# Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines

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**Few studies are available to inform duration of intravenous antibiotics for children and when it is safe and appropriate to switch to oral antibiotics. We have systematically reviewed antibiotic duration and timing of intravenous to oral switch for 36 paediatric infectious diseases and developed evidence-graded recommendations on the basis of the review, guidelines, and expert consensus. We searched databases and obtained information from references identified and relevant guidelines. All eligible studies were assessed for quality. 4090 articles were identified and 170 studies were included. Evidence relating antibiotic duration to outcomes in children for some infections was supported by meta-analyses or randomised controlled trials; in other infections data were from retrospective series only. Criteria for intravenous to oral switch commonly included defervescence and clinical improvement with or without improvement in laboratory markers. Evidence suggests that intravenous to oral switch can occur earlier than previously recommended for some infections. We have synthesised recommendations for antibiotic duration and intravenous to oral switch to support clinical decision making and prospective research.**

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## Introduction

Antibiotics are commonly prescribed for children in hospital, but few data are available to inform optimal duration of therapy. In view of the global crisis of antimicrobial resistance, the need for evidence-based recommendations for the optimal duration of intravenous and oral antibiotics, and when to switch from the intravenous to the oral route, is crucial (appendix reference [AR] 1). Shorter antibiotic courses can potentially affect antimicrobial resistance, and have already been advocated for a few infections (AR 2 and 3). So far, there has been no systematic review of the evidence guiding the minimum duration of intravenous antibiotics before switching to oral treatment for infections in children.

We aimed to determine, in children younger than 18 years with bacterial infections, the minimum intravenous and total antibiotic duration required to achieve outcomes similar to or better than those with traditional longer durations administered for specific infections. We then aimed to make evidence-based recommendations for optimal intravenous and total antibiotic duration and criteria for intravenous to oral switch.

## Methods

The Australian and New Zealand Paediatric Infectious Diseases Australasian Stewardship of Antimicrobials in Paediatrics (ANZPID-ASAP) group of the Australasian Society for Infectious Diseases collaborated on this study. Using 2009 PRISMA guidelines (appendix), the group systematically reviewed the literature on intravenous and total duration of antibiotics and the timing of switching from the intravenous to oral route for 36 infections in children younger than 18 years. Evidence-based recommendations synthesised from the review findings, relevant guidelines, and consensus opinion of the group were produced (appendix). There were four review coordinators (BJM, DA, DI, PAB) and 18 review contributors.

### Search strategy and selection criteria

The group searched MEDLINE from 1946 to Nov 21, 2014, and the Cochrane Central Register of Controlled Trials (up to Nov 21, 2014) using a standard overall strategy for all infections, and then separately with specific terms for each infection (appendix). Further information was obtained from secondary references identified from articles, and relevant guidelines. All study types published in peer-reviewed journals and published conference abstracts, except single case reports, were included. Studies were limited to those in human beings and reported in English, but no restrictions on year of publication were applied. Studies included were those of children younger than 18 years diagnosed with a bacterial infection for whom data about intravenous, oral, or total antibiotic duration and outcomes were reported. When data were scarce in children and the infection was likely to be similar in children and adults, relevant adult studies identified from other information sources were also reviewed. Interventions assessed were comparison between different intravenous antibiotic durations, comparison between different oral antibiotic durations, comparison between the use of intravenous and oral antibiotics, intravenous or oral antibiotic durations, and criteria for intravenous to oral switch. Outcome measures sought were clinical improvement or recovery and persistence of infection, complications, and recurrence of infection. No restriction was set on follow-up duration because of the differing natural histories of included infections. This study is registered with PROSPERO, number CRD42014015460.

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See Online for appendix

### Quality assessment and data extraction

The titles and abstracts of all studies resulting from the database search of each bacterial infection were screened and the full texts of all potentially relevant articles were reviewed by two independent investigators (one contributor and one coordinator), with disagreements resolved by discussion or a third coordinator. Risk of bias was assessed (appendix) at study level according to adapted grading of evidence and recommendations by the Australian National Health and Medical Research Council (NHMRC; AR 4). Risk of bias affected data synthesis by attributing weight according to the assessed bias in the study. No specific assessment was made for reporting bias, though it has been identified in our review where deemed possible. Negative studies were included. Data extracted and synthesised were ages of participants, underlying comorbidities (eg, immunocompromised), type of bacterial infection, duration of intravenous antibiotics, duration of oral antibiotics, persistent or recurrent infection, and complications of infection. The only simplification made was that if a systematic review included multiple similar studies with similar outcomes not all of them were independently cited. Data synthesis and recommendations incorporated the level of evidence and weighted the risk of bias accordingly.

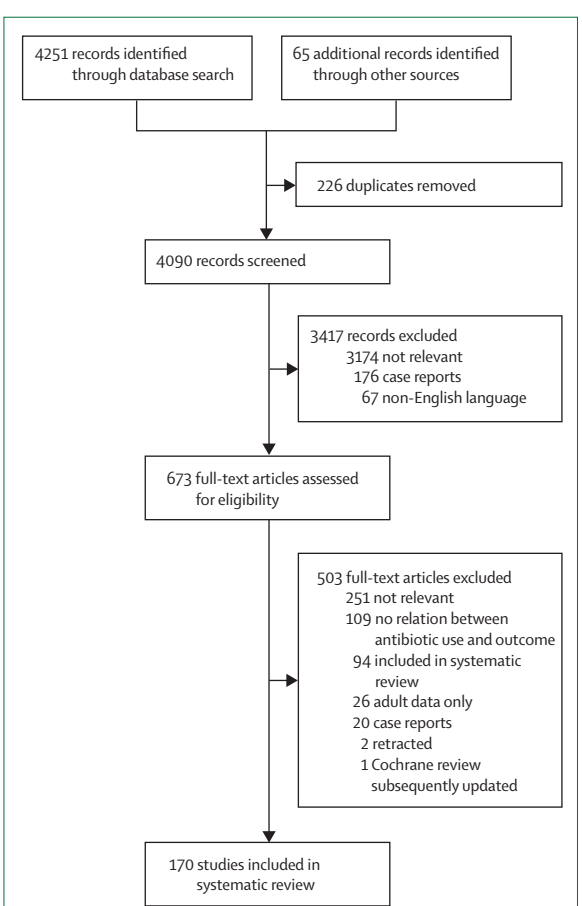


*Figure:* **Study profile**

### Guidelines

Evidence-graded recommendations were made for intravenous and total antibiotic duration and timing of intravenous to oral switch for bacterial infections in children. These guidelines were made on the basis of a synthesis of the literature from the systematic review, relevant current guidelines (AR 5–28), and expert consensus opinion from the ANZPID-ASAP group. In making recommendations, the group applied grading of evidence strength and consistency according to the adapted NHMRC criteria (appendix; AR 4).

