ARTICLE

Sterile Cerebrospinal Fluid Pleocytosis in Young Febrile Infants With Urinary Tract Infections

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Objectives: To determine the prevalence of and to identify risk factors for sterile cerebrospinal fluid (CSF) pleocytosis in a large sample of febrile young infants with urinary tract infections (UTIs) and to describe the clinical courses of those patients.

Design: Secondary analysis of a multicenter retrospective review.

Setting: Emergency departments of 20 North American hospitals.

Patients: Infants aged 29 to 60 days with temperatures of 38.0°C or higher and culture-proven UTIs who underwent a nontraumatic lumbar puncture from January 1, 1995, through May 31, 2006.

Main Exposure: Febrile UTI.

Outcome Measures: Presence of sterile CSF pleocytosis defined as CSF white blood cell count of 10/μL or higher in the absence of bacterial meningitis and clinical course and treatment (ie, presence of adverse events, time to defervescence, duration of parenteral antibiotic treatment, and length of hospitalization).

Results: A total of 214 of 1190 infants had sterile CSF pleocytosis (18.0%; 95% confidence interval, 15.9%-20.3%). Only the peripheral white blood cell count was independently associated with sterile CSF pleocytosis, and patients with a peripheral white blood cell count of 15/μL or higher had twice the odds of having sterile CSF pleocytosis (odds ratio, 1.97; 95% confidence interval, 1.32-2.94; $P=.001$). In the subset of patients at very low risk for adverse events (ie, not clinically ill in the emergency department and without a high-risk medical history), patients with and without sterile CSF pleocytosis had similar clinical courses; however, patients with CSF pleocytosis had longer parenteral antibiotics courses (median length, 4 days [interquartile range, 3-6 days] vs 3 days [interquartile range, 3-5 days]) ($P=.04$).

Conclusion: Sterile CSF pleocytosis occurs in 18% of young infants with UTIs. Patients with CSF pleocytosis at very low risk for adverse events may not require longer treatment with antibiotics.

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Urinary tract infections (UTIs) are the most common serious bacterial illnesses in febrile infants 29 to 60 days of age, occurring in 4% to 10% of these infants.[1-5] Although the presence of bacterial meningitis is rare in these patients,[6-13] previous studies[6,11,12,14] have reported a possible association between UTIs in young infants and sterile cerebrospinal fluid (CSF) pleocytosis. The prevalence of sterile CSF pleocytosis and its cause(s) in febrile infants with UTIs remains controversial, and the clinical and therapeutic implications are unclear. Prior investigations[6,11,12,15] have reported wide prevalence ranges of CSF pleocytosis in infants younger than 6 months (3%-19%), likely due to varied definitions of pleocytosis, inclusion of patients with traumatic lumbar punctures (LPs), and small sample sizes.

Although the clinical implications of sterile CSF pleocytosis in febrile infants with UTIs are not clear, it appears that these infants are often treated for longer periods with parenteral antibiotics when compared with infants without pleocytosis.[6,12] The potential causes of the sterile CSF pleocytosis include a systemic inflammatory response to infection and/or concomitant viral meningitis. Because prior studies lacked sufficient sample sizes, we aimed to determine a more precise estimate of the prevalence of sterile CSF pleocytosis in a large sample of febrile infants 29 to 60 days of age with

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UTIs. We also sought to identify potential risk factors for sterile CSF pleocytosis and to describe the clinical course and treatment of these infants. This information could shed light on the pathophysiology of sterile CSF pleocytosis in infants with UTIs and could inform the appropriate treatment of these patients, particularly regarding the duration of parenteral antibiotic treatment.

METHODS

We conducted a secondary analysis (ie, subanalysis) of data from a retrospective review of febrile (ie, temperature, ≥38.0°C) infants aged 29 to 60 days with culture-proven UTIs who had presented to any of 20 North American emergency departments (EDs) in the Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) of the American Academy of Pediatrics Section on Emergency Medicine from January 1, 1995, through May 31, 2006. The PEM CRC provides a framework for multicenter investigation, serving to support and facilitate the development of useful and rigorous collaborative research in pediatric emergency medicine. Collaborators for this study were recruited based on interest, availability of resources, and geographic diversity during the 2004 PEM CRC meeting in San Francisco, California. All investigators obtained approval for the study with waivers of informed consent from the institutional review boards at their respective institutions. In addition, site investigators obtained data-sharing agreements with the coordinating institution and the study data center in collaboration with the institutional review boards at their respective institutions. Full details of the study design and methods have been described previously.[16] In this article, we provide specific methods pertinent to this secondary analysis.

