.

Respiratory tract infections other than pneumonia

Bronchiectasis in adults and children

- Microbiological aetiology of bronchiectasis exacerbations in Australia.
- Randomised controlled trial evidence for the optimal antibiotic regimen for bronchiectasis exacerbations, particularly in children.
- Efficacy and safety of inhaled antibiotics, particularly their long-term impact on antibiotic resistance, and how this compares to antibiotics administered orally or intravenously for people with frequent exacerbations.
- Optimal antibiotic regimen to eradicate *Pseudomonas aeruginosa*, including efficacy of monotherapy versus dual therapy, and the impact of treatment on long-term outcomes for patients.

Chronic obstructive pulmonary disease (COPD) exacerbations

- Efficacy and potential harms (including development of antibiotic resistance) of azithromycin and erythromycin for long-term prophylaxis of COPD exacerbations.

Lung abscess

- Whether percutaneous biopsy in lung abscess without a microbiological diagnosis can direct antibiotic therapy or identify complications.

Parapneumonic effusion and thoracic empyema

- Utility and yield of pleural biopsy in determining a microbiological diagnosis of parapneumonic effusion or empyema, and directing antibiotic therapy.

Sepsis and septic shock

Community-acquired sepsis or septic shock of uncertain source in adults

- Head-to-head studies to determine the optimal antibiotic regimen for the empiric treatment of community-acquired sepsis of unknown source in adults.

Skin and soft tissue infections

- Whether shorter courses of antibiotic therapy can be used to treat boils and carbuncles, cellulitis and erysipelas, and, if they can, which patients would be suitable.
- Data supporting the efficacy of doxycycline for skin and soft tissue infections in patients who are at an increased risk of methicillin-resistant *Staphylococcus aureus* (MRSA).

Urinary tract infections (UTI)

Bacteriuria and UTI in pregnancy

- Optimal timing and frequency of antenatal screening for asymptomatic bacteriuria.
- Requirement for routine screening and treatment of asymptomatic bacteriuria in low-risk pregnant patients, considering the relative harms, benefits and cost-effectiveness.

Principles of aminoglycoside use

- Optimal aminoglycoside area under the concentration–time curve (AUC) target for pathogens with a low minimum inhibitory concentration (MIC).
- Maximum doses of gentamicin, tobramycin and amikacin are provided in the guidelines - data are needed to inform whether higher doses can be used and the toxicity threshold.
- Optimal amikacin dosage regimens in adults.
- Optimal weight descriptor to calculate aminoglycoside dose in adults (eg lean bodyweight, actual bodyweight, ideal bodyweight).
- Optimal aminoglycoside dose and method for monitoring in patients undergoing haemodialysis.
- In neonates and children, the optimal aminoglycoside dose for empirical and directed therapy.
- In neonates and children, the role of aminoglycoside trough plasma concentration monitoring to avoid toxicity.

Principles of vancomycin use

- Optimal vancomycin trough plasma concentration in children aged between 3 months and 2 years.
- Optimal vancomycin loading and maintenance dosage regimens in adults with obesity.
- Role of Bayesian *a priori* dosing of vancomycin to optimise vancomycin dosing.

Monitoring antimicrobial blood concentrations

- Whether trough plasma concentration or area under the concentration–time curve (AUC) is superior for fluconazole therapeutic drug monitoring.
- Optimal method for monitoring itraconazole plasma concentrations, in particular whether the target concentration should be the sum of the concentrations of drug and its active metabolites.
- Whether monitoring beta-lactam plasma concentrations in patients outside of the intensive care unit setting improves outcomes.
- Whether CYP2C19 genotype testing can guide initial voriconazole dosing and inform therapeutic drug monitoring targets.
- Whether posaconazole plasma concentration monitoring is required for patients using posaconazole tablets for prophylaxis to ensure that the patient has adequate plasma concentrations.
- The concentration above which posaconazole causes toxicity.

Antimicrobial hypersensitivity

- Management of hypersensitivity to antimicrobials other than penicillins (eg cephalosporins, macrolides, tetracyclines).
- Safety of delabeling antimicrobial allergies in primary care.
- Whether cephalosporins can be safely used in patients with a severe cutaneous adverse reaction (SCAR) to penicillin.
- Required fequency of benzathine benzylpenicillin desensitisation in patients with syphilis, in particular whether desensitisation needs to be repeated before each dose.