Is a Lumbar Puncture Necessary When Evaluating Febrile Infants (30 to 90 Days of Age) With an Abnormal Urinalysis?

Katryn Paquette, MD, Matthew P. Cheng, MD,* David McGillivray, MD,† Christina Lam, MD,* and Caroline Quach, MD, MSc, FRCPC*‡*

Objectives: Guidelines for the management of febrile infants aged 30 to 90 days presenting to the emergency department (ED) suggest that a lumbar puncture (LP) should be performed routinely if a positive urinalysis is found during initial investigations. The aim of our study was to assess the necessity of routine LPs in infants aged 30 to 90 days presenting to the ED for a fever without source but are found to have a positive urine analysis.

Methods: We retrospectively reviewed the records of all infants aged 30 to 90 days, presenting to the Montreal Children's Hospital ED from October 2001 to August 2005 who underwent an LP for bacterial culture, in addition to urinalysis and blood and urine cultures. Descriptive statistics and their corresponding confidence intervals were used.

Results: Overall, 392 infants were identified using the microbiology laboratory database. Fifty-seven patients had an abnormal urinalysis. Of these, 1 infant (71 days old) had an *Escherichia coli* urinary tract infection, bacteremia, and meningitis. This patient, however, was not well on history, and the peripheral white blood cell count was low at 2.9×10^9/L. Thus, the negative predictive value of an abnormal urinalysis for meningitis was 98.2%.

Conclusions: Routine LPs are not required in infants (30–90 days) presenting to the ED with a fever and a positive urinalysis if they are considered at low risk for serious bacterial infection based on clinical and laboratory criteria. However, we recommend that judicious clinical judgment be used; in doubt, an LP should be performed before empiric antibiotic therapy is begun.

Key Words: fever, infant, serious bacterial infection, urinary tract infection, lumbar puncture

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The assessment and management of febrile infants aged between 30 and 90 days presenting to the emergency department (ED) remain controversial. Infants in this population are more susceptible to infections than at any other age, particularly with respect to gram-negative bacteria.[1] Furthermore, they are not yet protected against serious bacterial infections (SBIs) caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type B, as the recommended immunization schedule is not yet completed. These factors increase their risk of generalized or fulminant infections. Alternatively, these young infants are often only mildly symptomatic even in the presence of an SBI, with fever being the sole manifestation of the infection. Yet, viral infections remain the most common cause of fever without a documented source in infants, whereas urinary tract infections (UTIs) are second.[2] However, it remains difficult to discriminate between a simple viral infection and an SBI.

Numerous methods for the evaluation of febrile infants, based on various signs and symptoms, have thus been devised and studied. The most commonly used approaches are based on protocols from Boston, Philadelphia, and Rochester.[3,4] In short, these protocols group febrile neonates into "high risk" and "low risk" groups for SBI according to their clinical appearance and baseline laboratory investigations. For example, the Rochester criteria deem that an infant is at low risk of having an SBI if he/she had a normal pregnancy and birth, was well since birth and nontoxic at ED presentation, had a normal physical examination, and investigations revealed a peripheral white blood cell (WBC) count between 5 and 15×10^9/L, a differential with bands of less than 1.5×10^9/L, and a urine analysis (UA) with less than 10 WBCs/high-power field (HPF).[5] As dictated by their risk category, the infants then undergo clinical and laboratory evaluations in an attempt to rule in or rule out disease.

The Rochester criteria suggest that if a patient meets the clinical and laboratory criteria for an infant at low risk of infection, a lumbar puncture (LP) is not necessary, by opposition to the Boston or Philadelphia criteria that deem an LP necessary in all cases. However, the Rochester criteria also suggest that if the urinalysis is positive, the infant must go through a full septic workup, including an LP, and use of antibiotics pending culture results.[5] However, an LP may be associated with potential adverse events and complications. Headache, bloody tap, dry tap, disk herniation, hypoxia, and ventilation-perfusion mismatches have all been reported in young children.[6] In fact, an estimated 10% to 35% of LPs tend to be traumatic,[7,8] associated with bleeding in the subarachnoid space. Conversely, abscess formation, ventriculitis, septic infarcts, hydrocephalus, subdural effusions, and death are potential consequences of untreated bacterial meningitis in the newborn.[9,10] Despite its flaws, the LP and subsequent cerebrospinal fluid (CSF) cultures remain the criterion standard for the diagnosis of bacterial meningitis.[11]

Controversy exists as to whether a well-looking infant 30 to 90 days of age who meets all the Rochester Criteria for being at low risk, with the exception of a positive urinalysis, should have a mandatory LP.

