RESEARCH ARTICLE

# Trends in US Hospital Stays for Listeriosis in Infants

Angela F. Veesenmeyer, MD, MPH,[a] M. Bruce Edmonson, MD, MPH[b]

ABSTRACT

**BACKGROUND AND OBJECTIVES:** Although listeriosis is rare in infants, it is common for young infants with suspected serious bacterial infection to be treated empirically with agents selected, in part, for their activity against *Listeria monocytogenes*. Our objectives were to describe the recent epidemiology of hospital discharges for listeriosis among infants in the United States and to precisely estimate the incidence of listeriosis according to infant age and meningitis status.

**METHODS:** We generated national estimates for listeriosis discharges in each of the 6 years for which samples were available in the Kids' Inpatient Database during the period 1997–2012. We used random-effects models to pool descriptive information and population rates across study years.

**RESULTS:** The cumulative number of US hospital discharges for listeriosis in infants was 344 (95% confidence interval [CI]: 290–397) over the 6 study years. The pooled annual incidence rate in infants (per 100 000 births) was 1.41 (95% CI: 1.01–1.80) after accounting for marked fluctuation in annual rates (range: 0.66–1.86; $I^2$ = 79.3%). Discharges for listeriosis without meningitis were particularly rare after the first week of life. Our models predicted only 2.7 (95% CI: 1.1–4.2) and 1.8 (95% CI: 0.0–3.6) such discharges per year in infants admitted at ages 7 to 28 days and 29 to 364 days, respectively.

**CONCLUSIONS:** From the perspective of providing coverage against listeriosis, the routine practice of including ampicillin in the empirical treatment of febrile infants should be reevaluated for those older than 1 week without clinical evidence of meningitis.

www.hospitalpediatrics.org
**DOI:**10.1542/hpeds.2015-0145


Address correspondence to Angela F. Veesenmeyer, MD, MPH, Department of Pediatrics, University of Utah, 295 Chipeta Way, Salt Lake City, UT 84108. E-mail: angela.veesenmeyer@hsc.utah.edu

FREE

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.

Drs Veesenmeyer and Edmonson conceptualized and designed the study, carried out the analyses, and drafted, reviewed, and revised the manuscript; and both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work

[a]Departments of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah; and [b]University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

*Listeria monocytogenes* infections are rare in newborns and infants, but these infections can cause sepsis, meningitis, and death.[1–6] Therefore, due in part to its activity against *Listeria*,[7,8] ampicillin is commonly included in empirical therapy for infants suspected of having a serious bacterial infection (SBI).[9–11] The rationale for the routine use of ampicillin in this setting has been questioned on the basis of the following: (1) the extreme rarity of listeriosis in case series of young infants evaluated for SBI,[5,7,9,12,13] (2) an apparent secular decline in foodborne outbreaks due to *Listeria* in the United States,[14] and (3) high levels of ampicillin resistance in Gram-negative pathogens isolated from newborns and young infants.[15,16]

Each year in the United States, thousands of newborns and young infants undergo evaluation for SBI outside the newborn nursery setting.[11,16–18] Most of these infants are older than 1 week and do not have clinical signs of bacterial meningitis or urinary tract infection (UTI).[8,10,18] These infants are often empirically treated for possible late-onset sepsis with the use of antimicrobial regimens that include ampicillin,[8,13,19] in part because of the agent's activity against *Listeria* and *Enterococcus*.[13,15] However, meningitis (not isolated sepsis) is the expected presentation on the rare occasion when late-onset listeriosis actually occurs.[5,20–22] To help evaluate the practice of routinely prescribing ampicillin for suspected late-onset sepsis in infants, we used multiple years of data in a national hospital discharge database to assemble information on >300 discharges of infants with listeriosis. Our objectives were as follows: (1) to describe a large, population-based series of hospital stays of infants with this rare disease; (2) to describe recent trends in the incidence of listeriosis among infants in the United States; and (3) to precisely estimate how often listeriosis, with and without meningitis, occurs in discrete age groups of infants.