### Role of the funding source

No funding was provided for this study.

## Findings

Our search identified 4090 abstracts. 671 potentially relevant articles were assessed for eligibility, of which 170 studies met the inclusion criteria (figure). Most studies were not of high quality, with only 61 (36%) being randomised controlled trials or systematic reviews (appendix). Specific infections were reviewed individually, and for most of them there were no systematic reviews or trials of antibiotic duration or intravenous to oral switch.

### Bacteraemia and endocarditis

Antibiotic duration for meningococcal bacteraemia can depend on coexistent meningococcal meningitis. In two trials of all-cause bacterial meningitis, children with meningococcal meningitis with or without meningococcaemia who were improving were randomised to short (4–5 days) versus long (7–10 days) duration of intravenous antibiotics; no deaths or relapses were recorded in either group.[1,2] In observational studies, 4 days of intravenous antibiotics for meningococcaemia is not associated with excess mortality or relapse.[3,4]

In two systematic reviews including several different study types and a large retrospective study of occult pneumococcal bacteraemia, no differences in serious complications between intravenous and oral antibiotics were recorded.[5–11] However, children who remained febrile at follow-up (median 33 h) were more likely to have developed focal infections or persistent bacteraemia if they were treated with oral antibiotics.[11] Results from another series showed that intravenous antibiotics given for fewer than 2 days and oral antibiotics for 10 days did not result in any complications.[12] For bacteraemia with associated pneumonia, initial intravenous antibiotics led to a lower admission rate than did oral-only antibiotics and improved condition at follow-up.[13]

In a small trial of neonates with *Staphylococcus aureus* bacteraemia, Chowdhary and colleagues[14] showed higher treatment failures with 7 days of intravenous antibiotics than with 14 days. Three retrospective series documented wide variations in median duration of intravenous antibiotics (5–162 days).[15–17] In a study of neonates with meticillin-resistant *S aureus* (MRSA) bacteraemia, the

mean duration of vancomycin treatment for those without any complications was 9·7 days (SD 5·1), although recurrences were greater with fewer than 14 days of antibiotics than with 14 days or longer.[18] Children with MRSA bacteraemia without endocarditis had a median antibiotic duration of 22 days (IQR 12–29), with bacteraemia persisting for a median of 6 days (IQR 2–7), despite effective antibiotics.[19]

Results from a retrospective study of uncomplicated Gram-negative bacteraemia (including *Pseudomonas aeruginosa*) in children showed no difference in mortality or recurrence between short (median 10 days, IQR 10–10) and longer course (14, 14–17) of intravenous antibiotics.[20] In Hakki and colleagues' retrospective study[21] of mostly adults with *P aeruginosa* bacteraemia after stem-cell transplantation, risk of recurrence was increased but not significantly so (p=0·06) when fewer than 14 days of antibiotics was compared with 14 days or more. The only data on antibiotic duration in multiresistant Gram-negative bacteraemia are from a study in critically ill adults: after onset of bacteraemia length of stay in hospital was the same for patients with sensitive (median 27 days, IQR 9–63·5) as with resistant Enterobacteriaceae bacteraemia (35 days, IQR 10–77), suggesting lack of need for long-term antibiotics with Gram-negative resistance (AR 29). Two studies of bacteraemia caused by non-typhoid salmonellae showed no difference in complications or recurrence between less than 7 days of antibiotics and 7 days or more.[22,23]

Outcomes in retrospective studies[24–26] of central venous catheter (CVC) infection with *S aureus* or Gram-negative organisms in children and adults vary: salvage can be successful if bacteraemia clears rapidly (AR 30 and 31). In two studies of CVC-associated *S aureus* bacteraemia in children, median intravenous antibiotic duration was 10 days[24] and 14 days,[26] with duration, CVC removal, and recurrence being unrelated. In adults, longer durations decrease complications.[16,27,28] After line removal for CVC infections with coagulase-negative staphylococci and *Bacillus* species, short intravenous courses (3–5 days and 5–7 days, respectively) are non-inferior than longer courses.[29–31] Results from small series in immunocompetent and immunocompromised children showed that CVC-associated bacteraemia resolved with 7–21 days of intravenous antibiotics, but no studies have compared antibiotic durations with line removal or retention.[32–36] A few studies of anti-infective locks have yielded mixed results, and larger studies are awaited.

No trials in childhood infective endocarditis exist, so practice is usually extrapolated from adult data. Results from retrospective studies in children show that antibiotic durations are unrelated to complications or recurrence (all-cause 4–6 weeks,[37,38] *S aureus* 2–6 weeks of intravenous with long-term oral use,[39] *Streptococcus pneumoniae* 4–8 weeks of intravenous use).[40] Guidelines for treatment of viridans streptococci rely on adult data, which show that shorter durations (2–4 weeks) are effective for susceptible isolates (AR 32–35). Oral antibiotics alone were used in six patients for a median of 6 weeks with no recurrences in one small study published in 1977.[41]

### CNS infections

In a systematic review of bacterial meningitis in children no difference in outcomes between 4–7 days and 7–14 days of antibiotics was recorded,[2,42–46] and results from observational studies show low failure rates with 4–7 days.[47,48] However, potential selection bias could reduce the applicability of the results. A large trial in resource-poor countries found similar outcomes with 5 or 10 days of ceftriaxone,[1] although the study lacked power to assess individual organisms. Failures have occurred after treatment for up to 14 days for *Listeria monocytogenes* meningitis,[49] and 21 days of treatment is recommended for Gram-negative meningitis (AR 36). Intraventricular antibiotics increase mortality so are not recommended (AR 37 and 38).

