Nonresponders: Prolonged Fever Among Infants With Urinary Tract Infections

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ABSTRACT. Background. The majority of young children with fever and urinary tract infections (UTIs) have evidence of pyelonephritis based on renal scans. Resolution of fever during treatment is 1 clinical marker of adequate treatment. Theoretically, prolonged fever may be a clue to complications, such as urinary obstruction or renal abscess.

Objective. Describe the pattern of fever in febrile children undergoing treatment of a UTI. Compare the clinical characteristics of those patients with prolonged fever to those who respond faster to therapy.

Setting. An urban pediatric hospital.

Design. Medical record review.

Methods. All children ≤2 years old admitted to the pediatric service with a primary discharge diagnosis of pyelonephritis or UTI were reviewed for 65 consecutive months. Patients with previous UTI, known urologic problems, or immunodeficiency were excluded. Only patients with an admitting temperature ≥38°C and those who met standard culture criteria were studied. Temperatures are not recorded hourly on the inpatient unit; therefore, they were assigned to blocks of time. Nonresponders were defined as those above the 90th percentile for the time to defervesce. Nonresponders were then compared with the balance of the study patients, termed responders.

Results. Of 288 patients studied, the median age was 5.6 months (interquartile range: 1.3–7.9 months old). Median admission temperature was 39.3°C (interquartile range: 38.5°C–40.1°C). Median time to defervesce ranged in the time block 13 to 16 hours. Sixty-eight percent were afebrile by 24 hours and 89% by 48 hours. Thirty-one patients had fever >48 hours (nonresponders). Nonresponders were older than responders (9.4 vs 4.1 months old) but had similar initial temperatures (39.8 vs 39.2°C), and the number of patients with "too numerous to count" white blood cell counts (12/28 vs 59/221), and nitrite-positive (8/28 vs 88/221), were similar. White blood cell counts per high power field (12/28 vs 1/31), nitrite-positive (8/28 vs 88/221), and the number of patients with "too numerous to count" white blood cell counts per high power field (12/28 vs 77/220). Nonresponders were as likely as responders to have bacteremia (3/31 vs 21/256), hydronephrosis by renal ultrasound (1/31 vs 12/223), and significant vesicoureteral reflux (more than or equal to grade 3; 5/26 vs 30/219). Escherichia coli was the pathogen in cultures of 28 of 31 (nonresponders) and 225 of 257 (responders) cultures. The number of cultures with ≥100 colony-forming units/mL was similar (25/31 nonresponders vs 206/257 responders). Repeat urine cultures were performed in 93% of patients during the admission; all culture results were negative. No renal abscesses or pyo-hydronephrosis was diagnosed.

Conclusions. Eighty-nine percent of young children with febrile UTIs were afebrile within 48 hours of initiating parenteral antibiotics. The patients who took longer than 48 hours to defervesce were clinically similar to those whose fevers responded faster to therapy. If antibiotic sensitivities are known, additional diagnostic studies or prolonged hospitalizations may not be justified solely based on persistent fever beyond 48 hours of therapy.

ABBREVIATIONS. UTI, urinary tract infection; IQR, interquartile range; CI, confidence interval; WBC, white blood cell.
The expected duration of fever with pyelonephritis has not been well-defined and has never before been the primary focus of a publication. The objectives of this manuscript were to describe the pattern of fever resolution of children undergoing treatment of a UTI, to review the clinical features of those patients with prolonged fever, and to judge the merit of the recommendations of the American Academy of Pediatrics for those patients with fever beyond 48 hours.