# METHODS

## Data Source

This study is a retrospective analysis of information on US hospital discharges in the Kids' Inpatient Database (KID). The KID is a public-use administrative database maintained by the Healthcare Cost and Utilization Project under the sponsorship of the Agency for Healthcare Research and Quality.[23] Beginning in 1997, a new KID data set is released every 3 years and consists of the following: (1) a 10% random sample of discharge records for uncomplicated births and (2) an 80% random sample of discharge records for all other pediatric inpatient stays in each nonfederal, short-term general and specialty hospital in participating states during the sample year. The KID includes discharge-level information on patient demographics, admission source, payers, hospital-assigned diagnosis and procedure codes, length of stay, total hospital charges, and discharge disposition. By accounting for its complex sampling design and incorporating poststratification sampling weights, each KID data set can be used to generate national estimates for short-term hospital discharges of children and adolescents in the United States during the sample year. For 2012, the KID sample contains information on 3.2 million (unweighted) discharges from 4179 US hospitals in 44 participating states, which corresponds to a national estimate of 6.7 million (weighted) discharges in persons under the age of 21 years.

## Definitions

We defined listeriosis and its manifestations using discharge diagnosis codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). Listeriosis was defined by the only code (027.0) available to indicate infection caused by *L monocytogenes*. This code excludes, by definition, congenital listeriosis (for which another, nonspecific code for congenital infection is recommended). The code for listeriosis does not indicate, by itself, which disease manifestation (eg, sepsis, bacteremia, or meningitis) occurred, and a supplementary code or codes are widely used to indicate their occurrence. Accordingly, listeriosis with meningitis was defined by (1) the code for listeriosis (027.0) and (2) a separate code for meningitis (320, 320.7, 320.89, 322.9). Similarly, listeriosis with bacteremia or sepsis was defined by (1) the code for listeriosis and (2) a separate code for bacteremia/sepsis (038, 038.9, 771.81, 771.83, 790.7, 995.91, 995.92). Due to a revision in ICD-9-CM coding that was first reflected in the 2003 KID sample, we were only able to collect consistent information about the occurrence of bacteremia or sepsis in infants with listeriosis for 2003–2012 discharges.

## Analysis

We limited our analysis to discharges that met the following inclusion criteria: (1) inpatient hospital discharge, (2) a principal or secondary diagnosis of listeriosis, and (3) patient age (in years) <1. To avoid "double counting" episodes of care in individual patients, we excluded records of hospital stays for which the discharge disposition was transfer (out) to another acute care hospital.[24]

The first step in our analysis was to separately generate national estimates (and their SEs) of listeriosis discharges in infants from each of the 6 available KID samples. Occasionally, a particular KID sample contained no discharge record associated with a particular event of interest (eg, in the 2012 sample, there was no discharge record for listeriosis associated with in-hospital death). In such cases, we used the Wilson score method to derive SE estimates from the corresponding 95% confidence intervals (CIs). The next step in our analysis was to estimate annual incidence rates (discharges per 100 000 live births) using data from Centers for Disease Control National Vital Statistics Reports for denominators.[25] We then applied standard meta-analysis methods[26] to pool national estimates (counts and rates) generated from each of the KID samples and relied on random-effects models to account for within-year variance (attributable to each KID sample) and between-year variance (attributable to any fluctuation in true incidence). The restricted maximum likelihood method was used to estimate model parameters. Due to the presence of rare events in some strata, we used equal weights to obtain unbiased estimates of pooled counts and rates.[27] Trends in incidence rates across sample years were evaluated with weighted least-squares regression. Reported *P* values were 2-sided, and $P < .05$ was used to define statistical significance. Heterogeneity in rates across sample years was assessed with the $I^2$ statistic, which describes the proportion (as a percentage) of total heterogeneity attributable to between-year differences in observed rates.[28]

Information was missing for several data elements. Information on admission age (in days) was missing for 10.6% (unweighted) of records that met the selection criteria. For these records, we were able to impute (with certainty) that admission age was 0 days when Healthcare Cost and Utilization Project data indicated a same-stay hospital birth. Information on age in days was administratively suppressed for all discharges of infants in the KID sample for 2012, which required us to rely on a single categorical data element indicating only whether admission age was neonatal (0–28 days) or not. Accordingly, after applying imputation and accounting for changes in data elements over time, we categorized patient age as follows: (1) 0 to 6 days, (2) 7 to 28 days, (3) 29 to 364 days, and (4) missing. Information was also missing for 2 other data elements, race/ethnicity and household income quartile, and we treated missing information categorically for these elements to avoid assuming that missingness was completely at random.

All analyses were conducted with procedures in SAS version 9.4 (SAS Institute, Cary, NC). The University of Wisconsin Health Sciences Internal Review Board determined that formal review of the study protocol was not required.

