



Bacterial meningitis in febrile young infants acutely assessed for presumed urinary tract infection: a systematic review

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Abstract

Urinary tract infections, the most common severe bacterial infections in young infants, may be associated with co-existing meningitis. There is no consensus on when to perform a lumbar puncture in these infants. Our aim was to quantify the frequency of co-existing bacterial meningitis in febrile young infants acutely assessed for presumed urinary tract infections. We systematically reviewed PubMed, EMBASE, and the Cochrane Library for studies including infants ≤ 3 months with suspected/confirmed urinary tract infections, who underwent a lumbar puncture. Two investigators independently reviewed articles for inclusion and extracted relevant data. Our outcomes were culture-confirmed meningitis and identification of low-/high-risk criteria of meningitis. Overall 20/2079 studies, including 4191 infants, met inclusion criteria. A total of 11 infants had bacterial meningitis (frequency between 0 and 2.1% across studies) and were mostly neonates. Of 253 infants meeting the low-risk criteria (well-appearing, age > 21 days, procalcitonin ≤ 0.5 ng/ml, and C reactive protein ≤ 20 mg/L) none developed meningitis, but only 15 underwent lumbar puncture.

Conclusion: Co-existing bacterial meningitis in febrile young infants with urinary tract infection is rare. In those meeting low-risk criteria, a lumbar puncture may not be indicated. A case by case assessment should be made in infants not meeting low-risk criteria.

Trial registration: CRD42018105339

What is known:

- When caring for febrile infants ≤ 3 months with urinary tract infections, clinicians may have uncertainty on whether to perform a lumbar puncture (LP) for possible co-existing meningitis

What is new:

- An up-to-date systematic review of 20 studies found the frequency of co-existing meningitis in this population to be between 0 and 2.1%
- Despite limited data, an LP may not be indicated in infants meeting low-risk criteria (being well-appearing, age > 21 days, procalcitonin ≤ 0.5 ng/ml, C reactive protein ≤ 20 mg/L). Ill-appearance and neonatal age appear to be significant risk factors of co-existing meningitis

Keywords Children · Emergency department · Meningitis · Urinary tract infection · Infants · Lumbar puncture

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Abbreviations

CI	Confidence interval
ED	Emergency department
LP	Lumbar puncture
UTI	Urinary tract infection

Introduction

Urinary tract infection (UTI) is the most common severe bacterial infection in infants [1, 2]. Up to 20% of febrile infants are diagnosed with a UTI [3, 4].

Although final diagnosis is made through a positive urine culture, an altered urinalysis accurately predicts UTI, even in the youngest patients [5, 6].

The American Academy of Pediatrics guidelines recommend inpatient treatment with parenteral antibiotic therapy for febrile infants less than 2 months old, due to the risk of adverse outcomes, of which bacteremia is the most frequent [6]. For this reason, blood cultures are routinely obtained when a UTI is suspected in these patients. However, more controversial is the indication for lumbar puncture (LP) [7].

Although several researchers have tried to determine the actual risk of meningitis secondary to UTI in febrile infants, most of the studies included small samples or had methodological limitations [8–11]. There is currently no consensus on which infants with suspected UTI are at higher risk of meningitis and should undergo an LP.

Our aim was to systematically review the existing literature and report on the frequency of co-existing bacterial meningitis in febrile young infants with presumed UTI based on their initial assessment. We also set out to identify studies describing clinical or laboratory criteria used to risk stratify these patients into low/high risk of co-existing meningitis. The ultimate goal of our systematic review is to support clinician decision making on whether to perform an LP in the acute assessment of febrile infants with a presumed UTI.

Methods

Study design

We conducted a systematic review of studies reporting on the frequency of bacterial meningitis in infants ≤ 3 months with a suspected or confirmed UTI based on samples collected in the acute care setting. Our study conforms to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines [12].