The aim of our study was to assess the necessity of performing routine LPs in infants aged 30 to 90 days, presenting to the ED with a fever without a source, and found to have a positive urinalysis, but who are otherwise well by clinical and laboratory

From the *Infectious Diseases Division, Department of Pediatrics; †Emergency Department; Department of Pediatrics; and ‡Department of Microbiology, The Montreal Children's Hospital, McGill University Health Center, McGill University, Montréal, Québec, Canada.

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Reprints: Caroline Quach, MD, MSc, FRCPC, Infectious Disease Division, Montreal Children's Hospital, 2300 Tupper St, Room C-1246, Montréal, QC, Canada, H3H 1P3 (e-mail: caroline.quach@mcgill.ca).

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assessment or, in other words, assess the usefulness of a urinalysis in the management of these infants.

METHODS

Patient Population

The Montreal Children's Hospital is a tertiary-care pediatric hospital whose ED sees an average of 200 children per day, with peaks during the winter months. Using the hospital's microbiology laboratory database, we retrospectively identified all infants aged between 30 and 90 days who presented to our ED between October 2001 and August 2005 and who underwent a full septic workup, including an LP for bacterial culture, in addition to blood and urine cultures. During this period, the ED's protocol was to do urine, blood, and CSF cultures on all febrile infants younger than 30 days and those 30 to 90 days of age who did not meet the Rochester low-risk criteria, or in whom the treating physician elected to do an LP. Premature infants (born before 35 weeks of gestation) and infants with chronic underlying medical conditions were excluded from the study.

Study Design

Ethics approval was obtained for this study. All CSF samples processed during the previously mentioned period were included. The charts of infants who met the inclusion criteria were reviewed to determine their maximal temperature (rectal temperature ≥38°C). A senior medical student (C.M.), unaware of the study's hypothesis, was the main chart reviewer, supervised by a specialist in infectious diseases and medical microbiology. A standardized case report form was used, no hypotheses were generated during data collection, no data were inferred, and if any significant clinical or microbiological data were missing or unavailable, the patient was not included in the study. We recorded the patients' symptoms at presentation and clinical information available in the ED chart (fever, ED discharge diagnosis, and clinical presentation), CSF parameters (biochemical, hematologic, and culture results), peripheral WBC counts and differential at the time of the LP, blood and urine culture results, UA results, and antibiotics given. Patients who received antibiotics before the cultures and those diagnosed with metabolic inherited diseases or immunologic deficiencies were excluded from the study. Infants with signs localizing an infection—for example, evidence of a skin and soft tissue infection or the presence of bulging, erythematous tympanic membrane—were excluded. The criteria used to define an abnormal urinalysis or one compatible with a UTI were the presence of a least 1 of the following: any level of positivity for leukocyte esterase and/or nitrites on dipstick tests, or more than 10 WBCs/HPF on microscopy.

