Duration of Fever Affects the Likelihood of a Positive Bag Urinalysis or Catheter Culture in Young Children

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Objective To test the hypothesis that there will be a clinically significant rise in the proportion of positive bag urinalyses and catheter cultures in young children with increasing duration of fever.

Study design This was a prospective cohort study of 818 infants and children age 3-36 months presenting to a tertiary care emergency department with documented fever without source. Following the documentation of fever from < 1 to ≥ 5 days, bag specimens were collected for urinalysis. The primary outcome was the yield of positive bag dipsticks by day, defined as positive for nitrates or more than trace leukocyte esterase. The secondary outcome was positive catheter cultures on each day of fever.

Results Positive bag urinalyses increased with duration of fever: 14.8% (35/237) on day 1 versus 26.4% (43/163) on day 3 (relative risk [RR] = 1.8; 95% confidence interval [CI] = 1.2-2.7; *P* = .004). Positive catheter cultures increased in the same fashion: 4.8% (11/229) on day 1 versus 12.6% (20/159) on day 3 (RR = 2.6; 95% CI = 1.3-5.3; *P* = .005).

Conclusions The yield of positive bag urinalyses and catheter cultures increased significantly in children with fever of 3 days or longer duration. *(J Pediatr 2010;156:629-33)*.

Even though most well-appearing young children with fever without source (FWS) have a nonspecific self-limited viral infection, urinary tract infection (UTI) remains an important consideration.[1] The reported pooled prevalence of UTI in febrile children around age 2 years is 7.0% (95% confidence interval [CI] = 5.5%-8.4%).[2] In their technical report on UTI, the American Academy of Pediatrics (AAP) stated that approximately 5% of children with FWS will have a UTI, and recommended considering a possible diagnosis of UTI in any infant or child age 2 months to 2 years old with FWS.[3] The report and the accompanying practice parameter provided no recommendation as to the duration of FWS necessary before the initiation of an investigation.[3,4] The published data are considered insufficient to identify the optimal time for evaluating UTI in this population.[5] Subsequent to the publication of the practice parameter, some studies have looked at duration of fever as one of several variables examined in girls with suspected UTI. To the best of our knowledge, the impact of the duration of fever on detection of fever has not been addressed as the primary outcome in boys and girls.[6-8]

The primary objective of this study was to determine the proportion of positive bag urinalyses in children age 3-36 months with FWS with varying duration of fever: < 1, 2, 3, 4, or ≥ 5 days. There is solid evidence supporting bag urinalysis as a valid screening tool for UTI in young children, given the fact that a positive bag dipstick tends to overestimate the risk of UTI[9] and that a negative dipstick for nitrites and leukocytes has a likelihood ratio (LR) of 0.2 (95% CI = 0.16-0.26) for a UTI.[10] Although suprapubic bladder aspiration is the gold standard for detecting UTI in young infants, we chose to use catheterization, because it is more commonly used in the emergency department (ED) environment. Our secondary objective was to determine the proportion of positive urine catheter cultures obtained on each day of fever. Our hypothesis was that there would be a clinically significant rise in the proportion of positive bag urinalyses and catheter cultures in infants and children with increasing duration of fever.

AAP	American Academy of Pediatrics
CFU	Colony-forming units
CI	Confidence interval
ED	Emergency department
FWS	Fever without source
HPF	High-power field
LR	Likelihood ratio
RR	Relative risk
UTI	Urinary tract infection
WBC	White blood cell

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Methods

We conducted a prospective cohort study of infants and children age 3-36 months presenting to a tertiary care pediatric ED with documented FWS between April 2005 and September 2007. The study received full approval from Montreal Children's Hospital's Ethics Committee and the Independent Review Board.

Bag urinalyses are ordered mainly by the nurse at triage or by a physician following assessment of a febrile, non–toilet-trained, nontoxic child age 3-36 months with FWS. At our center, nurses order approximately 80%-90% of the bag urines obtained. Urine bags are applied to the perineal area after cleansing with water. No bag urine specimens are sent for culture.

An automated Clinitek 100/200 analyzer (Bayer, Pittsburgh, Pennsylvania) and Multistix 10 SG reagent strip urine dipsticks (Bayer) were used for analysis of leukocyte esterase and nitrites. A positive result was defined as greater than trace amounts of leukocyte esterase or a positive nitrite test. A positive catheter urine culture was defined as growth of $\geq 10^7$ colony-forming units (CFU)/L or $\geq 10^4$ CFU/mL of a single pathogenic organism. Multiple organisms were not considered positive even if $>10^7$ CFU/L were present. These definitions are based on the AAP practice parameter for the diagnosis, treatment, and evaluation of initial UTI in febrile infants and young children.[4]

If the bag dipstick urinalysis was positive, then a catheter sample was obtained for urinalysis and culture. If the bag dipstick urinalysis result was negative, then no further testing was done.

