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# Use of Fever Duration to Guide Management of Urinary Tract Infection

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**Background:** The appropriate duration of antimicrobial therapy for febrile urinary tract infection (fUTI) in children has not been established. This study examined the optimal duration of treatment for fUTI in children.

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

**Results:** Of the 78 patients treated according to our protocol, data from 58 were analyzed—49 children (30 boys) had PN and nine (three boys) had AFBN. Blood test results showed that patients with AFBN had significantly higher white blood cell counts and C-reactive protein levels than did those with PN; however, urinary findings and causative bacteria did not differ between groups. Time to resolution of fever and duration of intravenous antibiotic administration were significantly longer in patients with AFBN than in those with PN. However, average duration of AFBN treatment was 14.2 days, which was shorter than the previously reported administration period of 3 weeks. No recurrence was observed in AFBN patients.

**Conclusions:** A protocol that used fever duration to determine the duration of antimicrobial treatment was useful. Invasive examinations, such as eCT, were not required.

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Key words: acute focal bacterial nephritis, child, contrast-enhanced computed tomography, intravenous antibiotic therapy, pyelonephritis

## Introduction

Febrile urinary tract infection (fUTI) is common in children. It requires careful management because renal scarring, a complication of failure of initial treatment of fUTI, can lead to hypertension and renal dysfunction<sup>1,2</sup>. 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)—a transitional stage between these two conditions—was first described by Rosenfield et al.<sup>3</sup> in 1979. Transvenous antibiotic therapy is longer for AFBN than for conventional  $PN^4$ .

International guidelines, such as those of the American Academy of Pediatrics (AAP)<sup>5</sup> and National Institute for Health and Care Excellence (NICE)<sup>6</sup>, have been used to determine initial fUTI treatment. In Japan, the Japanese Association for Infectious Diseases (JAID) and Japanese Society of Chemotherapy (JSC) have jointly developed *The Treatment of Infectious Diseases 2015—Urinary Tract Infections and Male Genital Tract Infections* (JAID/JSC Guide-

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lines), which are based on the AAP and NICE guidelines<sup>7</sup>. However, apart from renal abscesses, which require multidisciplinary treatment, the optimal method and duration of antimicrobial therapy for PN and AFBN have not been established because of limited evidence on the appropriate duration of antimicrobial therapy for pediatric patients with fUTI. According to the current standard, the recommended duration of treatment of UTIs in infants with fever is 7-14 days<sup>5,7</sup> but should be left to the discretion of the physician and facility. 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<sup>4</sup>. However, the gold standard for diagnosis of AFBN is contrast-enhanced computed tomography (eCT)<sup>8-10</sup>, which requires delayed contrastenhanced imaging in addition to normal imaging for a definitive diagnosis<sup>11,12</sup>. Radiation exposure and imaging timing are matters of concern because most patients with fUTI are infants. Therefore, the use of eCT in all fUTI cases is considered highly problematic.

Since April 2017, we have treated fUTI with our own protocol, which uses fever status to determine the duration of antibiotic administration, within the scope of JAID/JSC guidelines. In this study, we retrospectively reviewed data from patients treated with our 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, data from 58 were retrospectively analyzed. We excluded children younger than 1 month or older than 7 years at onset, those with positive blood cultures, those with a confirmed diagnosis of renal abscess, those with no resolution of fever after 1 week, and those who were transferred to our hospital after treatment was started at another hospital.

## Ethical approval

All procedures performed in this study of humans were conducted in accordance with 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.

#### Protocol

Figure 1 shows the treatment flowchart. Our protocol was designed to use fever onset to determine the method and duration of antibiotic administration. 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 whether PN or AFBN was diagnosed, 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 fever did not resolve within 1 week of changing to the appropriate antibiotic, as determined by culture results, treatment according to the protocol was discontinued, and alternative treatment methods were considered. If fever did not resolve within 60 h after the start of treatment, contrast-enhanced CT was performed if AFBN was suspected on ultrasonography or when deemed necessary by the attending physician. Important ultrasonographic findings were 1. renal enlargement, 2. a difference of >1 cm in the long axis diameters of the right and left kidneys, 3. a mass shadow with irregular margins (regardless of the brightness), and 4. suspected abscess formation. Cefotaxime sodium was used because distribution of other drugs (eg, cefmetazole sodium) was restricted owing to logistical challenges caused by earthquakes and other disasters.

#### Diagnosis

fUTI was diagnosed when a patient had a fever of  $37.5^{\circ}$ C or higher at the time of admission and a quantitative culture of catheterized urine yielded a bacteria count greater than  $1 \times 10^4$ . In the present study, we did not distinguish between cystitis and PN because of the difficulty of differentiating these diseases, particularly in infants<sup>13</sup>. AFBN was diagnosed when eCT revealed a defect, regardless of whether it was wedge-shaped (**Fig. 2a**) or mass-like (**Fig. 2b**).