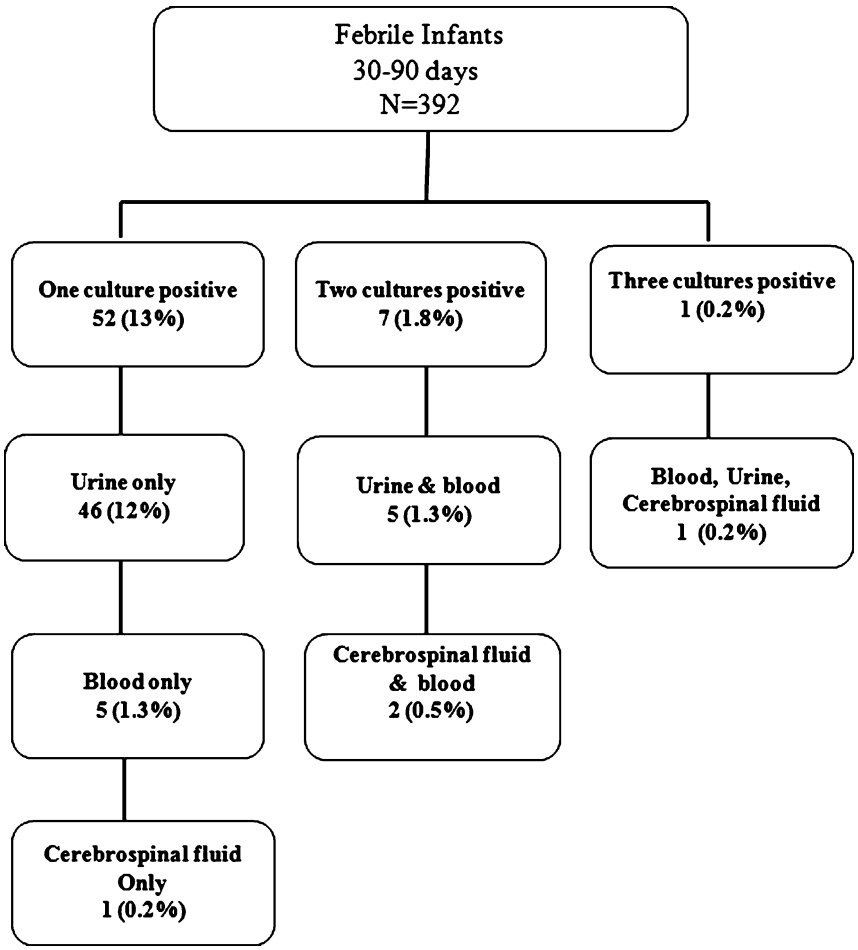

FIGURE 1. Distribution of culture results in febrile infants 30 to 90 days of age.

Statistical Analysis

Descriptive statistics, including average, median, and standard deviation (SD), were used to characterize the study population. The occurrences of UTI, bacteremia, and meningitis were calculated according to the results of the bacterial cultures. Finally, sensitivities, specificities, likelihood ratios (LRs), and their 95% confidence intervals (CIs) were computed to characterize the correlation between the results of urinalysis and the diagnosis of meningitis in infants aged 30 to 90 days.

RESULTS

Three hundred ninety-two patients were identified as having had an LP for fever without an apparent source while meeting the inclusion criteria. Of these, 241 (61.5%) were males. The infants ranged in age from 30 to 90 days, with a mean age of 56 ± 14 days (median, 48 days).

The complete culture results are shown in Figure 1. Only 1 patient in this group, a 71-day old female infant was diagnosed with both a UTI (positive leukocyte esterase, nitrites, and red blood cells) and meningitis. Further characteristics of patients with bacterial meningitis are found in Table 1. This patient was the only patient with meningitis of 57 infants 30 to 90 days of age who had an abnormal urinalysis (1/57; 1.8%). However, as detailed in Table 1, the case did not meet the other Rochester criteria for being at low risk of SBI. The 71-day-old female infant was rather unwell. In fact, she was irritable, lethargic, and feeding poorly, and her skin was cool and mottled. Furthermore, her peripheral WBC count of 2.9×10^9/L precluded her from meeting the Rochester criteria, as the count was not between 5 and 15×10^9/L. Thus, despite her abnormal urinalysis, she would have undergone a full septic workup before the administration of empiric antibiotic therapy for her UTI. As for the other children diagnosed with meningitis, all failed the Rochester criteria.

The causative organisms of UTIs were *Escherichia coli* (n = 41, 89%), *Enterococcus* spp (n = 3, 6.5%), *Klebsiella* spp (n = 1, 2.2%), and *Proteus mirabilis* (n = 1, 2.2%). The organisms cultured in the CSF of the infants were *E. coli* (n = 2, 50%), group B *Streptococcus* (n = 1, 25%), and *Neisseria meningitidis* (n = 1, 25%).

