Empiric *Listeria monocytogenes* Antibiotic Coverage for Febrile Infants (Age, 0-90 Days)

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The "Things We Do for No Reason" series reviews practices which have become common parts of hospital care but which may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent "black and white" conclusions or clinical practice standards, but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

Evaluation and treatment of the febrile infant 0 to 90 days of age are common clinical issues in pediatrics, family medicine, emergency medicine, and pediatric hospital medicine. Traditional teaching has been that *Listeria monocytogenes* is 1 of the 3 most common pathogens causing neonatal sepsis. Many practitioners routinely use antibiotic regimens, including ampicillin, to specifically target *Listeria*. However, a large body of evidence, including a meta-analysis and several multicenter studies, has shown that listeriosis is extremely rare in the United States. The practice of empiric ampicillin thus exposes the patient to harms and costs with little if any potential benefit, while increasing pressure on the bacterial flora in the community to generate antibiotic resistance. Empiric ampicillin for all infants admitted for sepsis evaluation is a tradition-based practice no longer founded on the best available evidence.

CASE REPORT

A 32-day-old, full-term, previously healthy girl presented with fever of 1 day's duration. Her parents reported she had appeared well until the evening before admission, when she became a bit less active and spent less time breastfeeding. The morning of admission, she was fussier than usual. Rectal temperature, taken by her parents, was 101°F. There were no other symptoms and no sick contacts.

On examination, the patient's rectal temperature was 101.5°F. Her other vitals and the physical examination findings were unremarkable. Laboratory test results included a normal urinalysis and a peripheral white blood cell (WBC) count of 21,300 cells/μL. Cerebrospinal fluid (CSF) analysis revealed normal protein and glucose levels with 3 WBCs/μL and a negative gram stain. Due to stratifying at higher risk for serious bacterial infection (SBI), the child was admitted and started on ampicillin and cefotaxime while awaiting culture results.

BACKGROUND

Evaluation and treatment of febrile infants are common clinical issues in pediatrics, emergency medicine, and general practice. Practice guidelines for evaluation of febrile infants recommend hospitalization and parenteral antibiotics for children younger than 28 days and children 29 to 90 days old if stratified at high risk for SBI.[1,2] Recommendations for empiric antibiotic regimens include ampicillin in addition to either gentamicin or cefotaxime.[1,2]

WHY YOU MIGHT THINK AMPICILLIN IS HELPFUL

Generations of pediatrics students have been taught that the 3 pathogens most likely to cause bacterial sepsis in infants are group B *Streptococcus* (GBS), *Escherichia coli*, and *Listeria monocytogenes*. This teaching is still espoused in the latest editions of pediatrics textbooks.[3] Ampicillin is specifically recommended for covering *Listeria*, and studies have found that 62% to 78% of practitioners choose empiric ampicillin-containing antibiotic regimens for the treatment of febrile infants.[4-6]

WHY EMPIRIC AMPICILLIN IS UNNECESSARY

In the past, *Listeria* was a potential though still uncommon infant pathogen. Over the past few decades, however, the epidemiology of infant sepsis has changed significantly. Estimates of the rate of infection with *Listeria* now range from extremely rare to nonexistent across multiple studies[4,7-15] (Table). In a 4-year retrospective case series at a single urban academic center in Washington, DC, Sadow et al.[4] reported no instances of *Listeria* among 121 positive bacterial cultures in infants younger than 60 days seen in the emergency department (ED). Byington et al.[7] examined all positive cultures for infants 0 to 90 days old at a large academic referral center in Utah over a 3-year period and reported no cases of *Listeria* (1298 patients, 105 SBI cases). A study at a North Carolina academic center found 1 case of *Listeria* meningitis among 72 SBIs (668 febrile infants) without a localizing source.[8] At a large group-practice in northern California, Greenhow et al.[9] examined all blood cultures (N = 4255) performed over 4 years for otherwise healthy infants 1 week to 3 months old and found no cases of *Listeria*. In a follow-up study, the same authors examined all blood (n = 5396), urine

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TABLE. Studies Reporting *Listeria* Cases in Infants

