Treatment strategies for urinary tract infections based on fever

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Abstract

Purpose

The duration of antimicrobial therapy for febrile urinary tract infections (fUTI) in children have not been established. This study aimed to explore the appropriate duration of the treatment for fUTI in children.

Methods

We created a protocol to determine the duration of antibiotic administration based on the fever. Transvenous antibiotics were administered for 3 days after the resolution of fever, followed by oral antibiotics for 1 week. Diagnosis of fUTI was based on a fever of 37.5°C or higher and a quantitative culture of catheterized urine showed $\geq 5 \times 10^4$ bacteria. Acute focal bacterial nephritis (AFBN) and pyelonephritis (PN) were diagnosed based on contrast-enhanced computed tomography (eCT) findings. We retrospectively reviewed the treatment outcomes.

Results

Of the 78 patients treated according to our protocol, 58 were included; 49 with PN (30 men) and nine with AFBN (three men). Blood test results showed that patients with AFBN had significantly higher white blood cell and C-reactive protein levels than those with PN; however, no differences were observed in the urinary findings and causative bacteria. The time to resolution of fever and duration of intravenous antibiotic administration were significantly longer in patients with AFBN than in those with PN. However, the average duration of AFBN treatment was 14.2 days, which was shorter than the previously reported 3-week administration and no recurrence was observed in AFBN patients.

Conclusions

The protocol created to determine the duration of antimicrobial treatment based on fever is useful. Invasive examinations, such as eCT, are not required.

Introduction

Febrile urinary tract infection (fUTI) is common in children, but it is a group of diseases that require careful management because renal scarring which is complicated by the failure of initial treatment of fUTI can lead to hypertension and renal dysfunction [1]. fUTI includes pyelonephritis (PN), a bacterial infection localized around the renal pelvis, and renal abscess, an abscess formed in the renal parenchyma. PN is treated with antibiotics, whereas renal abscess requires multidisciplinary treatment, including surgery. Acute focal bacterial nephritis (AFBN), which is considered a transitional stage between these two conditions, was first described by Rosenfield et al. in 1979 [2]; AFBN treatment requires more prolonged transvenous antibiotic therapy than the conventional PN treatment [3].
Internationally, guidelines, such as the American Academy of Pediatrics (AAP) [4] and the National Institute for Health and Care Excellence (NICE) [5], have been developed and used for the initial fUTI treatment. In Japan, based on the AAP and NICE guidelines, the Japanese Association for Infectious Diseases (JAID) and the Japanese Society of Chemotherapy (JSC) have jointly developed guidelines (JAID/JSC Guidelines) [6]. However, the method and duration of antimicrobial therapy for PN and AFBN have not been established because of a lack of substantial evidence to determine the appropriate duration of antimicrobial therapy for pediatric fUTI. Hence, according to the current method, the duration of treatment of UTIs with fever in infants should be 7–14 days [4, 6] and it should be set at the discretion of each physician. Furthermore, AFBN should be treated with a minimum of 2 weeks of intravenous antimicrobial therapy followed by oral therapy for a total of 3 weeks [3]. The gold standard for the AFBN diagnosis is contrast-enhanced computed tomography (eCT) [7, 8], however, performing eCT in all fUTI cases is considered highly problematic because patients with fUTI are mainly infants.

We have been treating fUTI since April 2017 by creating our treatment protocol that determines the duration of antibiotic administration based on fever within the scope of the JAID/JSC guidelines. In this study, we retrospectively reviewed the data of patients treated according to our treatment protocol and evaluated its usefulness.

Patients and Methods

Patients

Of the 78 patients with fUTI treated according to our protocol during the 5 years from April 1, 2017, to March 31, 2022, the data of 58 were retrospectively analyzed; those who were younger than 1 month or older than 7 years at onset, had positive blood cultures, had a confirmed diagnosis of renal abscess, had no resolution of fever for more than 1 week, and were transferred to our hospital after initiating treatment in another hospital were excluded.

