Risk of Meningitis in Infants Aged 29 to 90 Days with Urinary Tract Infection: A Systematic Review and Meta-Analysis

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Objective To determine the risk of bacterial meningitis in infants aged 29-90 days with evidence of urinary tract infection (UTI).

Methods PubMed (MEDLINE), Embase, and the Cochrane Library were systematically searched for studies reporting rates of meningitis in infants aged 29-90 days with abnormal urinalysis or urine culture. Observational studies in infants with evidence of UTI who underwent lumbar puncture (LP) reporting age-specific event rates of bacterial meningitis and sterile cerebrospinal fluid pleocytosis were included. Prevalence estimates for bacterial meningitis in infants with UTI were pooled in a random effects meta-analysis.

Results Three prospective and 17 retrospective cohort studies were included in the meta-analysis. The pooled prevalence of concomitant bacterial meningitis in infants with UTI was 0.25% (95% CI, 0.09%-0.70%). Rates of sterile pleocytosis ranged from 0% to 29%. Variation in study methods precluded calculation of a pooled estimate for sterile pleocytosis. In most studies, the decision to perform a LP was up to the provider, introducing selection bias into the prevalence estimate.

Conclusions The risk of bacterial meningitis in infants aged 29-90 days with evidence of UTI is low. A selective approach to LP in infants identified as low risk for meningitis by other clinical criteria may be indicated. *(J Pediatr 2019;212:102-10)*.

Urinary tract infection (UTI) is the most common serious bacterial infection in young infants, occurring in approximately 7% of febrile infants aged 0-3 months.[1] In infants younger than 3 months, bacteremia has been associated with UTI in up to 25% of cases,[2] with more recent studies reporting bacteremia rates of 4%-10%,[3-8] placing these infants at risk for hematogenous dissemination to the central nervous system.

Although febrile infants aged 0-28 days routinely undergo lumbar puncture (LP) during their initial evaluation, febrile infants aged 29-90 days often are stratified according to their clinical examination plus their complete blood count and urinalysis to determine their risk of serious bacterial infection before proceeding with LP.[9] The Rochester criteria suggest that febrile infants aged 0-60 days with a positive urinalysis should have cerebrospinal fluid (CSF) obtained to assess for concomitant bacterial meningitis.[10,11] Subsequent clinical prediction rules for febrile infants less than 60-90 days that do not include initial CSF testing continue to recommend LP for infants with an abnormal urinalysis or classify infants with an abnormal urinalysis outside the low-risk zone, leaving the decision to obtain CSF up to the treating provider.[12-14] In 1 cross-sectional study on the management of febrile infants aged 29-56 days in pediatric emergency departments (EDs), one-half of EDs had a clinical practice guideline recommending CSF testing in all patients and the other one-half recommended CSF testing only in high-risk patients based on history, physical findings, urine, and blood testing, resulting in LP for all infants with evidence of UTI irrespective of hospital protocol.[15] Despite these guidelines, practice patterns regarding acquisition of CSF for culture vary among infants with suspected UTI.[8,16]

Aseptic meningitis is common in infants with UTI, reported in up to 29% of patients.[17-19] Providers who initiate antibiotic therapy without obtaining CSF in infants with suspected UTI may decide to perform the LP later in the treatment course for infants with a positive blood culture or change in clinical status. Routine LP for all infants with suspected UTI avoids the challenge of determining

CSF	Cerebrospinal fluid
ED	Emergency department
LP	Lumbar puncture
UTI	Urinary tract infection

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Portions of this study were presented as a poster at the Pediatric Academic Societies Annual Meeting, April 30-May 3, 2016, Baltimore, Maryland.

0022-3476/$ - see front matter. Published by Elsevier Inc.
https://doi.org/10.1016/j.jpeds.2019.04.053

whether sterile CSF pleocytosis after antibiotic administration represents systemic inflammation related to the UTI or partially treated bacterial meningitis.

Previous studies have found that bacterial meningitis associated with UTI is a rare event.[3,4,7,18,20-22] However, owing to small sample sizes and often no case of meningitis, estimates for concomitant bacterial meningitis from individual studies are imprecise and the upper bounds of the 95% CIs are low but clinically significant. The purpose of this systematic review and meta-analysis was to determine the pooled prevalence of coexisting meningitis in young febrile infants aged 29-90 days with an abnormal urinalysis or urine culture. We hypothesize that young infants outside the neonatal period with UTI are at low risk for bacterial meningitis and that CSF pleocytosis in these infants is unlikely to reflect bacterial meningitis.

Methods

The systematic review and meta-analysis were performed according to the PRISMA Statement.[23] PubMed (MEDLINE), Embase, and the Cochrane Library were systematically searched from inception through August 20, 2018, for studies reporting rates of meningitis in infants aged 29-90 days with abnormal urinalysis or urine culture. The electronic search strategy for each database is shown in **Table I** (available at www.jpeds.com). The reference lists of identified studies were searched manually for additional studies not identified in the database search. The search was not limited by language. Studies were included if they reported rates of bacterial meningitis or sterile CSF pleocytosis in a population of infants aged 29-90 days with either an abnormal urinalysis or urine culture who had undergone LP. Studies were excluded if age-specific data for infants aged 29-90 days were not available or if the study did not report how many infants in this age group with evidence of UTI had undergone LP. For studies that did not provide age-specific data, the study's corresponding author was contacted and the study was included if the relevant information was obtained.