Study	Year	Design	Population	Setting	Outcome Measures	Results
Sadow et al.[4]	1999	Retrospective case series	Infants <60 days old seen in ED during 4-year period	Single urban university-affiliated ED in Washington, DC	Rates of all SBIs	0 case of *Listeria* among 121 isolated pathogens
Byington et al.[7]	2003	Retrospective case series	Febrile infants <90 days old evaluated for sepsis in ED during 3-year period	Single urban university-affiliated ED in Utah	Rates of all SBIs	0 case of *Listeria* among 105 SBIs in 1298 patients
Watt et al.[8]	2010	Retrospective case series	Febrile infants <90 days old without localizing source with blood culture in ED during 10-year period	Single university-affiliated ED in North Carolina	Rates of all SBIs	1 case of *Listeria* meningitis among 72 SBIs in 668 patients
Greenhow et al.[9]	2012	Retrospective case series	Previously healthy infants 1 week to 3 months old with blood culture collected in outpatient, ED, or inpatient setting during 4-year period	Large health maintenance organization practice in northern California	Rate of bacteremia	0 case of *Listeria* bacteremia among 93 positive cultures in 4255 total cultures
Biondi et al.[12]	2013	Retrospective case series	Febrile infants <90 days old with positive blood cultures admitted to general care unit during 7-year period	6 geographically diverse US healthcare systems	Rate of bacteremia	0 case of *Listeria* among 181 bacteremia cases
Greenhow et al.[10]	2014	Retrospective case series	Previously healthy infants 1 week to 3 months old with blood, urine, or CSF culture collected in outpatient, ED or inpatient setting during 7-year period	Large health maintenance organization practice in northern California	Rates of all SBIs	0 case of *Listeria* among: 129 positive cultures in 5396 blood cultures 823 positive cultures in 4599 urine cultures 16 bacterial meningitis cases in 1796 CSF cultures
Hassoun et al.[11]	2014	Retrospective case series	Infants <28 days old evaluated for SBIs in 2 EDs during 5-year period	1 ED at an urban children's hospital and 1 ED at a suburban academic hospital in Michigan	Rates of all SBIs	1 case of *Listeria* bacteremia among 72 SBIs in 1192 patients
Mischler et al.[13]	2015	Retrospective case series	Healthy febrile infants <90 days old admitted to general care unit during 8-year period	17 geographically diverse US healthcare systems	Rate of bacteremia	0 case of *Listeria* among 392 bacteremia cases
Leazer et al.[14]	2016	Meta-analysis	Studies of SBI rates in infants <90 days old	Studies conducted in United States between 1998 and 2014	Rates of all SBIs caused by *Listeria* or *Enterococcus*	16 studies in meta-analysis: 0.03% prevalence of *Listeria* bacteremia among 20,703 blood cultures 0.02% prevalence of *Listeria* meningitis among 13,775 CSF cultures 0 case of *Listeria* urinary tract infection among 18,283 urine cultures
Veesenmeyer & Edmonson[15]	2016	Retrospective cohort	Infants <1 year old with hospital discharge diagnosis of listeriosis, noncontinuous over 6-year period	Hospitals participating in Kids' Inpatient Database, a national (US) database	Cumulative discharges for listeriosis and pooled incidence rates of listeriosis	212 total *Listeria* cases in database during 6-year period were extrapolated to 344 total US cases, for pooled annual incidence of 1.41 in 100,000: In 40.1% of cases, infants were <7 days old In 77.6% of cases, infants were <28 days old 87.6% of infants 7-28 days old with listeriosis had meningitis

NOTE: Abbreviations: CSF, cerebrospinal fluid; ED, emergency department; SBI, serious bacterial infection.

(n = 4599), and CSF (n = 1796) cultures in the same population and found no *Listeria* cases.[10] Hassoun et al.[11] studied SBI rates among infants younger than 28 days with any blood, urine, or CSF culture performed over 4 years at two Michigan EDs. One (0.08%) of the 1192 infants evaluated had bacteremia caused by *Listeria*.

Multicenter studies have reported similar results. In a study of 6 hospital systems in geographically diverse areas of the United States, Biondi et al.[12] examined all positive blood cultures (N = 181) for febrile infants younger than 90 days admitted to a general pediatric ward, and found no listeriosis. Mischler et al.[13] examined all positive blood cultures (N = 392) for otherwise healthy febrile infants 0 to 90 days old admitted to a hospital in 1 of 17 geographically diverse healthcare systems and found no cases of *Listeria*. A recent meta-analysis of studies that reported SBI rates for febrile infants 0 to 90 days old found the weighted prevalence of *Listeria* bacteremia to be 0.03% (2/20,703) and that of meningitis to be 0.02% (3/13,375).[14] Veesenmeyer and Edmonson[15] used a national inpatient database to identify all *Listeria* cases among infants over a 6-year period and estimated listeriosis rates for the US population. Over the 6 years, there were 212 total cases, which were extrapolated to 344 in the United States during that period, yielding a pooled annual incidence rate of 1.41 in 100,000 births.