In a large retrospective study of childhood brain abscess, there was no difference in morbidity or mortality between patients who received less than 6 weeks, 6 weeks, or more than 6 weeks of antibiotics, and no difference in outcome by amount of intravenous versus oral antibiotics in patients who received 6 weeks of antibiotics in total.[50] In an observational study, children with positive cultures and clinical improvement received 2 weeks of intravenous antibiotics followed by 4 weeks of oral antibiotics with no increase in recurrence.[51] Studies mostly in adults have assessed intravenous durations of 1–2 weeks, with intravenous to oral switch based on clinical improvement and normalisation of C-reactive protein and found no recurrences (AR 39 and 40).[52]

Results of studies of ventriculoperitoneal shunt infection in children show that, irrespective of antibiotic duration, the highest chance of cure is with shunt removal.[53,54] For simple shunt infection the mean effective intravenous antibiotic duration was 9·7 days (SD 1·7) and with intraventricular antibiotics 6 days (SD 1·7) to 8 days (range 3–17).[55,56] For complicated shunt infection (eg, multicompartment hydrocephalus), 3 weeks of intravenous and 2 weeks of intraventricular antibiotics were effective.[57] In three studies, shunt reinfection was not associated with duration of antibiotics.[58–60] In one study with shunt retention, if there was no blockage or infection with *S aureus*, intravenous or intraventricular antibiotics for 14 days resulted in no recurrence by 6 months.[61]

### Respiratory infections

In pharyngitis and otitis media, either antibiotics are not needed or oral antibiotics are prescribed, so they are not included in this Review.

In a small trial in children and adults with drained peritonsillar abscess, a comparison of intravenous and oral antibiotics showed no difference in complications or recovery time.[62] In two studies of drainage and initial intravenous antibiotics the median length of stay was

2–3 days as a proxy for intravenous antibiotic duration, although no information about postdischarge antibiotics was given.[63,64] In adults, drainage followed by single-dose intravenous and 7 days of oral antibiotics is effective[65] (AR 41), although resolution can occur with drainage alone or antibiotics alone.[63,66]

In four retrospective series of children with drained retropharyngeal abscess the average intravenous duration was 3–6 days and oral duration 7–10 days, with no clinically significant complications.[67–70] 51 (75%) children in one study were managed with antibiotics alone.[68] Clinical symptoms such as return of neck mobility and toleration of oral fluids and diet were indications for intravenous to oral switch.[69,70] Oral durations varied from 7–9 days on the basis of symptom improvement to 3–6 weeks on the basis of CT resolution with no major complications with either duration, suggesting that 7–9 days is sufficient.[69,70]

Three retrospective and one prospective series with low complication, low recurrence rates, or both found average durations of treatment with intravenous antibiotics of 4·5–7 days for uncomplicated mastoiditis and 7·8–11 days for mastoiditis with mastoidectomy,[71–74] followed by an average of 7–9 days of oral antibiotics.[71,73] C-reactive protein and erythrocyte sedimentation rate (ESR) did not predict length of stay or oral antibiotic duration in one study in which patients without intracranial complications received 7–10 days of oral antibiotics after discharge and at least 15 days if there were intracranial complications.[75] No difference in rate of readmission to hospital between intravenous and oral outpatient treatment after mastoidectomy was found.[76]

Of four trials of acute sinusitis comparing 10–14 days of antibiotics with placebo, two favoured treatment and two found no difference in outcomes.[77–80] Results from two systematic reviews suggested that children with severe illness (fever >39°C, 3 days of purulent nasal discharge, headache, facial pain) can benefit from antibiotics[81] and that those with non-severe illness are likely to improve after 7 days with or without antibiotics.[82] Authors of a Cochrane review[83] and a systematic review[84] calculated that eight children needed to be treated with antibiotics to achieve one additional cure, and results from the systematic review showed that the efficacy of antibiotics was not established. A trial compared 3 with 5 days of azithromycin, and showed similar clinical resolution.[85] No difference in outcomes was found in a systematic review in adults comparing short (3–7 days) with longer durations of antibiotics (AR 42).

Only retrospective, hospital-based case series of acute cervical lymphadenitis have been published and most start intravenous antibiotics, but they probably represent a minority of cases.[86–88] Durations vary widely for intravenous use from 2 to 22 days and 7 to 10 days for oral use; longer durations were often associated with surgical drainage.[86–90] Recurrence rates in all studies were low.

A Cochrane review of children aged 2–59 months with non-severe pneumonia found no difference in outcomes for 3 versus 5 days of antibiotics.[91] Four additional trials in children aged up to 12–16 years found no difference between 3–5 days of antibiotics and longer durations.[85,92–94] In comparisons of intravenous with oral antibiotics for moderately severe pneumonia, three trials and a Cochrane review showed similar resolution of fever and oxygen requirement.[95–98] However, severe pneumonia (oxygen saturation <85%, shock requiring intravenous fluid bolus) or complicated disease (immunocompromised, chronic lung or heart disease, pleural effusion at diagnosis) were excluded. In their systematic review in children younger than 5 years in resource-poor settings, Lassi and colleagues[99] concluded that 3 days of oral antibiotics was sufficient for non-severe pneumonia.