The following information was independently extracted from each article by at least 2 of 3 investigators: study first author and publication year, study design, study years, study age group, subjects aged 29-90 days with UTI, subjects aged 29-90 days with UTI who underwent LP, definition of UTI, definition of bacterial meningitis, definition of CSF pleocytosis, prevalence of bacterial meningitis and sterile pleocytosis, and whether any subjects were pretreated with antibiotics before LP. Studies were critically appraised using a checklist adapted from the Newcastle Ottawa Scale[24] and the Joanna Briggs Institute quality assessment tool for systematic reviews of prevalence (**Figure 1**; available at www.jpeds.com).[25] Although the objective of some studies was not necessarily to report rates of concomitant meningitis in infants with UTI, the study was included if this information was available from the results. The critical appraisal checklist compared each study's characteristics with those of a high-quality study measuring the prevalence of concomitant meningitis and UTI in febrile infants. Study sample size was assessed according to the Joanna Briggs Institute tool[25] using a baseline risk of bacterial meningitis of 3 per 1000 infants aged 29-90 days.[26]

The primary outcome was the prevalence of bacterial meningitis in infants aged 29-90 days with either an abnormal urinalysis or urine culture who had undergone LP. The secondary outcome was the prevalence of sterile CSF pleocytosis in this same group of infants. For studies that provided CSF cell counts for subjects, pleocytosis was defined as 10 cells/μL or greater[27,28] with correction for traumatic LP, defined as a CSF red blood cell count of 10 000 cells/μL or greater, using the ratio of 1000 red blood cells for 1 white blood cell.[29] For studies that did not provide specific CSF cell counts for each subject, that study's criteria for CSF pleocytosis and correction for traumatic LP were used.

Prevalence estimates for bacterial meningitis were pooled in a random effects meta-analysis using the statistical software R (v 3.4.2, R Core Team, Vienna, Austria). We fit a generalized linear mixed model to the data using the logit transformation of the proportions (function 'metaprop' in R package 'metafor').[30] CIs for individual studies were calculated using the Agresti-Coull method; if a lower bound was negative, it was replaced by zero. Between-study statistical heterogeneity was assessed by the I^2 statistic. To account for probable cases of bacterial meningitis with negative CSF cultures, a sensitivity analysis was conducted in which probable cases were included in the prevalence estimate in addition to the culture-proven cases included in the primary analysis. Probable cases were infants with a negative CSF culture who were treated for bacterial meningitis owing to CSF pleocytosis with antibiotic pretreatment before LP. In a second sensitivity analysis, the pooled prevalence was calculated after excluding the low-quality studies. An additional analysis was performed in which individual studies were excluded 1 study at a time to determine the influence of each study on the pooled prevalence estimate. Subgroup analyses were conducted to report the pooled prevalence in infants with culture-confirmed UTI, infants with an abnormal urinalysis, and infants aged 29-60 days. The effects of differences in study design and inclusion criteria were explored using meta-regression (function 'metareg').

Results

Search Results

The flow diagram for search results is shown in **Figure 2** (available at www.jpeds.com). The literature search identified 3 prospective cohort studies[31-33] and 18 retrospective cohort studies for inclusion in the qualitative synthesis.[6,8,13,16,17,21,22,34-44] After excluding 1 study owing to overlapping data,[44] 20 studies were included in the meta-analysis. Two study authors provided additional data for inclusion.[8,31] The median number of included patients

per study was 61 (range, 3-1609). Age-specific event data were extracted for infants between 29 and 60 days in 8 studies[13,17,22,31-33,40,42]; 29 and 90 days in 11 studies[6,8,16,21,34-38,41,43]; and 29 and 99 days in 1 study.[39] Although this last study did not provide an event rate for infants aged 29-90 days, it was still included in the meta-analysis because the inclusion of infants up to 99 days in this study was not thought to significantly influence the results.

Study Characteristics

Table II describes the individual study methods, inclusion and exclusion criteria, and UTI definitions. Nine studies included only infants who had presented with fever and 11 studies included infants with evidence of UTI but not necessarily fever. Sixteen studies reported rates of meningitis in infants with culture-confirmed UTI. The remaining 4 studies provided data on infants with an abnormal urinalysis.[13,36,38,41] In the 3 prospective studies, LP was performed on all febrile infants.[31-33] In 1 retrospective study of febrile infants 29-56 days of age who had CSF cultures, hospital protocol followed the Philadelphia criteria, in which routine LP is recommended for all these febrile infants; however, the LP rates are not reported.[13] In another retrospective study of infants 30-90 days of age with abnormal urinalysis who had CSF cultures, hospital protocol followed the Rochester criteria in which all infants with positive urinalysis should have LP; however, LP rates are not known.[38] For all the other studies, the treating provider determined whether or not to perform the LP. The results of the quality assessment of individual studies are shown in Table III (available at www.jpeds.com). Quality scores ranged from 2 to 8 on a 10-point scale.

Antibiotic Pretreatment

Several studies addressed antibiotic treatment before LP. Four studies excluded infants who received antibiotics before culture acquisition.[31,37,38,40] One study used chart review and urine antibacterial activity testing to confirm that no infants had been pretreated with antibiotics.[34] Two studies reported a total of 4 probable cases of bacterial meningitis in infants who were pretreated with antibiotics, had sterile CSF pleocytosis, and were treated for bacterial meningitis.[16,22] Two other studies described a total of 5 infants with sterile CSF pleocytosis who had been pretreated with antibiotics, but had CSF samples with normal glucose, protein, and less than 45% neutrophils.[21,35] The remaining 11 studies do not explicitly address pretreatment or they acknowledge that pretreatment data are not available.

Prevalence of Bacterial Meningitis among Infants with UTI

There were 11 cases of bacterial meningitis among the 3868 infants with either an abnormal urinalysis or culture-confirmed UTI who underwent LP (0.28% or 2.8 per 1000). Random effects modeling of these 20 studies yielded a pooled prevalence of concomitant bacterial meningitis of 0.25% (95% CI, 0.09%-0.70%; Figure 3). There was moderate between-study heterogeneity (I^2 = 47%). For infants with culture-confirmed UTI, the pooled prevalence was 0.24% (95% CI, 0.07%-0.75%; Figure 4 available at www.jpeds.com). For infants with an abnormal urinalysis, the pooled prevalence was 0.40% (95% CI, 0.06%-2.80%; Figure 5 available at www.jpeds.com), with a prevalence of 0.68% (95% CI, 0.26%-1.81%) if the excluded study[44] is added for this subgroup analysis, because its overlapping study[8] was not included in the urinalysis subgroup. For the subgroup of infants aged 29-60 days, age-specific data were extracted from 12 studies for a pooled prevalence of 0.18% (95% CI, 0.07%-0.42%). Figure 6 shows the forest plot for rates of sterile CSF pleocytosis in infants with UTI, with notation regarding exclusion of traumatic LPs. Variability in individual study definitions of CSF pleocytosis precluded calculation of a pooled prevalence.