PATIENT IDENTIFICATION

We performed case ascertainment by querying laboratory databases at each participating institution for all urine cultures with bacterial growth in patients 29 to 60 days of age obtained in the ED from January 1, 1995, through May 31, 2006. *Lactobacillus*, *Micrococcus*, diphtheroids, *Bacillus* species, and *Staphylococcus epidermidis* were considered to be contaminants.

INCLUSION CRITERIA

We included patients with *UTIs*, defined as growth of a single pathogen with colony counts meeting at least 1 of 3 criteria: 1000 CFU/mL or more for urine cultures obtained by suprapubic aspiration, 50 000 CFU/mL or more from a catheterized specimen, or 10 000 CFU/mL for more and less than 50 000 CFU/mL from a catheterized specimen in association with positive urinalysis results.[17] We defined *positive urinalysis results* as those meeting any of the following criteria: any organisms visualized on Gram stain, trace or greater result for leukocyte esterase or nitrite on ED dipstick or laboratory-based urinalysis, or 5 or more white blood cells (WBCs) per high-power field (via standard microscopy) or per microliter (via hemocytometer) on a centrifuged or uncentrifuged urine specimen.[18-20]

EXCLUSION CRITERIA

For the main study in which we identified a group of febrile infants with UTIs at low risk for complications from their UTIs, we excluded patients for any of the following reasons: no measured temperature of 38.0°C or higher in the ED or at home within 24 hours of presentation to the ED, urine cultures that yielded multiple organisms, transfer from other hospitals with previously obtained laboratory results, or urine specimens obtained by techniques other than suprapubic aspiration or transurethral catheterization. For this secondary analysis, we also excluded patients with no LP performed, no CSF cell count obtained, a bloody LP (ie, a red blood cell count >1000/μL[11,12,21]), or the presence of bacterial meningitis.

On the basis of prior studies and to provide a conservative estimate of the rate of bacterial meningitis in our original study, we defined bacterial meningitis as "definite" or "probable." For the present study, we excluded patients who met either definition.[11,22,23] We defined *definite bacterial meningitis* as the growth of a known pathogen in the CSF. *Bacillus* species, *Propionibacterium* acnes, *Staphylococcus* non-*aureus*, and *Streptococcus viridans* were considered to be contaminants. For patients with no bacterial growth in the CSF cultures, we defined *probable bacterial meningitis* as meeting any of the following criteria:

1. The combination of sterile CSF pleocytosis (WBC count, ≥10/μL; to convert to $\times 10^9$/L, multiply by 0.001) *and* positive blood culture result and treatment consistent with bacterial meningitis (defined as ≥14 days of parenteral antibiotics not clearly administered for other reasons on review of inpatient records) or
2. The combination of positive CSF Gram stain result or positive latex agglutination test results and treatment consistent with bacterial meningitis or
3. The combination of pretreatment with antibiotics before LP, CSF pleocytosis (WBC count, ≥10/μL), and treatment consistent with bacterial meningitis.

DATA COLLECTION

We collected data from the medical records regarding patient demographics, medical history, symptoms at presentation to the ED, vital signs at triage, ED physical examination findings, presence of concomitant diseases, and ED disposition. We also obtained data regarding ED and inpatient treatment, the patient's clinical course, radiologic study results, and urine, blood, and CSF laboratory and microbiology results.

A priori, we created the variable "high-risk medical history," which included patients with known genitourinary abnormalities, prior laboratory evaluation for fever, prematurity of less than 37 weeks, history of a severe systemic disease (eg, complex heart, chronic lung, and metabolic or neurologic diseases), or previous UTI, bacteremia, or bacterial meningitis. Other past medical conditions, such as minor neonatal complications, jaundice, gastroesophageal reflux, or a history of a minor resolved acute illness, were not considered to represent a high-risk medical history.[16] We also created the variable "clinically ill in the ED," which was defined as an infant who was judged to be ill-appearing, dehydrated, or in respiratory distress or who had an acute concomitant disease diagnosed in the ED. We defined *acute concomitant disease* as an acute, focal infectious process distinct from the UTI, such as pneumonia, bronchiolitis, cellulitis, osteomyelitis, or septic arthritis. We did not consider acute gastroenteritis or acute otitis media as an acute concomitant disease because of variability in diagnosis. Because ours was a multicenter study that encompassed multiple regions of the United States, we used the US Centers for Disease Control and Prevention surveillance data to define *enteroviral season*, ie, June through October.[24]