A systematic review of all aspects of ventilator-associated pneumonia in children yielded no paediatric data for antibiotic duration, so on the basis of adult data the recommendation was to stop antibiotics after 3 days if cultures were negative or after 8 days with clinical or biomarker improvement (AR 43). All other studies are in adults: results from systematic reviews, trials, and a prospective study comparing short course (7–8 days) with longer course (10–15 days) antibiotics showed no difference in mortality (AR 44–49). In one study a higher recurrence rate of ventilator-associated pneumonia was recorded with 8 days of antibiotics than with 15 days if sputum culture yielded non-fermentative Gram-negative bacilli (eg, *Pseudomonas* spp, *Acinetobacter* spp), but this recurrence did not lead to higher mortality (AR 44). Declining inflammatory markers including C-reactive protein (AR 50) and procalcitonin (AR 51) are associated with better outcomes, but have not been used to guide intravenous to oral switch. A Cochrane review of short-course versus long-course antibiotics for hospital-acquired pneumonia in critically ill adults found no increase in mortality when procalcitonin was used to guide antibiotic cessation (AR 52).

No studies of antibiotic duration for pleural empyema in children exist. A systematic review of operative versus non-operative management found mean antibiotic durations of 12·8 days (SD 3·8) and 21·3 days (SD 7·9), respectively, although whether the route was intravenous or oral was not specified.[100] In another systematic review, length of stay in hospital (as a proxy for intravenous antibiotic duration) was similar with an average of 6 days for both groups.[101] In studies comparing different antibiotics but with the same duration, 14 days or more of intravenous antibiotics were used with relapse being uncommon.[102,103] In a retrospective series of *S pneumoniae* empyema, there was no difference in intravenous antibiotic duration and outcomes between penicillin-sensitive and penicillin-resistant strains, suggesting that longer durations for resistant bacteria are unnecessary.[104]

Few studies of lung abscess in children have been done. A comparison of antibiotics alone (with or without percutaneous drainage) with surgical drainage found a mean of 18 days of intravenous antibiotics in the medical

(antibiotic only) group compared with 26 days in the surgical group with similar mean oral durations (13–17 days), which were unrelated to clinical or radiological improvement or mortality.[105] Three other retrospective series found a mean total antibiotic duration ranging from 24 to 40 days.[106–108] Two trials in adults stipulated a minimum of 6 days of intravenous antibiotics, but did not relate duration to clinical improvement (AR 53 and 54).

### Musculoskeletal infections

In two systematic reviews, short course intravenous antibiotics (<7 days[109] and 3–4 days[110]) for uncomplicated acute osteomyelitis had similar cure rates to longer courses, with one of them[110] suggesting that a total of 3 weeks was sufficient.[109–112] In a large trial, after a median of 4 days of intravenous treatment, no difference in cure between 16 and 26 days of oral antibiotics was seen.[113] Some studies base intravenous to oral switch on clinical response and others include C-reactive protein.[113] Data are lacking for complicated acute osteomyelitis, but experts suggest longer-term intravenous duration. Although not powered to find a difference, an analysis of bacteraemic bone and joint infection in children showed no difference in mean intravenous antibiotic duration (4 days) or outcomes between patients with and without bacteraemia.[114]

The inadequate evidence available for subacute and chronic osteomyelitis in children was highlighted in a systematic review of 14 small observational studies; the conclusion was that long courses of antibiotics are no more effective than shorter courses, and that 2 days of intravenous plus 6 weeks of oral antibiotics will suffice.[115] A Cochrane review in adults found no difference between intravenous and oral antibiotics (AR 55). In a retrospective study, adolescents whose prosthetic spinal rod was removed because of chronic infection received 2–3 days of intravenous and 10 days of oral antibiotics with no recurrence.[116] There are no studies of antibiotic duration when prosthetic material remains.

Although the conclusion from a systematic review of acute septic arthritis in children was that the ideal antibiotic duration was not defined,[117] results from subsequent small trials and observational data showed that administration of 7 days or more of intravenous antibiotics followed by 3–4 weeks of oral antibiotics is effective and safe.[112,118–123] In a definitive large trial, children with culture-positive septic arthritis were randomised after 2–4 days of intravenous antibiotics to complete a total of either 10 or 30 days of oral antibiotics, and there were no differences in treatment success.[124] As with osteomyelitis, concurrent bacteraemia can be treatable with shorter duration intravenous antibiotics.[114]

For pyomyositis in children, in two retrospective series the mean duration of intravenous antibiotics was 11–13 days and of oral antibiotics 20–30 days,[125,126] whereas two other series described 4–7 days of intravenous antibiotics with a mean total of 2–6 weeks, all with low complication rates.[127,128] Intravenous to oral switch was based on clinical improvement and reduced inflammatory markers.[126–128] When surgery is required, intravenous antibiotics are usually continued until postoperatively.[126]

### Skin and soft tissue infections

The conclusion from a Cochrane review of adults and adolescents with cellulitis was that extended intravenous antibiotics were unnecessary.[129] In prospective studies of children with moderate or severe uncomplicated cellulitis (rapidly spreading erythema, tenderness, lymphangitis, systemic symptoms) initially treated with intravenous antibiotics, most have recorded successful switch to oral antibiotics after 2–3 days of intravenous antibiotics.[130,131] In retrospective studies, a median of 2 days of intravenous followed by 7 days of oral antibiotics did not result in complications.[132,133]

A prospective study including children with preseptal cellulitis found a median intravenous duration of 2 days (IQR 2–3) and oral 7 days (5–7) with no complications or recurrence.[131] Intravenous to oral switch was based on reduced swelling and erythema. Retrospective series have reported success without complications with 2–3 days of intravenous and 7–8 days of oral antibiotics.[132,134–137]

In two retrospective series of children with orbital cellulitis, a mean of 9·3 days (SD 3·6) of intravenous antibiotics (total 21·0 days, SD 3·0 days)[138] and median of 4 days (range 2–8) of intravenous antibiotics[139] were given with no long-term complications. One small study compared orally bioavailable antibiotics with historical intravenous cases, and although antibiotic durations were not reported no difference in mean length of stay or complications was noted.[140]

A study of MRSA skin abscesses of less than 5 cm diameter found no benefit from antibiotics for drained abscesses.[141] A larger trial in children of skin abscesses of all sizes and causal organisms compared 10 days of oral co-trimoxazole with placebo after incision and drainage.[142] There was no difference in failure rate, and a difference in new lesion formation at 10 days had disappeared by 3 months; treatment failure did not correlate with abscess size.