A sensitivity analysis, including the 4 probable cases in addition to the 11 culture-proven cases in the primary analysis, yielded the prevalence estimate of 0.37% (95% CI, 0.16%-0.84%) for concomitant bacterial meningitis with either an abnormal urinalysis or culture-confirmed UTI. In the second sensitivity analysis, in which each individual study was excluded and the overall prevalence estimate was recalculated, it is clear that 2 studies have significant influence on the results (Figure 7; available at www.jpeds.com).[8,22] One of these 2 studies is the largest cohort in the meta-analysis with 1609 (85%) of the 1895 febrile infants with UTI undergoing LP.[22] In the other study, 126 of the 566 infants (22%) with UTI underwent LP.[8] Differences in CSF culture acquisition rates may help to explain the between-study differences in event rates. An additional sensitivity analysis, excluding the lower quality studies with quality scores of 0-3, yielded a pooled prevalence of 0.22% (95% CI, 0.10%-0.46%). There were no significant subgroup differences in the prevalence of bacterial meningitis according to prospective or retrospective study design, presence of fever in study's inclusion criteria, and use of an abnormal urinalysis or urine culture for inclusion. Two studies on febrile infants with an abnormal urinalysis also described the rates of bacterial meningitis in febrile infants with a normal urinalysis.[38,44] Combining data from these 2 studies into a 2 × 2 table results in a positive likelihood ratio of 1.0, indicating that the probability of bacterial meningitis is unchanged when the urinalysis is positive.

Discussion

This systematic review and meta-analysis found that the prevalence of concomitant bacterial meningitis and UTI in infants aged 29-90 days is 0.25% (95% CI, 0.09-0.70%). Among infants in this age group with UTI, the number needed to investigate with LP to diagnose 1 case of bacterial meningitis is 400 infants (95% CI, 143-1111). Compared with the prevalence of bacterial meningitis of 0.2%-0.3%

Table II. Characteristics of studies

Authors	Year	Study type	Study years	Age	Inclusion diagnosis	Exclusions	UTI definition	No. aged 29-90 days with UTI+LP/No. aged 29-90 days with UTI	Pretreatment
Baker et al[32]	1990	P	1987-1988	29-56 days	Fever	None specified	Cath/SPA: ≥1K CFU	6/6	NA
Baker et al[33]	1999	P	1994-1996	29-60 days	Fever	Not immunocompetent	Cath: ≥1K CFU	17/17	NA
Kaplan et al[43]	2000	R	1993-1997	28-90 days	Fever and all 3 cultures sent	None specified	Cath/SPA: ≥10K CFU	165/165; study only includes patients who had blood, urine, and CSF cultures	NA
Syrogiannopoulos et al[37]	2001	R	1990-2001	≤90 days	UTI	Traumatic LP with ≥1000 RBC	Cath/SPA: positive culture	50/102	None
Adler-Shohet et al[35]	2003	R	1995-2000	<6 months	UTI or meningitis	Hospital-acquired UTI; UCx with >1 organism (unless patient had urinary tract abnormality or pyuria)	Cath: ≥10K CFU Bag: ≥100K CFU	126/166	Three infants with sterile pleocytosis pretreated (normal CSF glucose, protein, differential; not treated for BM)
Goldman et al[36]	2003	R	1997-2000	≤90 days	Fever and pyuria	Initial ED temperature <38°C	Pyuria: ≥10 WBC Cath: >50K CFU plus pyuria	73/132	NA
Vuillermin and Starr[16]	2007	R	1999-2003	≤90 days	UTI or meningitis	None specified	SPA: any pure growth Cath: >100K CFU CC: >10^8 CFU	51/127	One probable BM case with sterile pleocytosis pretreated
Shah et al[31]	2008	P	1999-2001	≤60 days	Fever and UTI	Received antibiotics within 48 hours of ED; no fever by history or in ED	SPA: ≥1K CFU Cath: ≥50K CFU Cath: ≥10K and <50K CFU plus positive UA	49/49	None
Yam et al[34]	2009	R	2004-2007	≤6 months	UTI	UCx and CSF culture not obtained on same day	CC/MSU: ≥10^8 CFU Cath/SPA: any growth from pure culture	64/64; study only includes patients who had LP at same time as UCx	None
Schnadower et al[22]	2010	R	1995-2006	29-60 days	Fever and UTI	Transfer from OSH; urine not collected by cath or SPA; UCx with >1 organism; no fever within 24 hours of ED	SPA: ≥1K CFU Cath: ≥50K CFU Cath: ≥10K and <50K CFU plus positive UA	1609/1895	Three probable BM cases with sterile pleocytosis pretreated
Schnadower et al[45]	2011	Secondary analysis of Schnadower 2010[22] to determine prevalence of sterile CSF pleocytosis in febrile infants aged 29-60 days with UTI				No LP performed; no CSF cell count obtained; bloody LP (>1000 RBC); presence of BM	—	1190/1895; 705 excluded: 286 no LP, 117 no CSF cell count, 297 bloody LP, 5 cases definite/probable BM	Excluded 3 probable BM cases with sterile pleocytosis that were pretreated
Paquette et al[38]	2011	R	2001-2005	30-90 days	Fever and all 3 cultures sent	Received antibiotics before cultures; history of prematurity or chronic condition; signs of localized infection; missing culture data	Abnormal UA: positive LE/nitrites on dipstick or >10 WBC on microscopy	57/57; study only includes patients who had complete sepsis workup (hospital protocol for LP on all febrile infants 1-3 months with abnormal UA; however, adherence not known)	None

(*continued*)