Studies identification

With the assistance of a medical librarian, we searched MEDLINE, EMBASE, and the Cochrane Library to include citations published before April 2018, without any limitations. Details of the search terms and combinations can be found in the Electronic Supplementary Material. In addition, we manually reviewed the cited references of the selected studies to identify additional potentially relevant studies.

Studies selection

After the initial search, two investigators (E.P. and L.Z.) independently screened identified titles and abstracts to exclude studies based on design (animal models, editorials, or other narrative reports), methods (urine bag as primary urine collection method or unreported method of urine collection), or patient populations (young infants who did not undergo an LP; young infants with sterile pleocytosis only; no separate data on febrile infants ≤ 3 months; infants treated with antibiotics prior to LP performance). We included observational studies, both prospective and retrospective, or case series with more than three eligible patients. When necessary, we translated potentially relevant non-English articles to determine study eligibility.

The full text of each of the remaining articles was manually reviewed by two investigators (E.P. and L.Z.) who were not blinded to the journal name, institution, or study authors. We excluded abstracts without full peer-reviewed publications as well as unavailable articles, as we could not determine the clinical outcomes of interest.

We selected original research studies that include all of the following: (1) febrile patients younger than 3 months of age with suspected or confirmed UTI based on urine dipstick/urine culture; (2) urine dipstick/urine culture were performed on samples collected in the acute care setting by bladder catheterization, suprapubic aspiration, or midstream sampling; (3) LP was performed in order to identify a possible meningitis.

We could distinguish two groups of studies, those that included children with a suspected UTI, namely infants with a positive dipstick, and those with a confirmed UTI, namely infants with a positive urine culture. Detailed information on the definition of positive urine dipstick and urine culture for each included study is reported in Table S1.

Data collection

We abstracted the following data from each eligible study: study setting and design, number of infants ≤ 3 months with positive urine dipstick/urine culture, urine collection method, number of patients who underwent LP, and number of culture-proven bacterial meningitis. When reported, we retrieved the clinical characteristics of children with co-existing bacterial meningitis, as well as the details on low-/high-risk criteria

for co-existing meningitis. For relevant studies, when the required data were not presented or unclear, we contacted the study corresponding author. If unable to clarify the needed data elements after this correspondence, we either excluded the article in its entirety or used the data only for outcomes that were clearly specified. Disagreements on study selection or on study details were resolved with the involvement of a third investigator (SB).

Quality assessment

We assigned a quality measure to each of the included studies, using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies 14-item checklist (see Table S2).

In accordance with the types of included studies, we omitted items 8 and 10 of the checklist because they were not applicable to the included observational studies. Using this rating system, two investigators (E.P. and L.Z.) rated each study overall as either poor, fair, or good. We then calculated the percentage of overall agreement between the two independent reviewers' assessments of study quality. Disagreements between investigators about studies quality were resolved through consensus with a third investigator, as per the data collection procedure.

Outcomes

Our primary outcome was the frequency of culture-proven bacterial meningitis in the study population. Our secondary outcome was the identification of low-/high-risk criteria of co-existing meningitis.

Results

After removal of duplicate studies, we identified 2079 potentially relevant publications for screening (Fig. 1). After screening the titles and abstracts, we identified 40 studies for full-text review. Following full-text review and the manual search of the articles included in the reference lists, we identified a total of 20 eligible studies meeting our inclusion criteria [8, 13–31].

Only five studies were prospective [13, 14, 21, 22, 31], and 15 were retrospective [8, 15–20, 23–30]. Three [14, 22, 23] were multicenter (Tables 1 and 2). Three studies included only neonates [27–29], and two only infants ≤ 2 months [13, 14].

Overall, the 20 eligible studies included a total of 6152 febrile infants ≤ 3 months who had a suspected or confirmed UTI diagnosis. Of these, 4191 (68%) successfully underwent an LP.

Eight studies (40%), six retrospective [15, 18, 20, 23, 27, 30], and two prospective [13, 22], reported on patients who had a suspected UTI based on positive urine dipstick results. These studies included 3361 infants, of whom 72% underwent an LP (Table 1).

