ARTICLE

Oral or intravenous antibiotics?

SUMMARY

Intravenous antibiotics are overused in hospitals. Many infections can be managed with oral antibiotics.

Oral antibiotics avoid the adverse effects of intravenous administration. They are also usually less expensive.

When intravenous antibiotics are indicated, it may be possible to switch to oral therapy after a short course. There are guidelines to aid the clinician with the timing of the switch so that there is no loss of efficacy.

Infections that may be suitable for a short course of intravenous antibiotic include pneumonia, complicated urinary tract infections, certain intra-abdominal infections, Gram-negative bacteraemia, acute exacerbations of chronic lung disease, and skin and soft tissue infections.

Bone and joint infections and infective endocarditis are managed with prolonged courses of intravenous antibiotics. However, there is research looking at the feasibility of an earlier switch to oral antibiotics in these conditions.

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Introduction

Selecting the most appropriate route of administration is part of the quality use of medicines. For many patients with bacterial infections who require treatment with an antibiotic, an oral formulation is the most appropriate choice. However, patients in hospital are often given intravenous antibiotics. While there are clinical circumstances when parenteral administration is indicated, for some infections oral therapy can be equally efficacious.

Intravenous antibiotics

Intravenous therapy is recommended, at least initially, for severe life-threatening infections and deep-seated infections because of concerns about not achieving adequate antibiotic concentrations at the site of infection. Patients who are unable to absorb or take oral drugs, for example because of vomiting, will require parenteral therapy. This route is also recommended in immunocompromised patients due to their reduced ability to fight infection.

The volume of community and hospital-based antibiotic use in Australia is higher than in comparator countries.[1] In 2017, almost one-third (32.7%) of the 21,034 prescriptions, for both oral and intravenous antibiotics, that were assessable for the voluntary hospital-based National Antimicrobial Prescribing Survey (NAPS) did not comply with either eTG Antibiotic or local guidelines.[2] A prospective study of all intravenous antibiotic use in a university-affiliated hospital found that one-third of almost 2000 days of antibiotic therapy was unnecessary.[3]

Using oral rather than parenteral antibiotics

Major advantages of oral over the intravenous route are the absence of cannula-related infections or thrombophlebitis, a lower drug cost, and a reduction in hidden costs such as the need for a health professional and equipment to administer intravenous antibiotics. Oral therapy may potentially enable an early discharge from the hospital[4,5] or directly from the emergency department.[6] For example, a single dose of intravenous antibiotic for paediatric uncomplicated urinary tract infections did not reduce the rate of representation or readmission. This suggests most children with a urinary tract infection can be managed with oral antibiotics alone.[7]

A key consideration is the bioavailability of oral antibiotics. This varies in comparison to intravenous formulations (Tables 1 and 2). Some oral antibiotics have equivalent bioavailability to the intravenous drug. They could be substituted, depending on the condition being treated and the required site of drug penetration.

In a small prospective trial, patients with moderately severe cellulitis were randomised to receive either oral cefalexin monohydrate or parenteral cefazolin. Parenteral administration was changed to oral once the cellulitis had stopped progressing and the patient was afebrile. There was no statistically significant

Table 1 **Intravenous to oral conversion for antibiotics with over 90% bioavailability**

Intravenous antibiotic	Oral antibiotic option	Oral formulations
Lincomycin or clindamycin	Clindamycin	Suspension (poor palatability) and capsules
Fluconazole	Fluconazole	Suspension and capsules
Metronidazole	Metronidazole	Suspension and capsules
Sulfamethoxazole/ trimethoprim	Sulfamethoxazole/ trimethoprim	Suspension and tablets
Doxycline	Doxycline	Tablets and capsules

Table 2 **Intravenous to oral conversion for antibiotics with 50–90% bioavailability**

Intravenous antibiotic	Oral antibiotic option	Oral formulations
Ampicillin or amoxicillin	Amoxicillin	Suspension and capsules
Benzylpenicillin	Amoxicillin	Suspension and capsules
Azithromycin	Azithromycin	Suspension and tablets
Amoxicillin/clavulanate	Amoxicillin/clavulanate	Suspension and tablets
Flucloxacillin	Flucloxacillin	Suspension (poor palatability) and capsules
	OR	
	Cefalexin	Suspension and capsules
Cefazolin	Cefalexin	Suspension and capsules
Ciprofloxacin	Ciprofloxacin	Tablets

difference in outcome between the two groups, however there were only approximately 20 patients in each arm of the trial.[8] Larger studies are required to support this result.

Shorter intravenous courses

Research is investigating whether infections that have traditionally been treated with a prolonged course of intravenous antibiotics can be managed with a shorter course of intravenous therapy. A multicentre randomised controlled trial of intra-abdominal infections, that had adequate control of the source of the infection, studied a composite outcome of surgical-site infection, recurrent intra-abdominal infection or death at 30 days. This outcome was similar in patients who only received 3–5 days of intravenous antibiotic therapy and patients who received longer courses based on cessation after resolution of physiological abnormalities.[9] This suggests that after adequate control of the source of infection the benefits of intravenous antibiotics are limited to the first few days of treatment. However, it is important to note that there were not many patients who were immunocompromised in this study.

Randomised controlled trials have looked at other infections and length of therapy. Short-course therapy may be just as effective as longer courses[10] for:

- community-acquired or ventilator-associated pneumonia
- complicated urinary tract infections
- complicated intra-abdominal infections
- Gram-negative bacteraemia
- acute exacerbations of chronic lung disease
- skin and soft tissue infections.