Table II. Continued

Authors	Year	Study type	Study years	Age	Inclusion diagnosis	Exclusions	UTI definition	No. aged 29-90 days with UTI+LP/No. aged 29-90 days with UTI	Pretreatment
Tebruegge et al[21]	2011	R	2001-2010	≤16 years	UTI	UCx with >1 organism; UCx with fungal organism; CSF not obtained within 48 hours of urine	SPA: ≥100 CFU Cath: ≥100 CFU CC: ≥1K CFU Bag: ≥100K CFU	304/304; study only includes patients with UTI who had CSF obtained	Two infants with sterile pleocytosis pretreated (normal CSF glucose, protein, differential)
Morley et al[40]	2012	R	2006-2008	≤60 days	Fever and had blood, urine, or CSF culture	Cultures done outside the ED, presence of VP shunt, patient already on antibiotics	≥100K CFU (urine sampling method not specified)	3/11	None
Peñalba Citores et al[41]	2012	R	2004-2010	<3 months	Abnormal UA or Gram stain	Urine sample not obtained in ED or not obtained by cath	Abnormal UA: >10 WBC or positive nitrites or microorganism on Gram stain	64/166	NA
Averbuch et al[42]	2014	R	2007	<2 months	UTI	None specified	UTI: Cath: >10K CFU Clinical symptoms of infection plus any pathogen from SPA or ≥10K CFU single pathogen by cath	17/24	NA
Greenhow et al[8]	2014	R	2005-2011	7-90 days	Blood, urine, or CSF culture sent	<37 weeks of gestation, underlying medical condition; additional cultures within 3 days of a positive or negative culture were not included unless they identified a new pathogen	7-60 d: Cath: ≥10K CFU 61-90 d: Cath: ≥50K CFU plus pyuria Bag: ≥100K CFU plus chart review	126/566	NA
Hernandez-Bou et al[6]	2015	R	2007-2012	<3 months	UTI	None specified	Cath: >10K CFU plus abnormal Gram stain	19/323	NA
Lee et al[39]	2017	R	2013-2016	29-99 days	UTI	None specified	Cath: ≥50K CFU	80/85	NA
Scarfone et al[13]	2017	R	2007-2014	29-56 days	Fever and LP in ED	CSF collected from VP shunt	UA normal if: negative or small LE, negative nitrite, <10 WBC, normal Gram stain	54/54; study only includes patients who had LP in ED (hospital protocol for LP on all febrile infants 29-56 days however adherence not reported)	NA
Thomson et al[17]	2017	R	2005-2013	≤60 days	UTI with CSF culture within 24 hours of presentation	Urine sample not obtained by cath	Cath: ≥50K CFU or 10-50K CFU with abnormal UA	934/934; study only includes patients with UTI who had CSF obtained	NA
Young et al[44]	2018	R	2007-2015	29-60 days	Fever, UA performed, and all 3 cultures sent	History of fever during birth admission; first documented fever >24 hours after admit	Abnormal UA: any LE or nitrites, ≥5 WBC Cath: ≥10K CFU Bag: ≥50K CFU	337/682	One BM case with sterile pleocytosis pretreated

BM, Bacterial meningitis; *Cath*, catheterization; *CC*, clean catch; *CFU*, colony-forming units; *LE*, leukocyte esterase; *MSU*, midstream urine; *NA*, not addressed or data not available; *OSH*, outside hospital; *P*, prospective; *R*, retrospective; *RBC*, red blood cell; *SPA*, suprapubic aspiration; *UA*, urinalysis; *UCx*, urine culture; *VP*, ventriculoperitoneal; *WBC*, white blood cell.

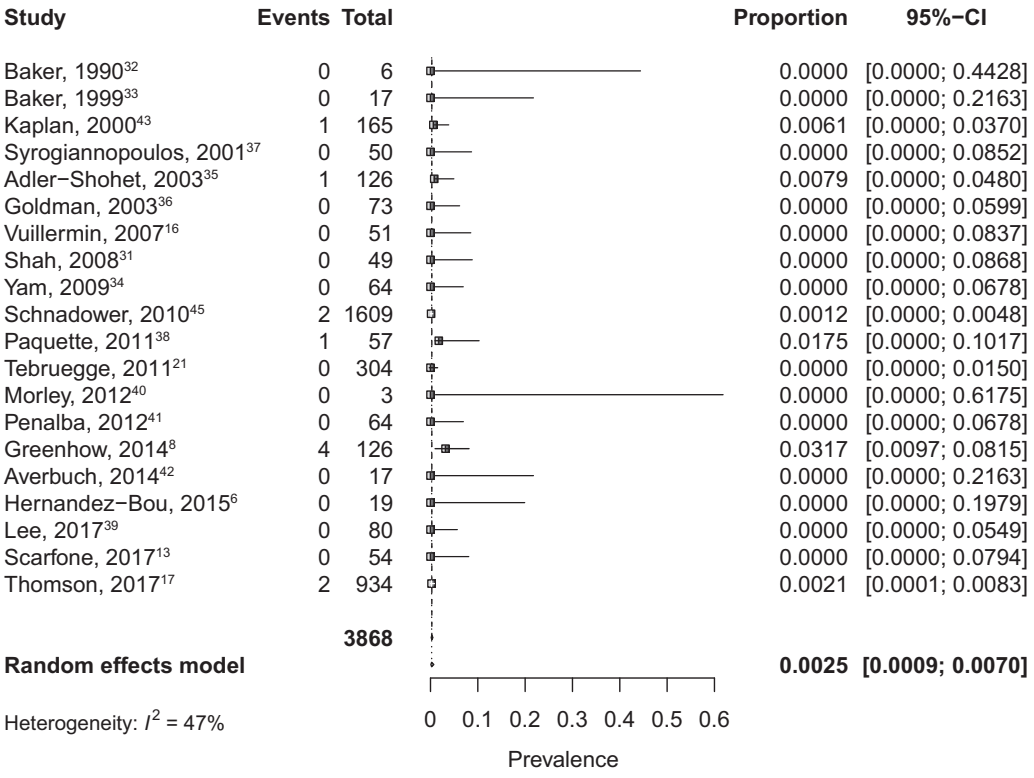

Figure 3. Prevalence of bacterial meningitis in infants aged 29-90 days with evidence of UTI.

reported in other cohorts of infants aged 29-90 days undergoing evaluation for serious bacterial infection, evidence of UTI alone does not significantly change the pretest probability of bacterial meningitis.[26,46,47] Although UTI is rarely associated with bacterial meningitis in this population, sterile CSF pleocytosis is common among infants with UTI who undergo LP, occurring in 18%-29% of patients in the 2 largest cohorts included in this review.[17,45]

Most studies included in this meta-analysis left the decision to obtain CSF up to the treating provider. This strategy introduces selection bias into the prevalence estimate of coexisting bacterial meningitis and UTI, because infants who seem to be sick are more likely to undergo LP than infants who seem to be well. Although 3868 infants with evidence of UTI who underwent LP comprised the denominator in the pooled prevalence estimate, at least an additional 1379 infants in the same age group with evidence of UTI from the individual studies did not have CSF obtained and therefore were not included in the meta-analysis. Young et al[44] described no infant with missed bacterial meningitis among 345 cases aged 29-60 days with fever and a positive urinalysis who were treated with antibiotics without LP, including 7 cases with bacteremia. Considering the recent literature reporting complete evaluations for sepsis in 25% of febrile infants aged 29-60 days and 5% of febrile infants aged 61-90 days without any cases of missed bacteremia or meningitis,[46] this meta-analysis provides a conservative estimate of bacterial meningitis associated with UTI in this age group; however, the true prevalence most likely is lower.