Results from a trial of systemic antibiotics versus placebo in superficial surgical site infection with local wound treatment showed that antibiotics increased bacterial clearance without clinical benefit.[143] The conclusion from a systematic review of adults with deep surgical site infection after spinal instrumentation was that spinal rod removal could shorten intravenous and oral antibiotic duration.[144] In children, small case series suggest that for removed prostheses 1–2 weeks of intravenous and 6 weeks of oral antibiotics are sufficient,[145,146] whereas for retained prostheses 4–6 weeks of intravenous and several months of oral antibiotics might be necessary.[147,148] In one study, normalisation of C-reactive protein and ESR was used to guide intravenous to oral switch.[147] Postsurgical mediastinitis is a specific deep surgical site infection for

which common durations of 4–6 weeks of intravenous antibiotics are extrapolated from scanty adult data (AR 56). In a retrospective study in children and neonates with postsurgical mediastinitis, the median duration of intravenous antibiotics was 11 days (range 7–28), with no recurrences or deaths.[149] Whether oral antibiotics were used after intravenous administration is unclear.

### Abdominopelvic infections

According to a Cochrane review of all ages after appendicectomy, prophylactic intravenous antibiotics were superior to placebo for prevention of wound infection and intra-abdominal abscess.[150] For paediatric studies the difference was no longer statistically significant but favoured single-dose preoperative antibiotics.[151] Studies of antibiotics versus surgery in children with appendicitis are too small to apply a recommendation (AR 57).

Results of a systematic review of complicated appendicitis in children showed that limiting total antibiotic duration to 3 days was not associated with higher complication rates.[152] In three trials and a retrospective review no difference in clinical improvement or complications were seen when shorter intravenous and total antibiotic durations were compared with longer durations, the shortest regimen being a mean of 3·4 days [SD 1·7] intravenous and no oral antibiotics.[153–156] No definitive criteria are available for stopping or switching intravenous antibiotics, but children[157] and adults (AR 58) with intra-abdominal sepsis have low complication rates if intravenous antibiotics are stopped when patients are afebrile and tolerating diet.

No outcome studies of antibiotic duration in acute cholangitis in children exist. In a study that included several children, failure to respond early to intravenous antibiotics was associated with mortality (AR 59). The only study that included children exclusively assessed clinical outcomes in acute cholangitis after the Kasai procedure (biliary bypass surgery for biliary atresia) according to institutional protocol: all antibiotics were administered intravenously for at least 2 weeks. After 1 week, 30 (75%) of the children had improved and no child needed more than 3 weeks of antibiotic treatment.[158]

There are no studies in children of either prophylaxis of infection in acute necrotising pancreatitis or treatment of established infection of pancreatic necrosis. A Cochrane review (AR 60), a systematic review (AR 61), and a trial (AR 62), all in adults only, found that antibiotics did not reduce mortality or pancreatic infection. Conversely one systematic review of antibiotics started within 72 h of symptoms showed reduced mortality compared with placebo (AR 63). However, since pancreatitis in adults is different from that in children, paediatric practice relies on expert experience and the use of prophylactic antibiotics is rare. Although antibiotic use is less controversial in established pancreatic

| | Minimum intravenous antibiotic duration (level of evidence*) | Criteria for switch to oral antibiotic | Minimum total antibiotic duration (level of evidence*) | Comments |
|---|---|---|---|---|
| **Bacteraemia and endocarditis** | | | | |
| Meningococcal bacteraemia | 4–5 days (C-III) | No oral switch | 4–5 days (C-III) | Duration applicable for uncomplicated bacteraemia |
| Pneumococcal bacteraemia | Occult afebrile at 24 h: 0 days (B-I);<br>occult febrile at 24 h: 1 day (C-IV);<br>non-occult/septic: 7–10 days (D-IV) | Oral only;<br>afebrile, rapid improvement;<br>no oral switch | 7–10 days;<br>7–10 days;<br>7–10 days | Occult: usually febrile, but not septic and no major focus. If ongoing fever repeat blood culture, consider other focal investigations (eg, lumbar puncture, chest imaging [C-IV]);<br>Non-occult: if associated pneumonia, initial intravenous until improvement then total 7–10 days (C-IV) |
| *Staphylococcus aureus* bacteraemia | 7–14 days (D-IV) | No oral switch | MSSA: 7–14 days (D-IV),<br>MRSA: 14 days (D-IV), longer if persistent positive cultures or complications (D-expert opinion) | If associated with endocarditis, refer to endocarditis guideline, if associated with osteomyelitis or septic arthritis, intravenous duration can be shortened to 4–7 days if condition is improving quickly and is uncomplicated, with remainder oral (C-III) |
| Gram-negative bacteraemia | 10 days (C-III) | No oral switch | 10 days (C-III)<br>specific bacteria:<br>pseudomonas in HSCT: 14 days (D-IV)<br>non-typhoidal salmonellae: 7 days (D-IV) | If multiresistant, duration is from first negative culture; if associated with UTI, intravenous duration may be shortened to 5–7 days if uncomplicated and improving quickly (D-IV), with remainder oral (D-expert opinion) |
| CVC-associated bacteraemia | 7 days (B-III)<br>CoNS in neonates, line removed, cultures cleared: 3–7 days (C-IV) | No oral switch | Additional duration dependent on the bacteria cultured (refer to relevant guideline) | CVC removal if blood cultures positive after 72 h of appropriate antibiotics (B-III); no bacteria absolutely necessitate CVC removal, but *Pseudomonas aeruginosa* and *Staphylococcus aureus* have been harder to clear in some studies |
| Bacterial endocarditis | 4–6 weeks depending on organism and antibiotic choice (C-III), except sensitive viridans streptococci | No oral switch | Viridans streptococci (D-IV)<br>MIC ≤0·12 mg/L: 2 weeks or 4 weeks<br>MIC >0·12–2 mg/L: 4–6 weeks<br>MIC >4 mg/L: 4–6 weeks<br>*S aureus* (D-IV)<br>MSSA uncomplicated: 4 weeks<br>MSSA complicated or MRSA: 6 weeks | For MIC ≤0·12 mg/L, 2 weeks if benzylpenicillin (or ceftriaxone) + gentamicin, 4 weeks if benzylpenicillin (or ceftriaxone) alone |