**METHODS**

Hospital records for all patients discharged from the medical service with the principal diagnosis of UTI, pyelonephritis, or urosepsis were retrospectively reviewed for 65 consecutive months. Inclusion criteria included the following: age ≥ 24 months, no previously identified urologic abnormality or immunodeficiency, fever as defined by an initial triage temperature ≥ 38.0°C, and a positive urine culture result as defined by standard criteria of ≥ 10,000 pure colony-forming units/mL on catheterized specimen and ≥ 1000 colony-forming units/mL from a suprapubic aspiration. Nosocomial infections were also excluded. For determining the duration of fever, time 0 was defined as the start of the first antibiotic dose. Because temperatures were not recorded continuously, the exact time to defervesce was assigned to time blocks. The time at which the patient became afebrile (rectal temperature ≤ 38.0°C; axillary temperatures adjusted by adding 1.0°C) and remained afebrile (through discharge from the hospital) was considered the endpoint for fever duration. Standard vital signs on medical admissions are performed every 4 hours; however, this is not enforced. Use of antipyretics was not considered.

For purpose of this study, nonresponders were defined as those patients who had persistent fever beyond the 90th percentile for the time to defervesce, and responders were defined as those patients who became afebrile in less than the 90th percentile for time to defervesce. Because times to defervesce were assigned to time blocks, the time cutoff closest to dividing the study group into the 90th and then upper 10th percentiles would be chosen.

Statistical analyses were conducted using Statistical Program for the Social Sciences, Version 6.1.1 (SPSS, Chicago, IL). Medians and interquartile ranges (IQR: 25th–75th percentile) were provided for non-normal data. Mean values of interval data were compared between groups by using a 2-tailed Student’s t test. χ² test and Fisher’s exact test were used to test nominal data. Confidence intervals (CIs) for proportions were calculated using Stata, Version 6 (Stata, College Station, TX).

**RESULTS**

**Study Group**

Five hundred seven cases were identified by age and discharge diagnosis, and of these, 481 of charts (95%) were available for review. One hundred ninety-three were excluded for history of urologic abnormality or previous UTI (n = 127), initial temperature < 38.0°C (even if fever was measured before or after initial temperature; n = 42), and missing data for determining the duration of fever (n = 24). Two hundred eighty-eight patients met all inclusion criteria. Forty-eight percent of the patients were males, and 77% of these were uncircumcised. The median age was 5.6 months (IQR: 1.3–7.9 months old), and median initial temperature was 39.3°C (IQR: 38.5°C–40.1°C). White blood cell (WBC) counts were obtained on admission in 287 patients; median WBC counts were 16 100/mm³ (IQR: 12 700–21 800/mm³).

**Fever Duration**

The median time to defervesce ranged in the time block of 13 to 16 hours. Sixty-eight percent were afebrile by 24 hours, 82% by 36 hours, 89% by 48 hours, and 97% by 72 hours. Only 9 patients (3%) were febrile beyond 72 hours. The duration of fever is graphically represented in Fig 1.

**Nonresponders Versus Responders**

Thirty-one patients (11%) had fever longer than 48 hours and were considered the nonresponders. The balance of patients (n = 257) defervesced in ≤ 48 hours and were termed responders. Table 1 compares the age, temperature, WBC counts, band counts, and results of the urinalysis of both groups. As indirect markers of illness severity, the frequency of vomiting, acidosis, and examination of cerebrospinal fluid are also compared in Table 1. Results of blood cultures (n = 265) and urine cultures (n = 288) are presented in Table 2. Renal ultrasounds were obtained in 263 of 288 patients (91%) during hospitalization including all the nonresponders. Hydronephrosis was noted in 13 patients (5%; 95% CI: 3–8).
and no patient had a renal abscess (0/288; 95% CI: 0–1.3). Results from voiding cystourethrograms obtained after hospitalization were available for 245 of 288 patients (85%). Grade 3 or higher reflux was seen in 35 of 245 (14%; 95% CI: 10–19). The presence of significant findings on ultrasound or VCUG is compared for responders and nonresponders in Table 2.

**Repeat Urine Cultures**

Repeat urine cultures were performed during the admission in 93% of patients including all nonresponders. The median time to repeat culture was 48 hours (IQR: 38–65 hours). All isolates were sensitive to 1 or more of the antibiotics administered. All repeat urine culture results were negative regardless of persistence of fever.