The ideal study to determine the prevalence of concomitant bacterial meningitis and UTI in febrile infants aged 29-90 days would require a large, prospective cohort of febrile infants in this age group, all of whom had both urine and CSF samples obtained simultaneously. Although 3 studies included in this review were conducted in this fashion, the small number of febrile infants with UTI included in these studies—49, 6, and 17 infants—precludes a precise risk estimate for concomitant bacterial meningitis.[31-33] A larger version of these studies is unlikely to be done. Pooling prevalence estimates in the included studies allows clinicians to quantify the risk of concomitant bacterial meningitis more precisely and may help to inform shared decision making between providers and families.

Based on a pretest probability of bacterial meningitis of 0.25% in infants with UTI, universal LP may not be appropriate and may actually expose the infant to unnecessary harm. Traumatic or unsuccessful LP is common in infants less than 3 months of age[48] and is associated with an increased likelihood of hospitalization and increased cost, even though infants with traumatic LP are not at increased risk for serious bacterial infection.[49] In addition, infants with UTI with sterile CSF pleocytosis who are otherwise well-appearing have similar clinical courses to those without CSF pleocytosis.[45] However, those with CSF pleocytosis tend

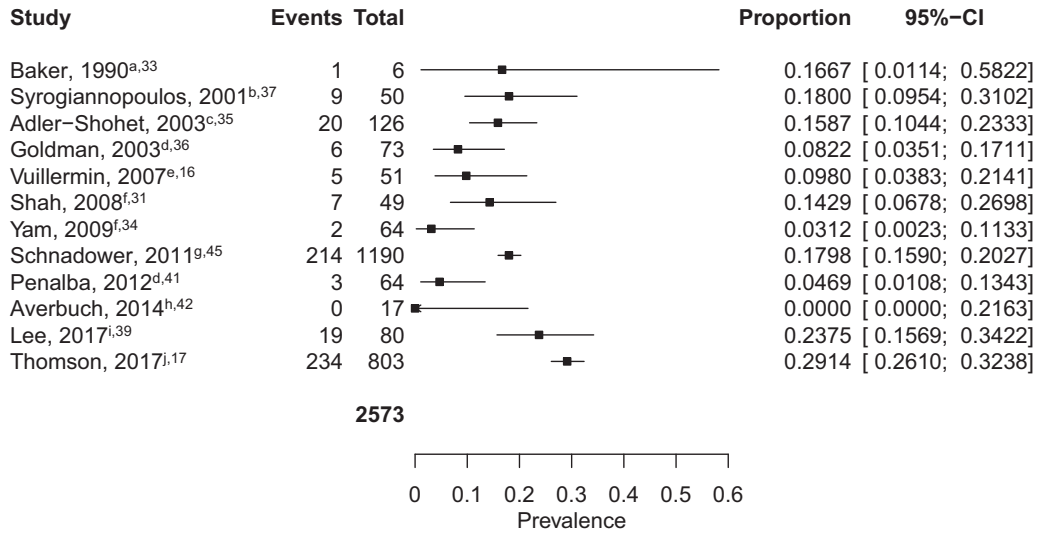

Figure 6. Prevalence of sterile CSF pleocytosis in infants aged 29-90 days with evidence of UTI. [a]CSF white blood cell (WBC) count of greater than 10, red blood cell (RBC) count of less than 100. [b]CSF WBC count of 21 or greater, absolute neutrophil count (ANC) of 3 or greater for 1-2 months; CSF WBC count of 15 or greater, ANC of 2 or greater for 2-3 months. Traumatic LP excluded. [c]CSF WBC count of greater than 10. For traumatic LP, CSF WBC count adjusted based on ratio of WBC and RBC counts in peripheral blood. [d]CSF WBC count of greater than 22 for 4-8 weeks; CSF WBC count of greater than 10 for more than 8 weeks. Traumatic LP excluded. [e]CSF WBC count of 22 of greater for 1-2 months; CSF WBC count of 10 or greater for 2-3 months. No correction for traumatic LP. [f]CSF WBC count of 10 or greater; 1:1000 correction for traumatic LP. Cell counts provided. [g]CSF WBC count of 10 or greater. Traumatic LP excluded. [h]CSF WBC count of greater than 10. None were traumatic. [i]CSF WBC count of 10 or greater; 1:700 correction for traumatic LP. Cell counts provided. [j]CSF WBC count of 9 of greater. No mention of traumatic LP.

to be treated with parenteral antibiotics for longer durations.[45] A judicious approach to LP in infants with UTI should help to decrease these adverse effects.

Several recent studies have sought to identify subgroups of infants with UTI who are at low risk for adverse events or invasive bacterial infections and might be managed less conservatively.[22,50,51] Schnadower et al[22] developed a prediction model in which infants aged 29-60 days with a positive urine culture who were well-appearing on examination and did not have a high-risk past medical history could be classified as very low risk for adverse events like shock, death, or meningitis with a negative predictive value of 99.9% (95% CI, 99.5%-100%). In the same study, a second model adding peripheral band count of less than 1250 cells/μL and peripheral absolute neutrophil count of 1500 cells/μL or greater to the other 2 variables decreased the probability of bacteremia to 3.2%. However, the authors did not consider this model successful at predicting which infants with UTI were at very low risk for bacteremia.[22] In a prospective study to determine which febrile infants younger than 90 days of age with an altered urinalysis were at low risk for invasive bacterial infections, defined as bacteremia or bacterial meningitis, Velasco et al[50] developed a model with a negative predictive value of 100% (95% CI, 97.5%-100%) for low-risk infants who were well-appearing on arrival to the ED, were less than 21 days of age, had a procalcitonin of less than 0.5 ng/mL, and had a C-reactive protein of less than 20 mg/L. External validation of this model performed well with a negative predictive value of 98.1% (95% CI, 93.3%-99.4%).[51] These models can help to guide clinicians taking a selective approach to LP in infants with UTI. Nevertheless, larger, prospective studies are needed to best discriminate which infants with UTI are at lowest risk for invasive bacterial infection. Based on the results of this meta-analysis, in the absence of other risk factors, evidence of UTI alone should not significantly impact the decision to perform an LP to assess for bacterial meningitis.

