Intravenous Antibiotic Durations for Common Bacterial Infections in Children: When is Enough Enough?

Alan R. Schroeder, MD1*, Shawn L. Ralston, MD2

1Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, California; 2Department of Pediatrics, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire.

Durations of intravenous antibiotic therapy for bacterial infections in hospitalized children sometimes extend well beyond clinical recovery and are often the primary determinants of length of stay. These durations, however, are not always based on solid evidence. Moreover, fixed durations are invariant to important individual factors. We review guidelines and the available evidence for durations of intravenous antibiotic therapy for meningitis, bacteremia, urinary tract infection, and osteomyelitis, conditions where intravenous antibiotics often extend beyond resolution of clinical symptoms. We propose a framework for the duration of therapy that is intended to serve as a guide when standards of care are either nonexistent, dated, conflicting, or contrary to evidence from published studies. This framework incorporates patient-centered factors such as severity of infection, response to therapy, ease of intravenous access, harms and costs of ongoing intravenous treatment, and family preferences. Journal of Hospital Medicine 2014;9:604–609. © 2014 Society of Hospital Medicine

Rationally defining the appropriate duration of intravenous (IV) antibiotics for children with bacterial infections is challenging. For example, how long should a 2-week-old infant with a urinary tract infection (UTI) caused by Escherichia coli (E. coli) be treated intravenously if the infant has responded to treatment and is back to baseline within 1 to 2 days? What if the blood culture was also positive for E. coli? What are the risks and benefits of continuing IV antibiotics?

Such questions are common for pediatric hospitalists. Bacterial infections remain a relatively frequent cause of pediatric hospitalization, especially in neonates where 5 of the top 10 causes of hospitalizations are related to bacterial infections.1 For some conditions, children remain hospitalized after clinical improvement simply for ongoing provision of IV antibiotics. Alternatively, some children are discharged home with a peripherally inserted central catheter (PICC) to complete an IV course.

The decision regarding the duration of IV antibiotics varies according to the condition for which the antibiotic is prescribed and often by practitioner or hospital. Many recommendations are numerically based (eg, 10 days for group B Streptococcus [GBS] bacteremia, 21 days for E. coli meningitis), without taking into account patient-level factors such as initial severity or response to therapy. These concrete recommendations may in fact be preferred by some practitioners, as suggested by a former chairman of the Committee on Infectious Disease for the American Academy of Pediatrics (AAP): “The Red Book is designed for people who make decisions. It cannot waffle on an issue. It has to make a positive recommendation even if the data are incomplete.”2 A potential downside of this mentality, however, is that some practitioners may then feel obligated to follow these recommendations despite the lack of supportive evidence.

EXTENDING IV ANTIBIOTICS BEYOND CLINICAL RECOVERY

What is the rationale for continuing IV antibiotics in infants whose symptoms have completely resolved? Several factors likely drive these decisions: prevention of recurrences, concerns about bioavailability of enteral antibiotics and patient compliance, adherence to expert recommendations/guidelines, and perhaps a general sense that more is better—that serious infections and/or their sequelae require more aggressive treatments.

Recurrence of a potentially life-threatening infection is an understandable concern. Even when symptoms have resolved and there is documented clearance of the infection, such clearance does not necessarily signify that the body has rid itself of the pathogen completely. Some infections are deep seated and may warrant continuing treatment despite apparent recovery. To some, the risks of prolonging IV therapy may seem inconsequential when juxtaposed to a potentially devastating recurrence. However, in many conditions, recurrences may be related to host issues or ongoing exposures rather than inadequate treatment of the original infection. Recurrent UTIs, for example, are
more likely in infants with urologic abnormalities, and recurrent GBS bacteremia has been associated with GBS colonization of maternal breast milk and/or maternal mastitis. Although it is tempting to extend IV courses to prevent recurrences, it is not clear that the benefits of such an approach outweigh the risks.

