

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

Alan R. Schroeder, MD,^{a,b} Kenneth B. Roberts, MD^c

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.^{1,2} However, recent evidence suggests that the modern epidemiology for bacteremia has shifted.^{3,4} *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).⁵ 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.⁶

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 al⁷ and Veessenmeyer et al⁸ 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 al⁷ 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.⁹

www.hospitalpediatrics.org

DOI:10.1542/hpeds.2016-0013

Copyright © 2016 by the American Academy of Pediatrics

Address correspondence to Alan R. Schroeder, MD, 751 S Bascom Ave, San Jose, CA 95128. E-mail: aschroe.md@gmail.com

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

FREE

^aDepartment of Pediatrics, Stanford University School of Medicine, Stanford, California; ^bDepartment of Pediatrics, Santa Clara Valley Medical Center, San Jose, California; and ^cDepartment of Pediatrics, University of North Carolina School of Medicine, Cone Health, Greensboro, North Carolina

Veesenmeyer et al⁸ 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,¹⁰ 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?¹¹ 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.¹² 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.

REFERENCES

1. McInerney TK. The infant with suspected infection. In: McInerney TK, Adam HM, eds. *Textbook of Pediatric Care*. Elk Grove Village, IL: American Academy of Pediatrics; 2009

2. Nield L, Kamat D. Fever without a focus. In: Kliegman RM, Stanton BMD, eds. *Nelson's Textbook of Pediatrics*. 20th ed. Philadelphia, PA: Elsevier Inc; 2016
3. Greenhow TL, Hung YY, Herz AM. Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics*. 2012;129(3). Available at: www.pediatrics.org/cgi/content/full/129/3/e590
4. Mischler M, Ryan MS, Leyenaar JK, et al. Epidemiology of bacteremia in previously healthy febrile infants: a follow-up study. *Hosp Pediatr*. 2015;5(6):293–300
5. Lee B, Newland JG, Jhaveri R. Reductions in neonatal listeriosis: "collateral benefit" of group B streptococcal prophylaxis? *J Infect*. 2016; 72(3):317–323.
6. Aronson PL, Thurm C, Alpern ER, et al; Febrile Young Infant Research Collaborative. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. *Pediatrics*. 2014;134(4):667–677
7. Leazer R, Perkins A, Shomaker K, Fine B. A meta-analysis of the rates of *Listeria monocytogenes* and *Enterococcus* in febrile infants. *Hosp Pediatr*. 2016;6(4).
8. Veesenmeyer A, Edmonson B. Trends in U.S. hospital stays for listeriosis in infants. *Hosp Pediatr*. 2016;6(4), In press
9. Schroeder AR, Chang PW, Shen MW, Biondi EA, Greenhow TL. Diagnostic accuracy of the urinalysis for urinary tract infection in infants <3 months of age. *Pediatrics*. 2015;135(6):965–971
10. Greenhow TL, Hung YY, Herz AM, Losada E, Pantell RH. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J*. 2014;33(6): 595–599
11. Pantell RH, Newman TB, Bernzweig J, et al. Management and outcomes of care of fever in early infancy. *JAMA*. 2004; 291(10):1203–1212
12. Prasad V, Ioannidis JP. Evidence-based de-implementation for contradicted, unproven, and aspiring healthcare practices. *Implement Sci*. 2014;9:1

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

Alan R. Schroeder and Kenneth B. Roberts

Hospital Pediatrics 2016;6;252

DOI: 10.1542/hpeds.2016-0013 originally published online January 1, 2016;

Updated Information & Services	including high resolution figures, can be found at: http://hosppeds.aappublications.org/content/6/4/252
Supplementary Material	Supplementary material can be found at:
References	This article cites 7 articles, 3 of which you can access for free at: http://hosppeds.aappublications.org/content/6/4/252#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Fetus/Newborn Infant http://www.hosppeds.aappublications.org/cgi/collection/fetus:newborn_infant_sub Hospital Medicine http://www.hosppeds.aappublications.org/cgi/collection/hospital_medicine_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.hosppeds.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.hosppeds.aappublications.org/site/misc/reprints.xhtml

Hospital Pediatrics®

AN OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Alan R. Schroeder and Kenneth B. Roberts

Hospital Pediatrics 2016;6;252

DOI: 10.1542/hpeds.2016-0013 originally published online January 1, 2016;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hosppeds.aappublications.org/content/6/4/252>

Hospital Pediatrics is an official journal of the American Academy of Pediatrics. Hospital Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