Protocol

Figure 1 shows the treatment flowchart. Our protocol was designed to determine the method and duration of antibiotic administration based on the onset of fever. The timing of fever resolution was defined as the first time a body temperature of 37.5°C or lower was recorded for at least 48 h. Transvenous antibiotic therapy was initiated regardless of the diagnosis of PN or AFBN, and intravenous antibiotic therapy was administered until 72 h after fever resolution, at which time the patient was switched to oral antibiotic therapy for 1 week. If the fever did not resolve within 1 week of changing to the appropriate antibiotic based on the culture results, treatment according to the protocol was discontinued, and alternative treatment methods were considered. Contrast-enhanced CT was performed if AFBN was suspected on ultrasonography if fever did not resolve within 60 h after the initiation of treatment, or when deemed necessary by the attending physician. The significant ultrasonographic findings were: 1. renal enlargement, 2. a difference of > 1 cm in the long axis diameter between the right and left kidneys, 3. mass shadow with irregular margins (regardless of the brightness), and 4. suspected abscess formation.
Cefotaxime sodium was used because the distribution of other drugs (e.g., Cefmetazole sodium) was restricted owing to earthquakes and other disasters.

Figure 1

Diagnosis

fUTI diagnosis was made when the patient had a fever of 37.5°C or higher at the time of admission, and a quantitative culture of catheterized urine showed more than $5 \times 10^4$ bacteria. In the present study, we did not distinguish between cystitis and PN because of the difficulty of discriminating between these diseases, particularly in infants [9]. AFBN was diagnosed when eCT revealed a defect, regardless of whether it was wedge-shaped (Fig. 2a) or mass-like (Fig. 2b).

Parameters

The following data were collected: 1. Laboratory data at admission (serum leukocytes, CRP, urine leukocyte esterase, nitrite, protein, and occult blood), 2. the time from the onset of fever to the start of treatment (days), 3. from admission to the resolution of fever (days), 4. duration of intravenous antibiotic administration (days), and 5. information on treatment failures. Treatment failure was defined as the occurrence of complications, such as a renal abscess or bacteremia, during treatment. Furthermore, treatment failure was considered when patients had recurrent UTIs within 6 months and caused by the same pathogen that was responsible for the initial infection.

Statistics

Statistical comparisons between the PN and AFBN groups were performed using the R ver. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Fisher's exact and the Mann–Whitney U tests were used to analyze qualitative and numerical variables, respectively.

Results

During the observation period, 78 patients were admitted and treated at our hospital. Of these, two patients were < 1 month old, seven were > 7 years, six had positive blood cultures, one had no fever resolution for > 1 week, and four were transferred from other hospitals where the initial treatment had already been started. No patient was diagnosed with renal abscess on admission. None of the patients developed renal abscesses or any other serious conditions during treatment. After excluding 20 patients, 58 patients were included in the study.

The median patient age was 3.0 months. The study included 33 boys. Contrast enhancement CT was performed in 14 patients and nine of them showed defects, indicating AFBN. Table 1 shows the observations made for the PN and AFBN groups. The median age of the PN group was 3.0 months and had 30 boys and 19 girls. The median times from fever to the start of treatment were 1.0 day. The median time from initiation of treatment to fever resolution was 1.0 day. The median duration of intravenous
antibiotic therapy was 4.0 days. Four children had recurrent UTIs. Table 2 shows the clinical information of children with recurrent UTIs.

In contrast, nine patients were diagnosed with AFBN. The median age of these nine patients was 14 months; the median age of these patients was significantly (p = 0.037) higher than those of the PN group. The AFBN group had more girls than boys compared with the PN group and significant difference (p < 0.01) was observed between the two groups. The median time to start treatment were 1.0 day, which was not significantly different from the PN group (p = 0.49). However, the median time to fever resolution was significantly (p < 0.01) longer than those of the PN group, and the median time to intravenous antibiotic administration was also significantly (p < 0.01) longer than that for PN group. No recurrence was observed in the patients diagnosed with AFBN.

Ultrasound examinations were performed on all patients and voiding cystourethrography (VCG) was performed on 43 patients who consented to participate. In the PN group, one patient had Society for Fatal Urology (SFU) 4th grade, one patient had SFU 3rd grade, and one patient had SFU 2nd grade hydronephrosis. The patient with SFU 3rd-grade hydronephrosis had ipsilateral 4th-degree vesicoureteral reflux (VUR). Dwarf kidneys were observed in two patients; one of these patients had ipsilateral 3rd-degree VUR and the other had no reflux but ipsilateral hydroureter and ureterovesical junction stenosis. A total of 11 patients had VUR. In addition, one patient had a horseshoe kidney and one had a single kidney. In the AFBN group, all patients underwent VCG. The results of the ultrasound and VCG are summarized in Table 3. The AFBN group had a higher complication rate (77.8%) of severe VUR, obstructive urinary tract abnormalities, and other congenital anomalies of the kidney and urinary tract (CAKUT); however, no statistically significant difference (p = 0.064) was observed between the PN and AFBN groups.