The remaining 12 studies (60%), nine retrospective [8, 16, 17, 19, 24–26, 28, 29] and three prospective [14, 21, 31] (Table 2), included only patients who had a confirmed UTI diagnosis based on a positive urine culture. These studies included a total of 2791 infants ≤ 3 months, of whom 63% successfully underwent an LP.

Definitions of altered urinalysis (i.e., suspected UTI) and positive urine culture (namely confirmed UTI diagnosis) differed across studies (see Table S1).

Decision making on LP performance for patients with UTI also varied widely across studies. Overall, the 10 studies conducted in North America reported high percentages of LP performance (between 68 and 100%) [14–18, 20, 26–28, 30], followed by Australian studies (between 47 and 100%) [8, 24, 25] and studies conducted in Europe (between 23 and 57%) [21–23, 29, 31].

On the 3-level quality scale, we judged all of the included studies to be fair or good (see Tables S3 and S4). For overall study quality, the reviewers' classifications were concordant for 17 of 20 studies [percentage agreement 85.0%; 95% confidence interval (CI) 62.1–96.8%]. The two studies with discordant reviewer assessment were reviewed by a third investigator (SB) and a consensus quality measure was assigned.

For our primary outcome, a total of 11 febrile infants with suspected or confirmed UTI who underwent an LP were finally diagnosed with bacterial meningitis, with a frequency ranging from 0 to 2.1% across studies. The frequency range of bacterial meningitis diagnosis varied between 0.6 to 2.1% in studies of infants with suspected UTI and between 0.4 to 1.2% in those of infants with confirmed UTI. The clinical characteristics of patients with meningitis were available for eight out of 11 patients. Of these, six were neonates (Table 3). The most common pathogen involved was *Escherichia coli*, with only one case each of *Staphylococcus aureus* and *Klebsiella oxytoca*.

With regard to our secondary outcome, only two studies [22, 23] reported on the risk stratification of febrile infants with an altered urinalysis to identify those with invasive bacterial infections (IBI), a combined outcome including co-existing bacteremia and/or meningitis. None of 253 febrile infants, who were included in the two studies and met all low-risk criteria (i.e., well-appearing infants, age > 21 days, procalcitonin ≤ 0.5 ng/ml, C reactive protein ≤ 20 mg/L), were diagnosed with IBI. However, only 15 of these infants underwent an LP (Table 4). All infants received antibiotic therapy in the ED.

None of the other 18 studies aimed to stratify patients with presumed UTI based on the risk of IBI. However, when we tried to apply the low-risk criteria developed by Velasco et al. [22, 23] to the patients with bacterial meningitis (Table 3), seven out of eight could not be classified as low risk, as they did not meet one or more low-risk criteria. For one patient, the information available was insufficient to determine whether or not he/she could be classified as low risk.