Switching from intravenous to oral therapy

To develop guidelines, there was a study of switching to oral therapy after 48–72 hours of intravenous therapy. The main bacterial infections studied were respiratory tract infections, urinary tract infections, cholangitis, abdominal abscess and erysipelas. In the six weeks after completing the antibiotic course there was no recurrence of infection or readmissions due to reinfections. It was estimated that switching therapy avoided more than 6000 doses of intravenous antibiotics.[11]

A retrospective study of skin infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) evaluated the treatment of hospitalised patients across 12 European countries. It estimated that more than one-third of the patients could have been changed from intravenous antibiotics to oral therapy earlier than occurred in practice.[12]

In a single tertiary hospital a printed checklist was placed in patients' charts to encourage appropriate switching from intravenous to oral antibiotics at day three of treatment. The conditions predominantly studied were lower respiratory tract infections, urinary tract infections and intra-abdominal infections. Of the patients who were suitable for switching to oral antibiotics 61.4% were switched in response to the checklist. They had no increase in complications.[13]

There has been a systematic review of the evidence for the minimum intravenous and total antibiotic duration in children younger than 18 years with bacterial infections.[14] It compared shorter courses with traditionally longer durations. In many conditions such as respiratory, skin and soft tissue and genitourinary infections long durations of intravenous antibiotics might be unnecessary and the switch from intravenous to oral can occur earlier.

When considering a change to oral therapy it is important to evaluate the clinical situation. This includes the response to treatment, the patient's immune status, comorbidities, allergies and their ability to absorb and tolerate oral drugs. Knowing the causative pathogens and resistance patterns is important or, if available, the patient's microbiological results. Regarding the antibiotic to use consider its:

- spectrum of activity
- bioavailability
- penetration to the site of infection
- potential adverse effects.

Australian guidelines

eTG Antibiotic includes guidance for timely switching from intravenous to oral antibiotics. There has to be clinical improvement, resolving fever and no unexplained haemodynamic instability (see Box).[15]

The Australian paediatric infectious diseases community has collaborated in a systematic review of the evidence for switching from intravenous to oral therapy in 36 childhood infections. The aim of the review was to give clinicians the confidence to change children to oral antibiotics and to send them home earlier. It found that for some infections the switch from intravenous therapy can occur sooner than previously recommended.[14]

Prolonged intravenous therapy

Some conditions, such as bone and joint infections and endocarditis, are managed with prolonged courses of intravenous antibiotics. There is little evidence to guide the duration of intravenous therapy and whether oral antibiotics can be used.

Bone and joint infections

The Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) trial was conducted at multiple centres across the UK.[16] It compared early switching (within one week) from intravenous to oral therapy to continuing intravenous antibiotics for at least six weeks. It included all adults with suspected bone and joint infections, irrespective of surgical intervention or antibiotic choice, who were planned to receive at least six weeks of antibiotic therapy. Comparing the outcomes at one year suggested that appropriately selected oral therapy is non-inferior to intravenous therapy. However, there are several important caveats:

- the trial was not powered to evaluate the outcome between different types of infection
- Gram-negative infections were under-represented
- most patients had surgical management of the infection
- rifampicin was used as a treatment option in approximately one-third of the cohort
- the clinicians managing the patients were specialist-led teams.

Although the events were not necessarily related to the antibiotics, one in four patients experienced a serious adverse event. This shows that ongoing monitoring is still required even with an oral antibiotic regimen.[16,17] Further studies are required to look more closely at the different types of infection and the varying antibiotic regimens. Ideally these trials should be performed in the Australian healthcare system.

Endocarditis

The Partial Oral Treatment of Endocarditis (POET) trial was a study of left-sided endocarditis caused by streptococci, *Enterococcus faecalis*, *Staphylococcus aureus* or coagulase-negative staphylococci. The patients were randomised to either receive intravenous drugs for the full course of therapy, or for a minimum of 10 days followed by oral therapy. Patients were clinically stable before the switch and required transoesophageal echocardiography to confirm the response to treatment. Oral antibiotic regimens were designed to include at least two drugs with different mechanisms of action and were based on pharmacokinetic–pharmacodynamic analyses to enhance synergy and decrease the risk of resistance.[18]

There was no difference in a composite end point of all-cause mortality, unplanned cardiac surgery, embolic events or relapse of bacteraemia from the

Box **Guidance for intravenous to oral switch**

It is often appropriate to switch a patient's therapy from the intravenous to oral route when all of the following apply:*

- clinical improvement
- fever resolved or improving
- no unexplained haemodynamic instability
- tolerating oral intake with no concerns about malabsorption
- a suitable oral antimicrobial with the same or similar spectrum, or an oral formulation of the same drug, is available. For children, a suitable paediatric formulation is available.

* Does not apply to infections that require high tissue concentrations or prolonged intravenous therapy (e.g. meningitis, endocarditis).

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primary pathogen. A subsequent analysis at 3.5 years showed similar results.[18,19]

Important caveats on these results included the heterogeneity in the bacterial pathogens being treated and the antibiotic combinations used and the lack of infections with multiresistant organisms. Few patients had cardiac devices or were injecting drug users. The study was also led by physicians in specialist centres.[20]

Antibiotic resistance

The overuse of antibiotics has contributed to the emergence and dissemination of antimicrobial-resistant nosocomial and community pathogens. Reducing intravenous antibiotic use and shortening the duration of antibiotic courses will contribute to overall less antibiotic use and thus may reduce the development of antibiotic resistance. The appropriate use of oral antibiotics, particularly those with good bioavailability, is also essential to maintain their usefulness.

Conclusion

For many infections oral antibiotics can be as effective as intravenous drugs. Shorter durations of intravenous antibiotic therapy and switching to oral therapy should be important considerations in patient management. They have the potential to improve outcomes for patients by avoiding the adverse effects of intravenous drugs and may facilitate early discharge from hospital. ⋖

Conflict of interest: none declared

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