REVIEW ARTICLE

A Meta-analysis of the Rates of *Listeria monocytogenes* and *Enterococcus* in Febrile Infants

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ABSTRACT

CONTEXT: A change in the epidemiology of pathogens causing serious bacterial infection (SBI) has been noted since original recommendations were made for the empirical antibiotic choices for young infants with fever.

OBJECTIVE: To assess the prevalence of SBI caused by *Listeria monocytogenes* and *Enterococcus* species.

DATA SOURCES: A literature search was conducted on keywords related to SBI, *L. monocytogenes,* and *Enterococcus* spp. infections.

STUDY SELECTION: Eligible studies were those conducted in the United States and published between January 1998 and June 2014 focusing on SBI in infants ≤90 days of age.

DATA EXTRACTION: The rates of urinary tract infection, bacteremia, and meningitis for each pathogen were recorded for each study. Meta-analysis was performed to calculate the prevalence for each pathogen in a random effects model with 0.5 continuity correction added to studies with zero events.

RESULTS: Sixteen studies were included. A total of 20 703 blood cultures were included, with weighted prevalences for *L. monocytogenes* and *Enterococcus* spp. bacteremia of 0.03% and 0.09%, respectively. A total of 13 775 cerebrospinal fluid cultures were included with event rates (unweighted prevalences) for *L. monocytogenes* and *Enterococcus* spp. meningitis of 0.02% and 0.03%, respectively. A total of 18 283 urine cultures were included, with no cases of *L. monocytogenes* and a weighted prevalence for *Enterococcus* spp. urinary tract infection of 0.28%.

LIMITATIONS: There may have been reporting bias or incomplete retrieval or inadvertent exclusion of relevant studies.

CONCLUSIONS: SBI caused by *L. monocytogenes* and *Enterococcus* spp. in febrile infants is rare, and therefore clinicians may consider a change in empirical antibiotic choices.

www.hospitalpediatrics.org
DOI:10.1542/hpeds.2015-0187

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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.

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Fever often prompts evaluation for serious bacterial infection (SBI) in infants, and a subset may be admitted to the hospital and placed on empirical antibiotics while awaiting bacterial culture results. For otherwise healthy infants outside the intensive care setting, empirical antibiotic coverage has classically included the combination of ampicillin and either gentamicin or a third-generation cephalosporin.[1,2] These regimens were adopted when group B *Streptococcus* (GBS) was the predominant pathogen causing SBI and *Listeria monocytogenes* was more commonly encountered as a neonatal pathogen. Since these regimens were initially determined, there have been changes in the epidemiology of pathogens causing SBI in young infants. The most notable changes have been the decline in cases of infections with GBS and *L. monocytogenes* and a rise in infections caused by *Staphylococcus aureus* and *Enterobacteriacae*.[3–5] The etiology of these changes is probably multifactorial, with proposed influences being changes in food handling in the United States,[6,7] the implementation of intrapartum GBS prophylaxis, vaccination for other previously common pathogens such as *Haemophilus influenzae,* and trends in antibiotic use in the community.

Although changes in the epidemiology of SBI in febrile infants have been demonstrated in several studies, meningitis and bacteremia are rare events, and the epidemiology of infections is often regional. With small sample sizes in previous studies, it has therefore been difficult to recommend a change in the empirical antibiotic choice for febrile infants, and practitioners often continue to include empirical antibiotic coverage for *L. monocytogenes* and *Enterococcus* spp. Stronger evidence supporting a low rate of invasive infections caused by *Enterococcus* spp. and *L. monocytogenes* in febrile infants is needed to inform practitioners in choosing empirical antibiotic regimens. This meta-analysis was performed to determine the prevalence of SBI caused by *L. monocytogenes* and *Enterococcus* spp. in otherwise healthy febrile infants ≤90 days of age in the United States.

METHODS

The Meta-Analysis of Observational Studies in Epidemiology[8] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses[9] guidelines were used in formulating this review.