There was variation in the inclusion criteria among studies. Nine of the 20 studies only included infants with fever plus evidence of UTI, whereas the other 11 studies included infants who had UTI but not necessarily fever. The subgroup analysis based on whether or not the study required fever in the inclusion criteria showed that there was no significant difference in pooled prevalence estimate. Most studies included infants with culture-confirmed UTI. Four studies, however, included infants with an abnormal urinalysis, thereby simulating the clinical decision making that must occur based on a suspicious urinalysis without the urine culture results. Although there was no significant difference in the pooled prevalence between studies that used an abnormal urinalysis compared with studies that used a positive urine culture, the precision of the prevalence estimate in the abnormal urinalysis subgroup is limited by the smaller sample size. Urine sampling technique varied

across studies, including bag and clean catch specimens, which could lead to contaminants being considered true infections. Studies also applied different definitions for UTI, positive urine culture, and abnormal urinalysis. Consistent with the diagnostic criteria recommended by the American Academy of Pediatrics UTI guideline for children aged 2-24 months,[52] 1 study required pyuria plus a positive urine culture for a UTI diagnosis in infants over 2 months of age.[8] None of the studies required an abnormal urinalysis to diagnose a UTI in infants less than 2 months of age, which reflects past literature suggesting that the urinalysis may not be reliable for identifying infants less than 2 months of age with UTI.[53,54] In light of recent evidence showing that an abnormal urinalysis is highly sensitive even in the youngest infants, particularly for bacteremic UTI,[55,56] our results support the practice that patients with a normal urinalysis who develop a positive urine culture do not need to undergo LP to assess for bacterial meningitis. It is possible that some cases of culture-confirmed UTI without an associated urinalysis may represent asymptomatic bacteriuria[57]; however, our inclusion of only patients with a paired CSF sample limits this effect because the perception of toxicity and abnormal biomarkers that prompt providers to obtain CSF would not be expected with asymptomatic bacteriuria.

The risk of coexisting bacterial meningitis in infants aged 29-90 days with evidence of UTI is low. A more selective approach to LP in those infants identified as low risk by other clinical criteria may be indicated. Quantifying the risk of concomitant bacterial meningitis in these infants with good precision will help to inform the decisions of providers and families facing this clinical dilemma. ■

We thank Steven Howard for his assistance and guidance on meta-analysis methodology and R implementation.

Submitted for publication Jan 11, 2019; last revision received Apr 11, 2019; accepted Apr 25, 2019.

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(1) Was the sample representative of the target population?

1 star: Study includes infants aged 29-90 days with abnormal urinalysis or UTI who presented with fever.

0 stars: Study includes infants aged 29-90 days with abnormal urinalysis or UTI who did not necessarily present with fever.

(2) Were study participants recruited in an appropriate way?

1 star: Study patients were identified prospectively.

0 stars: Study patients were identified retrospectively.

(3) Sample size *

2 stars: ≥5107 infants aged 29-90 days with UTI underwent LP.

1 star: ≥1277 infants aged 29-90 days with UTI underwent LP.

0 stars: <1277 infants aged 29-90 days with UTI underwent LP.

(4) Quality of descriptive statistics reporting

1 star: Reports descriptive statistics about the population (minimum: age, gender).

0 stars: No descriptive statistics about the population provided.

(5) Selection bias: Is the data analysis conducted with sufficient coverage of the identified sample?

2 stars: All infants aged 29-90 days with UTI underwent LP.

1 star: ≥50% of infants aged 29-90 days with UTI underwent LP.

0 stars: <50% of infants aged 29-90 days with UTI underwent LP. 0 points if retrospective review of only infants who had both UTI and CSF collected but no mention of infants with UTI who did not get LP.

(6) Ascertainment of UTI

1 star: Reports diagnostic criteria for UTI and/or abnormal UA and requires catheterized urine or SPA.

0 stars: Fails to report diagnostic criteria for UTI and/or abnormal UA or allows clean-catch or bag cultures.

(7) Assessment of outcome

1 star: Reports diagnostic criteria for bacterial meningitis and/or sterile pleocytosis.

0 stars: Fails to report diagnostic criteria for bacterial meningitis and/or sterile pleocytosis.

(8) Adequacy of follow-up

1 star: Complete culture data was available for all patients or if loss to follow-up was <10%, then authors address reasons for loss to follow-up

0 stars: ≥10% of patients had incomplete culture data or were lost to follow-up or if loss to follow-up was <10%, the authors fail to discuss reasons for loss to follow-up.

*** Sample Size Calculation:**

$$n = Z^2 P(1\text{-}P) / d^2$$

n = sample size
Z = Z statistic for a level of confidence (Z=1.96 for 95% CI)
P = Expected prevalence as a proportion of one (P=0.003, or case rate of 3 per 1000 for bacterial meningitis)
d = precision or width of confidence interval's upper and lower bounds (d=0.0015 for bacterial meningitis)

Goal *n* = 5107 for bacterial meningitis with estimated prevalence of 0.3% +/- 0.15%
Goal *n* = 1277 for bacterial meningitis with estimated prevalence of 0.3% +/- 0.3%

Figure 1. Critical appraisal tool.