Concerns over enteral absorption and bioavailability are also understandable, especially in young infants. The superior efficacy of IV over oral antibiotics in general is well accepted for many pediatric conditions, and in some cases (e.g., septic shock) it would be unethical to perform a head-to-head trial. However, the lack of any published trials (to our knowledge) in pediatrics confirming the superiority of IV therapy. Further trials in developed countries are needed.

BACTERIAL MENINGITIS

The Infectious Disease Society of America and the British National Institute for Clinical Evidence have both published guidelines with pediatric recommendations for duration of therapy in bacterial meningitis, though the recommendations differ somewhat for 3 of the 4 most common pathogens, and are not always concordant with evidence from randomized controlled trials (Table 1). A recent meta-analysis on duration of therapy in meningitis included 5 open-label trials of ceftriaxone for bacterial meningitis in children. These trials included the 3 most common pathogens and were categorized as short-course (4–7 days, n = 196 patients) and long-course (7–14 days, n = 187 patients) therapy. There was no significant difference in clinical success or long-term neurological complications between groups. Subsequently, a multicountry trial enrolled over 1000 children 2 months to 12 years of age with meningitis caused by *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, or *Neisseria meningitidis* who were stable after 5 days of IV ceftriaxone therapy and randomized them to receive placebo or an additional 5 days of ceftriaxone. Patients with persistence of seizures, bacteremia, abscess or distant infections, or who were judged to be deteriorating or still severely ill at the 5-day point were excluded (~4.7% of the children who were recruited on day 0). There were no significant differences in bacteriologic failures, clinical failures, or clinical sequelae in survivors. The authors concluded that ceftriaxone can be discontinued in children with bacterial meningitis who are clinically stable after 5 days of IV therapy.

### TABLE 1. Recommended Duration of Intravenous Antibiotics for Meningitis in Children

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>IDSA</th>
<th>NICE</th>
<th>Minimum Range</th>
<th>Achieving Equivalent Outcomes in Recent Randomized Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Group B Streptococcus</em></td>
<td>14–21 days</td>
<td>14 days</td>
<td>None available</td>
<td></td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td>7 days</td>
<td>7 days</td>
<td>1–5 days</td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae type b</em></td>
<td>7 days</td>
<td>10 days</td>
<td>4–5 days</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
<td>10–14 days</td>
<td>14 days</td>
<td>4–5 days</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Abbreviations: IDSA, Infectious Disease Society of America; NICE, National Institute for Clinical Excellence.

### BACTEREMIA

Because of routine vaccination against *H influenzae* type b and *S pneumoniae*, bacteremia beyond the first few months of life in otherwise healthy children is now rare. Even in infants too young to benefit directly from vaccination, the epidemiology of bacteremia has changed considerably over the last few decades, with *E coli* and GBS constituting the majority (65%–77%) of cases. We will limit this review on bacteremia to these 2 organisms in young infants.

Most cases of *E coli* bacteremia are associated with UTI (91%–98%), and most bacteremic UTIs (88%–92%) are caused by *E coli*. There are no official recommendations for the duration of treatment of bacteremic UTI, and only a limited amount of evidence can be gleaned from existing studies. In a trial of oral cefixime for infants aged 1 to 24 months with UTI, all 13 infants with bacteremia fared well whether they received oral cefixime only or IV cefotaxime for 3 days followed by oral cefixime. In a study on length of IV antibiotic therapy in over 12,000 infants <6 months old with UTI, the presence of bacteremia predicted longer IV treatment length (bacteremia was present in 0.5% of the short IV group vs 0.8% of the long IV group, *P* = 0.02) but did not predict treatment failure, defined as readmission within 30 days. In a multicenter investigation of 229 infants <3 months old with bacteremic UTI, the duration of parenteral antibiotics was extremely variable (range, 1–17 days) and was not associated with treatment failure, defined as recurrent UTI caused by the same organism within 30 days (mean duration 7.8 days in the treatment-failure group vs 7.7 days in the no-failure group, *P* = 0.99). In summary, there is no
evidence to support a prolonged course (ie, >3–5 days) of IV antibiotics for bacteremic UTI.