Children who met all of the following criteria were eligible for study entry: age 3-36 months, rectal temperature of ≥ 38 °C recorded in the ED or by parental report, FWS, and bag urinalysis initiated by the nurse at triage or requested by the child's physician. Exclusion criteria included toxic appearance, known renal disease, immunocompromised status, the need to proceed directly to catheterization, and antibiotic use in the previous 10 days. Data collected included age, sex, race, circumcision status in males, highest reported fever by the parents or documented in the ED, duration of fever, laboratory results on the bag urine specimen (leukocyte esterase and nitrites on dipstick), and the culture results obtained on all catheter urine specimens.

Definitions

FWS was defined as either fever with no identified etiology following a detailed history and physical examination, or fever with equivocal etiology where the potential source of fever was either nonspecific (eg, early viral illness) or of low clinical severity (eg, mild gastroenteritis or otitis media).

Fever was defined as a rectal temperature of ≥ 38 °C recorded in the ED or by parental report. Parental report was used to categorize duration of fever in days, from < 1 day to ≥ 5 days. This was considered a practical and realistic measurement tool. In a population of 244 infants, Bonadio et al[11] reported a 92% concordance between home-reported fever and hospital-measured rectal fever as long as the home-reported temperature was a rectal temperature.[11]

Statistical Analyses

The primary outcome was the proportion of positive bag urinalyses by fever duration, that is, < 1 day, 2, 3, 4, or ≥ 5 days of fever. We also studied infants and children with fever of ≤ 2 days versus ≥ 3 days duration based on work by Gorelick, Shaw, and coworkers.[6,7] The secondary outcome was the proportion of positive urine catheter cultures by duration of fever. A sensitivity analysis was conducted to evaluate the significance of those infants who had a positive bag urinalysis but did not have a urine culture. The χ^2 test was used to compare the proportions of positive bag urinalyses and catheter cultures for the 5 different durations of fever, the proportions for fever of 1 day versus fever of 3 days, and the proportions for the dichotomized time periods (≤ 2 days vs ≥ 3 days of fever). The level of significance used was $P < .05$. Relative risk (RR) and 95% confidence intervals (CIs) were calculated. The statistical program used for this study was SPSS version 11.0 (SPSS, Chicago, Illinois).

Results

Of the 818 bag urine dipsticks analyzed in this study, 152 (19%) were positive. As shown in Table I, there were no significant differences in duration of fever by sex, circumcision status, age 3-12 months, Caucasian female, Caucasian race, or mean temperature. A significant increase in positive bag urinalysis results over time was observed ($P = .02$; Figure 1). Patients with fever of 3 days duration had the highest proportion of positive urinalyses. On day 1, 14.8% (35/237) of the urinalyses were positive, compared with 26.4% (43/163) on day 3 (RR = 1.8; 95% CI = 1.2-2.7; $P = .004$). When duration of fever was dichotomized into ≤ 2 days versus ≥ 3 days of fever, the children with longer duration of fever had a greater risk of having a positive bag urinalysis (14.6% [64/438] vs 23.2% [88/380]; RR = 1.6; 95% CI = 1.2-2.1; $P = .002$).

A total of 120 patients (79%) with a positive bag urinalysis had a urine culture obtained by catheterization. The proportion of positive catheter urine cultures based on the total number of bag urines collected showed a significant increase over

Table I. Characteristics of patients by days of fever

	Duration of fever, days				
	< 1	2	3	4	> 5
Number of children/day	237	201	163	99	118
Female sex, %	42	47	53	41	56
Uncircumsized, %	66	71	69	88	86
Caucasian race, %	62	54	52	60	46
Caucasian female, %	26	22	29	36	24
Age 3-12 months, %	46	43	44	46	37
Average temperature, °C	39.1	39.3	39.1	39.1	39.1

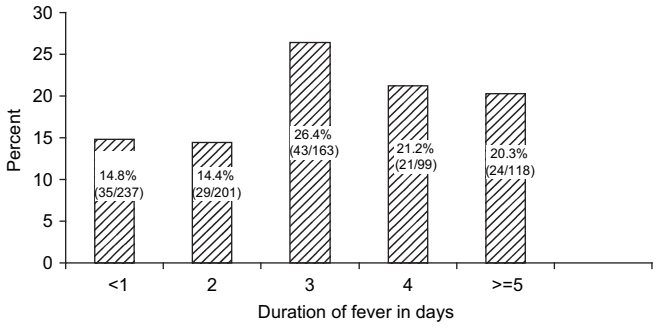

Figure 1. Number and percentage of positive bag urinalyses based on duration of fever.

time (P = .02; Figure 2). The percentage of positive cultures was lowest on day 1 (4.8%; 11/229) and highest on day 3 (12.6%; 20/159) (RR = 2.6; 95% CI: 1.3-5.3; P = .005). When duration of fever was dichotomized into ≤ 2 days versus ≥ 3 days of fever, the children with longer duration of fever were at greater risk of having a positive bag catheter culture (5.0% [21/421] vs 11.1% [41/367]; RR = 2.2; 95% CI = 1.3-3.7; P = .001).