OUTCOMES

Sterile CSF Pleocytosis

The main outcome for this study was sterile CSF pleocytosis. In accordance with prior reports and using published 95th-percentile age-specific values for CSF WBC counts,[6,10,11,21] we

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defined *sterile CSF pleocytosis* as a CSF WBC count of 10/μL or higher. However, to allow for comparisons with prior studies[3,11,12,15] of patients in this age range, we also report the prevalence of sterile CSF pleocytosis when defined as a CSF WBC count of 16/μL or higher and a CSF WBC of 21/μL or higher.

Clinical Course and Treatment

We described and compared patients with and without CSF pleocytosis on the following: time to defervescence, length of parenteral antibiotic treatment, length of hospitalization, and presence of adverse events (ie, death, shock, admission, or transfer to a higher level of care [ie, an intensive care unit or a step-down intensive care unit]), need for ventilatory support, or any other severe clinical outcomes, such as the need for surgery.[16]

Statistical Analysis

We described the prevalence of CSF pleocytosis as proportions with 95% confidence intervals (CIs). We described categorical data as frequencies and proportions, normally distributed continuous variables as means with standard deviations, and nonnormally distributed data as medians with interquartile ranges (IQRs).

We used the following variables to assess potential risk factors for CSF pleocytosis: patient age, season, medical history, history of feeding difficulty, vomiting, seizures, clinical appearance in the ED, presence of acute concomitant disease, vital signs at triage, peripheral WBC count, peripheral blood absolute neutrophil count (ANC), peripheral blood band count, and peripheral blood immature:total neutrophil ratio.

To study the association between the variables of interest and the presence of CSF pleocytosis, we first conducted bivariate analyses using the Pearson χ^2 test for categorical variables and 2-tailed *t* test and Mann-Whitney test for normally and nonnormally distributed continuous variables, respectively. Subsequently, after testing all variables for colinearity and assessing the role of outliers, we constructed multivariate logistic regression models to assess for independent factors associated with sterile CSF pleocytosis. We chose potential predictors based on their biological plausibility or previous study suggesting associations with the outcomes of interest.[6,11,12,15] We assessed the following variables for model inclusion: bacteremia, enteroviral season, high-risk medical history, clinical appearance in the ED, highest recorded temperature, the presence of a seizure, urine WBC count, peripheral blood WBC count, ANC, and absolute band count. We performed goodness-of-fit analyses with the Hosmer-Lemeshow test.[25] For ease of clinical interpretation, we subsequently dichotomized continuous variables found to be associated with sterile CSF pleocytosis by exploring frequency distributions and performing receiver operating characteristic curve analysis and single-variable recursive partitioning analyses to determine the optimal predictive cut points. We then rounded the dichotomized variable to a clinically sensible cutoff.

Finally, based on the results of our previous analysis,[16] we stratified patients according to their apparent risk of adverse events. In this prior analysis, infants at very low risk of adverse events were those who were not clinically ill in the ED and were without a high-risk medical history, as previously defined. We then compared the clinical courses and treatment of patients with and without CSF pleocytosis in the subgroup of patients at very low risk for adverse events. We used CART pro statistical software (version 6; Salford Systems, San Diego, California) to conduct the recursive partitioning analyses and SPSS statistical software (version 16; SPSS Inc, Chicago, Illinois) for all other analyses.