For bacteremia caused by GBS, although the Red Book Committee on Infectious Disease recommends 10 days of IV antibiotics,\textsuperscript{22} to our knowledge there are no experimental or observational investigations to support this recommendation. Although available studies suggest that IV courses of at least 10 days are generally provided,\textsuperscript{7,23} no studies have compared outcomes of infants treated with short versus long courses. However, in a study that included 29 full-term neonates with GBS bacteremia, all 29 had responded initially to 48 hours of intravenous antibiotics (defined as being “asymptomatic” and fed enterally), and were then treated successfully with high-dose oral amoxicillin for the remainder of the course, with no recurrences.\textsuperscript{8} Although recurrences are estimated to occur in 0.5% to 3% of babies treated for GBS infections, many recurrences are associated with exposure factors such as GBS colonization of the breast milk.\textsuperscript{4–7} In summary, although 10 or more days of IV antibiotic therapy remains a common published recommendation, there is no supportive evidence. More research is needed to assess whether shorter IV courses are safe.

**UTI**

Most UTIs can be treated with oral antibiotics.\textsuperscript{24} In its practice parameter on febrile UTIs in infants 2 months to 2 years of age, the AAP recommends oral antibiotics for well-appearing children.\textsuperscript{25} This recommendation is supported by a recent Cochrane review on the topic,\textsuperscript{26} and at least 3 additional trials that have demonstrated that long IV courses do not yield better outcomes than shorter IV courses or oral only courses.\textsuperscript{27–29}

However, all of these trials exclude infants <1 month old, and there are no published recommendations for the <2-month-old age group. The study by Brady et al. on >12,000 infants <6 months old with UTI demonstrated no significant differences in UTI readmission rates between infants who were given ≥4 days of IV antibiotics versus those who were given ≤4 days.\textsuperscript{3} There were 3,383 infants <30 days old in this study, and about one-third of these babies received a short IV course. Failure rates were nearly identical in each group (2.3% in short course vs 2.4% in long course) even after risk adjustment (personal communication with Patrick Brady, MD, on February 7, 2014). Magin et al. describe 172 neonates (median age 19 days) with UTI who were treated intravenously for a median duration of 4 days (interquartile range, 3–6 days) and did not experience treatment failures or relapses.\textsuperscript{30}

In summary, most cases of UTI can be managed with oral antibiotics. Uncertainty remains over the optimal approach for infants <1 to 2 months old, an age range not considered in current published guide-

**ACUTE OSTEOMYELITIS**

Given the excellent blood supply to rapidly growing tissues in children, shorter durations of IV therapy have been studied with increasing frequency. A 2002 systematic review included 12 prospective cohort studies with at least 6 months of follow-up.\textsuperscript{31} Studies were stratified into ≤7 days or >7 days IV therapy, and there were no differences in cure rates. Subsequently, a large Finnish trial reported on 131 children who received an initial short IV course (2–4 days) followed by 20 versus 30 total days of therapy with very low treatment failure rates.\textsuperscript{32}

The largest study from the United States to date analyzed nearly 2000 cases of osteomyelitis from 29 hospitals.\textsuperscript{33} This study defined a prolonged IV course by placement of a central venous catheter. The rates of prolonged IV therapy varied significantly across hospitals, ranging from 10% to 95% of patients, without detectable differences in outcomes. Furthermore, the readmission rate for catheter related complications (3%) was nearly as high as the overall treatment failure rate (4%–5%). Recently, Arnold et al. reported 8 years’ experience with a management algorithm to guide the transition to oral antibiotics in pediatric osteoarticular infections in a patient specific manner.\textsuperscript{34} This study included 194 patients (154 uncomplicated and 40 complicated cases), all with culture-proven disease. Transition to oral antibiotics occurred based on resolution of fever and pain, improved function of the affected region, and a C-reactive protein level of <3 mg/dL, and occurred at an average of 10 days into the treatment course. These authors also provided extensive information about complications to demonstrate that the proposed strategy can be used with a wide range of patients and pathogens. There was a single microbiologic treatment failure after oral step-down therapy in a complicated osteoarticular infection, with a retained bony fragment. This study represents a successful example of a patient-centered approach to IV antibiotic duration.