Search Strategies

The PubMed database was searched by the primary author with guidance from institutional librarians using combinations of the terms "infant," "fever," "serious bacterial infection," "*Enterococcus,*" "*Listeria monocytogenes,*" "sepsis," "urinary tract infection," "bacteremia," and "meningitis." To include recent and relevant epidemiologic data, search limitations included studies published over ∼15 years, between January 1998 and June 2014. Additional limitations included studies performed in humans and those published in English. References from studies included in data analysis were reviewed by 3 of the authors for additional relevant citations.

Study Selection

Studies were screened by the primary author through title or abstract review to include studies focusing on the intended population of otherwise healthy febrile infants in the United States. Studies were therefore excluded if performed outside the United States, if there was specific focus on preterm infants, if cultures drawn in the ICU setting or the newborn nursery were included, or there was focus on 1 pathogen or disease process (eg, SBI associated with pneumonia). The remaining studies were then excluded upon abstract or full-text review if the specific data for infants ≤90 days of age were not available, or if pathogens causing SBI or the total number of positive blood, urine, or cerebrospinal fluid (CSF) cultures were not included in reported results. For studies that otherwise met inclusion criteria but did not describe specific age group characteristics or culture data in the text, the primary author was contacted and the study was included if the necessary information was subsequently obtained. Study dates, authors, and institutions were used to cross-reference studies for duplicate data sets. For publications with duplicate data sets, only the study with the larger data set was included for analysis. Because the purpose of this review is to evaluate rates of occult infections caused by *L. monocytogenes* and *Enterococcus* spp., only cases of urinary tract infection (UTI), bacteremia, and meningitis were included as SBIs.

Data Collection Process

The primary outcomes for this review were the prevalence rates of UTI, bacteremia, and meningitis caused by *L. monocytogenes* and *Enterococcus* spp. in febrile infants ≤90 days of age. The results from each included study were reviewed, and prevalence rates of UTI, bacteremia, and meningitis caused by each pathogen were recorded.

Study Quality Assessment

Studies were assessed for risk of bias via a 13-item assessment tool developed from recommendations published by the Agency for Healthcare Research and Quality for observational studies.[10] From the Agency for Healthcare Research and Quality question bank, applicable questions were chosen in the domains of Selection, Performance, Attrition, Reporting, and Conflict of Interest. Each study was independently assessed by 3 authors (R.L., B.F., and K.S.) and discussed until consensus was reached for each question.

Data Synthesis and Analysis

Heterogeneity between the studies was assessed via the Cochran Q test and I^2. Negative values for I^2 or lower confidence limits were set to 0. Because the included studies had low event rates and zero event rates were common, heterogeneity testing may not be a reliable assessment to determine the most appropriate method for a meta-analysis. In addition, study populations were assumed to differ from each other, and therefore a random effects model was consistently used with the assumption of at least moderate heterogeneity between studies. Meta-analysis was performed to calculate the prevalence for each pathogen. To adjust for the occurrence of zero events, a continuity correction of 0.5 was added to studies with zero events. Weighted prevalence rates (including lower and upper 95%

confidence limits) and the number needed to screen (NNS) to find 1 positive culture caused by *L. monocytogenes* or *Enterococcus* spp. were calculated for each pathogen. The data were analyzed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) and SAS 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Search Results

A flow diagram of search results is shown in Supplemental Fig 4. A total of 3081 studies were identified through initial search methods, and 16 articles were included in the analysis.

Included Study Characteristics

Sixteen studies met inclusion criteria.[4,5,11–24] The characteristics of each study and included data are detailed in Tables 1, 2, and 3. Although publication dates were restricted to studies published in the last 15 years, the dates during which the studies were performed vary and are listed in the tables. The included studies are observational, with the majority being retrospective in design. All included studies used a rectal temperature of ≥38.0°C as a criterion for fever. Unless specifically indicated in the tables, the species of *Enterococcus* was not specified in the results for each study. The quality assessment of each included study is detailed in Supplemental Table 4. Although 1 study was deemed low-quality because of the proposed conclusions, the data collection and results were sound and were therefore included in the analysis.

