5, 7, 10 or 14 days: appropriate duration of treatment for bacteraemia or an example of 'antimicrobial bingo'?

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Concern about serious bacterial infection is a common reason for children to be admitted to hospital, many of whom are given parenteral antibiotics. Once children are converted to oral antibiotics, they are usually discharged home, so the length of parenteral antibiotic treatment is a major determinant of length of stay and total cost of care (unless children can be discharged home on outpatient parenteral antibiotic therapy). The excellent bioavailability of some oral antibiotics (quinolones, clindamycin) means these drugs can rapidly achieve adequate blood levels, making a switch to oral antibiotics more appealing.

The duration and route of antimicrobial treatment required for many childhood infections is often based on expert opinion and rarely on evidence. This is particularly true for the duration of parenteral antibiotics for children with Gram-negative blood stream infections. The Infectious Diseases Society of America guidelines for the treatment of catheter-related bloodstream infections acknowledge the lack of evidence in this area, but suggest 7–14 days of intravenous antibiotics should be given for central venous catheter infections due to Gram-negative bacilli.[1] This expert opinion has been taken by some to suggest that up to 14 days of intravenous antibiotics should be given for all blood stream infections due to Gram-negative bacilli in children, such as *Escherichia coli*. However, no guidance exists for duration of parenteral antibiotic treatment for children who are bacteraemic with a urinary tract infection (UTI).

UTIs are the commonest bacterial infection in young infants. Infection can spread from the urinary tract into blood and the meninges. Between 3% and 17% of young infants with UTI also have bacteraemia, with younger infants being more likely to be bacteraemic. Infants with bacteraemic UTIs tend to be given longer courses of parenteral antibiotics than non-bacteraemic children with UTI (6 vs 2 days). Around 1.2% of neonates with UTI have coexisting bacterial meningitis.[2] Clinicians should have a low threshold to perform a lumbar puncture in neonates with UTI. Beyond the neonatal period, the risk of meningitis is small and a more selective approach is warranted.

Guidelines for managing UTI in children highlight the evidence that oral antibiotic treatment is as effective as parenteral,[3] although data on oral therapy are limited in very young infants. Some guidelines suggest that parenteral treatment may be required in children with UTI who are 'toxic' or who have a 'complicated' UTI (high creatinine, fever or abdominal mass), until the child is improving.[3] However, no national or international guidelines give any advice about duration or route of antibiotics for children with bacteraemic UTIs.

The linked study by Schroeder *et al*[4] shows marked variation in the duration of parenteral antibiotics given by paediatricians to treat infants with bacteraemic UTIs in 11 US centres. The duration of parenteral antibiotics mostly seemed to depend on local practice, with each institution having a different mean duration (5, 7, 10 or 12 days). Duration of parenteral antibiotics did not seem to be influenced much by clinical features (fever, comorbidities, ill appearance), but was influenced by age, if the child had a second positive blood culture and if the organism causing the UTI was not *E. coli*. Duration of parenteral treatment thus seemed most influenced by local practice, rather than other features.

Despite this variation, duration of parenteral antibiotic treatment did not seem to influence outcome or relapse of infection. Recurrence of UTI was influenced by anatomical factors such as veiscoureteric reflux, not duration of parenteral antibiotics. Only one child had a relapse of bacteraemia, despite receiving 11 days of parenteral treatment.

Why is there such variation in practice? No guidelines are available to guide clinicians in this infrequent situation. The institutions in the study saw 1–5 infants with bacteraemic UTI per year, meaning few clinicians saw this presentation on a regular basis. No studies compare 7 vs 10 vs 14 days of antibiotic treatment for children with UTI,[3] and studies comparing antibiotic duration in bacteraemic children with UTIs will be difficult to do because of the infrequent occurrence of the condition.

HOW SHOULD WE MANAGE YOUNG INFANTS WITH BACTERAEMIC UTIS?

Standard duration of treatment

Some clinicians choose to complete a 'standard' duration of intravenous antibiotics, despite the patient being clinically well. Infectious disease specialists tend to suggest longer durations than other doctors.[5] This could be 'evidenced based' if there are studies that define the optimal duration of therapy—however, this is rarely the case.

The optimal duration of therapy for bacteraemia has been poorly defined. A meta-analysis of bacteraemic patients receiving shorter (5–7 days) versus longer (7–21 days) antibiotic therapy found no significant difference in clinical cure, microbiological cure or survival.[6] However, only 13 of the 227 patients included had bacteraemia due to UTI.

While standard duration of treatment is appealing, without evidence to base decisions on clinicians pick a seemingly random duration (5, 7, 10 or 14 days). I sometimes liken this to calling out numbers in a game of bingo!

Clinically determined duration of treatment

Alternatively, some clinicians attempt to 'treat the patient', by switching to oral antibiotics when the patient is 'clinically stable'. This is often assessed as clinical improvement, 'source control' (ie, drainage or removal of focus of infection), ability to take oral medication, being afebrile for 24–48 h and/or having a reduction in inflammatory (bio-)markers.

Many clinicians use resolution of fever as a guide to switching to oral antibiotics or stopping antibiotics. This may be valid in bacteraemic UTIs. Schroeder *et al* found few children who were afebrile for 24 h on antibiotic therapy had positive blood cultures (2/8 infants—0.9% of all infants with repeat cultures).

Biomarkers

There is increasing interest in using biomarkers (such as C-reactive protein or procalcitonin) for improving decisions about antibiotic therapy. Studies are needed to demonstrate whether biomarkers can be used to reliably predict when it is safe to stop parenteral antibiotics in children with

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blood stream infections. A systematic review examined the use of procalcitonin to guide duration of antibiotic treatment in intensive care unit patients with severe sepsis and septic shock. This found no increase in mortality rates or length of stay in those who stopped antibiotics once procalcitonin was below a certain level. This group did have a significantly reduced duration of antibiotics.[7] However, these studies have limitations including high rates of patient exclusion, high rates of algorithm over-ruling and large variations in the duration of antibiotic therapy in controls. The costs associated with regular measurement of procalcitonin may also be a drawback, with some suggesting a cheaper and widely available alternative (C-reactive protein).

Summary

In an infant older than 1 month with bacteraemic UTI, the duration of parenteral antibiotics could be guided by clinical features commonly used to decide whether patients can be switched to oral antibiotics; suitable oral agent, child-tolerating oral feeds, afebrile for 24–48 h, clinical improvement and reduced inflammatory markers.

Treating individual infants on the basis of their clinical response (with validated biomarkers) may be more appropriate than blind adherence to a duration based purely on expert opinion.

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REFERENCES

1 Mermel LA, Allon M, Bouza E, *et al*. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;49:1–45.
2 Tebruegge M, Pantazidou A, Clifford V, *et al*. The age-related risk of co-existing meningitis in children with urinary tract infection. *PLoS ONE* 2011;6:e26576.
3 Roberts KB, Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics* 2011;128:595–610.
4 Schroeder AR, Shen MW, Biondi EA, *et al*. Bacteremic urinary tract infection: management and outcomes in young infants. *Arch Dis Child* 2016;101:125–30.
5 Daneman N, Shore K, Pinto R, *et al*. Antibiotic treatment duration for bloodstream infections in critically ill patients: a national survey of Canadian infectious diseases and critical care specialists. *Int J Antimicrob Agents* 2011;38:480–5.
6 Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. *Crit Care* 2011;15:R267.
7 Prkno A, Wacker C, Brunkhorst FM, *et al*. Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock–a systematic review and meta-analysis. *Crit Care* 2013;17:R291.