Of the 388 infants without a meningitis, 56 (14%) had an abnormal UA. Of the 4 infants in this age group with meningitis, only 1 had an abnormal urinalysis. Thus, the positive and negative LRs are 1.8 (95% CI, 0.3–9.6) and 0.87 (95% CI, 0.5–1.5), respectively. Ultimately, the negative predictive value of an abnormal urinalysis for the absence of meningitis was 98.2% and 100% when the Rochester criteria for defining infants to be at low risk are properly applied.

DISCUSSION

Of the 392 infants aged 30 to 90 days who presented to the Montreal Children's Hospital's ED from October 2001 to August 2005 with a fever of unknown origin, 4 were ultimately diagnosed with bacterial meningitis. As previously mentioned, only 1 of those children had an abnormal urinalysis.

The positive and negative LRs of an abnormal UA for the diagnosis of meningitis were found to be 1.8 (95% CI, 0.3–9.6) and 0.87 (95% CI, 0.5–1.5), respectively, and low and unlikely to modify a clinician's decision to do an LP. The negative predictive value of an abnormal urinalysis for the absence of meningitis was 98.2%. However, it is not unreasonable to assume that the negative predictive value is in fact stronger when the Rochester criteria are strictly applied.

The most commonly used clinical tools to assess the pretest probability of infants having an SBI are based on protocols from Boston, Philadelphia, and Rochester. The Rochester criteria categorize infants as low risk based on their prior history, physical examination, WBC count and differential, and UA. The Boston criteria, in turn, define low-risk infants as appearing well, not having localized signs of infection, a UA with less than 10 WBCs/HPF, CSF with WBCs of less than 10/mL, no infiltrate on chest radiograph, WBCs of less than 20,000/mL, and no recent antibiotic use. The Philadelphia criteria similarly require CSF analysis. The Rochester and Philadelphia protocols are designed for infants younger than 2 months, whereas the Boston criteria are aimed at those aged 28 to 89 days. Their sensitivities to detect SBIs are 92%, 98%, and not assessed, whereas their specificities are 50%, 42%, and 94.6%, respectively.[12] We chose to use the Rochester criteria as they do not include CSF parameters. Although the Boston and Philadelphia criteria are widely recognized as useful clinical tools, we could not use a method that inherently required CSF analysis to determine the usefulness of a routine LP in infants with a fever without a focus.

TABLE 1. Characteristics of Infant With Meningitis

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age, d	71	49	41	33
Clinical	38.5°C (rectally), mottled skin, cool extremities, irritability, lethargy, and decreased feeding	39.7°C (R), hypotension responsive to bolus, lethargy, petechial rash	38.6°C (R), shortness of breath, grunting; resuscitated and intubated in ED	38.6°C (R), somnolent, fussy, dehydrated, and decreased feeding
Peripheral WBC count, $\times 10^9$/L	2.9	3.0	1.3	14.8
Blood culture	*E. coli*	*N. meningitidis* group B	Group B *Streptococcus*	Negative
Urinalysis	Leukocyte esterase positive, nitrite positive, 6 RBCs/HPF, 4 WBCs/HPF	Negative	Negative	Negative
Urine culture	*E. coli* $>10^8$/L	Negative	Negative	Negative
CSF culture	*E. coli*	*N. meningitidis* group B	Negative after antibiotics (LP: WBCs, 1592; 68% neutrophils; proteins, 2.38 mmol/L)	*E. coli*

RBC indicates red blood cells.

The clinical practice guidelines currently in use are unambiguous with regard to the treatment of neonates. In fact, all infants aged 1 to 30 days presenting with a fever in the absence of localizing symptoms should and would receive a full septic workup. However, the situation is not as clear for older infants aged 30 to 90 days. In the latter age group, however, more and more ED physicians will withhold performing an LP if a relatively well-looking febrile infant who otherwise is not deemed at high risk of SBI as per the Rochester criteria has an abnormal urinalysis. Adhering only to the abnormal UA criteria in infants 30 to 90 days old, in our study, 1 infant with meningitis and an abnormal UA would have been misdiagnosed. Applying the Rochester criteria, however, completely remedies the situation. In short, routine LPs are not necessary, as all cases of meningitis were diagnosed using Rochester criteria and the results of the UA. However, not finding a case of meningitis among our older infants with an abnormal UA who met the Rochester criteria does not necessarily mean that the risk is absent. In the event of a zero numerator, one can estimate the upper 95% confidence limit of risk by using Hanley and Lippman-Hand's[13] "rule of three," where the approximation of risk is 3/n. If n is the number of patients assessed with an abnormal UA, then the estimated maximal risk of meningitis in febrile infants aged 30 to 90 days would be 5.3% (3/57).