Meta-analysis

A total of 20 703 blood cultures were included in the analysis, with a weighted prevalence of bacteremia of 2.68% (95% confidence interval [CI], 2.00%–3.36%). There were 2 cases of *L. monocytogenes* and 22 cases of *Enterococcus* spp. causing bacteremia. The weighted prevalence of *L. monocytogenes* bacteremia was 0.03% (95% CI, 0.00%–0.06%) with an NNS of 3440. The weighted prevalence of *Enterococcus* spp. bacteremia was 0.09% (95% CI, 0.04%–0.14%) with an NNS of 1132. Figures 1 and 2 show the forest plots for bacteremia caused by *Enterococcus* spp. and *L. monocytogenes* with individual study event rates.

A total of 13 775 CSF cultures were included in the analysis, with a weighted prevalence of meningitis of 0.98% (95% CI, 0.48%–1.48%). There were 3 cases of *L. monocytogenes* and 4 cases of *Enterococcus* spp. causing meningitis. The event rates (unweighted prevalences) for

TABLE 1 Study Details for Bacteremia

Source	Type	Time Frame	Setting	Age, d	Total Study Subjects	Total Blood Cultures	Total Bacteremia	Total *Enterococcus*	Total *Listeria*	Comments
Bachur 2001[13]	R	1993–1999	ED	≤90	5279	4645	59	2	0	Both *E. faecalis*
Baker and Bell 1999[12]	P	1994–1996	ED	≤28	254	254	8	1	1	*Listeria* case occurred in 1996
Baker 1999[11]	P	1994–1996	ED	29–60	422	422	9	0	0	
Byington 2003[5]	P	1999–2002	ED	≤90	1298	1298	28	2	0	
Caviness 2008[14]	R	2001–2005	ED	≤28	960	893	71	7	0	
Evans 2013[15]	R	2007–2011	ED, clinic, inpatient	≤90	—	2092	38	2	0	Both *E. faecalis*
Greenhow 2014[4]	R	2005–2011	ED, clinic, inpatient	7–90	6232	5636	129	3	0	
Herr 2001[16]	R	1999–2000	ED	≤60	344	344	7	0	0	Excluded ill-appearing infants from subject group
Kadish 2000[17]	R	1993–1996	ED	≤28	372	372	12	0	0	
Levine 2004[18]	P	1998–2001	ED	≤60	1248	1235	25	1	0	
Maniaci 2007[19]	P	2005–2007	ED	≤90	234	234	6	0	0	
Morley 2012[20]	R	2006–2008	ED	≤60	207	205	4	0	0	
Pantell 2004[22]	P	1995–1998	Clinic	≤90	3066	2250	54	3	1	Blood and CSF data from PROS Febrile Infant Study All 3 isolates *E. faecalis*. *Listeria* case occurred in 1996
Watt 2010[23]	R	1997–2006	ED	<90	—	668	18	1	0	
Woelker 2012[24]	P	2004–2007	ED	2–60	155	155	3	0	0	
Totals						20 703	471	22	2	

ED, emergency department; P, prospective; R, retrospective. —, not applicable.

TABLE 2 Study Details for Meningitis

	Type	Time Frame	Setting	Age, d	Total Study Subjects	Total CSF Cultures	Total Meningitis	Total *Enterococcus*	Total *Listeria*	Comments
Bachur 2001[13]	R	1993–1999	ED	≤90	5279	4117	17	2	0	Both *E. faecium*
Baker and Bell 1999[12]	P	1994–1996	ED	≤28	254	254	4	0	1	*Listeria* case occurred in 1996
Baker 1999[11]	P	1994–1996	ED	29–60	422	422	5	0	0	—
Byington 2003[5]	P	1999–2002	ED	≤90	1298	1298	9	0	0	Specific culture information obtained from contacting author
Caviness 2008[14]	R	2001–2005	ED	≤28	960	874	21	1	0	Specific culture information obtained from contacting author
Evans 2013[15]	R	2007–2011	ED, clinic, inpatient	≤90	—	1159	7	1	0	*E. faecium*
Greenhow 2014[4]	R	2005–2011	ED, clinic, inpatient	7–90	6232	1796	16	0	0	—
Herr 2001[16]	R	1999–2000	ED	≤60	344	344	2	0	0	Excluded ill-appearing infants from subject group
Kadish 2000[17]	R	1993–1996	ED	≤28	372	372	5	0	0	—
Levine 2004[18]	P	1998–2001	ED	≤60	1248	1189	8	0	0	—
Maniaci 2007[19]	P	2005–2007	ED	≤90	234	234	0	0	0	—
Morley 2012[20]	R	2006–2008	ED	≤60	207	130	1	0	0	—
Pantell 2004[22]	P	1995–1998	Clinic	≤90	3066	1012	14	0	1	Blood and CSF data from PROS Febrile Infant Study *Listeria* case occurred in 1996
Watt 2010[23]	R	1997–2006	ED	<90	—	468	3	0	1	*Listeria* case occurred between 1997–2001
Woelker 2012[24]	P	2004–2007	ED	2–60	155	106	0	0	0	—
Totals						13 775	112	4	3	