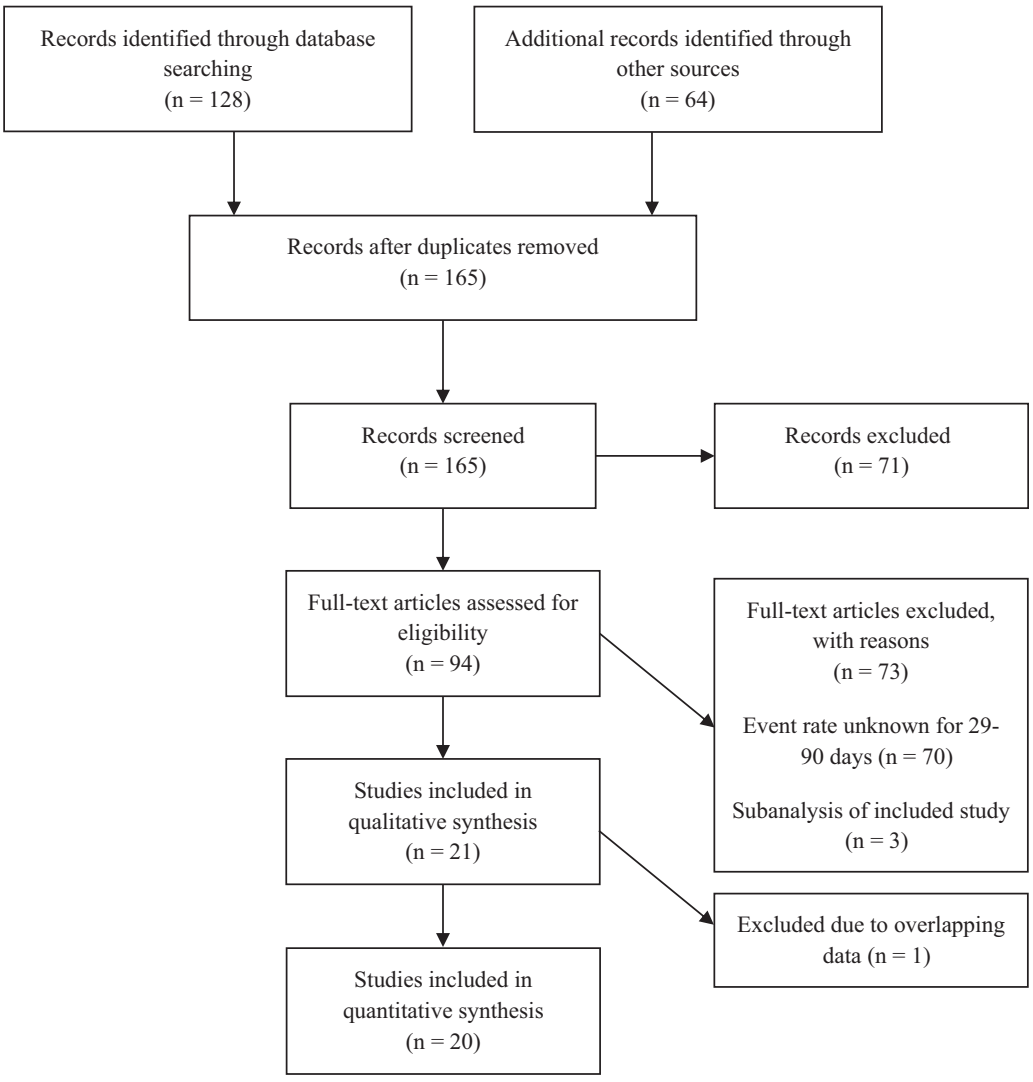

Figure 2. Flow diagram for identifying studies on the prevalence of meningitis among infants with UTIs.

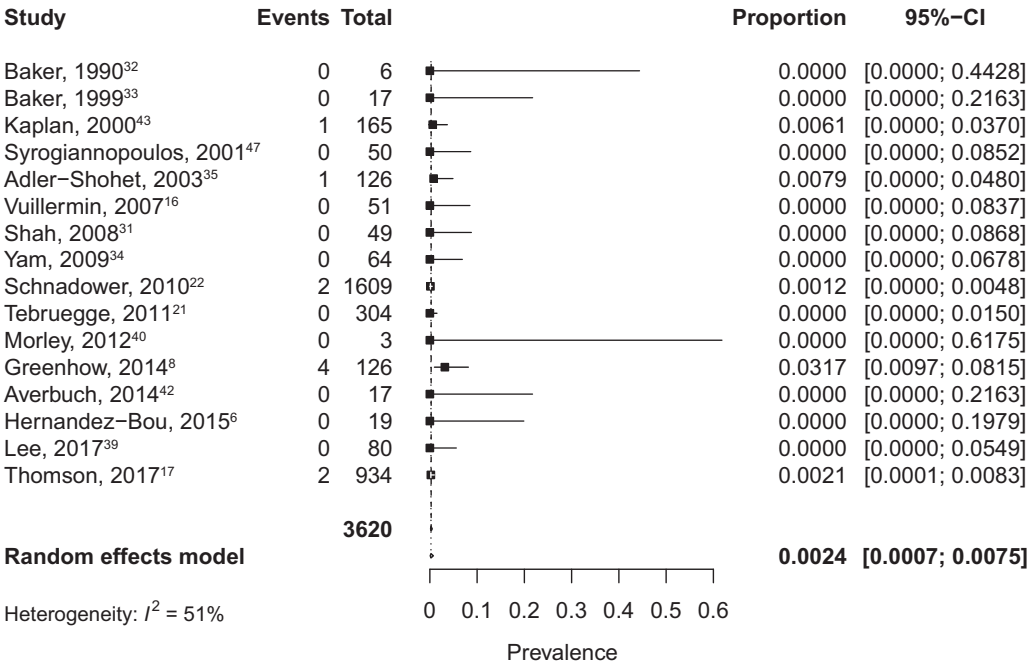

Figure 4. Prevalence of bacterial meningitis in infants aged 29-90 days with culture-confirmed UTI.