To account for the 30 patients with a positive bag urinalyses in whom a catheter urine culture was not obtained, we performed a further sensitivity analysis by attributing the missing catheter cultures to each of their respective days and making 3 separate assumptions about the missed cultures; all cultures were negative, all cultures were positive, and all missing cultures had the same proportion of positive cultures each day as was found in the catheter urine cultures obtained in the study (Table II). All 3 assumptions continued to demonstrate that the proportion of positive cultures increased over time. If all of the missing catheter cultures were positive (an unlikely scenario), the result would not be statistically significant, however.

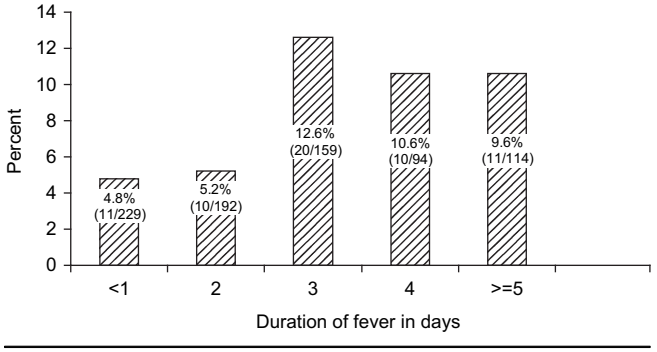

Figure 2. Number and percentage of positive catheter urine cultures based on duration of fever (assuming that children with a negative bag urinalysis would have had a negative catheter culture if done).

Discussion

FWS is a common complaint in young children in the ED and other ambulatory care settings. Although investigations in unwell children are clearly indicated, regardless of duration of fever, in the otherwise well child with fever of short duration, controversy continues regarding the need, timing, and extent of investigations. Specifically, current data on the impact of duration of fever in the diagnosis of UTI is both incomplete and conflicting. In a study on the prevalence of UTI in young febrile children in the ED, Shaw et al[8] found no increase in the likelihood of a UTI in children with fever of > 48 hours duration (LR = 1.3; 95% CI = 0.8-1.9). This study was done on all infants age < 12 months and girls age < 2 years who presented to the ED with fever ≥ 38.5 °C. In contrast, in 2000, Gorelick and Shaw,[6] using a combination approach, published a clinical decision rule to identify febrile young girls (age < 2 years) at risk for UTI. They showed that FWS for 2 days or more was one of 5 clinical variables related to the presence of a UTI in the study population.[6] The other variables included age < 12 months, Caucasian race, temperature ≥ 39°C, and FWS. Their clinical decision rule suggested that any combination of 2 or more risk factors indicated the need for bladder catheterization urine testing. This rule would identify 95% of patients with UTI and eliminate 30% of unnecessary (negative) urine cultures. When analyzed separately, fever of ≥ 2 days duration by history was not significant (RR = 1.5; 95% CI = 0.9-2.6; P = .10). This clinical decision rule was further evaluated in a retrospective case-control study of 98 girls age 1 month to 2 years with UTI and a random sample of 114 girls with negative urine culture.[7] In that study, fever of > 2 days duration was strongly associated with presence of a UTI.[7] To date, the decision rule has been limited to girls and has not been validated prospectively. Thus, the relationship between duration of fever and risk of UTI remains unclear.

In the present prospective cohort study, we observed that febrile young children with FWS who had a bag urinalysis to screen for UTI were more likely to have a positive bag urinalysis and positive catheter culture if the duration of fever was prolonged for ≥ 3 days. This study is unique in that it includes both boys and girls age 3-36 months, specifically uses the bag urine as an initial screen for UTI with a follow-up urine catheter culture to confirm UTI, and includes a large number of children enrolled on each day of fever.