(Table continues on next page)

| | Minimum intravenous antibiotic duration (level of evidence*) | Criteria for switch to oral antibiotic | Minimum total antibiotic duration (level of evidence*) | Comments |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| **Central nervous system infections** | | | | |
| Bacterial meningitis | 7–21 days depending on organism (D-IV) | No oral switch (D-IV) | *Neisseria meningitidis*: 5–7 days (B-II)<br>*Haemophilus influenzae*: 7–10 days (C-II)<br>*Streptococcus pneumoniae*: 10–14 days (C-II)<br>Group B streptococci: 14–21 days (D-IV)<br>Gram-negative bacilli: 21 days (D-IV)<br>*Listeria monocytogenes*: 21 days (D-IV) | Nil |
| Brain abscess and subdural empyema | 2–4 weeks (B-III) | Clinical improvement (afebrile, normal conscious level), CRP normal (C-III) | 6 weeks (C-III) | Pus drainage where possible (B-III), ideally before antibiotics. Antibiotic duration is likely to be longer when drainage cannot occur (D-expert opinion); decision to switch to oral includes antibiotic CNS penetration and adherence |
| Ventriculoperitoneal shunt infection | Uncomplicated: 10 days (C-III); complicated: 21 days (C-III) | No oral switch; no oral switch | Uncomplicated: 10 days intravenous (with or without intraventricular antibiotics); Complicated: 21 days intravenous (with or without intraventricular antibiotics); might need longer, aiming for 7 days post CSF clearance (D-expert opinion) | Shunt removal (B-III), with alternative CSF drainage; if conservative treatment in CoNS infection, shunt should be removed if CSF not sterilised (D-expert opinion); Complicated: multi-compartmental hydrocephalus, ventriculitis, multiple organisms, severe peritonitis, or remaining prosthetic material. Intraventricular antibiotics (particularly aminoglycosides) should be avoided in neonates (A-I) |
| **Respiratory infections** | | | | |
| Peritonsillar abscess (quinsy) | 1–2 days following successful drainage (C-IV) | As soon as tolerated | 10 days (A-I) | Nil |
| Retropharyngeal abscess | 3–5 days for conservative or surgical management (D-IV) | Afebrile, neck mobility, tolerating oral diet (D-IV) | 10–14 days (D-expert opinion) | Even if abscess is drained, intravenous antibiotics needed for surrounding tissue involvement |
| Mastoiditis | 5 days (D-IV) | Clinical improvement | 12–15 days based on clinical progress (D-expert opinion) | Longer courses might be required for intracranial complications; refer to brain abscess guideline |
| Acute bacterial sinusitis | 0 days (C-I)<br>Systemically unwell or high risk of suppuration: 1–2 days (D-expert opinion) | Clinical improvement | Moderate or severe: 7 days after improvement in symptoms (C-I); usually 10–14 days (D-expert opinion) | Nil |
| Acute cervical lymphadenitis | 0 days (D-expert opinion)<br>Systemically unwell or rapid progression: 2–3 days (D-IV) | Clinical improvement including reduction in fever, pain, and size | 5–7 days (D-expert opinion) | May be longer if slow progression or abscess formation (D-IV) |
| Community-acquired pneumonia | 0 days (A-I)<br>Severe or complicated: initial intravenous treatment (D-expert opinion) | Clinical improvement | Mild: 3 days (A-I)<br>Moderate or severe uncomplicated: ≤7 days of antibiotics (B-I) | Oral antibiotics can be used in most children including children requiring hospital admission (A-I); if associated with bacteraemia refer to the relevant guideline<br>Severe or complicated: $O_2$ sats <85%, shock receiving intravenous bolus, immunocompromised, chronic lung or heart disease |
| Ventilator-associated pneumonia | Initial treatment (D-expert opinion) | No bacteraemia, clinical improvement, toleration of oral drugs | Good clinical response: 7 days (B-II)<br>Non-fermentative Gram-negative bacilli in sputum: 10 days (D-expert opinion) (eg, *Pseudomonas* spp, *Acinetobacter* spp) | Although there is no minimum intravenous duration most patients will start intravenous antibiotics because they are ventilated; if associated with bacteraemia refer to the relevant guideline |
| Pleural empyema | Initial treatment (D-expert opinion) | Afebrile for 1–2 days, chest drain removed | 7 days (D-expert opinion) | Patients can remain febrile for several days on adequate treatment; antibiotic duration might need to be much longer (up to 6 weeks) dependent on disease severity |
| Lung abscess | Initial treatment (D-expert opinion) | Afebrile, clinical improvement | 4–6 weeks (D-expert opinion) | Abscess >6 cm: continue until resolved or cavity small and stable size (D-expert opinion) |
| **Musculoskeletal infections** | | | | |
| Acute osteomyelitis | Uncomplicated: 3–4 days (A-I) | Afebrile, clinical improvement, CRP or ESR decreasing (A-II) | 3–4 weeks (A-II)<br>Complicated (delayed presentation, associated wound or abscess): longer duration intravenous administration is likely to be required (D-expert opinion) | If associated with bacteraemia, initial intravenous but may be shortened to 4–7 days if improving quickly and uncomplicated, with remainder oral for total duration as for non-bacteraemic infection (C-III) |
| Subacute or chronic osteomyelitis | Clinically well and no prosthetic material: 0 days (D-expert opinion);<br>prosthetic material: initial treatment (D-expert opinion) | As soon as tolerated; clinical improvement (D-expert opinion) | No evidence to support a minimum total duration;<br>no evidence to support a minimum total duration | If prosthetic material is present, biofilm active antibiotics for a long duration are likely to be necessary (D-expert opinion); cure might not be possible without removal of prosthetic material |