### Discussion

Based on the JAID/JSC guidelines, we created a protocol for fUTI treatment. The average duration of intravenous antibiotic therapy was 5.2 days, and even with the addition of 1 week of oral therapy, treatment was completed in 12.2 days; for AFBN cases, the average duration was 14.2 days, which was approximately 1 week shorter than the previously reported 3-week treatment. Conversely, the PN group had four cases of relapse, but this could be attributed to underlying CAKUT or the initiation of drug resistance rather than the short treatment period. Therefore, it is questionable to perform eCT from the beginning of admission, as mentioned in a systematic review [10], and to administer antibiotics to a child diagnosed with AFBN for more than 3 weeks, as previously reported [3]. Although the number of cases was small, the time required for resolution tended to be shorter for wedge-shaped defects (Table 3), suggesting that diagnosing AFBN, especially with wedge-shaped defects, and administering antibiotics for a total of 3 weeks is likely to result in overtreatment.

The initial treatment of UTI is often performed worldwide according to the AAP [4] and NICE [5] guidelines and children >2–3 months would be treated with oral antibiotics in an outpatient office. In contrast, the
JAID/JSC guidelines state that intravenous antibiotic therapy is the standard of care. This is because prompt antibiotic treatment is important in the initial treatment of fUTI [11]. Although it is difficult to make a blanket statement because the medical conditions and insurance systems in each country differ from those in Japan, as well as the types and doses of antibiotics approved by the insurance, intravenous administration is probably the safest initial treatment.

AFBN was reported by Rosenberg [2], but the strict diagnosis is difficult. Diagnosis of AFBN is generally based on eCT defects [7, 12, 13]. However, PN has also been reported to exhibit wedge-shaped defects on eCT [13, 14]. Delayed enhancement CT has been reported to be useful in detecting pathological changes in the renal parenchyma [12], and delayed eCT imaging is necessary to strictly distinguish between PN and AFBN. However, the radiation dose is naturally doubled; therefore, the indications for delayed eCT should be avoided in infants. Ultrasonography is also useful for the diagnosis of AFBN [15, 16] because it shows renal enlargement, a shadow of the mass, and a lack of blood flow in the same area. However, the diagnostic sensitivity of ultrasonography for AFBN remains unclear. Clinically, blood tests showed significantly higher levels of CRP and WBC in AFBN than those in cases of PN, but no significant differences were observed in the pathogens or urinary findings (Table 1); therefore, distinguishing between PN and AFBN is difficult.

Thus, the exact diagnosis of AFBN is difficult while Chen CT recommended long-term antibiotic therapy for AFBN [3]. Because AFBN lesions are not contrasted on delayed eCT, blood flow may be largely absent. Therefore, it is theoretically correct to increase the duration of drug administration to allow sufficient antibiotic doses to act on the AFBN lesions. We believe that the effect of antibiotics reflects the blood flow in the lesion; therefore, the duration of fever is a more pathognomonic factor than the diagnosis of PN and AFBN by eCT and is an important factor in determining a more appropriate duration of treatment. Our results showed that transvenous antibiotics were administered significantly longer in AFBN than in PN (Table 1), and no recurrence was observed, suggesting that this is a valid concept. Unless new therapies are developed to inhibit renal scar formation, there is little advantage in using eCT to differentiate AFBN.

Two patients who recurred during follow-up after completion of the initial treatment had renal urinary tract abnormalities (Table 2). Extended-spectrum-lactamase (ESBL)-producing E. coli was detected in one of the two patients with no renal-urinary tract abnormalities. The fever resolved once after the initiation of treatment, but the patient developed fever again while receiving intravenous antimicrobials. The other child had no complications but relapsed during follow-up after the treatment was completed. It is not clear from the present study whether these four children would have benefited from antibiotics for a longer period. It remains unclear whether a longer course of antibiotics is necessary, particularly in the presence of complicated malformations.