**DISCUSSION**

UTIs represent the most commonly diagnosed bacterial infection in young febrile infants other than otitis media. Renal scans have shown that two thirds of febrile children with UTIs have pyelonephritis, and symptoms, examination findings, and noninvasive diagnostic studies cannot predict which patients have pyelonephritis. Although admission for parenteral antibiotics was recommended in the past for febrile young children with UTIs, outpatient therapy after an initial single dose of parenteral antibiotics as well as oral antibiotics alone have been discussed. Although some authors have anecdotally noted that the fever associated with pyelonephritis will resolve in 24 to 48 hours under appropriate antibiotic therapy, the pattern of fever resolution has not been previously detailed in the medical literature. Not only has the presence of fever been used as an admission criteria, but persistence of fever after initial outpatient therapy has led to hospitalization in some children.

Persistence of fever beyond 48 hours in those being treated for a UTI has led to recommendations for radiologic studies and repeat urine cultures—presumably to investigate the possibility of urologic complications such as renal abscess or urinary obstruction. I undertook this study to better evaluate the logic of radiologic studies and repeat urine cultures in patients who have prolonged fever.

In a recent publication reporting on comparing oral and parenteral therapy for pyelonephritis, Hoberman et al noted a mean duration of fever of 24 (standard deviation: 23) and 25 (standard deviation: 23) hours for those patients treated with parenteral and oral antibiotics, respectively (P = .39). In the current study of infants ≤2 years of age who were treated with parenteral antibiotics, the median duration of fever ranged in the time block of 13 to 16 hours; 68% and 89% were afebrile at 24 and 48 hours, respectively. The 11% of patients with fever beyond 48 hours did not differ with regard to any clinical parameter except that the nonresponders were older than those whose fever resolved before 48 hours. Of note, repeat urine cultures performed during admission were all sterile regardless of the fever duration. Hydronephrosis was seen equally between patients who defervesced before or after 48 hours. Renal ultrasounds did not demonstrate any complete obstruction (pyohydronephrosis) or renal abscess, but the prevalence of such complications could be as high as 1.3% with our sample size. In describing the lack of differences between responders and nonresponders, it is fair to acknowledge that the power to recognize differences was limited by the sample size. For example, the study had 80% power (α = .05, 2-tailed) to detect a difference in WBC count of 2000/μL, a difference of .8°C in initial temperature, a difference of 25% for bacteremia, and a difference of 19% for hydronephrosis. Obviously, smaller differences may be clinically significant but missed in this study.

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**TABLE 1.** Comparisons of Responders and Nonresponders at Presentation

<table>
<thead>
<tr>
<th>Marker of illness severity</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>39% (80/203)</td>
<td>36% (10/28)</td>
<td>1% (−12, 10)</td>
<td>.9</td>
</tr>
<tr>
<td>HCO$_3^-$ &lt;20 mEq/L</td>
<td>37% (60/164)</td>
<td>29% (6/21)</td>
<td>−1% (−16, 14)</td>
<td>.9</td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>68% (163/239)</td>
<td>68% (21/31)</td>
<td>2% (−5, 9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>86% (211/246)</td>
<td>79% (23/29)</td>
<td>7% (−1, 14)</td>
<td>.5</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
<td>40% (88/221)</td>
<td>29% (8/28)</td>
<td>11% (2, 21)</td>
<td>.25</td>
</tr>
<tr>
<td>&gt;50 WBCs/high-power field</td>
<td>35% (77/220)</td>
<td>43% (12/28)</td>
<td>8% (−10, 24)</td>
<td>.41</td>
</tr>
</tbody>
</table>

