

# What is the risk of bacterial meningitis in infants who present to the emergency department with fever and pyuria?

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## ABSTRACT

**Objective:** To determine the rate of bacterial meningitis among febrile infants in the emergency department (ED) who have pyuria detected in an initial catheterized urine specimen.

**Methods:** This retrospective chart review, conducted at the Hospital for Sick Children, Toronto, Ont., involved all children aged 0 to 3 months who presented to the ED with fever and pyuria ( $\geq 10$  white blood cells/mm<sup>3</sup>) over a 3-year period. Cerebrospinal fluid (CSF) was evaluated using standard methods, and the rate of meningitis in children with pyuria was determined.

**Results:** The study sample included 211 infants with fever and pyuria — 79 of these under 1 month of age. Eighty-one percent (171/211) had positive urine cultures, and 143 underwent lumbar puncture to rule out meningitis. Of these, 140 CSF samples were culture negative and 3 grew coagulase negative *Staphylococcus* — 2 because of contamination and 1 because of a ventriculo-peritoneal shunt infection. Both children with CSF contamination grew *Escherichia coli* in the urine. The rate of bacterial meningitis in the study sample was 0% (95% confidence interval, 0%–2.6%).

**Conclusions:** In this study of febrile children under 90 days of age with fever and pyuria, the incidence of concurrent meningitis was 0%. This suggests that recommendations for mandatory lumbar puncture in such children should be reconsidered. However, until larger prospective studies define a patient subset that does not require CSF analysis, it is prudent to rule out meningitis, administer parenteral antibiotics for urinary tract infection, and admit for close observation.

**Key words:** meningitis; pyuria; urinary tract infection; children; emergencies

## RÉSUMÉ

**Objectif :** Déterminer le taux de méningites bactériennes parmi des nourrissons fébriles au département d'urgence (DU) chez qui une pyurie est décelée lors de l'analyse initiale d'un échantillon d'urine par cathéter.

**Méthodes :** Cette revue de dossiers rétrospective, menée au Hospital for Sick Children à Toronto, Ontario, incluait tous les enfants âgés entre 0 et 3 mois reçus au DU avec des symptômes de fièvre et de pyurie (103 leucocytes/mm<sup>3</sup>) au cours d'une période de trois ans. Le liquide céphalo-rachidien (LCR) fut évalué à l'aide de méthodes standard et le taux de méningite chez les enfants atteints de pyurie fut déterminé.

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Received: June 9, 2003; final submission: Aug. 6, 2003; accepted: Aug. 12, 2003

*This article has been peer reviewed.*

*Can J Emerg Med* 2003;5(6):394-9

**Résultats :** L'échantillon à l'étude incluait 211 nourrissons atteints de fièvre et de pyurie, dont 79 étaient âgés de moins d'un mois. Quarante-vingt-un pour cent des bébés (171/211) présentaient une culture d'urine positive et 143 subirent une ponction lombaire pour écarter le diagnostic de la méningite. Parmi ceux-ci, les résultats de la culture de 140 échantillons de LCR furent négatifs et trois permirent d'isoler des staphylocoques à coagulase négative, soit deux découlant de la contamination et un découlant d'une infection par shunt ventriculo-péritonéal. On isola *Escherichia coli* dans l'urine des deux enfants dont le LCR était contaminé. Le taux de méningite bactérienne au sein de l'échantillon à l'étude était de 0 % (intervalle de confiance de 95 %, 0 %-2,6 %).

**Conclusions :** Dans cette étude auprès d'enfants âgés de moins de 90 jours atteints de fièvre et de pyurie, l'incidence de méningite coexistante était de 0 %. Cette constatation soulève la possibilité de revoir la recommandation de ponction lombaire obligatoire chez de tels enfants. Cependant, jusqu'à ce que des études prospectives de plus grande envergure définissent un sous-groupe de patients qui ne nécessitent pas d'analyse du LCR, il est prudent d'écarter le diagnostic de méningite, d'administrer des antibiotiques par voie parentérale pour l'infection urinaire et de garder l'enfant à l'hôpital sous surveillance étroite.