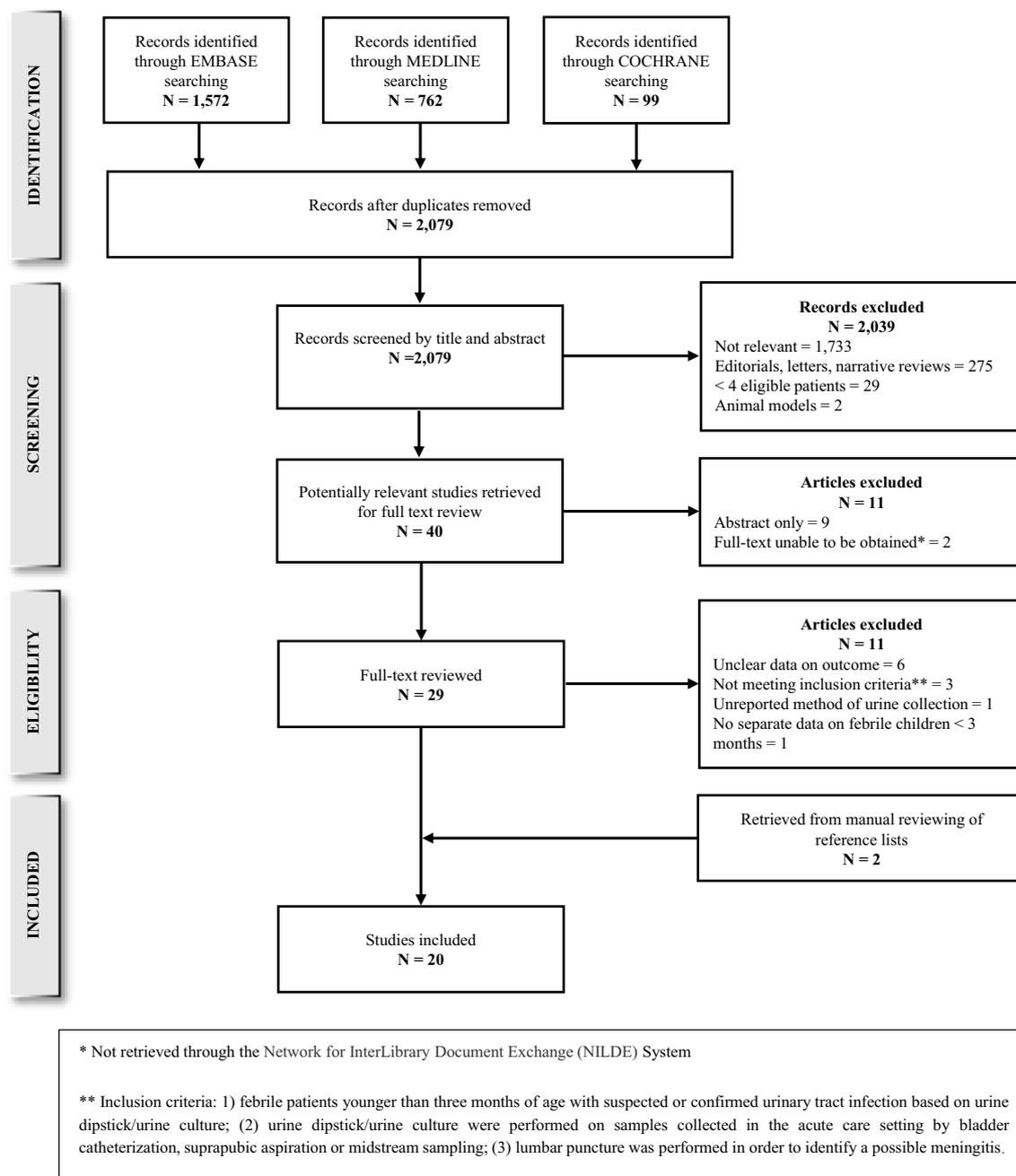


Fig. 1 Flowchart of study selection process

Discussion

Our comprehensive systematic review provides up-to-date results on the frequency of co-existing bacterial meningitis in infants younger than 3 months of age with suspected UTI. UTIs can be associated with meningitis as a result of bacterial dissemination to the central nervous system through the blood stream. An early diagnosis of co-existing meningitis considerably impacts decision making on antibiotics administration and treatment duration. However, LP is an invasive procedure

and bears some downsides associated with pain and possible complications, besides parents' distress [32]. Our findings show that the risk of co-existing meningitis is very low in young infants with suspected UTI, especially beyond the neonatal period. This is consistent with the higher risk of bacteremia and meningitis in the overall population of febrile neonates compared with older infants [33].