We excluded patients younger than 1 month from our study because neonates with UTI should be evaluated for associated systemic infections. Additionally, our protocol excluded serious infections, such as bacteremia and renal abscesses. We do not recommend the treatment protocol reported here for
children who are also at risk of infection of multiple organs or who have already developed serious bacterial complications on admission.

The fact that the children who were diagnosed with AFBN were relatively older does not preclude the possibility that they had repeated UTI and were diagnosed with AFBN based on scarring that had already developed. In addition, because eCT was not performed in all patients, we cannot rule out the possibility that AFBN was included in the PN group. However, we believe that these factors do not interfere with our assertion that fever duration determines the treatment strategy.

**Conclusion**

We created an effective protocol to determine the duration of antibiotic therapy based on the duration of the fever. This protocol allows patients to complete treatment with antimicrobial agents for a shorter period than previously possible. Additionally, our protocol does not necessarily require eCT to differentiate AFBN, thereby reducing the need for invasive diagnostic procedures in children.

**Declarations**

**Acknowledgement**

We would like to thank all the staff who worked with our patients during their hospital stay and Honyaku Center Inc. for English language editing.

**Compliance with Ethical Standards**

**Conflict of interest:** The authors declare no conflict of interest.

**Ethical approval:** All procedures performed in this study involving human participants were following the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Nippon Medical School (Approval number: M-2022-075).

**Informed Consent:** As this was a research study using medical records, written or oral consent was not obtained from the patients. However, to disclose the Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects and allow patients or their surrogates to refuse participation in the research, materials regarding opt-outs were posted.

**Funding declaration**

We have not received any funding or goods in the course of carrying out our research.

**Contributorship**
Takeshi Yanagihara contributed to the design of the study, data analysis, and interpretation of the results and writing the manuscript. Koichi Kobayashi and Yujiro Tanabe worked with inpatients at the Nippon Medical School hospital and collected data. Emi Yanai and Hikaru Takeshita worked with inpatients at the Nippon Medical School Musashikosugi hospital and collected data. Yasuhiro Ito contributed to interpretation of the result and critically reviewed the manuscript. All authors finally approved the final version of manuscript.

References


Tables
Table 1 Clinical observations of patients with PN and AFBN

<table>
<thead>
<tr>
<th>age (month) (median)</th>
<th>PN (n=49)</th>
<th>AFBN (n=9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>30</td>
<td>3</td>
<td>0.01 &gt;</td>
</tr>
<tr>
<td>f</td>
<td>19</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>pathogen *</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><em>E. coli</em></td>
<td>38</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><em>E. coli</em> (ESBL)</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><em>E. faecalis</em></td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella spp.</em></td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Serum (median)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>5.0</td>
<td>13.1</td>
<td>0.012</td>
</tr>
<tr>
<td>WBC (/ μL)</td>
<td>16600</td>
<td>24540</td>
<td>0.01 &gt;</td>
</tr>
<tr>
<td>Urine (median)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pro</td>
<td>+</td>
<td>+</td>
<td>0.31</td>
</tr>
<tr>
<td>OB</td>
<td>+</td>
<td>+</td>
<td>0.37</td>
</tr>
<tr>
<td>WBC</td>
<td>3+</td>
<td>2+</td>
<td>0.15</td>
</tr>
<tr>
<td>Nit</td>
<td>-</td>
<td>+</td>
<td>0.27</td>
</tr>
<tr>
<td>Period (median)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>1.0</td>
<td>1.0</td>
<td>0.49</td>
</tr>
<tr>
<td>P2</td>
<td>1.0</td>
<td>3.0</td>
<td>0.01 &gt;</td>
</tr>
<tr>
<td>P3</td>
<td>4.0</td>
<td>7.0</td>
<td>0.01 &gt;</td>
</tr>
</tbody>
</table>

* There are overlaps

P1 interval from onset to admission (day)
P2 febrile period (day)
P3 duration of antibiotic treatment through intravenous injection (day)

WBC, white blood cell; Pro, protein; OB, occult blood; Nit, nitrous acid
Table 2. Clinical observations of children with recurrent UTI

