

# Is Tradition Trumping Evidence in the Treatment of Young, Febrile Infants?

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Ask a pediatric trainee which organisms should be targeted in empiric therapy for febrile infants <1 month of age, and we will bet you a carton of raw milk that the answer will include *Listeria*. Traditional teaching is that the 3 most common pathogens in neonatal sepsis are group B *Streptococcus* (GBS), *Escherichia coli*, and *Listeria*, and current textbooks continue to promote these organisms as the leading pathogens.<sup>1,2</sup> However, recent evidence suggests that the modern epidemiology for bacteremia has shifted.<sup>3,4</sup> *E. coli* has now surpassed GBS, and in multiple reports *Listeria* has gone from rare to exceedingly rare or nonexistent (a decrease that may be explained by enhanced regulation around food safety or a “collateral benefit” of GBS screening and prophylaxis).<sup>5</sup> Nonetheless, ampicillin is still included in most current empiric regimens, presumably to cover for *Listeria* or *Enterococcus*. Between 2011 and 2013, the regimen for 71% of infants <28 days old hospitalized at 37 children’s hospitals for fever was ampicillin with a third-generation cephalosporin.<sup>6</sup>

Because bacteremia and bacterial meningitis in young infants are potentially life-threatening infections, high numbers needed to treat (NNTs) generally have been considered acceptable. However, in considering the addition of ampicillin to cefotaxime, just how high an NNT are we talking about? Given that ampicillin does not confer additional benefit to cefotaxime against *E. coli* or GBS and other concerns about known and unknown risks of antibiotics in neonates, is the NNT now too high to justify routine ampicillin use? Until the recent investigations published in this month’s *Hospital Pediatrics*, we did not have precise data on the exact incidence of *Listeria* or *Enterococcus* in febrile infants, making estimates of these NNTs challenging. The articles by Leazer et al<sup>7</sup> and Veessenmeyer et al<sup>8</sup> use different methods: meta-analysis of retrospective studies and national hospitalization data collected over 15 years. In a situation like this, with an uncommon outcome and changing epidemiology, it would be preferable to have contemporaneous data from a large, multicenter collaborative to avoid overrepresenting an era that may have passed. Nevertheless, the 2 articles arrive at the same conclusion: Organisms necessitating ampicillin are extremely rare in febrile young infants, prompting a reconsideration of the routine use of this antimicrobial.

Leazer et al<sup>7</sup> conducted a meta-analysis of studies published between 1998 and 2014 to assess the probability of infections with *Listeria* and *Enterococcus* in febrile infants in the first 90 days of life. Their search resulted in the inclusion of 16 studies involving ~21 000 blood cultures, 14 000 cerebrospinal fluid cultures, and 18 000 urine cultures. *Listeria* was exceedingly rare, with a weighted prevalence for bacteremia and meningitis, respectively, of 0.03% (NNT = 3440) and 0.02% (NNT not calculated to because of an excess of zero events, but somewhere in the vicinity of 5000), and no cases of urinary tract infection (UTI). Numbers were similarly low for *Enterococcus*, with the exception of UTI (0.28%, NNT = 363), although in most studies the definition of UTI did not require a positive urinalysis or used fairly low colony count thresholds, suggesting that some of the “UTIs” might reflect asymptomatic bacteruria or contamination.<sup>9</sup>

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Veesenmeyer et al<sup>8</sup> analyzed data from 6 separate years between 1997 and 2012 from the Kids' Inpatient Database (KID), enabling the investigators to estimate the incidence of listeriosis on a population level. Expressed per 100 000 births, there were an estimated 0.56, 0.53, and 0.18 discharges per year for infants age 0 to 7 days, 7 to 28 days, and 29 to 364 days, respectively. Infants with listeriosis in the 7- to 28-day range were substantially more likely to have meningitis than infants the 0- to 7-day age range (88% vs 27%), confirming the distinction between early-onset and late-onset disease, seen also with GBS.

Each study design has its strength and weaknesses. As noted earlier, neither study may accurately represent the epidemiology of the last 3 years. Although the meta-analysis included studies published as recently as 2014, those studies generally contain data that are at least a few years old. Similarly, the most recent KID analyzed was 2012, in which the numbers were far lower than in previous years (without evidence of a statistically significant temporal trend). The KID analysis relied on International Classification of Diseases, Ninth Revision codes for listeriosis, but it is unknown whether these codes are specific or sensitive. It is possible that a baby with listeriosis would receive an alternative code, such as "sepsis" or "meningitis" without mention of the organism, leading to an underestimate of the listeriosis incidence.

The meta-analysis, on the other hand, evaluated studies that include organism types, thereby providing a more reliable estimate for the probability of *Listeria* in febrile young infants. However, the largest study in the meta-analysis excluded infants <1 week of age,<sup>10</sup> the age range where the rate of listeriosis was most common according to the KID. Therefore, any implications from these studies for a reduction in ampicillin use may not apply to infants <1 week of age.

Justifiably, proponents of an ampicillin plus cefotaxime regimen may voice a "What's the big deal about ampicillin?" argument. Yes, the NNT is high, but these are potentially fatal infections, and the antibiotic is cheap and safe. Viewed in the context of an infant who is already hospitalized, already needs

an intravenous line, and is already receiving an antimicrobial, ampicillin may be perceived as fairly inconsequential in terms of harms and costs. And there may indeed be bigger fish to fry; for example, do all low-risk febrile infants <28 days old need hospitalization?<sup>11</sup> The impact a substantial reduction in hospitalizations would have on health care value would far exceed the impact of even a meaningful decrease in ampicillin use in hospitalized infants.

Nonetheless, moving away from the ampicillin plus cefotaxime combination in low-risk infants is still a worthy endeavor (discussions will continue, as they should, over whether the preferred initial regimen should be ampicillin plus gentamicin or cefotaxime alone, and whether reports of recent *Listeria* outbreaks should factor into this decision). Febrile infant hospitalizations are common, and although a few doses of ampicillin may not seem like a big deal at the individual patient level, when summed up nationally, the costs and harms do add up. We are entering a new era of health care, one that emphasizes value over volume, evidence-based medicine over eminence-based medicine, and one in which routine practices should be questioned routinely. The fact that our trainees continue to be taught that *Listeria* is a "top 3" pathogen is emblematic of just how challenging deimplementation can be.<sup>12</sup> Routine ampicillin to cover *Listeria* or *Enterococcus* in low-risk infants challenges the basic tenet of evidence-based medicine that a treatment should be provided only when the probability of the condition being treated exceeds a predefined threshold. Based on these 2 new investigations, this threshold would have to be exceedingly low to justify ampicillin in the majority of cases of young infants with fever.

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