(Table continues on next page)

| | Minimum intravenous antibiotic duration (level of evidence*) | Criteria for switch to oral antibiotic | Minimum total antibiotic duration (level of evidence*) | Comments |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Septic arthritis | 2–4 days (A-II) | Afebrile, clinical improvement, CRP or ESR decreasing (A-II) | 2–3 weeks (A-II)<br>Complicated (delayed presentation, associated wound or abscess): longer duration intravenous route is likely to be required (D-expert opinion) | If associated with bacteraemia, initial intravenous route but may be shortened to 4–7 days if improving quickly and uncomplicated, with remainder oral route for total duration as for non-bacteraemic infection (C-III) |
| Pyomyositis | 2–5 days (C-IV) | Clinical improvement | 2–3 weeks (C-IV) | Pus should be drained (C-IV) |
| **Skin and soft tissue infections** | | | | |
| Cellulitis | Mild: 0 days;<br>moderate or severe: 1–3 days (C-IV) | Clinical improvement: reduction in fever and erythema | 5–7 days (C-IV) | If associated with deep infection or osteomyelitis, refer to relevant guideline;<br>moderate or severe: rapidly spreading erythema, tenderness, lymphangitis, systemic features |
| Preseptal (periorbital) cellulitis | 2–3 days (C-IV) | Clinical improvement: reduction in fever and erythema | 7–10 days (C-IV) | Nil |
| Orbital cellulitis | 3–4 days (C-IV) | Clinical resolution of fever, erythema, and pain | 7–10 days (C-IV) | Intraorbital abscesses should be drained, with non-operative management in selected patients (C-IV); if symptoms persist intravenous antibiotics should continue while investigating for complications (D-expert opinion) |
| Skin abscesses and boils | If effectively drained: 0 days (B-II) | As soon as tolerated | 0 days (B-II) | If associated with cellulitis, refer to relevant guideline. Treatment recommendations unaffected by abscess size |
| Superficial surgical site infection | 0 days (B-II) | As soon as tolerated | If started, 5–7 days (D-expert opinion) | Local wound management and delay starting antibiotics, especially if symptoms occur within 48 h of surgery (B-II) |
| Deep surgical site infection | No prosthetic material: initial treatment (B-III);<br>prosthetic material: 4–6 weeks (D-expert opinion) | No oral switch if short duration;<br>clinical improvement | No minimum recommendation, duration dependent on clinical improvement;<br>if prosthetic material present, very long-term antibiotics might be necessary (D-expert opinion) | Wound should be surgically debrided (B-III). Mediastinitis might be treatable with shorter than 4–6 weeks' antibiotics, but there is insufficient evidence for this recommendation; prosthetic material should be removed if possible |
| **Abdominopelvic infections** | | | | |
| Appendicitis: uncomplicated | Single preoperative dose (A-I) | No oral switch | Single preoperative dose only (A-I) | Surgical prophylaxis; non-operative antibiotic management has been used but studies are too small to recommend this approach |
| Appendicitis: complicated, intra-abdominal infection | Initial treatment (B-III) | Clinical improvement, normal bowel function (B-III) | 3–7 days (B-III); stop when signs of infection have resolved (B-III) | Complicated: perforation, peritonitis, pus in peritoneum. Antibiotics do not need to be changed on the basis of culture results if improving (B-III) |
| Acute cholangitis | Initial treatment (C-III) | No recommendation | No minimum duration, depends on clinical improvement (D-expert opinion) | If there is accompanying bacteraemia refer to the relevant guideline |
| Pancreatitis | Prevention of infection: 0 days (C-I);<br>treatment of infection: initial treatment (D-IV) | Not applicable;<br>no recommendation | 0 days (C-I);<br>no minimum duration, dependent on clinical improvement (D-expert opinion) | The only evidence for antibiotic use for pancreatitis in children is for treatment of established infection. If complications of bacteraemia or pneumonia occur refer to the relevant guideline; .. |
| Necrotising enterocolitis | 7-10 days (C-IV) | No oral switch | 7–10 days (D-expert opinion) with further duration if lack of clinical improvement | Antibiotics can be discontinued after 2–3 days if necrotising enterocolitis is thought unlikely (D-expert opinion) |
| **Genitourinary infections** | | | | |
| Lower UTI | 0 days<br>Age <3 months: initial treatment | Clinical improvement | 3–4 days (A-I) | If associated with bacteraemia, refer to bacteraemia guideline |
| Pyelonephritis | 0 days (A-I)<br>Age <3 months or not tolerating orals: initial treatment | Clinical improvement, or as soon as tolerating orals | 10 days (A-I)<br>In a child who rapidly improves 7 days may be sufficient (D-expert opinion) | If associated with bacteraemia, refer to bacteraemia guideline |
| Epididymitis | 0 days | Clinical improvement | Negative urinalysis: no antibiotic (C-III)<br>Positive urinalysis: oral antibiotic (B-III) for 2 weeks (D-expert opinion) | Nil |

MSSA=meticillin-sensitive *S aureus*. MRSA=meticillin-resistant *S aureus*. UTI=urinary tract infection. HSCT=haemopoietic stem-cell transplantation. CVC=central venous catheter. MIC=minimum inhibitory concentration. CoNS=coagulase-negative staphylococci. CRP=C-reactive protein. CSF=cerebrospinal fluid. *Grading of evidence is shown in appendix.

***Table:*** **Recommendations for minimum intravenous and total duration of antibiotics and timing of intravenous to oral switch**

infection, no studies in adults or children have addressed duration of antibiotics in this condition.

A Cochrane review of antibiotics for necrotising enterocolitis identified only two studies that assessed antibiotic choice but not duration (AR 64). However, one study specified 10–14 days of intravenous antibiotics in each arm,[159] and a retrospective study compared two different intravenous regimens administered for 7–10 days,[160] both of which had low complication rates. Oral antibiotics are not recommended.