## RESULTS

There were 207 (unweighted) records for discharges of infants with listeriosis in KID samples for 1997, 2000, 2003, 2006, 2009, and 2012; and the corresponding national (weighted) estimate was 344 (95% CI: 290–397) discharges cumulatively over 6 years. Table 1 shows selected characteristics of these discharges. Most discharges were for infants admitted in the first month of life, and approximately half of the discharges in neonates were associated with admission in the first week of life. A plot of discharges by admission age in weeks (see Fig 1), shows that

**TABLE 1** Characteristics of US Hospital Discharges for Listeriosis in Infants Based on National Estimates from 1997, 2000, 2003, 2006, 2009, and 2012

| Characteristic | Aggregated Estimates for 6 Years | | |
|---|---|---|---|
| | Discharges ($N$ = 344), $n$ | Pooled Proportion[a] | |
| | | % | (95% CI) |
| Discharge year | | | |
| 1997 | 61 | 17.7 | (10.3–25.1) |
| 2000 | 72 | 20.9 | (12.4–29.5) |
| 2003 | 52 | 15.1 | (9.4–20.8) |
| 2006 | 56 | 16.3 | (10.6–22.0) |
| 2009 | 77 | 22.4 | (16.1–28.6) |
| 2012 | 26 | 7.6 | (4.1–11.0) |
| Age on admission | | | |
| 0–6 days | 138 | 40.1 | (31.5–48.6) |
| 7–28 days | 129 | 37.5 | (27.8–47.2) |
| 29–364 days | 45 | 13.1 | (6.3–19.9) |
| Data missing[b] | 32 | 9.3 | (4.2–14.4) |
| Gender | | | |
| Female | 150 | 43.6 | (33.9–53.3) |
| Male | 194 | 56.4 | (45.0–67.8) |
| Race/ethnicity | | | |
| White | 111 | 32.3 | (22.6–42.0) |
| Black | 31 | 9.0 | (3.9–14.1) |
| Hispanic | 80 | 23.3 | (17.0–29.5) |
| Other | 27 | 7.8 | (4.4–11.3) |
| Data missing[b] | 95 | 27.6 | (19.6–35.6) |
| Primary payer | | | |
| Medicaid | 214 | 62.2 | (50.3–74.2) |
| Private | 105 | 30.5 | (23.4–39.6) |
| Other | 25 | 7.3 | (3.6–10.4) |
| Patient household income by zip code quartile | | | |
| First (lowest) | 106 | 30.8 | (22.8–38.8) |
| Second | 90 | 26.2 | (18.2–34.1) |
| Third | 66 | 19.2 | (12.9–25.5) |
| Fourth (highest) | 65 | 18.9 | (11.5–26.3) |
| Data missing[b] | 17 | 5.2 | (1.8–8.6) |
| Hospital region | | | |
| Northeast | 66 | 19.2 | (12.9–25.5) |
| Midwest | 65 | 18.9 | (10.9–26.8) |
| South | 138 | 40.1 | (29.8–50.3) |
| West | 75 | 21.8 | (15.5–28.1) |
| Admission source | | | |
| Same-stay hospital birth | | | |
| Yes | 86 | 25.0 | (18.7–31.3) |
| No | 258 | 75.0 | (60.7–89.2) |
| Transfer from another hospital | | | |
| Yes | 94 | 27.3 | (18.8–35.9) |
| No | 250 | 72.7 | (60.1–85.2) |

**TABLE 1** Continued

| Characteristic | Aggregated Estimates for 6 Years | | |
|---|---|---|---|
| | Discharges ($N$ = 344), $n$ | Pooled Proportion[a] | |
| | | % | (95% CI) |
| Additional indicated diagnoses | | | |
| Bacteremia/sepsis[c] | | | |
| Yes | 119 | 56.4 | (43.4–69.4) |
| No | 92 | 43.6 | (31.5–55.7) |
| Meningitis | | | |
| Yes | 207 | 60.2 | (47.1–73.3) |
| No | 137 | 39.8 | (31.0–48.1) |
| Same-stay hospital death | ≤10 | ≤2.9 | —[d] |

[a] Estimated by pooling proportions across study years with a random-effects model (see Methods).
[b] Age in days missing, age (in years) <1.
[c] Information limited to discharges in 2003–2012.
[d] Data suppressed according to data use agreement with the Healthcare Cost and Utilization Project.

discharges rapidly declined in number after week 1 and occurred only sporadically after week 5. Disproportionately large numbers of discharges occurred in male infants and in infants with Medicaid (versus private) insurance (see Table 1). We failed to find a statistically significant difference in the relative contributions of non-Hispanic white infants and in Hispanic infants to total discharges, although information was frequently missing for race and ethnicity. Discharges of infants from poorer households predominated (linear trend across household income quartiles, $P$ = .01). Hospitals in the South accounted for more discharges (40.1%) than any of the other 3 census regions. The cumulative number of in-hospital deaths was low (≤10) during the study period, and a statistically stable case-fatality rate could not be estimated.