One previous review [11] had investigated the association between UTI and meningitis in 15 studies including 3479 children up to 2 years of age. This study found that 0–2% of

Table 1 Included studies of febrile infants with suspected urinary tract infection who underwent lumbar puncture

Age range	Study	Journal	Country	Time period	Study design	Setting *	No. of febrile infants ≤ 3 m with suspected UTI	No. of febrile infants with suspected UTI who underwent LP (%)	No. of infants with bacterial meningitis	% of bacterial meningitis in infants with suspected UTI who underwent LP
< 1 m	Bonadio et al. 2014	Pediatr Infect Dis J	USA	2004–2013	Retrospective	Single center ED	100	100 (100)	0	0
< 2 m	Lin et al. 2000	Pediatrics	Taiwan	1997–1998	Prospective	Single center Pediatric Clinic & ED	162	162 (100)	0	0
< 3 m	Bonsu et al. 2007	BMC Pediatrics	USA	1993–1999	Retrospective	Single center ED	1516	1516 (100)	1	0.1
	Goldman et al. 2003	Can J Emerg Med	Canada	1997–2000	Retrospective	Single center ED	211	143 (68)	0	0
	Meehan et al. 2008	Pediatr Emerg Care	USA	A period of 4 years	Retrospective	Single center ED	158	158 (100)	0	0
	Paquette et al. 2011	Pediatr Emerg Care	Canada	2001–2005	Retrospective	Single center ED	57	57 (100)	1	1.8
	Velasco et al. 2015#	Pediatr Infect Dis J	Spain	2011–2013	Prospective	Multicenter ED	766	195 (25)	1	0.5
	Velasco et al. 2016#	Eur J Clin Microbiol Infect Dis	Spain	2013–2015	Retrospective	Multicenter ED	391	95 (24)	2	2.1

m months, *ED* emergency department, *LP* lumbar puncture, *UTI* urinary tract infection

*All tertiary care settings

Studies included for secondary outcome, as they reported on low-risk criteria of invasive bacterial infection [well-appearing infants, > 21 days of age, procalcitonin ≤ 0.5 ng/ml, C reactive protein ≤ 20 mg/L]. Invasive bacterial infection was defined as bacteremia/sepsis and/or meningitis

Table 2 Included studies of febrile infants with confirmed urinary tract infection who underwent lumbar puncture

Age range	Study	Journal	Country	Time period	Study design	Setting*	No. of febrile infants ≤ 3 m with confirmed UTI	No. of febrile infants ≤ 3 m with confirmed UTI who underwent LP (%)	No. of infants with bacterial meningitis	% of bacterial meningitis in infants with confirmed UTI who underwent LP
< 1 m	Magin et al. 2007	Pediatr Emerg Care	Spain	1997–2002	Retrospective	Single center	172	75 (44)	0	0
	Wallace et al. 2017	J Pediatr	USA	2005–2013	Retrospective	Single center	236	180 [¶] (76)	0	0
< 2 m	Shah et al. 2008	J Pediatr	USA	1999–2001	Prospective	Multicenter	91	82 (90)	1	1.2
< 3 m	Dayan et al. 2004	Pediatr Emerg Care	USA	1995–2000	Retrospective	Single center	128	125 (98)	1	0.8
	Doby et al. 2013	Pediatr Infect Dis J	USA	2004–2011	Retrospective	Single center	162	162 (100)	0	0
	Mintegi et al. 2018	ADC	Spain	2003–2016	Prospective	Single center	660	151 [§] (23)	1	0.7
	Nosrati et al. 2014 [#]	Pediatr Int	Israel	2006–2008	Retrospective	Single center	43	43 (100)	0	0
	Syrogiannopoulos et al. 2001	Pediatr Infect Dis J	Greece	1990–2001	Prospective	Single center	206	117 (57)	0	0
	Vuillermin et al. 2007	Emerg Med Australas	Australia	1999–2003	Retrospective	Single center	161	75 (47)	0	0
< 6 m	Yam et al. 2009	J Paediatr Child Health	Australia	2006–2007	Retrospective	Single center	79	79 (100)	0	0
	Adler-Shohet et al. 2003	Pediatr Infect Dis J	U.S.A.	1995–2000	Retrospective	Single center	386	209 (54)	1	0.5
0–16 y	Tebuegge et al. 2011	PLoS One	Australia	2001–2010	Retrospective	Single center	467	467 (100)	2	0.4