A possible explanation for our results is that the duration of fever itself may select the patients, so that those with simple viral infections are less likely to present after 2-3 days, given that most of these patients experience spontaneous resolution of illness and fever within 3 days. Thus, the population presenting with fever of 3 days duration may be more likely to have a UTI than those with fever of shorter duration. A second possible explanation could be a delay between the onset of infection and the inflammatory response required to demonstrate a positive urinalysis, with a positive urinalysis less likely to appear early on in the illness. Previous studies

Table II. Sensitivity analysis for the proportion of positive catheter urine cultures from patients with bag urines obtained on each day of fever, making assumptions for the 30 patients with positive bag urinalysis who did not have a catheter culture done

	Assumptions/days, n (%)					
	< 1	2	3	4	5	*P* value
Actual study	**4.8 (11/229)**	**5.2 (10/192)**	**12.6 (20/159)**	**10.6 (10/94)**	**9.6 (11/114)**	**.02**
Number missing	**3.8 (9/237)**	**4.5 (9/201)**	**2.5 (4/163)**	**5 (5/99)**	**3.4 (4/118)**	**.82**
All positive	8.4 (20/237)	9.4 (19/201)	14.7 (24/163)	15.1 (15/99)	12.3 (15/118)	.19
Proportionate	5.0 (12/237)	5.4 (11/201)	12.9 (21/163)	13.1 (13/99)	12.7 (15/118)	.005
All negative	4.6 (11/237)	5.0 (10/201)	12.3 (20/163)	10.1 (10/99)	9.3 (11/118)	.02

Actual study results are in bold. The sensitivity analysis is in regular type.

have used different age and sex criteria when looking at different predictors of UTI, not just duration of fever as we have done in this study.[6-8,12] We excluded febrile infants age < 3 months with fever, because we believe that these very young infants should have a catheter urinalysis at the time of the first visit to the ED, because they are at higher risk than older infants with FWS. Newman et al[12] reported an odds ratio of 1.8 (95% CI = 1.2-2.8) for the diagnosis of UTI after 24 hours of fever in infants age ≤ 3 months, and that 10% of 167 infants with a UTI had bacteremia.

The present study has some limitations. Opinions vary as to the appropriateness of using a bag urinalysis, because a negative bag screen does not invariably rule out UTI. However, in a recent meta-analysis, Whiting et al[10] reported that a negative dipstick for leukocyte esterase and nitrites had a LR of 0.2 (95% CI = 0.16-0.26) for UTI.[10] It is a practical reality that in febrile but nontoxic children age 3-36 months, bag urinalysis is often used as a screen for UTI to determine the need for a confirmatory catheter culture. The advantages of using bag dipstick urinalysis for screening are that it is more readily available in most clinical settings, is less invasive, and has a higher sensitivity for determining a UTI in infants age > 90 days than catheter urinalysis,[9] and also provides a rapid result from the laboratory. The dipstick often is used as a quick screen in the office-based setting, where it is more difficult to obtain a microscopic result in a timely fashion. The disadvantage is that it has lower specificity and must be followed up with a catheter culture if positive. By including both bag urinalysis and catheter cultures in our study, we believe that the information will be potentially useful to 2 groups of physicians: those who screen first with a bag urine dipstick with or without a microscopic examination and those who proceed directly to a catheter culture.

We cannot automatically extrapolate the results from this study to the potential results from a true longitudinal study in which the same child underwent repeat urine sampling, by bag and catheterization, on each day of fever. Such a study would be neither feasible nor ethical. Because each child was eligible to contribute only 1 observation regarding the duration of fever, we are unable to discern whether the 21/438 infants with a positive urine culture after bag urine screening on day 1 and day 2 would still have had a positive urinalysis and culture had the screening been delayed until day 3 or longer. Similarly, the design of the present study does not allow us to speculate as to whether the individual children with positive urinalyses presenting after more than 2 days of fever would have had positive screening studies had they presented earlier in the course of their illness. Nonetheless, given that more than 400 children were evaluated after a short duration of fever, our results remain clinically relevant and clearly demonstrate that the overall yield of urine testing was significantly higher in those presenting with fever of ≥ 3 days duration.

An additional limitation of this study is that children with a negative bag urinalysis did not undergo our gold standard test for UTI—catheter urine culture. To find these false-negative results, we would have needed to catheterize 656 additional children (80% of our patient population). Beyond age 3 months, the false-negative rate of bag urinalysis decreases substantially.[9,10]Bag urinalysis appears to be a helpful screening tool in nontoxic, non–toilet-trained patients in the office or ED setting and in settings in which staff are not trained to perform catheterization on children under age 3 years. The finding of an increase in positive bag urinalysis over time is supported by our secondary outcome showing an increase in positive catheter cultures over time.

Recent prospective studies have suggested that a delay in treating pyelonephritis was not associated with increased risk of scarring.[13,14] This issue remains controversial, however,[15] and further research is needed before we can recommend a delayed testing approach in well children with FWS. The decision to perform a urine test on well children presenting with FWS on day 1 or 2 of fever depends on individual physician judgment, the health care setting, specific risk factors for UTI, and the reliability of follow-up care. ■

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