During the study period, annual discharge rates for listeriosis in infants ranged between 0.66 per 100 000 births (in 2012) and 1.86 per 100 000 births (in 2009). The pooled mean annual rate was 1.41 (95% CI: 1.01–1.80) discharges per 100 000 births per year, although there was considerable heterogeneity in rates across study years ($I^2$ = 79.3%). Although discharges occurred at their lowest rate in 2012, we failed to find a stepwise pattern or a statistically significant linear trend in rates ($P$ = .12).

Notably, when discharges were stratified by admission age and meningitis status, there were striking age-related differences (see Table 2). For discharges of infants admitted at age 0–6 days, 26.8% (95% CI: 15.4%–38.2%) of records included a separate code for meningitis. For discharges of those admitted at age 7 to 28 days, 87.6% (95% CI: 63.3%–100%) of records indicated meningitis. When age-specific incidence rates were applied to a hypothetical US birth cohort of 4 million (Table 2), the expected number of hospital

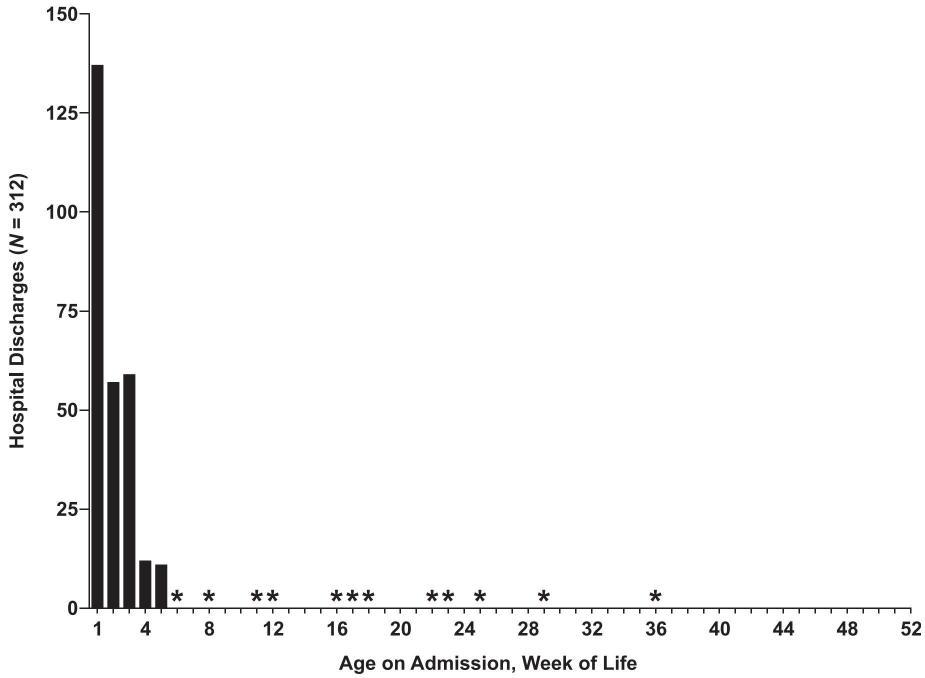


**FIGURE 1** Age distribution of infants with a hospital discharge for listeriosis. Discharges are aggregated from national estimates for 6 years spanning the period 1997–2012. Discharges by transfer to another hospital or with missing information on patient age in days were excluded. *Indicates suppressed data (≤10 discharges).