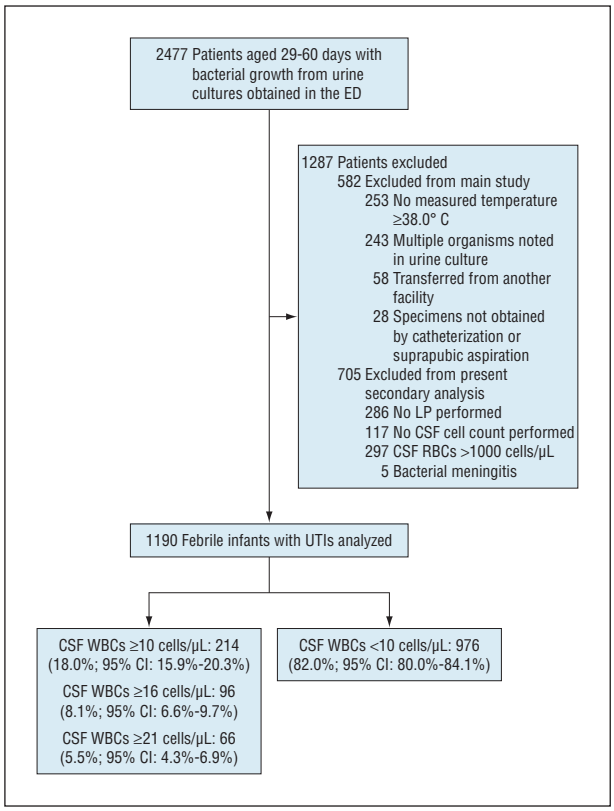

Figure. Study flow. CI indicates confidence interval; CSF, cerebrospinal fluid; ED, emergency department; LP, lumbar puncture; RBCs, red blood cells; UTI, urinary tract infection; and WBCs, white blood cells To convert WBCs to $\times 10^9$/L, multiply by 0.001.

RESULTS

Of 2477 potentially eligible patients identified by laboratory database ascertainment, 1287 were excluded (**Figure**). Five excluded patients had bacterial meningitis; 2 had culture-positive bacterial meningitis (both *Escherichia coli*); and 3 patients were pretreated with antibiotics, were found to have CSF pleocytosis, and were treated for bacterial meningitis (eTable; http://www.archpediatrics.com). Of the remaining 1190 patients included in this analysis, the median CSF WBC count was 4/μL (IQR, 2-8/μL; range, 0-1251/μL), with similar medians across enteroviral (4/μL; IQR, 2-9/μL; range, 0-1251/μL) and nonenteroviral (4/μL; IQR, 2-7/μL; range, 0-775/μL) seasons.

Two hundred fourteen had CSF WBC counts of 10/μL or higher (18.0%; 95% CI, 15.9%-20.3%). The proportion of patients with sterile CSF pleocytosis decreased to 8.1% and 5.5% when the sterile CSF pleocytosis thresholds were changed to a WBC count of 16/μL or higher and 21/μL or higher, respectively.

RISK FACTORS FOR STERILE CSF PLEOCYTOSIS

Presentation during enteroviral season, height of fever, peripheral WBC count, peripheral blood ANC, and peripheral blood band count were associated with the presence of CSF pleocytosis on bivariate analyses (**Table 1**). Multiple logistic regression analyses, however, only identified peripheral blood WBC count ($\beta = .065$, $P = .02$, Hos-

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Table 1. Bivariate Comparison of Infants With Urinary Tract Infections With and Without Sterile CSF Pleocytosis

Characteristic	No. (%) of Infants[a] With Pleocytosis (CSF WBC Count, ≥10/μL) (n=214)	No. (%) of Infants[a] Without Pleocytosis (CSF WBC Count, <10/μL) (n=976)	*P* Value
Age, mean (SD), d	43.3 (9.1)	44.4 (8.8)	.10
Male sex	141/214 (65.9)	596/976 (61.1)	.39
Enteroviral season (June-October)	109/214 (50.9)	411/976 (42.1)	.02
High-risk medical history	31/214 (14.5)	143/969 (14.8)	.92
Clinically ill in the ED	49/207 (23.7)	206/957 (21.5)	.50
Highest temperature, mean (SD), °C	39.1 (0.6)	38.9 (0.6)	.002
Seizure	2/214 (0.9)	9/976 (0.9)	.99
Urine WBC count, median (IQR), /μL	37 (10-100)	25 (10-100)	.26
Peripheral blood WBC count, mean (SD), /μL	16.8 (6.9)	14.3 (6.4)	<.001
Peripheral blood ANC, mean (SD), /μL	8029.0 (4760.0)	7118.0 (4337.0)	.007
Peripheral blood band count, median (IQR), /μL	1200 (337-2527)	840 (300-1700)	.008
Peripheral blood immature:total neutrophil ratio, mean (SD)	0.2 (0.2)	0.2 (0.2)	.17

