An End in Sight: Shorter Duration of Parenteral Antibiotics in Neonates

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Prescribing the appropriate duration of antibiotic therapy is at the top of mind for the Centers for Disease Control and Prevention, hospital systems, and individual providers alike because it has a resounding impact on antimicrobial resistance.[1] In this month's issue of *Pediatrics*, Desai et al[2] have taken on the duration of parenteral antibiotics for infants ≤60 days old with bacteremic urinary tract infection (UTI). This is a critical piece of a complicated puzzle that not only includes minimum duration of parenteral antibiotic treatment but also involves bioavailability of antimicrobial agents in infants and total treatment duration, which includes parenteral and oral antibiotic therapy. They have written a methodologically sound multicenter study and propose that a short course of parenteral antibiotics is no less effective than a long course in infants ≤60 days old with bacteremic UTIs.

This study uniquely affords granularity with respect to the patient population, including a physician's documented clinical assessment providing information such as temperature, ill appearance, or presence of a known genitourinary condition, which allowed for ascertainment of critical clinical information that influenced management decisions. Ultimately, these clinical characteristics, along with baseline demographics and past medical history, were used to develop propensity scores and inverse probability weighting to account for confounding by indication, thereby strengthening the study findings.

Antimicrobial bioavailability in infants impacts antibiotic choice in neonates who are infected. Drug pharmacokinetics in neonates is influenced by a multitude of physiologic and disease-related factors. Gastrointestinal absorption of orally administered drugs is influenced by gastric pH, gastric emptying time, intestinal absorption, bacterial colonization of the gut, and diet composition.[3] Parenteral antibiotics are relied on in infants, as in children and adults, to ensure optimal bioavailability and tissue penetrance to combat severe infections and when patients are unable to tolerate oral therapy. Clinicians often start with parenteral antibiotics, but in infants who are tolerating oral intake, the value of a prolonged parenteral antibiotics course is unclear. In young children who are fragile and often are on the precipice of severe consequences from infection, we are hesitant to risk any chance that they could acutely worsen if started on oral antibiotics and bioavailability becomes suboptimal. When Gras-Le Guen et al[4] evaluated bioavailability of amoxicillin in term infants with Group B *Streptococcus* (GBS) infections, they found that after an initial 48-hour course of intravenous amoxicillin, all 29 patients with bacteremia who transitioned to oral amoxicillin maintained therapeutic levels. Three months after discharge, none of the patients, including >150 GBS-positive infants who were not bacteremic, were GBS-positive. Furthermore, infants who were transitioned to oral antibiotics reduced their hospital length of stay by 5 days.[4] Studies such as these suggest that after an initial short course of parenteral

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antibiotics, bioavailability of oral and parenteral antibiotics are equal, and therefore a shorter duration of parenteral antibiotics is effective and adequate.

Given that bacteremia is a perilous diagnosis with morbidities that include severe sepsis and death, it is not surprising that infants with bacteremia receive a greater proportion of their total treatment parenterally than those without bacteremia, although there are no available published recommendations on duration of parenteral treatment. So, what is the appropriate duration? Desai et al[2] used a relatively arbitrary cutoff of 7 days on the basis of the distribution of antibiotic course among their patient population; however, this is likely more a reflection of clinical practice than it is evidence based, as demonstrated by the dramatic variability in prescription patterns, which ranged from 1 to 24 days depending on the treatment location of the patient. Two studies revealed similar variation in duration of parenteral antibiotics for treatment of UTI and bacteremic UTI respectively, with Brady et al[5] reporting that 15% to 87% of clinicians prescribe ≥4 days of parenteral antibiotics for nonbacteremic UTI.[6] These same studies also revealed that the total duration of parenteral therapy had no impact on the rate of treatment failure or rate of readmission. For >10 years, Lewis-de Los Angeles et al[7] performed a retrospective analysis of otherwise healthy infants with UTI younger than 60 days and identified an increasing trend toward short-course parenteral antibiotics and also no difference in readmission rates as parenteral antibiotic duration shortened. Total antibiotic course was not analyzed.[7] Clinical parameters certainly play a role in duration of parenteral antibiotic therapy. For example, when a patient defervesces or when the urine culture indicates bacterial sensitivity to antibiotics that are available orally, it is often reasonable to transition to appropriate oral antibiotics. However, a first step toward evidence-based guidelines related to total duration of therapy (parenteral and oral antibiotic therapy) is to elucidate whether patients can tolerate a shorter course of parenteral antibiotics before we place this in a larger context.

Desai et al[2] provide further evidence that a short course of parenteral antibiotics in infants ≤60 days old with bacteremic UTI is safe and effective. Although the current study does not address total duration of antibiotics, it does shine a light on where we should focus future research endeavors.

ABBREVIATIONS

GBS: Group B *Streptococcus*
UTI: urinary tract infection

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