[¶] Six patients were excluded as they received antibiotic therapy prior to lumbar puncture performance. Two of these six patients had a traumatic tap and had *E. coli* isolated from CSF as well as blood culture. As contamination from blood could not be excluded, these patients were diagnosed with probable meningitis

[#] Patients aged 1–3 months (this study excluded neonates)

[§] In seven patients the LP was not successful

*All tertiary care settings

[¶] All tertiary care settings

[§] In seven patients the LP was not successful

Table 3 Characteristics of infants diagnosed with a co-existing bacterial meningitis

Age	Sex	Study	Clinical characteristics	Laboratory characteristics	Microbiology	
					Urine culture	Blood culture CSF culture
71 days	F	Paquette et al. 2011	38.5 °C, mottled skin, cool extremities, irritability, lethargy, and decreased feeding	<ul style="list-style-type: none"> Blood markers: WBC $2.9 \times 10^9/L$ Urinalysis: Leukocyte esterase positive, nitrite positive, 6 RBCs/HPF; 4 WBCs/HPF CSF: NR 	<i>E. coli</i> ($> 10^8/L$)	<i>E. coli</i>
22 days	NR	Shah et al. 2008	[Bacterial meningitis]	<ul style="list-style-type: none"> Blood markers: not reported Urinalysis: leukocyte esterase positive; nitrite positive CSF: 20 CSF white blood cells/mm³ 	Enterobacter species	Enterobacter species 20 CSF white blood cells/mm ³
19 days	M	Tebnuegge et al. 2011	Pyrexia, poor feeding, irritability, and lethargy	<ul style="list-style-type: none"> Blood markers: WBC $12.06 \times 10^9/L$; N $9.06 \times 10^9/L$; CRP < 8 mg/L Urinalysis: leukocyte esterase positive, nitrite positive CSF: WBC 230/μL; RBC 700/UI; protein 1.62 g/L; glucose 4.2 mmol/L 	<i>E. coli</i> CFU $> 10^2/mL$ (suprapubic aspiration)	NR <i>E. coli</i>
15 days	M	Tebnuegge et al. 2011	Bilateral renal dysplasia antenatally, pyrexia, poor feeding, irritability, and lethargy	<ul style="list-style-type: none"> Blood markers: WBC normal; CRP 36 mg/L Urinalysis: leukocyte esterase positive, nitrite positive CSF: WBC $> 19/\mu$L 	<i>S. aureus</i> CFU $> 10^2/mL$ (suprapubic aspiration)	NR <i>S. aureus</i>
33 days	F	Velasco et al. 2015	38.3 °C, not-well appearance (altered Pediatric Assessment Triangle)	<ul style="list-style-type: none"> Blood markers: WBC normal; CRP 4.8 mg/L Urinalysis: leukocyte esterase positive, nitrite positive CSF: L 36/μL 	<i>E. coli</i>	None <i>E. coli</i>
20 days	M	Velasco et al. 2016	38 °C, well-appearing	<ul style="list-style-type: none"> Blood markers: WBC $20.5 \times 10^9/L$ (N $11.5 \times 10^9/L$); CRP 48.3 mg/L, procalcitonin 0.39 ng/ml Urinalysis: leukocyte esterase positive, nitrite negative CSF: > 25 cells/ L 	<i>E. coli</i>	None <i>E. coli</i>
25 days	M	Velasco et al. 2016	38.5 °C, well-appearing	<ul style="list-style-type: none"> Blood markers: WBC normal; CRP 17.4 mg/L, procalcitonin 9.5 ng/ml Urinalysis: leukocyte esterase positive, nitrite positive CSF: > 25 cells/μL 	<i>K. oxytoca</i>	<i>K. oxytoca</i> <i>K. oxytoca</i>
22 days	M	Mintegi et al. 2018	38.5 °C, well-appearing	<ul style="list-style-type: none"> Blood markers: CRP 12.02 mg/dL, PCT 8.3, WBC 18,800, ANC 9200 Urinalysis: leukocyte esterase pos/neg; nitrite pos/neg, leukocyturia (cath) CSF: protein 120 mg/dL. Glucose 60 mg/dL. RBC 36,000/mm³. WBC 90/mm³ (lymfocytes 35%, ANC 62%) 	<i>E. coli</i>	<i>E. coli</i> <i>E. coli</i>