Several articles in the literature likewise illustrated the minute risk of a combined meningitis and UTI, in addition to the lack of empiric data supporting routine LPs in older infants. Indeed, Vuillermin and Starr[14] demonstrated the occurrence of 1 case of combined meningitis and UTI in a pool of 322 infants 90 days or younger with a UTI. This infant with meningitis was 90 days old and, although had CSF parameters compatible with meningitis, never had a positive CSF culture. Similarly, culture-proven UTIs in conjunction with culture-proven bacterial meningitis were found to occur in less than 1% of cases in this age group,[15,16] whereas no case appears to have been published in a child older than 2 months.[17] Alternatively, Bachur and Harper[12] determined that decision tree models based on age, temperature, peripheral WBC count, UA, and clinical picture may appropriately be used with reasonable predictive values in settings where complete sepsis workups are not routinely performed. Furthermore, Brik et al,[18] through retrospective analysis of 492 infants younger than 90 days, concluded that those designated as at low risk for SBI without focal symptoms of disease did not require an LP. Mintegi et al,[19] in turn, retrospectively assessed 685 infants 3 months or younger and confirmed that "the decision to perform the LP in previously healthy and well-appearing infants with fever without known source attended by an experienced pediatric emergency physician can be individualized with no subsequent adverse outcomes."

However, given the difficulty in reliably discriminating between an SBI and other infectious etiologies, when the clinical picture remains difficult to interpret, conservative management may be warranted, and the physician may have to use his/her own judgment, despite the laboratory results. This choice should always remain an option in the clinical decision making on infants and children. A case in point, should the LP be performed with the initial workup, the cultures can be used to rule in or rule out the presence of bacterial meningitis, regardless of whether the tap is traumatic. In our study, 55 (14.3%) of negative LPs were traumatic. Had they been performed after antibiotic treatment, these infants would have undergone unnecessary treatment with a prolonged hospital stay. Of note, the association between CSF pleocytosis and UTI is controversial. Some studies have illustrated an association between aseptic meningitis and a UTI.[20,21] Shah et al[22] in a multicenter study found that CSF pleocytosis was uncommon in infants with UTIs and could usually be attributed to traumatic LP, whereas Yam et al[23] stated that CSF pleocytosis in infants with a UTI may simply be inflammatory. Thus, even a nontraumatic LP in an infant with UTI on antibiotics may be noninterpretable, as the abnormal biochemical parameters may be due to viral or other causes of aseptic meningitis.

There are some limitations to our study; the small sample size decreased our power to identify the potential case of meningitis that could have occurred in a 30- to 90-day infant with an abnormal urinalysis. However, we tried to estimate the upper limit of the 95% CI bound given a zero numerator. Moreover, as this study was done retrospectively, it became impossible to ensure that all children with fever who did not fulfill the Rochester criteria for being considered as low risk did in fact undergo a full septic workup, including an LP. We suspect, however, that ED physicians are more cautious than less and would have done more septic workup than clearly indicated by the criteria. Only a prospective study could solve this potential bias.

CONCLUSIONS

This study's findings will be helpful in the management of infants 30 to 90 days of age presenting to the ED with a fever and the refinement of the Rochester criteria. Urinalysis is not adding any additional information to the pretest probability of an SBI in a 30- to 90-day-old infant with fever that the other Rochester criteria are not already capturing. Routine LPs may not be required in infants aged 30 to 90 days if their urinalysis is compatible with a UTI and if they are considered low risk according to the Rochester criteria. In fact, we observed that the negative predictive value of an abnormal urinalysis alone for meningitis was 98.2%. However, we recommend that judicious clinical judgment be used; in the event of uncertainty, an LP should be performed before empiric antibiotic therapy is begun.

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