**A PATIENT-CENTERED APPROACH**

Returning to the example above of the 2-week-old with UTI (with or without bacteremia), there are no published guidelines and only limited available evidence to help guide the duration of IV antibiotics in this case. When standards of care (eg, from published guidelines, review articles, textbooks, or local expert guidance) are nonexistent, conflicting, dated, or contrary to existing evidence, patient-level factors can be incorporated into the decision-making process (Table 2). In these cases, tailoring the IV antibiotic course to the individual’s response (referred to in 1 review as
was a fever. Similarly, most practitioners would be reluctant to stop IV antibiotics and discharge a patient with a bacterial infection who is persistently febrile or vomiting. Although the use of inflammatory markers and other clinical symptoms to guide therapy has been limited to osteomyelitis, this approach might be useful and should be studied in other conditions.

**SHARED DECISION MAKING**

Shared decision making can also be employed. Parents of sick, hospitalized children generally prefer to be involved in the decision-making process. For a parent who has concerns about their child’s well-being in the hospital, or has multiple other children at home, competing career obligations, and/or limited family support, the burden of ongoing hospitalization can be significant, and should be factored into decision making. Involving parents in medical decisions may lead to a reduction in utilization for some conditions.

**ASSESSMENT OF RISKS/COSTS**

The risks and costs of pediatric hospitalization and prolonged IV antibiotics are well described in the literature and are summarized in Table 3. Although the benefits of prolonging IV antibiotics in a child who has recovered from an acute bacterial infection are largely theoretical, many of the risks are concrete and quantifiable. For example, a young infant being treated for a bacteremic UTI may run out of potential IV sites and need a PICC line to continue IV therapy, which according to a recent review of 2574 PICC lines has a 21% complication rate. This rate is even higher in children for whom the PICC line indication was provision of antibiotics (27%) and for infants <1 year of age (44%). Moreover, this procedure often requires sedation or anesthesia for placement, which has both known and unknown risks, including concerns about subsequent adverse effects on development in young children. Nosocomial exposure to

Table 2. Additional Considerations for the Duration of Intravenous Antibiotics When Guidelines Are Conflicting, Absent, Dated, or Contrary to Existing Evidence

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of initial infection</td>
<td>If concern of recurrence is the justification for a longer IV course, then a more prolonged course might be considered for a more severe initial presentation (eg, septic shock, multisystem organ failure, intensive care unit admission).</td>
</tr>
<tr>
<td>Response to therapy</td>
<td>Continued IV antibiotics might be warranted in patients who are still symptomatic (eg, fever, vomiting). Inflammatory markers have been used to guide therapy in osteomyelitis.</td>
</tr>
<tr>
<td>Patient compliance</td>
<td>If a child does not tolerate oral antibiotics or there are concerns about family adherence, a longer IV course may be considered.</td>
</tr>
<tr>
<td>Family preferences</td>
<td>Shared decision making can be employed, especially when there is no clear evidence supporting a specific duration.</td>
</tr>
<tr>
<td>Assessment of harms of ongoing hospitalization and/or prolonged IV therapy</td>
<td>See Table 3</td>
</tr>
</tbody>
</table>

*NOTE: Abbreviations: IV, intravenous.*

“the ultimate bioassay of the therapy”2), while also weighing risks and benefits of ongoing therapy, is a logical approach.