## Introduction

When a patient is under 1 month of age, fever may be the only manifestation of meningitis; therefore lumbar puncture (LP) is recommended for all febrile neonates.<sup>1,2</sup> In infants from 1–3 months of age, LP is recommended if the fever is over 39°C, if the child appears unwell or has abnormal mentation, or if laboratory tests suggest bacterial infection.<sup>2</sup> When assessing the need for LP, physicians typically look for infection elsewhere — particularly in the urine.

Previous studies suggest that 0%–7.5% of children with culture-proven urinary tract infection (UTI) have concurrent meningitis,<sup>3–9</sup> so positive urine cultures do not eliminate the need for LP but they reduce the likelihood of meningitis, particularly in children without clinical evidence of central nervous system infection. Because emergency physicians rarely have access to culture results, they often modify early diagnostic decisions based on microscopic examination of the urine. This is probably a valid practice, since the finding of white blood cells (WBC) in catheterized urine samples is sensitive and specific for UTI,<sup>10</sup> but concurrent meningitis remains a concern, and previous studies have not documented the prevalence of meningitis in children who present to the emergency department (ED) with fever and pyuria.

The purpose of this study was to estimate the prevalence of meningitis in children <90 days of age who present to the ED with fever and pyuria. Our hypothesis was that the prevalence of meningitis in these children is close to zero. If this is the case, and if admission for intravenous antibiotics is the recommended management, the need for LP might be reconsidered, particularly in children with a low clinical suspicion of meningitis.

## Methods

### *Setting and patients*

This retrospective study was conducted in the ED of the Hospital for Sick Children, Toronto, Ont. All children aged 0–3 months who presented to the ED between Oct. 1, 1997, and Oct. 31, 2000, and who had catheterized urine specimens reported in the hospital's electronic laboratory database were identified. Charts were reviewed, and patients were considered eligible for inclusion if their initial documented ED temperature was >38°C. Patients were excluded if the urine WBC count was <10 cells/mm<sup>3</sup>.

### *Urine analysis*

In our hospital, catheterization is the sole method of obtaining urine specimens for culture. Between 0700 and 1900, our hospital laboratory analyzes urine immediately; after 1900, urine samples were often refrigerated and analyzed the next morning. Unspun specimens were examined microscopically for bacteria and WBCs, and pyuria was reported as the number of leukocytes per mm<sup>3</sup> based on hemocytometer count. Urine was cultured quantitatively with 0.01-mL calibrated loops on blood agar and 0.001-mL calibrated loops on MacConkey plates. The plates were incubated at 35°C and read after a minimum of 16 hours of incubation. Organisms were identified according to standard methods.<sup>11</sup>

### *Cerebrospinal fluid analysis*

Cerebrospinal fluid (CSF) was examined for bacteria and WBCs by light microscopy with a hemocytometer. The WBC differential count was done on CSF stained with Fuchs stain. Culture specimens were inoculated onto sheep-blood agar and chocolate agar plates, incubated in

5% CO<sub>2</sub>, and read at 24 and 48 hours. Organisms were identified according to standard methods.<sup>12</sup> Viral isolation by cell culture and polymerase chain reaction for herpes simplex virus were performed based on methods described by Johnson and colleagues.<sup>13</sup>

### Definitions

Pyuria was defined as the presence of  $\geq 10$  WBC/mm<sup>3</sup>. "Positive urine culture" was defined as pyuria plus the growth of a single urinary pathogen with  $>50 \times 10^6$  CFU (colony forming units)/L ( $50 \times 10^3$  CFU/mL).<sup>14</sup> CSF pleocytosis was defined as  $>35$  WBC/mm<sup>3</sup> for infants younger than 4 weeks,  $>22$  WBC/mm<sup>3</sup> for infants 4–8 weeks, and  $>10$  WBC/mm<sup>3</sup> for infants older than 8 weeks.<sup>11</sup> Bacterial meningitis was considered present if an infant had a positive bacterial CSF culture. Herpes simplex meningitis was considered present if an infant had a positive CSF polymerase chain reaction.