**TABLE 2** Hospital Discharge Rates for Listeriosis in Infants, by Age Group and Meningitis Status: United States, 1997–2012

| Rate | Age Group | | | | | |
|---|---|---|---|---|---|---|
| | 0–6 Days | | 7–28 Days | | 29–364 Days | |
| | Estimate | (95% CI) | Estimate | (95% CI) | Estimate | (95% CI) |
| Discharges per 100 000 births | | | | | | |
| With meningitis | 0.15 | (0.07–0.24) | 0.46 | (0.27–0.66) | 0.14 | (0.04–0.24) |
| Without meningitis | 0.41 | (0.28–0.54) | 0.07 | (0.03–0.11) | 0.04 | (0.00–0.09) |
| Discharges per 4 000 000 births in hypothetical US birth cohort | | | | | | |
| With meningitis | 6.1 | (2.9–9.4) | 18.5 | (10.7–26.3) | 5.5 | (1.5–9.6) |
| Without meningitis | 16.4 | (11.4–21.6) | 2.7 | (1.1–4.2) | 1.8 | (0.0–3.6) |

discharges for listeriosis without meningitis declined with age on admission from 16.4 to 2.7 to 1.8 discharges per year in infants admitted at age 0 to 6 days, 7 to 28 days, and 29 to 364 days, respectively.

## DISCUSSION

We report results of a US population–based analysis of listeriosis in infants that was designed to collect information on a large number of cases and to precisely estimate the current incidence of this rare disease according to infant age group and meningitis status. Most previous epidemiologic descriptions of listeriosis in infants were statistically underpowered due to the rarity of the condition.[5,8,16,17,29,30] Our results failed to show a decline in the incidence of listeriosis in infants during 1997–2012, despite a decline in overall rates of foodborne listeriosis over the past decade.[14,30–32] Our results did show, however, that listeriosis without meningitis is extremely rare among US infants admitted after the first week of life, accounting for only 2.7 (95% CI: 1.1–4.2) and 1.8 (95% CI: 0.0–3.6) discharges per year in infants admitted at ages 7 to 28 days and at 29 to 364 days, respectively.

The incidence of early-onset (0–6 days of age) listeriosis in our study was 0.53 per 100 000 births, which is similar to an aggregated rate of 0.92 per 100 000 based on a total of 13 cases reported in 3 recently reported population-based studies of early-onset sepsis.[33–35] The incidence of listeriosis in older age groups (eg, 7–28 days, 29–89 days) has been estimated in previous studies, but these estimates have generally been based on extremely small or zero numerators.[8,16,20] Various studies have reported the relative rarity of listeriosis cases among newborns and infants evaluated for SBI.[7,33–38] The extreme rarity of listeriosis without meningitis after the first week of life in our study is consistent with and supported by previous studies that analyzed fever evaluations in neonates and young infants.[9,13,16,17,39]

Previous studies showed that listeriosis disproportionately affects the poor, but these did not specifically look at this phenomenon in young infants.[40,41] We found that infants with Medicaid (versus private) insurance[42] and infants living in a lower-income household were overrepresented among those discharged for listeriosis (see Table 1). Multiple studies have shown a relationship between Hispanic ethnicity and listeriosis.[2,29,31,32,43] Information on race/ethnicity is frequently missing in KID data, however, and we were unable to confirm this association.

Current practice for empirical antibiotic treatment of febrile infants includes ampicillin in combination with gentamicin or in combination with a third-generation cephalosporin to maintain adequate coverage of both *Listeria* and *Enterococcus* while simultaneously providing effective treatment of the more common causes of neonatal sepsis.[8,11,19,44,45] Current guidelines for the prevention of perinatal group B streptococcal disease recommend intrapartum administration of either penicillin or ampicillin to pregnant women.[46] Glasgow et al[47] found that in infants with late-onset sepsis, those with ampicillin-resistant organisms were more likely to have been exposed to intrapartum antibiotics. The prevalence of ampicillin resistance in infants with SBI has been reported to be 36% to 62%, and the widespread adherence to intrapartum antibiotics guidelines for the prevention of group B streptococcal disease will likely result in increased prevalence of ampicillin resistance.[13,15,16] It has been repeatedly questioned whether empirical treatment with ampicillin is necessary for febrile infants being evaluated for sepsis.[8,9,12,13,15–17,47] Nevertheless, ampicillin is used frequently in this scenario. Aronson et al[11] found that 62% of febrile infants <90 days of age presenting with fever received ampicillin empirically. In addition, almost 50% of infants between 29 and 56 days of age received both ampicillin and a third-generation cephalosporin. Similarly, Sadow et al[13] found that >70% of the initial antibiotic regimens for treatment of SBI in infants <60 days of age included ampicillin, with 38% of these patients receiving ampicillin in combination with a third-generation cephalosporin. Cantey et al[19] found that 78% of infants younger than 28 days with SBI received empirical ampicillin. Historically, group B streptococcal isolates have been broadly susceptible to third-generation cephalosporins.[48–50] Therefore, empirically treating suspected sepsis in infants after the first week of life with cephalosporin monotherapy may be a reasonable approach.

