BENDING THE VALUE CURVE

Considering Cultures and Consequences: The Relevance of Bacteremia in Infant UTIs

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A 2-week-old male infant presented to a children's hospital emergency department (ED) after having a rectal temperature to 38.6°C at home. He was born at term via normal spontaneous vaginal delivery. There were no complications during pregnancy or delivery. His mother was negative for group B *Streptococcus* and herpes simplex virus. He was feeding well and voiding and stooling normally. In the ED, he was febrile to 38.1°C and underwent a laboratory evaluation with a complete blood cell count, blood culture, urinalysis, urine culture, and cerebral spinal fluid (CSF) culture. His complete blood cell count had a white blood cell (WBC) count of 25.2×10^6/L with 2% bands and 60% neutrophils. CSF analysis revealed 3 WBCs with a normal protein and glucose. Urinalysis revealed 3+ leukocyte esterase, >100 WBCs, and many bacteria. He was started on ampicillin and gentamicin in the ED and admitted to a general pediatric service.

Within 24 hours, his urine culture revealed Gram-negative rods, ultimately identified as >100 000 colony-forming units of pan-sensitive *Escherichia coli*, at which time his antibiotic therapy was narrowed to intravenous (IV) cefazolin. He subsequently had normal results from renal and bladder ultrasound and continued to be afebrile and well appearing after the first dose of IV antibiotics. Results from his blood and CSF cultures remained negative. Per our institutional pathway for neonatal urinary tract infection (UTI), he received a total of 7 days of IV antibiotics, requiring placement of 3 separate peripheral IV lines. He was transitioned to oral cephalexin and discharged from the hospital to complete a total of 14 days of antibiotics with close outpatient follow-up.

INFANTS, IV ANTIBIOTICS, AND COMPLICATIONS OF BACTEREMIC UTIS

UTIs are the most common cause of bacterial infections in infants <90 days of age.[1–3] Of these infants with a febrile UTI, ∼8% have culture-proven bacteremia,[1,2,4] and are often treated with longer courses of IV antibiotics, because of the presumption of an increased risk of complications.[5–8] Given the concern for false-negative blood culture results and the potential for decreased enteral absorption, many infants <30 days with a UTI are routinely treated with prolonged IV antibiotics. The following discussion evaluates 3 assumptions behind this rationale. The first assumption is that infants with a UTI should be presumed bacteremic regardless of blood culture results. The second assumption is that bacteremia in the setting of a UTI is clinically significant. The third assumption is that IV antibiotics are superior to oral antibiotics.

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ASSUMPTION 1: INFANTS WITH A UTI SHOULD BE PRESUMED BACTEREMIC REGARDLESS OF BLOOD CULTURE RESULTS

The volume of blood that is obtained for a blood culture is the most important variable in recovering bacteria from patients with bloodstream infections.[9] Obtaining blood cultures in infants can be technically challenging, resulting in smaller than optimal volumes collected. In many cases, often there is <0.5 mL of blood collected for such blood cultures. These small volumes increase the likelihood of false-negative culture results.[10]

A microbiology study by Schelonka et al[10] in 1996 found that when as little as 0.5 mL of blood was inoculated with 4 colony-forming units/mL of *E coli*, the resultant culture had positive results 81% of the time, meaning that 19% of known bacteremic samples had false-negative results. If we apply this assumption to UTIs, then an 8% rate of bacteremia is capturing only 81% of true bacteremic cases. This would mean the "true" bacteremia rate would be closer to 10% and that 2 in 100 infants with a UTI and a blood culture with negative results would be expected to have bacteremia.

If we accept a false-negative blood culture result rate of 2%, then consider the impact for 100 well-appearing infants with a UTI and a blood culture with negative results. Two of these 100 infants who have false-negative blood culture results will actually have a bacteremic UTI. Currently, at our institution, all 100 are being treated with 7 days of IV antibiotics. Because most infants <30 days old will remain hospitalized for 2 days while awaiting final CSF culture results, 5 of those 7 days are potentially unnecessary for 98 of 100 infants. In other words, 500 days of IV antibiotics need to be administered to treat 2 infants with presumed bacteremia. If the average cost per night to stay at a nonprofit hospital is $2413,[11] then for every 100 infants hospitalized with negative blood culture results, a total expenditure of $1 206 500 would be spent to cover the 2 infants with potential bacteremia ($2413 × 500 days = $1 206 500).