### Outcome assessment

Two of the authors (R.D.G., L.L.) reviewed the electronic records of all eligible children, documenting the reported urine WBC counts, red blood cell counts and culture results, as well as the CSF WBC counts, red blood cell counts, protein and glucose levels, culture results, and polymerase chain reactions for viruses. Our primary outcome was the rate of documented meningitis in the study population of children with pyuria on initial catheterized urine sample.

### Data analysis

Data were entered into Microsoft Excel 2000 (Microsoft Corporation, Redmond, Wash.). Interobserver reliability for key outcomes was not assessed because none involved subjective data elements. Standard descriptive statistics, including means, standard deviations, were determined. Statistical analysis was performed using SPSS for Windows 10.0. The statistical significance of observed differences in categorical outcomes (e.g., culture results) was assessed using the chi-squared test, while the significance of observed differences in continuous outcome variables (e.g., cell counts) was assessed using Student's *t*-test. *P* values  $<0.05$  were considered significant. InStat (version 2.04, Knoll Pharma Inc.) was used to calculate 95% confidence intervals (CIs) for key study outcomes, including meningitis rates.

## Results

Figure 1 shows that 651 infants had catheterized urine specimens reported in the hospital's electronic laboratory

database and that 217 (33%) of these were eligible for inclusion based on significant pyuria. Six patients were excluded because reviewers were unable to retrieve their charts, leaving 211 in the study sample, including 170 (81%) boys and 41 (19%) girls. The mean age was  $43 \pm 26$  days, with a range of 2–89 days. Seventy-nine children (38%) were less than 29 days old, and 132 (63%) were 29–90 days old.

### Urine specimens

All children had  $\geq 10$  WBC/mm<sup>3</sup> and 164 children (78%) had  $\geq 100$  WBC/mm<sup>3</sup>. The 47 children (22%) with 10–100 WBC/mm<sup>3</sup> had an average of 33 WBC/mm<sup>3</sup>. Red blood cells were seen in 67 samples (32%) and bacteria in 153 samples (73%). Table 1 shows that 171 children (81%) had UTIs confirmed by positive cultures. An additional 7 patients grew mixed organisms, and 33 had negative urine cultures.

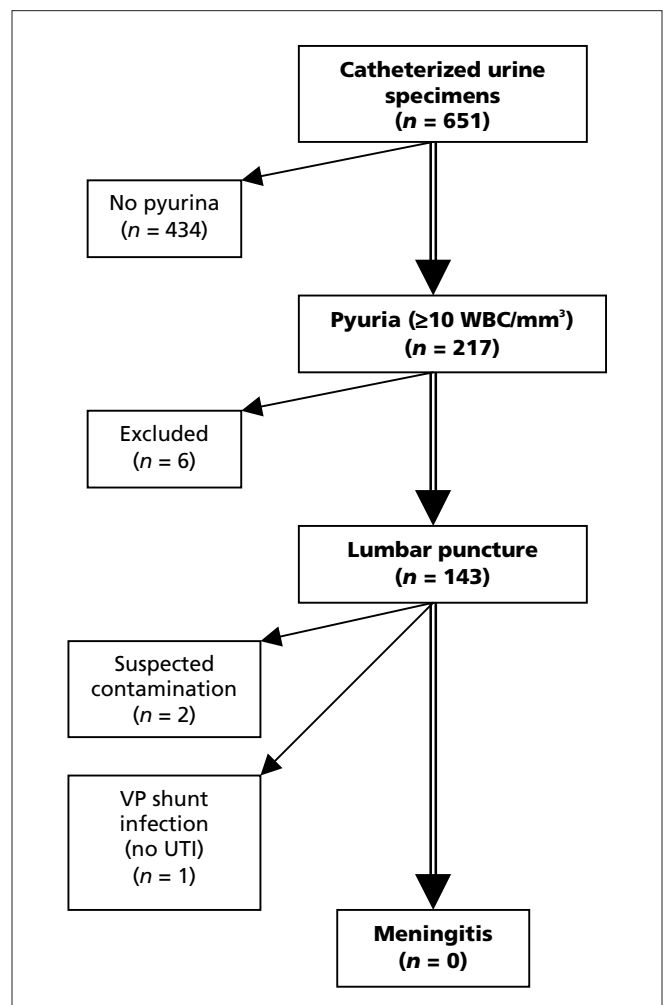


Fig. 1. Study flowchart. WBC = white blood count; VP = ventriculo-peritoneal; UTI = urinary tract infection.