<table>
<thead>
<tr>
<th>age (month)</th>
<th>sex</th>
<th>pathogen</th>
<th>serum</th>
<th>urine (fast tape)</th>
<th>VCUU</th>
<th>ultrasound</th>
<th>eCT</th>
<th>others</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>f</td>
<td><em>E. coli</em></td>
<td>10.12</td>
<td>21760</td>
<td>1+ 1+ 3+ -</td>
<td>0 3 6</td>
<td>Lt. renal enlargement</td>
<td>n.p.</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td><em>E. coli</em></td>
<td>7.06</td>
<td>24270</td>
<td>+/- - 3+ -+</td>
<td>1 1 3</td>
<td>rt. VUR 3°</td>
<td>n.p.</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td><em>E. coli</em></td>
<td>3.52</td>
<td>10500</td>
<td>+/- +/- 3+ -</td>
<td>0 1 4</td>
<td>n.p.</td>
<td>n.p.</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td><em>E. coli</em> ESBL</td>
<td>3.36</td>
<td>8500</td>
<td>2+ 3+ 3+ -</td>
<td>0 1 7</td>
<td>n.p.</td>
<td>n.p.</td>
</tr>
</tbody>
</table>

P1 interval from onset to admission (day)
P2 febrile period (day)
P3 duration of antibiotic treatment through intravenous injection (day)
WBC, white blood cell; Pro, protein; OB, occult blood; Nit, nitrous acid
VCUG, voiding cystourethrography; eCT, contrast enhancement computed tomography
VUR, vesicoureteral reflux; Lt., left; rt., right; n.p., not particular

Table 3. Characteristics of patients with AFBN

<table>
<thead>
<tr>
<th>age (month)</th>
<th>sex</th>
<th>pathogen</th>
<th>P2</th>
<th>Ultrasound</th>
<th>VCUU</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>f</td>
<td><em>E. coli</em></td>
<td>3</td>
<td>high echoic SOL</td>
<td>VUR rt. 3°</td>
<td>rt. Wedge-shaped defect</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td><em>E. coli</em></td>
<td>3</td>
<td>high echoic SOL</td>
<td>n.p.</td>
<td>bil. tumor-like defects</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td><em>E. faecalis</em></td>
<td>3</td>
<td>hydrenephrosis</td>
<td>VUR lt. 3°</td>
<td>rt. 5°</td>
</tr>
<tr>
<td>20</td>
<td>f</td>
<td><em>E. coli</em></td>
<td>4</td>
<td>bil. renal enlargement reduced blood flow lesion</td>
<td>bladder diverticulum</td>
<td>bil. renal enlargement</td>
</tr>
<tr>
<td>54</td>
<td>f</td>
<td><em>E. coli</em></td>
<td>2</td>
<td>reduced blood flow lesion</td>
<td>VUR lt. 2°</td>
<td>lt. wedge-shaped defect</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td><em>E. coli</em></td>
<td>3</td>
<td>reduced blood flow lesion</td>
<td>n.p.</td>
<td>VUR rt. 2°</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td><em>E. coli, E. faecalis</em></td>
<td>2</td>
<td>n.p.</td>
<td>n.p.</td>
<td>n.p.</td>
</tr>
<tr>
<td>52</td>
<td>f</td>
<td>Klebsiella pneumoniae</td>
<td>3</td>
<td>n.p.</td>
<td>VUR lt. 4°</td>
<td>rt. 3°</td>
</tr>
<tr>
<td>56</td>
<td>f</td>
<td><em>E. coli</em></td>
<td>4</td>
<td>n.p.</td>
<td>VUR lt. 4°</td>
<td>n.p.</td>
</tr>
</tbody>
</table>

P2, febrile period (day)
VCUG, voiding cystourethrography; eCT, contrast enhancement computed tomography
SOL, space occupied lesion; VUR, vesicoureteral reflux
bil., bilateral; Lt., left; rt., right; n.p., not particular

Figures
Figure 1

Our protocol was designed to determine the timing of eCT and duration of antibiotic administration based on the patient's fever period.
Figure 2

(a) shows wedge-shaped defects (arrows) and (b) shows tumor-like defects (arrowheads). Both patterns of defects were diagnosed as acute focal bacterial nephritis in this study.