ASSUMPTION 2: HAVING BACTEREMIA IN THE SETTING OF A UTI IS CLINICALLY SIGNIFICANT

Historically, bacteremic UTIs have been treated with longer courses of IV antibiotics because of concerns for severity of infection, renal scarring, hospital readmission, and recurrent UTIs.[5–8] Although there is no published evidence to propose a standard duration of IV therapy for bacteremia associated with infant UTIs,[12] the authors of current literature suggest that bactermic UTIs, regardless of age, do not increase these risks.[13] In 2016, Schroeder et al[12] examined 251 infants <90 days with bacteremic UTIs, finding no relationship between the length of parenteral antibiotic therapy and treatment failure or relapse. Additionally, on further examination of cases of relapsed UTI, they reported 0 cases of relapsed bacteremic UTI and no cases of clinical deterioration (ICU transfer or development of meningitis during acute treatment or within 30 days of treatment).[12] In a randomized clinical trial of 309 infants 1 to 24 months old with fever and UTI, patients received initial therapy with either oral cefixime alone or IV cefotaxime. Thirteen infants, after randomization, were found to be bacteremic. The study found no significant differences in time to defervescence, symptomatic reinfection, or renal scarring at 6 months, regardless of the presence of bacteremia.[13] Most significantly, in this study, none (0 of 13) of the infants with bacteremia had renal scarring at 6 months, but 10% (26/288) of the nonbacteremic population did. Lastly, the authors of a Finnish study looked at 134 children with bacteremic UTI matched with children with UTIs and negative blood culture results. They found infants with bacteremia had no difference in clinical presentation or recovery and that the presence of positive culture results did not add new microbiologic information.[7]

ASSUMPTION 3: IV ANTIBIOTICS ARE SUPERIOR TO ORAL ANTIBIOTICS (ESPECIALLY IN INFANTS)

The presumption that IV antibiotics are superior to oral antibiotics remains a driving force for the treatment in many pediatric and neonatal conditions.[14] Yet, in studies in which neonates are specifically addressed, oral antibiotic therapy has not been associated with treatment failure or recurrence of infection, despite concerns of decreased enteral absorption.

In 2007, Gras-Le Guen et al[15] found that 29 infants >36 weeks' gestational age with early-onset group B streptococcal bacteremia were able to achieve and maintain therapeutic blood levels of oral antibiotics after only 2 days of IV therapy, even in cases of initial evidence of shock. There were no cases of treatment failure or infection recurrence after completion of oral therapy.[15] In 2007, Magín et al[6] reviewed 172 infants (median age: 19 days) with UTI, finding that early transition to oral antibiotics had no increased rate of treatment failure, relapses, or renal complications. In 2010, Brady et al[8] conducted a retrospective study of 3383 infants <30 days admitted to the hospital for UTI and examined the duration of parenteral antibiotic therapy across 24 children's hospitals. Patients were divided into short (≤3 days) or long (≥4 days) courses of IV antibiotics. By using propensity scoring adjustments to account for confounding variables, the study found that early transition to oral therapy was not predictive of treatment failure.[8]

REEVALUATING UTIS AS SERIOUS BACTERIAL INFECTIONS

If the presence of bacteremia does not impact outcomes for infants with a UTI, perhaps it is time we reconsider whether a UTI should be classified as a serious bacterial infection requiring prolonged parenteral therapy. Given the harms of hospitalization, including fear of pain,[16] multiple placements of peripheral IV catheters, complications associated with peripherally inserted central catheters,[17] nosocomial infections,[18] and increased cost, the treatment of febrile infant UTI provides an opportunity to use the literature to inform and improve evidence-based practice.

In the context of "more care does not necessarily mean delivering a higher value of care,"[19] we have attempted to follow the

assumptions made about this population to a logical conclusion. Because of the increasing evidence that the detection of bacteremia drives costly and potential harmful interventions in infants with UTI, without any apparent favorable impact on outcomes, we suggest that "routine" blood cultures in all infants treated for a UTI should be reevaluated.

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