Because ampicillin is used to treat infections due to *Enterococcus* as well as those due to *Listeria*, we recognize that the (extremely low) risk of listeriosis in infants older than 1 week is not the only determinant of empirical antibiotic choice.[8,15,19] However, many cases of enterococcal infections in young infants include UTI, and isolated sepsis in the absence of UTI or meningitis appears to be extremely rare. Biondi et al[9] found only 7 cases of enterococcal bacteremia (1 with concomitant UTI and 1 with meningitis) out of 2901 blood cultures from febrile infants <90 days of age admitted to general inpatient units. Greenhow et al[17] reported a total of 3 cases of enterococcal bacteremia (with or without UTI) in 5396 febrile infants ages 1 week to 3 months from a total birth cohort of 224 553 (for an estimated incidence of 1.2 [95% CI: 0.4–3.6] per 100 000 infants). Hassoun et al[8] described 1192 infants aged <28 days evaluated for SBI and found 1 case of enterococcal bacteremia without UTI or meningitis. Similarly, Watt et al[12] studied 668 infants <90 days of age presenting with fever and found a single case of enterococcal bacteremia without UTI or meningitis. On the basis of the results of our study and the literature on isolated sepsis due to enterococcus, the incidence of isolated enterococcal sepsis is likely to be in the same order of magnitude as that of *Listeria* sepsis. Therefore, we propose that the empirical use of ampicillin in infants beyond the first week of life undergoing evaluation for sepsis be reconsidered, particularly when there is no clinical evidence of meningitis or UTI.

The use of a hospital discharge database is subject to certain limitations. The KID database is a discharge-level database and does not contain identifiers for unique patients or episodes of care. Accordingly, we restricted our analysis to discharges of infants who were not transferred (out) to another hospital to avoid "double counting" hospital stays by infants who were transferred between hospitals. Age on admission was missing for 9.3% of discharges that were included in our analytic data set; therefore, our age-specific incidence estimates may be slightly low. In addition, we were limited by the accuracy of the various ICD-9-CM codes we used to define the diagnostic groups. Although there is only a single code available to indicate listeriosis, the code excludes "congenital infection" due to listeriosis. It is possible that we failed to detect cases of listeriosis that were coded (nonspecifically) as congenital infection, which may have caused us to underestimate the incidence of listeria in the youngest age group (0–6 days). Another limitation of the database is the reliance on secondary codes for bacteremia and meningitis, because there is no way to validate these codes in the context of listeriosis. However, the proportion of discharges in the 7- to 28-day age group for which a secondary code indicated meningitis was high, which is consistent with previously published case series based on direct medical record review.[5,22]

## CONCLUSIONS

By using a national hospital discharge database to characterize a rare infection, we report US population–based estimates for the current incidence of listeriosis with and without meningitis in discrete age groups of infants. We confirmed that listeriosis in infants is rare and can confidently state that isolated *Listeria* bacteremia in infants after the first week of life occurs at extremely low rates. Strictly from the perspective of providing coverage for *Listeria*, ampicillin for empirical therapy for infants older than 7 days with suspected sepsis may no longer be warranted. Choosing an empirical therapy for a febrile infant should take into consideration the infant's age, clinical status, suspected etiology, local resistance patterns, and care setting.


## Acknowledgments

The authors thank Jens C. Eickhoff, Ph.D., and Qianqian Zhao, MS, both of the Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, for statistical assistance.