Abbreviations: ANC, absolute neutrophil count; CSF, cerebrospinal fluid; ED, emergency department; IQR, interquartile range; WBC, white blood cell.
SI conversion factor: To convert WBC counts to $\times 10^9$/L, multiply by 0.001.
[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Table 2. Clinical Course and Outcomes of Infants With Febrile Urinary Tract Infections With and Without Sterile CSF Pleocytosis

Variable	No. (%) of Patients[a] With Pleocytosis (CSF WBC Count, ≥10/μL) (n=214)	No. (%) of Patients[a] Without Pleocytosis (CSF WBC Count, <10/μL) (n=976)	*P* Value
Temperature, <38.0°C in <24 h	156/203 (76.8)	673/863 (78.0)	.73
Presence of bacteremia	17/212 (8.0)	60/972 (6.2)	.32
Adverse events[b]	11/210 (5.2)	16/952 (1.7)	.002
Death	1	1	
Shock	0	3	
ICU or SD-ICU care	10	9	
Ventilatory support	0	2	
Other[c]	1	4	
IV antibiotics, median (IQR), d	4 (4-6)	3 (3-5)	.005
IV antibiotics for ≥7 d	50/214 (23.4)	134/976 (13.7)	<.001
LOS, median (IQR), d	3 (3-5)	3 (2-5)	.047

Abbreviations: CSF, cerebrospinal fluid; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; LOS, length of stay; SD-ICU, step-down intensive care unit; WBC, white blood cell.
SI conversion factor: To convert WBC counts to $\times 10^9$/L, multiply by 0.001.
[a] Presented as number (percentage) of patients unless otherwise indicated.
[b] One patient may have more than 1 adverse event.
[c] Includes surgery, seizures, and apneic episodes.

mer Lemeshow test $P=.99$) to be independently associated with sterile CSF pleocytosis when controlled for the presence of bacteremia, enteroviral season, high-risk medical history, clinical appearance in the ED, highest recorded temperature, presence of seizures, urine WBC counts, peripheral blood ANC, and peripheral blood band count. When dichotomized, patients with peripheral WBC counts of 15/μL or higher had almost twice the odds of having sterile CSF pleocytosis as those with lower peripheral WBC counts (odds ratio, 1.97; 95% CI, 1.32-2.94; $P=.001$).

CLINICAL COURSE AND TREATMENT

Most patients with sterile CSF pleocytosis were afebrile within 24 hours of presentation to the ED. Patients with sterile CSF pleocytosis had similar likelihoods of bacteremia as patients without CSF pleocytosis (8.0% and 6.2%, respectively; $P=.32$) but had higher rates of adverse events (5.2% and 1.7%, respectively; $P=.002$). Patients with sterile CSF pleocytosis were treated with intravenous antibiotics for longer periods than those without CSF pleocytosis (median treatment length, 4 days; IQR, 4-6 days) vs 3 days (IQR, 3-5 days), respectively ($P=.005$) (**Table 2**). In the subset of patients at very low risk of adverse events (ie, not clinically ill in the ED and without a high-risk medical history), no significant differences in clinical course were noted between those with and without CSF pleocytosis, but those with CSF pleocytosis were treated with parenteral antibiotics for longer periods (median length of treatment, 4 days; IQR, 3-6 days) vs 3 days (IQR, 3-5 days), respectively ($P=.04$) (**Table 3**).

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Table 3. Clinical Course and Outcomes of Infants With Urinary Tract Infections at Very Low Risk of Adverse Events With and Without Sterile CSF Pleocytosis[a]

Variable	No. (%) of Patients[b]		P Value
	With Pleocytosis (CSF WBC Count, ≥10/μL) (n=137)	Without Pleocytosis (CSF WBC Count, <10/μL) (n=665)	
Temperature <38.0°C in <24 h	107/129 (82.9)	465/579 (80.3)	.28
Presence of bacteremia	11/136 (8.1)	35/663 (5.3)	.20
Adverse events[c]	0	0	>.99
Duration of parenteral antibiotics, median (IQR), d	4 (3-6)	3 (3-5)	.04
IV antibiotics for ≥7 d	29/137 (21.2)	86/665 (12.9)	.006
LOS, median (IQR), d	3 (2-5)	3 (2-5)	.20

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; IV, intravenous; LOS, length of stay; WBC, white blood cell.
SI conversion factor: To convert WBC counts to $\times 10^9$/L, multiply by 0.001.
[a] Very low risk of adverse events indicates not clinically ill in the ED and without a high-risk medical history.
[b] Data are presented as number (percentage) of patients unless otherwise indicated.
[c] Defined as death, shock, admission or transfer to a higher level of care (ie, intensive care unit or step-down intensive care unit), need for ventilatory support, or any other severe clinical outcomes, including surgery, seizures, and apneic episodes.