Ampicillin offers no significant improvement in coverage for GBS or *E coli* beyond other β-lactam antibiotics, such as cefotaxime. Therefore, though the cost and potential

harms of 24 to 48 hours of intravenous ampicillin are low for the individual patient, there is almost no potential benefit. Using the weighted prevalence of 0.03% for *Listeria* bacteremia reported in the recent meta-analysis,[14] the number needed to treat to cover 1 case of *Listeria* bacteremia would be 3333. In addition, the increasing incidence of ampicillin resistance, particularly among gram-negative organisms,[4,7,9] argues strongly for better antibiotic stewardship on a national level. A number of expert authors have advocated dropping empiric *Listeria* coverage as part of the treatment of febrile infants, particularly infants 29 to 90 days old.[16,17] Some authors continue to advocate empiric *Listeria* coverage.[6] It is interesting to note, however, that the incidence of *Staph aureus* bacteremia in recent case series is much higher than that reported for *Listeria*, accounting for 6-9% of bacteremia cases.[9,11,13] Yet few if any authors advocate for empiric *S. aureus* coverage.

WHEN EMPIRIC AMPICILLIN COVERAGE MAY BE REASONABLE

The rate of listeriosis remains low across age groups in recent studies, but the rate is slightly higher in very young infants. In the recent national database study of listeriosis cases over a 6-year period, almost half involved infants younger than 7 days, and most of these infants showed no evidence of meningitis.[15] Therefore, it may be reasonable to include empiric *Listeria* coverage in febrile infants younger than 7 days, though the study authors estimated 22.5 annual cases of *Listeria* in this age range in the United States. Eighty percent of the *Listeria* cases were in infants younger than 28 days, but more than 85% of infants 7 to 28 days old had meningitis. Therefore, broad antimicrobial coverage for infants with CSF pleocytosis and/or a high bacterial meningitis score is reasonable, especially for infants younger than 28 days.

Other potential indications for ampicillin are enterococcal infections. Though enteroccocal SBI rates in febrile infants are also quite low,[7-9,11,12] if *Enterococcus* were highly suspected, such as in an infant with pyuria and gram positive organisms on gram stain, ampicillin offers good additional coverage. In the case of a local outbreak of listeriosis, or a specific exposure to *Listeria*-contaminated products on a patient history, antibiotics with efficacy against *Listeria* should be used. Last, in cases in which gentamicin is used as empiric coverage for gram-negative organisms, ampicillin offers important additional coverage for GBS.

Some practitioners advocate ampicillin and gentamicin over cefotaxime regimens on the basis of an often cited study that found a survival benefit for febrile neonates in the intensive care setting.[18] There are a number of reasons that this study should not influence care for typical infants admitted with possible sepsis. First, the study was retrospective and limited by its use of administrative data. The authors acknowledged that a potential explanation for their results is unmeasured confounding. Second, the patients included in the study were dramatically different from the group of well infants admitted with possible sepsis; the study included neonatal critical care unit patients treated with antibiotics within the first 3 days of life. Third, the study's results have not been replicated in otherwise healthy febrile infants.

WHAT YOU SHOULD USE INSTEAD OF AMPICILLIN FOR EMPIRIC *LISTERIA* COVERAGE

For febrile children 0 to 90 days old, empiric antibiotic coverage should be aimed at covering the current predominant pathogens, which include *E coli* and GBS. Therefore, for most children and US regions, a third-generation cephalosporin (eg, cefotaxime) is sufficient.

RECOMMENDATIONS

- Empiric antibiotics for treatment of febrile children 0-90 days should target *E. coli* and GBS; a third generation cephalosporin, (e.g. cefotaxime) alone is a reasonable choice for most patients.
- Prescribing ampicillin to specifically cover *Listeria* is unnecessary for the vast majority of febrile infants
- Prescribing ampicillin is reasonable in certain subgroups of febrile infants: those less than seven days of age, those with evidence of bacterial meningitis (especially if also <28 days of age), those in whom enterococcal infection is strongly suspected, and those with specific *Listeria* exposures related to local outbreaks.

CONCLUSION

The 32-day-old infant described in the clinical scenario was at extremely low risk for listeriosis. Antibiotic coverage with a third-generation cephalosporin is sufficient for the most likely pathogens. The common practice of empirically covering *Listeria* in otherwise healthy febrile infants considered to be at higher risk for SBI is no longer based on best available evidence and represents overtreatment with at least theoretical harms. Avoidance of the risks associated with the side effects of antibiotics, costs saved by forgoing multiple antibiotics, a decrease in medication dosing frequency, and improved antibiotic stewardship for the general population all argue forcefully for making empiric *Listeria* coverage a thing of the past.

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Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason?" Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and Liking It on Facebook. We invite you to propose ideas for other "Things We Do for No Reason" topics by emailing TWDFNR@hospitalmedicine.org.

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