**TABLE 2.** Clinical Characteristics of Responders and Nonresponders

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Responders</th>
<th>Nonresponders</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>8% (21/256)</td>
<td>10% (3/31)</td>
<td>1% (−12, 10)</td>
<td>.9</td>
</tr>
<tr>
<td>Urine culture ≥100 000 colony-forming units/mL</td>
<td>80% (206/257)</td>
<td>81% (25/31)</td>
<td>−1% (−16, 14)</td>
<td>.9</td>
</tr>
<tr>
<td><em>Escherichia coli</em> as urinary pathogen</td>
<td>88% (225/257)</td>
<td>90% (28/31)</td>
<td>−2% (−13, 9)</td>
<td>.6</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>5% (12/232)</td>
<td>3% (1/31)</td>
<td>2% (−5, 9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Vesicoureteral reflux ≥ grade 3</td>
<td>14% (30/219)</td>
<td>8% (5/62)</td>
<td>6% (−5, 17)</td>
<td>.9</td>
</tr>
<tr>
<td>Positive repeat urine culture result</td>
<td>0% (0/237)</td>
<td>0% (0/31)</td>
<td>0% (−4, 4)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Although complications such as renal abscess have been reported in the pediatric literature, most references represent single case reports or case series, therefore, the prevalence of renal abscess as a complication of pyelonephritis has not been determined. Furthermore, in these reports, up to one half of these patients with renal abscesses presented with normal urinalyses or negative urine culture results; this implies a different population than my study patients. In a study evaluating ultrasound evidence of focal renal infection in children with presumed pyelonephritis, Klar et al noted focal nephritis in 23 of 210 hospitalized children with UTI, and 25% of those with focal findings developed a renal abscess by computed tomography; the authors noted that abscess formation may be underdiagnosed without such imaging strategies, but the significance of its detection is speculative. In circumstances where renal ultrasounds will be eventually performed as part of the urologic investigation, then the ultrasounds might as well be performed during acute infection if readily obtainable. However, when ultrasounds are relatively unavailable or when patients are managed exclusively as outpatients, ultrasounds seem to have low yield with regard to information that would alter therapy.

Finally, renal scarring, the long-term outcome measure of pyelonephritis, was not investigated in our study. Theoretically, prolonged fever during treatment could be a marker of more serious infection with a higher likelihood of scarring, but evidence for this phenomenon is lacking. Miller and Phillips noted as well as Winter et al noted that renal scarring was more likely in patients with a longer duration of fever before antibiotics and in those “inadequately treated.” In the study by Hoberman et al, renal scarring was higher in patients with a longer duration of fever before therapy and in those who took longer to defervesce once therapy was initiated, although neither of these findings reached statistical significance with their study size. More importantly, maintaining a patient on intravenous antibiotics or oral antibiotics did not influence the rate of scar formation.

Based on the results of this study, clinicians can expect resolution of fever by 48 to 72 hours with adequate therapy. Even under effective therapy, proven with repeat urine cultures, fever may persist for up to 3 days. As with other deep infections, inflammation and release of pyrogens may perpetuate fever despite apparent eradication of infection. Although each temperature recording between admission and the time to defervesce were not graphed, it is possible that the response to therapy would be more obvious based on the actual duration, frequency, or the height of temperature elevations rather than just the endpoint of being afebrile. Certainly, the rare patient with fever beyond 3 days needs to have further evaluation. Fortunately, antibiotic sensitivities of the urinary pathogen are usually available by 48 to 72 hours; therefore, antibiotics can be adjusted if needed. Repeat urine cultures are certainly not indicated for patients who have the expected response to therapy. Patients with immunodeficiency, known urologic abnormalities, or history of infections with multiply-resistant bacteria need to be considered differently.

CONCLUSION

Eighty-nine percent of febrile young children with UTIs will be afebrile within 48 hours of initiating parenteral therapy. Patients who took longer than 48 hours to defervesce are clinically similar to those who responded faster. Additional diagnostic studies or prolonged hospitalizations may not be justified solely based on fever for >48 hours, especially when antibiotic susceptibilities of the urinary pathogen are known.

REFERENCES

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