### Cerebrospinal fluid specimens

LPs were performed on 143 (70%) of the 211 children, including 89% (70/79) of those in the 0–28-day age group and 55% (73/132) of those in the 29–90-day age group. All CSF samples were cultured, but only 65 (45%) had WBC counts reported because the remainder were contaminated with blood, were clotted or were of insufficient volume. The median WBC count was 7 cells/mm<sup>3</sup> (range 0–300), and 39 of 65 infants (60%) had WBC counts <10 cells/mm<sup>3</sup>. Six children had WBC counts above the pre-defined study thresholds (>35 WBC/mm<sup>3</sup> under 4 weeks, >22 WBC/mm<sup>3</sup> for infants 4–8 weeks, and >10 WBC/mm<sup>3</sup> for infants older than 8 weeks). This included 5 infants aged 4–8 weeks and 1 infant older than 8 weeks.

CSF cultures were negative in all but 3 cases, and these patients, aged 35, 39 and 45 days, all grew coagulase negative *Staphylococci*. Two of these were considered contaminants (one had a CSF WBC count of 76/mm<sup>3</sup>, and the second had an insufficient CSF volume for a cell count). Both children grew *Escherichia coli* in their urine cultures, both became afebrile after 1 day of antibiotic treatment, and both were discharged with no complications on day 5. The third child had severe congenital hydro-

cephalus with an infected ventriculo–peritoneal shunt. His urine sample had 34 WBC/mm<sup>3</sup>, no red blood cells, no bacteria and negative cultures. Blood cultures, CSF viral cultures and polymerase chain reaction for herpes simplex were negative in all 3 patients who grew coagulase negative *Staphylococci* in their CSF. Based on these findings, the rate of meningitis in the study sample was 0% (95% CI, 0%–2.6%).

### Discussion

This study suggests that, in febrile children less than 90 days of age, if there is no clinical evidence of meningitis and pyuria ( $\geq 10$  WBC/mm<sup>3</sup>) is present on a catheterized urine sample, the likelihood of concurrent meningitis is extremely low and LPs are unlikely to alter management. Previous studies have described meningitis rates in febrile children with positive urine cultures, but culture results take 36–72 hours and are not helpful in making ED decisions. This is the first study to assess the likelihood of meningitis in febrile infants who have pyuria documented during their ED visit.

### Previous literature

Most authors have found that in febrile children with proven UTI concurrent meningitis is uncommon or non-existent (Table 2). In a series of 100 5-day to 8-month-old children, Ginsburg and McCracken found no cases of meningitis,<sup>4</sup> and in a similar study of 22 febrile infants younger than 8 weeks, Lin and coworkers also found no cases of meningitis.<sup>8</sup> Hoberman and colleagues reported 1 case of meningitis among 50 children less than 1 year of age,<sup>6</sup> while Wiswell found 3 cases of meningitis in a series of 88 uncircumcized boys under 1 month of age.<sup>5</sup> In the latter study, however, no data were provided on the

**Table 1. Organisms cultured from the urine of 171 infants in retrospective study of 211 infants with fever and pyuria**

Organism	No. of infants
<i>Escherichia coli</i>	145
<i>Klebsiella</i>	8
<i>Enterococcus</i> sp	3
<i>Enterobacter cloacae</i>	3
<i>Streptococcus agalactiae</i>	3
<i>Staphylococcus coagulase negative</i>	3
Others	6

**Table 2. Studies assessing meningitis rates in children with proven urinary tract infections**

Study, year	Age	No. of UTI cases	LP positivity	Meningitis rate,* %
Bergstrom et al, <sup>3</sup> 1972	Neonates	80	6 / 31†	7.5
Ginsburg and McCracken, <sup>4</sup> 1982	5 d–8 mo	100	0 / 88	0.0
Wiswell and Geschke, <sup>5</sup> 1989	<30 d	88	3 / 88	3.4
Hoberman et al, <sup>6</sup> 1993	<12 mo	50	1 / 50	2.0
Bachur and Caputo, <sup>7</sup> 1995	<2 yr‡	354	4 / 244	1.1
Lin et al, <sup>8</sup> 2000	<8 wk	22	0 / 22	0.0
Dayan et al, <sup>9</sup> 2002	<60 d	131	1 / 131	0.8

UTI = urinary tract infection; LP = lumbar puncture

\*Meningitis rates are calculated using the no. of positive LPs as the numerator and the no. of children in the study as the denominator.