ED, emergency department; P, prospective; R, retrospective. —, not applicable.

meningitis caused by *L. monocytogenes* and *Enterococcus* spp. were 0.02% (95% CI, 0.00%–0.77%) and 0.03% (95% CI, 0.00%–0.89%), respectively. Forest plots, weighted prevalence, and NNS were not generated for meningitis because of an excess of zero events.

A total of 18 283 urine cultures were included in the analysis, with a weighted prevalence of UTI of 9.34% (95% CI, 6.93%–11.75%). There were no cases of *L. monocytogenes* and 68 cases of *Enterococcus* spp. causing UTI. The weighted prevalence for UTI caused by *Enterococcus* spp. was 0.28% (95% CI, 0.18%–0.38%), with an NNS of 363. Figure 3 shows the forest plot for UTI caused by *Enterococcus* spp. with individual study event rates.

There were a total of 3 infants with *L. monocytogenes* infections, 2 with bacteremia and meningitis, and 1 with meningitis alone. In the included articles, there were no reported cases of *L. monocytogenes* after 2001. The details for cases of *L. monocytogenes* infections are in Tables 1 and 2.

DISCUSSION

This meta-analysis demonstrates an NNS for bacteremia caused by *L. monocytogenes* of 3440, with reported event rates too low to calculate an NNS for meningitis. In addition, there were no reported infections in the included studies after 2001. Although there are still sporadic outbreaks of *L. monocytogenes* in the United States, this pathogen typically causes infections in neonates subsequent to maternal infection and, when present, is most often noted postmortem after in utero infant demise or

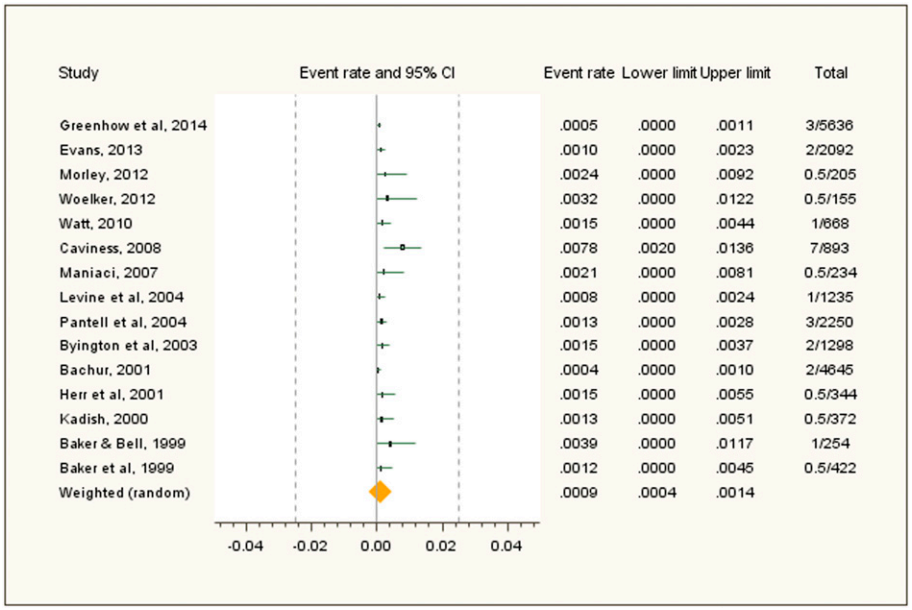

FIGURE 1 Forest plot for event rates for bacteremia caused by *Enterococcus* spp.

in infants delivered prematurely because of maternal infection. As with other rare diseases, clinicians may ask screening questions to determine a patient's risk for infections with *L. monocytogenes* and consider empirical therapy in certain populations such as premature infants and those exposed to high-risk foods or travel.