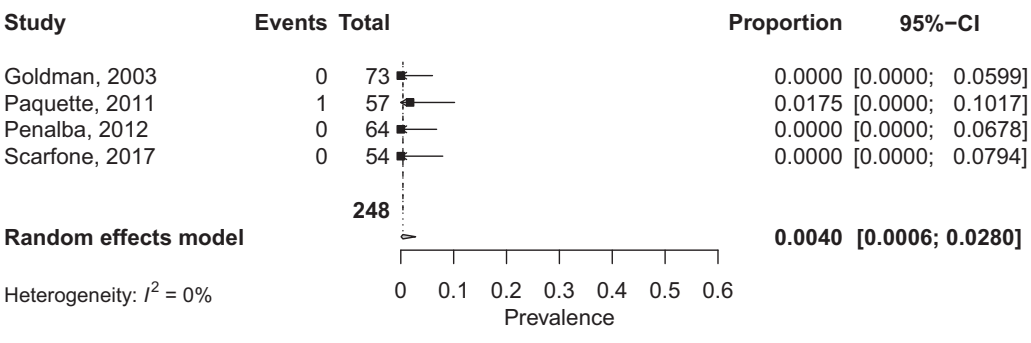

Figure 5. Prevalence of bacterial meningitis in infants aged 29-90 days with abnormal urinalysis.

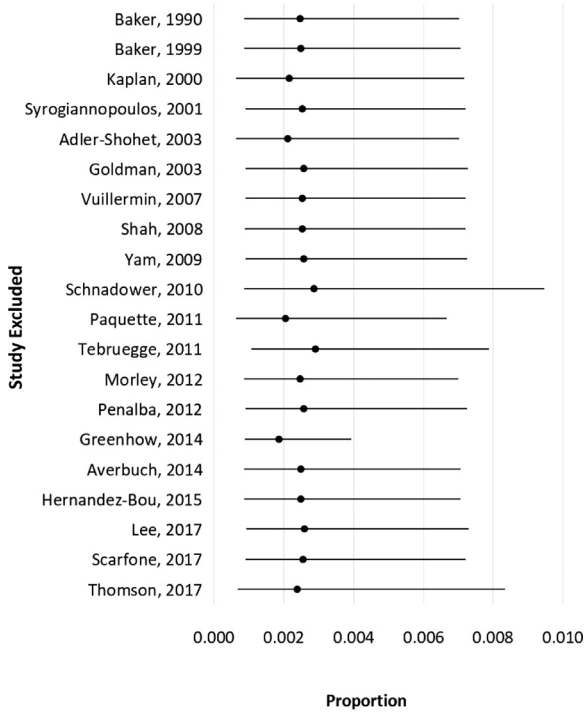

Figure 7. Sensitivity analysis displaying impact on pooled prevalence confidence bounds after excluding each study in turn.

Table I. Search strategies for PubMed (MEDLINE), Embase, and the Cochrane Library

PubMed (MEDLINE)

(Urinary Tract Infections[MeSH] OR urinary tract infection* OR uti OR pyelonephriti* OR Pyelonephritis[MeSH] OR cystiti* OR Cystitis[MeSH]) AND (meningiti* OR Meningitis [MeSH] OR pachymeningiti* OR meningoencephaliti* OR cerebromeningiti* OR encephalomeningi* OR Leukocytosis[MeSH] OR leukocytos* OR pleocytos* OR sepsis OR bacteremia* OR urosepsis OR pyemia* OR pyohemia* OR pyaemia* OR septic* OR blood poison* OR central nervous system infection* OR cns infection* OR Central Nervous System Infections[MeSH]) AND (lumbar puncture* OR spinal puncture* OR spinal tap* OR Spinal Puncture[MeSH]) AND (infants OR newborn*)

Embase

('urinary tract infection'/exp OR 'urinary tract infection*' OR uti OR 'pyelonephritis'/exp OR pyelonephriti* OR 'cystitis'/exp OR cystiti*) AND (meningiti* OR pachymeningiti* OR meningoencephaliti* OR cerebromeningiti* OR encephalomeningi* OR pleocytos* OR 'pleocytosis'/exp OR leukocytos* OR bacteremia* OR 'leukocytosis'/exp OR 'sepsis'/exp OR sepsis OR urosepsis OR pyemia* OR pyohemia* OR pyaemia* OR septic* OR 'blood poison*' OR 'central nervous system infection*' OR 'cns infection*' OR 'central nervous system infection'/exp) AND ('puncture'/exp OR 'lumbar puncture'/exp OR 'lumbar puncture*' OR 'spinal puncture*' OR 'spinal tap*') AND ('infant'/exp OR infant OR infants OR newborn*)

Cochrane Library

(urinary tract infection* or uti or pyelonephriti* or cystiti*) and (meningiti* or pachymeningiti* or meningoencephaliti* or cerebromeningiti* or encephalomeningi* or leukocytos* or pleocytos* or sepsis or bacteremia* or urosepsis or pyemia* or pyohemia* or pyaemia* or septic* or blood poison* or central nervous system infection* or cns infection*) and (lumbar puncture* or spinal puncture* or spinal tap*) and (infant or infants or newborn*)

Table III. Results of critical appraisal checklist for studies included in meta-analysis

Authors	Year	Was the sample representative of the target population? (0-1 stars)	Were study participants recruited prospectively? (0-1 stars)	Sample size (0-2 stars)	Quality of descriptive statistics reporting (0-1 stars)	Selection bias (0-2 stars)	Ascertainment of UTI (0-1 stars)	Assessment of outcome (0-1 stars)	Adequacy of follow-up (0-1 stars)
Baker et al[33]	1990	★	★		★	★★	★	★	★
Baker et al[32]	1999	★	★		★	★★	★	★	★
Kaplan et al[43]	2000	★			★	★	★	★	★
Syrogiannopoulos et al[37]	2001						★	★	★
Adler-Shohet et al[35]	2003				★	★		★	★
Goldman et al[36]	2003	★			★	★	★	★	★
Vuillermin and Starr[16]	2007				★			★	★
Shah et al[31]	2008	★	★		★	★★	★	★	★
Yam et al[34]	2009							★	★
Schnadower et al[22]	2010	★		★	★	★	★	★	★
Paquette et al[38]	2011	★			★			★	★
Tebruegge et al[21]	2011				★			★	★
Morley et al[40]	2012	★			★			★	
Peñalba Citores et al[41]	2012				★		★	★	★
Averbuch et al[41]	2014				★	★	★	★	★
Greenhow et al[8]	2014				★			★	★
Hernandez-Bou et al[6]	2015				★		★	★	★
Lee et al[39]	2017				★	★	★	★	★
Scarfone et al[13]	2017	★				★		★	
Thomson et al[17]	2017				★		★	★	★
Young et al[44]	2018	★			★			★	★