## REFERENCES


1. Gellin BG, Broome CV, Bibb WF, Weaver RE, Gaventa S, Mascola L; Listeriosis Study Group. The epidemiology of listeriosis in the United States—1986. *Am J Epidemiol*. 1991;133(4):392–401
2. Centers for Disease Control and Prevention. Vital signs: Listeria illnesses, deaths, and outbreaks—United States, 2009-2011. *MMWR Morb Mortal Wkly Rep*. 2013;62(22):448–452
3. Committee on Infectious Diseases. Listeria monocytogenes infections. In: LK Pickering, ed. *Red Book: 2012 Report of the Committee on Infectious Diseases*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012
4. Hsieh WS, Tsai LY, Jeng SF, et al. Neonatal listeriosis in Taiwan, 1990-2007. *Int J Infect Dis*. 2009;13(2):193–195
5. Kessler SL, Dajani AS. Listeria meningitis in infants and children. *Pediatr Infect Dis J*. 1990;9(1):61–63
6. McLauchlin J. Human listeriosis in Britain, 1967-85, a summary of 722 cases. 1. Listeriosis during pregnancy and in the newborn. *Epidemiol Infect*. 1990;104(2):181–189
7. Brown JC, Burns JL, Cummings P. Ampicillin use in infant fever: a systematic review. *Arch Pediatr Adolesc Med*. 2002;156(1):27–32
8. Hassoun A, Stankovic C, Rogers A, et al. Listeria and enterococcal infections in neonates 28 days of age and younger: is empiric parenteral ampicillin still indicated? *Pediatr Emerg Care*. 2014; 30(4):240–243
9. Biondi E, Evans R, Mischler M, et al. Epidemiology of bacteremia in febrile infants in the United States. *Pediatrics*. 2013;132(6):990–996
10. Ashkenazi-Hoffnung L, Livni G, Amir J, Bilavsky E. Serious bacterial infections in hospitalized febrile infants aged 90 days or younger: the traditional combination of ampicillin and gentamicin is still appropriate. *Scand J Infect Dis*. 2011; 43(6–7):489–494
11. 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
12. Watt K, Waddle E, Jhaveri R. Changing epidemiology of serious bacterial infections in febrile infants without localizing signs. *PLoS One*. 2010;5(8): e12448
13. Sadow KB, Derr R, Teach SJ. Bacterial infections in infants 60 days and

younger: epidemiology, resistance, and implications for treatment. *Arch Pediatr Adolesc Med*. 1999;153(6): 611–614

14. Bennion JR, Sorvillo F, Wise ME, Krishna S, Mascola L. Decreasing listeriosis mortality in the United States, 1990-2005. *Clin Infect Dis*. 2008;47(7):867–874
15. Byington CL, Rittichier KK, Bassett KE, et al. Serious bacterial infections in febrile infants younger than 90 days of age: the importance of ampicillin-resistant pathogens. *Pediatrics*. 2003; 111(5 pt 1):964–968
16. 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
17. 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
18. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993; 329(20):1437–1441
19. Cantey JB, Lopez-Medina E, Nguyen S, Doern C, Garcia C. Empiric antibiotics for serious bacterial infection in young infants: opportunities for stewardship. *Pediatr Emerg Care*. 2015;31(8):568–571
20. Gaschignard J, Levy C, Romain O, et al. Neonatal bacterial meningitis: 444 cases in 7 years. *Pediatr Infect Dis J*. 2011; 30(3):212–217
21. Doorduyn Y, de Jager CM, van der Zwaluw WK, et al. Invasive Listeria monocytogenes infections in The Netherlands, 1995-2003. *Eur J Clin Microbiol Infect Dis*. 2006;25(7):433–442
22. Posfay-Barbe KM, Wald ER. Listeriosis. *Semin Fetal Neonatal Med*. 2009;14(4): 228–233
23. Healthcare Cost and Utilization Project (HCUP). HCUP Kids' Inpatient Database (KID). Available at: www.hcup-us.ahrq.gov/kidoverview.jsp. Accessed May 19, 2015
24. Westfall JM, McGloin J. Impact of double counting and transfer bias on estimated rates and outcomes of acute myocardial infarction. *Med Care*. 2001; 39(5):459–468
25. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2012. *Natl Vital Stat Rep*. 2013;62(9): 1–68
26. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008–2012
27. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med*. 2007;26(1): 53–77
28. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414): 557–560
29. Silk BJ, Date KA, Jackson KA, et al. Invasive listeriosis in the Foodborne Diseases Active Surveillance Network (FoodNet), 2004-2009: further targeted prevention needed for higher-risk groups. *Clin Infect Dis*. 2012;54(suppl 5):S396–S404
30. Tappero JW, Schuchat A, Deaver KA, Mascola L, Wenger JD. Reduction in the incidence of human listeriosis in the United States: effectiveness of prevention efforts? The Listeriosis Study Group. *JAMA*. 1995;273(14):1118–1122
31. Jackson KA, Iwamoto M, Swerdlow D. Pregnancy-associated listeriosis. *Epidemiol Infect*. 2010;138(10):1503–1509
32. Voetsch AC, Angulo FJ, Jones TF, et al; Centers for Disease Control and Prevention Emerging Infections Program Foodborne Diseases Active Surveillance Network Working Group. Reduction in the incidence of invasive listeriosis in foodborne diseases active surveillance network sites, 1996-2003. *Clin Infect Dis*. 2007;44(4):513–520
33. Puopolo KM, Eichenwald EC. No change in the incidence of ampicillin-resistant, neonatal, early-onset sepsis over 18 years. *Pediatrics*. 2010;125(5). Available at: www.pediatrics.org/cgi/content/full/125/5/e1031
34. Weston EJ, Pondo T, Lewis MM, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005-2008. *Pediatr Infect Dis J*. 2011;30(11):937–941
35. Stoll BJ, Hansen NI, Sánchez PJ, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B streptococcal and E. coli disease continues. *Pediatrics*. 2011;127(5):817–826
36. Baker MD, Bell LM. Unpredictability of serious bacterial illness in febrile infants from birth to 1 month of age. *Arch Pediatr Adolesc Med*. 1999;153(5):508–511
37. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. *Pediatrics*. 2005;116(3):595–602
38. Ferrera PC, Bartfield JM, Snyder HS. Neonatal fever: utility of the Rochester criteria in determining low risk for serious bacterial infections. *Am J Emerg Med*. 1997;15(3):299–302
39. Biondi EA, Mischler M, Jerardi KE, et al; Pediatric Research in Inpatient Settings (PRIS) Network. Blood culture time to positivity in febrile infants with bacteremia. *JAMA Pediatr*. 2014;168(9): 844–849
40. Signs RJ, Darcey VL, Carney TA, Evans AA, Quinlan JJ. Retail food safety risks for populations of different races, ethnicities, and income levels. *J Food Prot*. 2011;74(10):1717–1723
41. Gillespie IA, Mook P, Little CL, Grant KA, McLauchlin J. Human listeriosis in England, 2001-2007: association with neighbourhood deprivation. *Eur Surveill*. 2010;15(27):7–16
42. Barrett ML-GL, Hines A, Andrews R, Jiang J. An examination of expected payer coding in HCUP databases. HCUP Methods Series Report 2014-03. Updated Dec 17, 2014. Available at: www.hcup-us.