CFU colony-forming unit, CRP C reactive protein, CSF cerebrospinal fluid, F female, M male, RBC red blood cell, WBC white blood cell, NR not reported

Table 4 Summary of studies reporting on the secondary outcome—low-risk criteria for co-existing meningitis

Study	Journal	Country	Time period	Study design	Setting	No. of febrile infants ≤ 3 m with suspected UTI	No. of patients classified as low risk*	No. of low-risk patients who underwent LP (%)	No. of infants with bacterial meningitis in the low-risk group
Velasco et al. 2015	Pediatr Infect Dis J	Spain	2011–2013	Prospective	Multicenter ED	766	149	15	0
Velasco et al. 2016	Eur J Clin Microbiol Infect Dis	Spain	2013–2015	Retrospective	Multicenter ED	391	104		

ED emergency department, LP lumbar puncture, UTI urinary tract infection

*To be classified as low risk, patients had to meet all the following criteria: well-appearing, > 21 days of age, procalcitonin ≤ 0.5 ng/ml, C reactive protein ≤ 20 mg/L

infants ≤ 3 months with UTI had co-existing bacterial meningitis. Although our results are similar to this previous work, our study differs in several important ways. First, we wanted to provide an up-to-date overview of what has been published in recent years on this topic. Nine recent studies [8, 17, 19, 20, 22, 23, 27, 28, 31] included in our review had not been published at the time of the review performed by Tebruegge et al. [11]. In addition, our study is the first to selectively review data of patients with a suspected and confirmed UTI, excluding those whose samples were primarily collected by urine bag. This criterion allows greater certainty in our report, as data are not affected by overestimated rates of UTI in febrile children. We also limited our systematic review to patients under 3 months of age, who represent the greatest challenge for clinicians, as older patients have a lower risk of severe and invasive bacterial infections and usually receive outpatient treatment [32]. We also excluded from our review patients who had received antibiotics prior to LP, which may influence the results of the cerebrospinal fluid culture. For this review, we decided not to consider patients with sterile pleocytosis, as this is not pertinent to decision-making on whether or not to perform an LP in the acute care setting. Despite these differences, our results align with the findings of previous work.

In our systematic review, the proportion of patients with UTI undergoing an LP varied between 23 and 100% across the included studies. According to Goldman et al. [30], clinicians often choose not to perform LPs, either due to the child's favorable clinical status or a high perceived likelihood that a UTI is the only source of fever. Indeed, not all infants have the same risk of developing IBIs [34, 35]. This is why it appears essential to identify a group of patients with low risk of adverse events that might be suitable for outpatient management [22, 36, 37]. The secondary outcome of our study was the identification of low-/high-risk criteria of co-existing meningitis in febrile infants with a presumed UTI focus. Two studies by the same research team reported on low-risk criteria for IBI (co-existing bacteremia and/or meningitis) [22, 23], showing both prospectively and retrospectively that none of 253 febrile infants meeting these criteria (i.e., well-appearing infants, age > 21 days, procalcitonin ≤ 0.5 ng/ml, C reactive protein ≤ 20 mg/L) had co-existing meningitis. However, only 6% (15) of these infants underwent an LP to identify co-existing meningitis. Following a sequential approach, the predictive model first recommends to exclude patients who are not well appearing or are under 21 days old from the low-risk group. Biomarkers can be used at this point to select which patients are less likely to develop an IBI. Although a follow-up of each patient was performed 1 month after inclusion in these studies [22, 23], the fact that all of them received antibiotic therapy in the ED does not allow to draw definitive conclusions on the accuracy of these criteria in predicting the risk of co-existing meningitis.