Invasive infections caused by *Enterococcus* spp. are also rare, with an unweighted prevalence of meningitis of 0.02% and weighted prevalence for bacteremia of only 0.09%. The NNS to identify 1 case of bacteremia caused by *Enterococcus* spp. was 1132, and reported event rates were too low to calculate an NNS for meningitis.

The majority of infections with *Enterococcus* spp. are found in the urinary tract. Although the weighted prevalence of enterococcal UTI was 0.28%, it should be noted that the definition of UTI used in several of the included studies may overestimate the prevalence of UTI given the currently accepted definition described in the

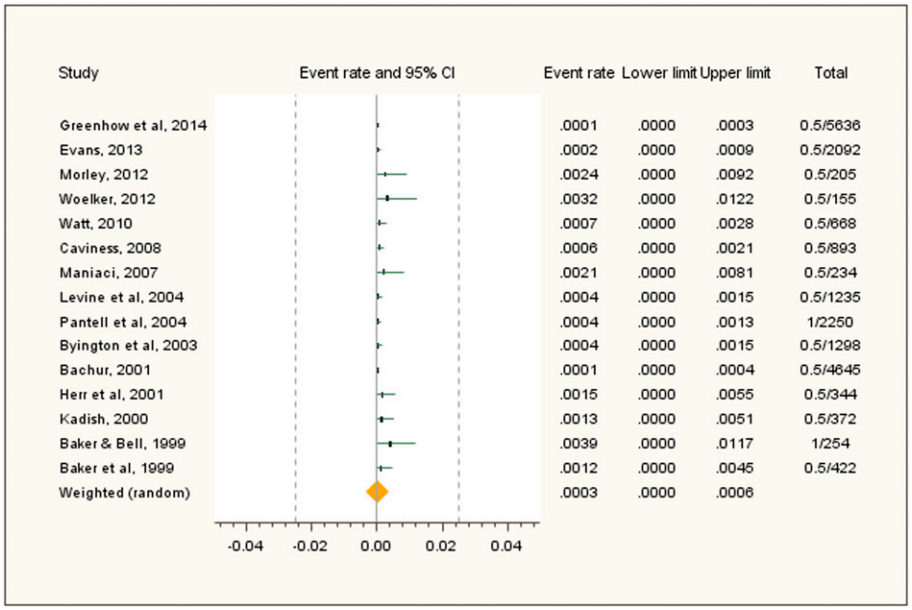

FIGURE 2 Forest plot for event rates for bacteremia caused by *L. monocytogenes*.