†6 positive LPs for bacterial meningitis. Nine patients had viral meningitis, urine not catheter specimens.

‡All children in this series were <6 months old.

number of patients who had LPs, on whether pleocytosis was found, or the identity of the organisms involved. Bachur and Caputo published the largest series, involving 354 children, of whom 3 (all younger than 1 month) had *E. coli* meningitis.<sup>7</sup> Two of these had positive blood cultures for *E. coli*, while a third had CSF pleocytosis and a positive blood culture for *Enterobacter cloacae*; however, the authors noted that the CSF culture was mishandled in this case. The most alarming data were published in 1972 by Bergstrom and colleagues,<sup>3</sup> who reported 6 cases of purulent meningitis in a series of 80 febrile neonates with UTIs. Unfortunately, the urine cultures in this study were not obtained in sterile fashion, and no organisms were specified.

### **Fever and urinary tract infections**

From 1%–20% of children who present for evaluation of fever in the outpatient setting have a UTI.<sup>15–18</sup> Ninety-five percent of children with UTI have pyuria or bacteriuria, and these findings have high positive predictive value (85%) for the identification of positive urine cultures.<sup>15</sup> Conversely, low urinary WBC counts are associated with sterile urine cultures.<sup>16,19</sup> In febrile infants younger than 8 weeks, urine WBC counts determined by hemocytometer are better predictors of UTI than (peripheral blood) WBC counts, c-reactive protein, erythrocyte sedimentation rates or microscopic analysis of urine.<sup>8</sup> The presence of pyuria in catheterized urine has been advocated as a marker to determine which febrile infants require urine cultures,<sup>15</sup> but it is important to note that pyuria can occur in other conditions, including trauma, dehydration, appendicitis, glomerulonephritis, viral infection and fever.<sup>20</sup> This may explain the 33 infants in our study who had pyuria and negative urine cultures.

### **Concurrent meningitis in infants with UTI**

Because of concerns that meningitis may be missed in patients with UTI, LPs are recommended for febrile infants from 29–90 days old who have suspected UTIs.<sup>2</sup> In the current study, LPs were performed on 70% of the 211 children, including 89% in the 0–28-day age group and 55% in the 29–90-day age group. Clearly, despite current recommendations, clinicians often choose not to perform an LP, perhaps due to the child's favourable clinical status or perhaps based on a high perceived likelihood that UTI was the only source of fever. Our data also show that physicians were more willing to trust clinical judgement and defer the LP in older children. Given the 0% meningitis rate seen, this practice of selective LP may be reasonable in patients with pyuria who are otherwise clinically well and those

who are going to be admitted for parenteral therapy and close observation.

### **Limitations**

In this and previous studies, not all children with fever and pyuria underwent LP; therefore it is conceivable that some children had concurrent meningitis and were successfully treated by the antibiotics used to treat UTI. While we did not see cases of missed or partially-treated meningitis in the study sample, it is possible that patients who did not have LPs subsequently deteriorated and presented to another facility, but this is unlikely since we are the only regional pediatric hospital. Finally, although we found a 0% incidence of meningitis in our study sample, the upper boundary of the 95% CI was 2.6%, a small but significant risk; therefore a larger sample of febrile children with pyuria would be necessary to achieve a higher level of certainty.

### **Conclusion**

In this study of febrile children under 90 days of age with fever and pyuria, the incidence of concurrent meningitis was 0%. This suggests that recommendations for mandatory LP in such children should be reconsidered. However, until larger prospective studies define a patient subset that does not require CSF analysis, it is prudent to rule out meningitis, administer parenteral antibiotics for UTI and admit for close observation.

**Competing interests:** None declared.

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