ahrq.gov/reports/methods/methods.jsp. Accessed February 19, 2016

43. Pouillot R, Hoelzer K, Jackson KA, Henao OL, Silk BJ. Relative risk of listeriosis in Foodborne Diseases Active Surveillance Network (FoodNet) sites according to age, pregnancy, and ethnicity. *Clin Infect Dis*. 2012;54(suppl 5):S405–S410

44. FUS Team, Cincinnati Children's Hospital Medical Center. Evidence-based clinical care guideline for fever of uncertain source in infants 60 days of age or less. Available at: www.cincinnatichildrens.org/workarea/linkit.aspx?linkidentifier=id&itemid=87913&libid=87601. Accessed February 19, 2016

45. Kourtis AP, Sullivan DT, Sathian U. Practice guidelines for the management of febrile infants less than 90 days of age at the ambulatory network of a large pediatric health care system in the United States: summary of new evidence. *Clin Pediatr (Phila)*. 2004;43(1):11–16

46. Verani JR, McGee L, Schrag SJ. Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59(RR-10):1–36

47. Glasgow TS, Young PC, Wallin J, et al. Association of intrapartum antibiotic exposure and late-onset serious bacterial infections in infants. *Pediatrics*. 2005;116(3):696–702

48. Hall MA, Ducker DA, Lowes JA, et al. A randomised prospective comparison of cefotaxime versus netilmicin/penicillin for treatment of suspected neonatal sepsis. *Drugs*. 1988;35(suppl 2):169–177

49. Lin FY, Azimi PH, Weisman LE, et al. Antibiotic susceptibility profiles for group B streptococci isolated from neonates, 1995-1998. *Clin Infect Dis*. 2000;31(1):76–79

50. Wells TG, Trang JM, Brown AL, Marmer BC, Jacobs RF. Cefotaxime therapy of bacterial meningitis in children. *J Antimicrob Chemother*. 1984;14(suppl B):181–189

HOSPITAL Pediatrics

**Trends in US Hospital Stays for Listeriosis in Infants**

Angela F. Veesenmeyer and M. Bruce Edmonson

*Hospital Pediatrics* originally published online January 1, 2016;