**SEVERITY OF INITIAL INFECTION AND RESPONSE TO THERAPY**

The severity of the initial infection, whether in terms of presentation or clinical recovery, can factor into the duration of therapy. Provision of a longer IV course to prevent (albeit theoretically) a recurrence makes more logical sense in an infant with GBS bacteremia who was ill enough to warrant intensive care unit admission than in an infant whose only symptom

Table 3. Harms Associated With Intravenous Antibiotic Therapy

<table>
<thead>
<tr>
<th>Harm of Intravenous Antibiotic Therapy</th>
<th>Description or Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications from peripheral IV catheter</td>
<td>Leading source of pain and distress for hospitalized children.44 Serious complications can occur following IV infiltrates.45</td>
</tr>
<tr>
<td>Complications from PICC line</td>
<td>Approximately 20% overall complication rate (44% in infants &lt; 1 year old).37 Complications led to rehospitalization of 3% of children being treated with prolonged antibiotics for osteomyelitis.33</td>
</tr>
<tr>
<td>Risk of nosocomial infection while hospitalized</td>
<td>When thrombosis occurs (up to 9% risk in neonates46), 3 months of anticoagulation is recommended.47 Complications may arise from sedation/anesthesia necessary to place catheter. Anesthesia has been associated with adverse behavioral or developmental outcomes in children &lt;4 years of age.38</td>
</tr>
<tr>
<td>Medication error</td>
<td>An estimated 6% of hospital RSV infections are nosocomial, which are associated with a more prolonged LOS than hospitalizations for community-acquired RSV.39</td>
</tr>
<tr>
<td>Emotional and financial burdens</td>
<td>In 1 investigation, serious medication errors occurred in 22 per 1,000 patient-days in a large children’s hospital.48</td>
</tr>
<tr>
<td>Financial costs to healthcare system</td>
<td>Hospitalization can pose a significant strain on the child, parents, and siblings.</td>
</tr>
<tr>
<td>Harms associated with prolonged courses of antibiotics in general (IV or PO)</td>
<td>In 2003, infection-related hospitalizations in infants had an average cost of $4,000 (average LOS 3.5 days).1 Antibiotic resistance, diarrhea (including Clostridium difficile), allergic reactions, increased costs.49</td>
</tr>
</tbody>
</table>

*NOTE: Abbreviations: IV, intravenous; LOS, length of stay; PICC, peripherally inserted central catheter; PO, per os (by mouth); RSV, respiratory syncytial virus.*
seasonal viruses poses an additional risk to hospitalized children.39
These additional considerations for the duration of IV antibiotics are not evidence based and should not be used to justify an IV duration that differs dramatically from an accepted standard of care. These are merely considerations that incorporate clinical judgment and a comprehensive analysis of risks and benefits in situations where the available evidence is suboptimal. This approach can be adopted both as a framework for future research and directly in clinical practice.

CONCLUSION
In an era of increasing focus on overtreatment/waste,40 patient safety,41 and patient-centered care,42 the duration of IV antibiotics for common bacterial infections is a prime target for improving pediatric healthcare value. As emphasized by Michael Porter recently in The New England Journal of Medicine, “value should always be defined around the customer.”43 A high-value approach to IV antibiotic duration incorporates a rigorous assessment of risks and benefits that focuses on best evidence and patient-level factors.

In discussing published guidelines in a review on bacterial meningitis therapy, Michael Radetsky noted that “[R]ecommended criteria, even if provisional, may inadvertently become invested with an independent power to force submission and prohibit deviation. The danger is that sensitivity to individual responsiveness and variability will be lost.”44 Guidelines are useful tools in pediatrics and should continue to be used to direct IV antibiotic durations for bacterial infections in children. However, the emphasis on fixed durations of IV antibiotics might not always serve the best interest of the patient. When guidelines are lacking or contradictory, patient factors should also be considered.

Acknowledgements
The authors thank Ellen R. Wald, MD, and Kenneth B. Roberts, MD, for their thoughtful and valuable additions to this review.

Disclosure: Nothing to report.

References
33. Zouzos T, Localio AR, Sutherland S, Bertoch D, Keren J. Prolonged intravenous therapy versus early transition to oral