COMMENT

In this large multicenter sample, we found that CSF pleocytosis occurs in 18% of febrile infants 29 to 60 days of age with UTIs (at a CSF WBC count threshold of ≥10/μL) and is associated with elevation of the peripheral blood WBC count. The prevalence of sterile CSF pleocytosis in our patient population is comparable to that observed in 3 prior studies.[6,11,12] Comparisons to previous studies are difficult, however, due to the varied definitions of CSF pleocytosis used by different investigators, seasonality, the inclusion of different age groups (including neonates), and the inclusion of patients with traumatic LPs. Our sample size far exceeds that of prior studies of infants in the 29- to 60-day age group, enabling a more precise estimate of the prevalence of sterile CSF pleocytosis in this population. Although controversial, we chose CSF WBC counts of 10/μL or higher to define pleocytosis because this value represents the recently identified upper limit of normal in this age group and is a common cut point used by physicians.[2,21,26,27] Interestingly, the proportion of patients with sterile CSF pleocytosis decreased substantially when the WBC count cut point was changed from 10/μL to 16/μL and 21/μL; this result was also found in 1 prior study.[11]

Because of the large sample studied, we were able to assess factors for independent association with sterile CSF pleocytosis using multivariable statistical methods. Although bivariate analysis suggested several associations (including enteroviral season), we found that only peripheral WBC count was independently associated with the risk of CSF pleocytosis. This finding may suggest a possible inflammatory cause of sterile CSF pleocytosis. Previous studies[6,12,28-32] have suggested that sterile CSF pleocytosis in patients with UTIs and other bacterial infections might be explained by the release of bacterial antigens and inflammatory mediators, which result in local meningeal cytokine release and upregulation of genes that control the innate immune response of the brain.

Finally, similar to the findings of 2 previous reports,[6,12] the presence of sterile CSF pleocytosis appears to affect clinical decision making. In our sample, more than 20% of the infants with UTIs and sterile CSF pleocytosis who did not have a high-risk medical history and were not clinically ill in the ED received at least 7 days of intravenous antibiotics. However, these patients defervesced as rapidly and were no more likely to have adverse events when compared with those without sterile CSF pleocytosis, suggesting that prolonged antibiotic therapy is unnecessary.

Our study had several possible limitations. We only included patients 29 to 60 days of age because this was the population of interest for the primary study. Our results do not necessarily apply to neonates or older infants. Ours was also a retrospective study, with inherent limitations in data availability and completeness. We attempted to minimize biases by creating a detailed manual of operations that included specific keywords to interpret subjective findings and by conducting interrater reliability analyses of subjective variables.[16] These efforts, however, would not account for physician documentation biased by prior knowledge of laboratory results or clinical courses.

Also, we queried microbiology databases rather than identifying patients who presented to the ED and had positive results on urinalyses, which was not feasible. Therefore, our results are applicable to those patients for whom urine culture results are known and cannot necessarily be extrapolated to those for whom only the results of preliminary (ie, screening) tests for UTI are known.

Finally, most patients in our sample did not have viral studies of the CSF performed. Instead, we used presentation during enteroviral season as a surrogate marker for viral meningitis. Because enterovirus infection can occur outside its typical season[33] and many other viruses may cause viral meningitis, we cannot comment on the true prevalence of CSF viral coinfections in our sample.

In conclusion, sterile CSF pleocytosis occurs in 18% of febrile infants 29 to 60 days of age with UTIs. Sterile CSF pleocytosis in these patients is associated with an elevated peripheral WBC count, suggesting a systemic inflammatory origin. However, patients with sterile CSF

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pleocytosis at very low risk for adverse events (ie, not clinically ill in the ED and without a significant medical history) appear to have similar clinical courses compared with those without CSF pleocytosis and may not require longer treatment with parenteral antibiotics.

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