### Genitourinary infection

In a Cochrane review of childhood lower urinary tract infection no difference in persistent bacteriuria or recurrence was noted between 2–4 days and 7–14 days of oral antibiotics.[161] Results from a subsequent Cochrane review showed that single-dose antibiotic was associated with more persistent bacteriuria than was 10 days of antibiotics, although no difference in symptom duration or recurrence occurred.[162] A large retrospective study of infants younger than 6 months found no difference in treatment failure between intravenous antibiotics for 3 days or less and 4 days or more.[163]

A Cochrane review and trial of acute pyelonephritis in children treated with 10–14 days of antibiotics, found no difference in duration of fever or renal damage between all intravenous antibiotics, 3 days of intravenous followed by oral antibiotics, or all oral administration.[164,165] Similarly, a Cochrane review in all ages with pyelonephritis found no difference between different routes of administration.[166] Some data on antibiotic duration for urinary tract infection with Gram-negative bacteraemia suggest that shorter intravenous durations than recommended for bacteraemia alone (ie, 10 days) could be sufficient (eg, a mean of 6 days with varying subsequent oral durations; AR 65).[167,168] In a trial comparing 3 days of intravenous antibiotics with no intravenous administration, followed by 14 days of oral antibiotics for febrile urinary tract infection, there was no difference in recurrence rate between groups, even with bacteraemia.[168] However, only 13 of 306 patients had bacteraemia, so numbers are too small to recommend a minimum duration this short. In the largest retrospective multicentre study of infants with bacteraemic urinary tract infection, no relapses occurred with a mean intravenous antibiotic duration of 7·8 days (SD 4·0), with the lowest mean duration at any institution of 5·5 days (SD 3·0), suggesting that shorter courses could be appropriate in healthy infants who have recovered.[169]

There are no studies of antibiotic duration in epididymitis, but the question of whether antibiotics are needed at all has been addressed. In prepubescent boys, antibiotics are usually recommended for epididymitis associated with abnormal urine (AR 11). Two retrospective studies of urinalysis in epididymitis found low rates of abnormal urine (1–7%), although in one of them 128 boys (91%) received antibiotics (AR 66 and 67). In a prospective study, 36 (84%) of 43 boys without pyuria received no antibiotics, while the five (10%) with pyuria received antibiotics, although duration was not stated.[170] At a mean follow-up of 3 months, there were no complications in the group that did not receive antibiotics.

## Discussion

We have reviewed the evidence for minimum intravenous and total antibiotic duration in children younger than 18 years with bacterial infections, comparing shorter courses with traditionally longer durations. In many infections, especially when clinical improvement is rapid, emerging data suggest that traditional long durations of intravenous antibiotics might be unnecessary and that intravenous to oral switch can occur earlier. In most of the other infections evidence for routine longer courses is sparse. The frequent use of traditionally longer courses indicates the paucity of evidence and lack of consensus guidelines and, in the face of this gap, natural clinical instincts to take a conservative approach with patient care. However, longer durations of antibiotics are associated with increased antimicrobial resistance, so the cost must be weighed against the potential benefits, especially if these benefits are unproven.

We have therefore derived evidence-based recommendations for minimum intravenous and total antibiotic duration for all bacterial infections reviewed, and graded the recommendation according to the quality of the evidence (table). We have also taken into account information from available guidelines (AR 5–28). Although the evidence is generalisable for most patients, recommendations should be used as a framework to tailor treatment individually in the context of each patient's condition, including underlying immunodeficiency, infection severity, and rate of

***Panel:* General principles guiding intravenous to oral switch of antibiotics**

**Clinical condition**

- Clinically stable without signs of severe sepsis (fever alone need not prevent switch)

**Ability to absorb oral antibiotics**

- Able to tolerate oral medication (not vomiting or nil by mouth)
- No impairment to absorption (eg, mucositis)
- Older than 28 days (<28 days not an absolute contraindication, but absorption variable)

**Availability of an appropriate oral antibiotic**

- Antibiotic treats the identified or expected organism
- Antibiotic available in appropriate or palatable paediatric formulation
- Antibiotic has sufficient penetration of affected tissues

**Practical issues**

- Adherence to oral antibiotics
- The family agrees with the plan

recovery. For example, immunocompromised patients might need longer total durations for some infections because of diminished immune defences to combat infection.

In addition to recommendations for specific infection, review of the contributing articles has highlighted general principles that should be considered when deciding whether the switch from intravenous to oral antibiotics is suitable, including clinical condition, ability to absorb oral antibiotics, and availability of an appropriate oral choice for children (panel).

In an era of increasing antimicrobial resistance, strategies to reduce antibiotic overuse are crucial. Optimising the duration of intravenous and oral antibiotics aims to provide the shortest safe duration of antibiotics to treat infection. By reviewing the available evidence systematically, we have synthesised recommendations in the context of available guidelines for antibiotic duration and criteria for intravenous to oral switch. These recommendations can be used to support clinical decision making and, where data are scarce, as a basis for prospective research on optimal antibiotic durations.

#### Contributors

BJM coordinated contributors to review one or more infections, completed one or more topics as described for all other authors, collated the search and review data in PRISMA format from all contributors, independently verified the searches and reviews, substantially edited the reviews and recommendations, and compiled and approved the final report. DA conceived the project, compiled the list of topics, coordinated the search strategy, coordinated contributors to review one or more infections, and completed one or more topics as described for all other authors, and approved the final report. DI conceived the project, substantially edited the reviews and recommendations, and approved the final report. PAB completed one or more topics as described for all other authors, collated the search and review data in PRISMA format from all contributors, independently verified the searches and reviews, substantially edited the reviews and recommendations, and compiled and approved the final report. All other authors completed one or more topic literature reviews as follows: performed the search, screened and selected relevant studies, synthesised the data, and drafted the literature review and recommendations. They also reviewed the final report to ensure consensus and approved the final report.

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#### Declaration of interests

We declare no competing interests.

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