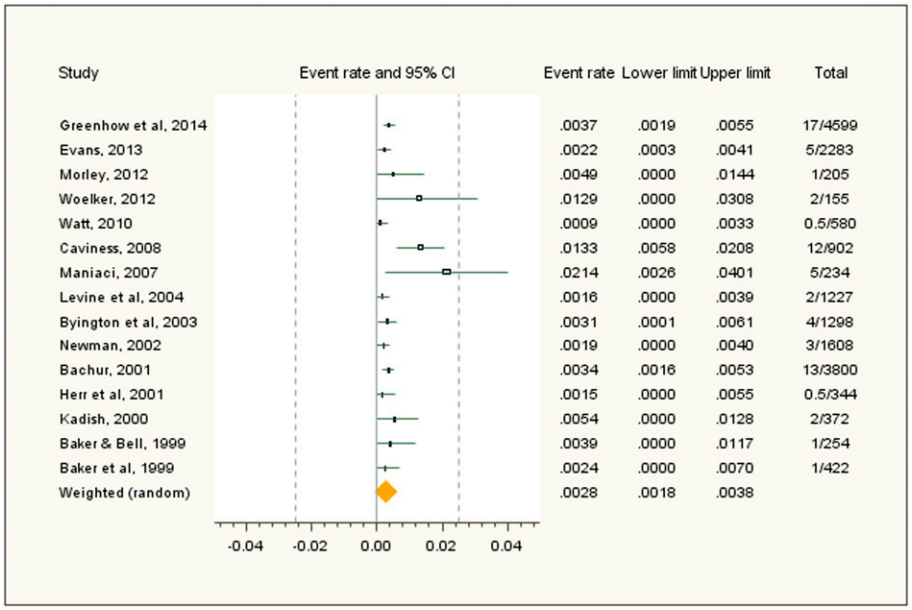

FIGURE 3 Forest plot for event rates for UTI caused by *Enterococcus* spp.

American Academy of Pediatrics UTI guidelines.[25] In particular, the studies contributing the highest number of cases in this analysis of *Enterococcus* spp. causing UTI defined a positive culture as a catheterized specimen with >10 000 colony-forming units (CFUs) of bacterial growth.[4,13,14]

The decrease in infections caused by *L. monocytogenes* is specific to the United States, whereas other countries continue to report infection in neonates.[6,7] In 1987, the Food Safety and Inspection Service of the US Department of Agriculture instituted a zero-tolerance policy prohibiting the sale of ready-to-eat foods contaminated with *L. monocytogenes,* and the policy has been strengthened with each outbreak identified since that time. There have also been public education campaigns targeting pregnant women and populations with a higher than expected consumption of at-risk foods. With these implemented changes, there has been an overall decrease in laboratory confirmed listeriosis and a decrease in pregnancy-associated cases in the United States.[26]

Infections with *Enterococcus* spp. occur most often in patients with anatomic defects or indwelling catheters or in the hospital setting.[27] Because multiple studies have demonstrated the low rate of progression from UTI to bacteremia or meningitis and a low rate of adverse events from UTI when infants are well appearing,[28,29] immediate coverage for this pathogen may not be needed. In addition, antibiotic therapy is often changed once a pathogen is identified,[30] and hospitalized patients are under close observation with the ability to broaden antibiotic coverage if the patient shows clinical decline or an SBI is definitively identified. If there is high suspicion for UTI in an ill-appearing patient or the infant has a known urologic defect, practitioners may consider screening with enhanced urinalysis and broadening the empirical antibiotic regimen while awaiting culture results.

This meta-analysis excluded studies performed in ICU settings and in infants with defined sites of infection; therefore the data from this study do not necessarily apply to ill-appearing infants or those with a high likelihood of focal infection such as meningitis or osteomyelitis. It has been demonstrated that the rate of SBI in ill-appearing infants is collectively higher than in well-appearing infants, so clinicians should consider broader empirical antibiotic coverage for this population.

Only studies performed in the United States were included in this meta-analysis, because the epidemiology of pathogens is expected to vary between countries along with differences in environmental factors such as food preparation and sales regulations. Studies published >15 years before the review were excluded to ensure that only recent epidemiologic reports were included. Other causes of SBI such as gastroenteritis and osteomyelitis were not included in the reported results because they are unlikely sites for infection with *L. monocytogenes* and *Enterococcus* spp., and these patients would not be the targeted population for more narrow empirical antibiotic therapy. In addition, this review excluded studies performed in the NICU and those with medical hardware in place, because these populations are at greater risk for SBI caused by *L. monocytogenes* and *Enterococcus* spp. Although this analysis demonstrates a historically low rate of SBI caused by *L. monocytogenes* and *Enterococcus* spp., it is imperative that each practitioner be familiar with his or her own region's bacterial epidemiology and resistance patterns to appropriately choose empirical antibiotic coverage.