Vuillerman et al. [24] in commenting their study results as well as existing literature on UTI and invasive infections suggest there are three groups of young infants with a working diagnosis of UTI who are likely to be at higher risk of co-existing bacterial meningitis and should definitely undergo LP: infants with specific signs suggestive of meningitis (bulging fontanelle, meningism, paradoxical irritability, and high-pitched cry); infants with features of sepsis (lethargy, pallor, tachycardia, and inadequate perfusion), and neonates (28 days of age or less). Similarly to the risk criteria assessed by Velasco et al. [22, 23], infants who are not well appearing and who have a younger age are considered at higher risk. As neonates have an inherent high risk of both bacteremia and meningitis, an LP should be performed regardless of the urine dipstick and/or urinalysis results.

The results of our systematic review must be interpreted in the context of its limitations. First, we limited our search to three main databases. Unpublished studies and unreported data were not included. However, the inclusions of additional small unpublished studies are unlikely to substantially alter our findings. To maximize study identification, we utilized a broad search strategy and manually reviewed references of included studies to capture additional eligible studies. Second, although this systematic review was performed using rigorous methodology [12], the findings are limited by the methodological heterogeneity of the included studies (e.g., study design and population). Our aim was to provide clinicians with a broad overview of up-to-date research data on the risk of co-existing meningitis in febrile infants ≤ 3 months of age with UTI and we did not perform a meta-analysis, which would have to focus on separate age groups, given the differences in the populations of available studies. Third, even though we included both prospective and retrospective studies, 12 studies included only patients with a confirmed UTI diagnosis based on a positive urine culture, and did not provide data on the larger denominator of patients with a working UTI diagnosis based on urine dipstick results. These are the only results available at the time of decision making on LP in the ED, while urine culture is pending. Fourth, the exclusion of samples collected by urine bag cannot eliminate the risk of sample contamination, given the non-negligible contamination rate reported for midstream and catheter urine collection [38]. Frequency of UTI might be therefore affected by sample contamination in some studies. However, in the Electronic Supplementary Material (see Table S4), we provided details on the urine collection methods used in each included study for a better interpretation of our results.

Despite these limitations, the results from this systematic review provide a more accurate estimate on the risk of co-existing meningitis in young infants with suspected or confirmed UTI, compared with previous work. Based on our findings, a routine LP might not be necessary in all febrile infants younger than 3 months with a presumed focus of

UTI based on urine dipstick or urinalysis results. Both tests have shown excellent sensitivity ($> 90\%$) and specificity (90%) for diagnosing UTIs in young febrile infants in the ED [5, 39]. However, the consequences of a missed bacterial meningitis or a too short antibiotic treatment can be devastating and clinicians should carefully consider the need for an LP in febrile infants with a presumed UTI focus despite the low frequency of co-existing bacterial meningitis found in our study.

Conclusions

In conclusion, the frequency of co-existing bacterial meningitis in young infants with a presumed focus of UTI is low and a routine LP might not be necessary for all these infants. In those meeting low-risk criteria an LP may not be indicated; however, data are limited and further studies are needed to better define their accuracy in predicting the risk of co-existing meningitis. A case by case assessment should be made in patients not meeting low-risk criteria, although ill-appearance and neonatal age appear to be the most significant risk factors. Given the devastating consequences of a missed bacterial meningitis clinicians should carefully consider the need for an LP in febrile infants with a presumed UTI focus despite the low frequency of co-existing meningitis found in our study.

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Authors' contributions Elisa Poletto and Lorenzo Zanetto designed the study protocol and built the search strategy, searched the literature and undertook selection of retrieved articles, performed data extraction and quality assessment of selected studies, drafted the initial manuscript, and reviewed and revised the manuscript.

Roberto Velasco reviewed the study protocol, contributed to drafting the manuscript, and critically reviewed and revised the manuscript for important intellectual content.

Liviana Da Dalt reviewed the study protocol, co-supervised the study conduct, and critically reviewed and revised the manuscript for important intellectual content.

Silvia Bressan conceptualized the study and designed the study protocol, supervised study selection, data extraction, and quality assessment of selected studies, drafted the initial manuscript, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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