Limitations and Bias

Although efforts were taken to include all relevant studies, there is a possibility of incomplete retrieval of relevant studies or

TABLE 3 Study Details for UTI

Source	Type	Time Frame	Setting	Age, d	Total Study Subjects	Total Urine Cultures	Total UTI	Total *Enterococcus*	Total *Listeria*	UTI Definition	Comments
Bachur 2001[13]	R	1993–1999	ED	≤90	5279	3800	316	13	0	≥1000 CFUs SPA or ≥10 000 cath	Specific culture information obtained from contacting author
Baker and Bell 1999[12]	P	1994–1996	ED	≤28	254	254	17	1	0	≥1000 CFUs	—
Baker 1999[11]	P	1994–1996	ED	29–60	422	422	17	1	0	≥1000 CFUs	—
Byington 2003[5]	P	1999–2002	ED	≤90	1298	1298	78	4	0	≥100 000 CFUs or ≥50 000 CFUs and positive UA	Specific culture information obtained from contacting author
Caviness 2008[14]	R	2001–2005	ED	≤28	960	902	177	12	0	≥10 000 CFUs	Specific culture information obtained from contacting author
Evans 2013[15]	R	2007–2011	ED, clinic, inpatient	≤90	—	2283	111	5	0	As determined by treating physician	—
Greenhow 2014[4]	R	2005–2011	ED, clinic, inpatient	7–90	6232	4599	778	17	0	In 7- to 60-d-old ≥10 000 CFUs in 61- to 90-d-old pyuria and ≥50 000 CFUs	—
Herr 2001[16]	R	1999–2000	ED	≤60	344	344	25	0	0	≥50 000 CFUs	Excluded ill-appearing infants from subject group
Kadish 2000[17]	R	1993–1996	ED	≤28	372	372	32	2	0	≥50 000 CFUs	—
Levine 2004[18]	P	1998–2001	ED	≤60	1248	1227	112	2	0	≥1000 CFUs SPA, ≥50 000 cath, or ≥10 000 cath and positive UA	—
Maniaci 2007[19]	P	2005–2007	ED	≤90	234	234	26	5	0	≥50 000 cath or ≥10 000 cath and positive UA	2 *Enterococcus* defined "definite" and 3 "possible" UTIs for low CFU counts
Morley 2012[20]	R	2006–2008	ED	≤60	207	205	19	1	0	≥10 000 CFUs	—
Newman 2002[21]	P	1995–1998	Clinic	≤90	3066	1608	167	3	0	≥100 CFUs SPA, ≥20 000 cath or ≥100 000 clean catch	Urine data from PROS Febrile Infant Study
Watt 2010[23]	R	1997–2006	ED	<90	—	580	58	0	0	≥ 100 000 CFUs or ≥10 000 CFUs and positive UA	—
Woelker 2012[24]	P	2004–2007	ED	2–60	155	155	11	2	0	≥50 000 cath or ≥10 000 cath and positive UA	—
Totals						18 283	1944	68	0		

cath, catheter; ED, emergency department; P, prospective; R, retrospective; SPA, suprapubic aspiration; UA, urinalysis. —, not applicable.

exclusion upon abstract review of articles that may have affected the outcome of our analysis. There is also the possibility of reporting bias, with this analysis undertaken to assess the need for a change in antibiotic regimen. We attempted to mitigate these limitations with the inclusion of several authors performing the search and discussion of results.

Several of the studies included in this meta-analysis did not report any infections with *L. monocytogenes* or *Enterococcus* spp. We recognize the limitation of including studies with zero events in standard methods of meta-analysis and have therefore included a continuity correction factor of 0.5 for those studies with no reported events. In addition, although the calculated statistical heterogeneity between studies was low, a random-effects model was used given the anticipated poor performance of heterogeneity calculations when there are a low number of events.

CONCLUSIONS

This meta-analysis demonstrates that serious bacterial infections caused by *L. monocytogenes* and *Enterococcus* spp. are rare in febrile infants ≤90 days of age outside the ICU setting, suggesting that an update in the empirical antibiotic regimen chosen for febrile infants admitted to the hospital during evaluation for SBI may be warranted. A longitudinal, multicenter study focusing on the epidemiology of SBI in febrile infants would provide additional evidence to support a change in recommended empirical antibiotic regimens.

Acknowledgments

Special thanks to Dr Shawn Ralston for her mentorship and to Drs Carrie Byington, Tara Greenhow, A. Chantal Caviness, Kevin Watt, Ravi Jhaveri, M. Douglas Baker, Tom Newman, and Richard Bachur for reviewing the data sets used for the included studies to retrieve the information needed for this review. We also acknowledge our librarians, Esther Sarino and Jin An, for their help in performing the literature search.

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