#### Variables

The following data were collected: 1. laboratory data at admission (serum leukocytes, CRP, urine leukocyte esterase, nitrite, protein, and occult blood), 2. time from onset of fever to start of treatment (days), 3. time from admission to resolution of fever (days), 4. duration of intravenous antibiotic administration (days), and 5. information on treatment failures. Treatment failure was defined as development of complications such as renal abscess

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eCT, contrast enhancement computed tomography

CTX, cefotaxime sodium

Fig. 1 Our protocol was designed to use fever duration to determine the timing of eCT and duration of antibiotic administration. The gold standard for diagnosing AFBN is eCT, but eCT is not necessary if other techniques can be used.

and bacteremia during treatment, or recurrence within 6 months of UTI caused by the same pathogen responsible for the initial infection.

#### Statistics

The PN and AFBN groups were compared by using R ver. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Fisher's exact test and the Mann-Whitney U test were used to analyze qualitative and numerical variables, respectively.

#### Results

During the observation period, 78 patients were admitted and treated at our hospital. Two patients were younger than 1 month, seven were older than 7 years, six had

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positive blood cultures, one had no fever resolution after 1 week, and four were transferred from hospitals where initial treatment had been started. No patient had a renal abscess on admission, and no patient developed renal abscesses or any other serious condition during treatment. Children with multiple chromosomal or other congenital abnormalities were excluded. 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 for 14 patients, nine of whom had defects indicating AFBN. **Table 1** shows the observations for the PN and AFBN groups. The median age of the PN group was 3.0 months and the group comprised 30 boys and 19



Fig. 2 (a) shows wedge-shaped defects (arrows) and (b) shows tumor-like defects (arrowheads). Both defect patterns were considered to indicate acute focal bacterial nephritis in this study.

		PN (n=49)	AFBN (n=9)	p value	
age (months)		8.0 (3.0)***	23.1 (14.0)	0.037	
sex	m	30	3	0.01	
	f	19	6	0.01>	
pathogen*	E. coli	38	7		
	E. coli (ESBL)	4	0		
	E. faecalis	6	2		
	Klebsiella spp.	1	1		
	P. mirabillis	1	0		
Serum	CRP (mg/dL)	6.5 (5.0)	11.9 (13.1)	0.012	
	WBC (/µL)	17,257 (16,600)	24,186 (24,540)	0.01>	
Urine**	Pro	0.95 (1.0)	1.3 (1.0)	0.31	
	OB	1.3 (1.0)	1.1 (1.0)	0.37	
	WBC	2.8 (3.0)	2.1 (2.0)	0.15	
	Nit	0.47 (0)	0.78 (1.0)	0.27	
Period	P1	1.6 (1.0)	1.7 (1.0)	0.49	
	P2	1.4 (1.0)	3.0 (3.0)	0.01>	
	P3	4.8 (4.0)	7.2 (7.0)	0.01>	

Table 1 Clinical data for patients with PN and AFBN

\* Some patients had more than one pathogen

\*\* Results of test tape

-, 0; +/-, 0.5; +, 1.0; 2+, 2.0; 3+. 3.0

\*\*\* mean (median)

P1 interval from onset to admission (days)

P2 febrile period (days)

P3 duration of antibiotic treatment through intravenous injection (days) WBC, white blood cell; Pro, protein; OB, occult blood; Nit, nitrous acid

girls. The median time from fever to start of treatment was 1.0 days. The median time from start of treatment to fever resolution was 1.0 days. The median duration of intravenous antibiotic therapy was 4.0 days. Four children had recurrent UTIs. **Table 2** shows the clinical information for children with recurrent UTIs.

AFBN was diagnosed in nine patients. The median age of these nine patients was 14 months, which was significantly (p=0.037) higher than that of the PN group. The proportion of girls was significantly higher in the AFBN group than in the PN group (p<0.01). The median time to start of treatment was 1.0 days, which was not significantly different from the PN group (p=0.49). However, the median time to fever resolution was significantly longer (p<0.01) than in the PN group, and median time to intravenous antibiotic administration was also significantly longer (p<0.01) than in the PN group. No recurrence was observed in patients with AFBN.

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		serum		urine (test tape)											
(months)	sex	pathogen	CRP (mg/dL)	WBC (/µL)	Pro	OB	WBC	Nit	P1	P2	P3	VCUG	ultrasound	eCT	others
3	f	E. coli	10.12	21,760	1+	1+	3+	_	0	3	6	ureterocele	lt. renal enlargement ureterocele	double pelvis and ureter ipsilateral giant ureter	
4	m	E. coli	7.96	24,270	+/-	-	2+	2+	1	1	3	rt. VUR 3°	n.p.	n.p.	buried penis
2	m	E. coli	3.62	12,600	+/-	+/-	3+	-	0	1	4	n.p.	n.p.	n.p.	
2	m	E. coli ESBL	3.96	8,500	2+	3+	3+	-	0	1	7	n.p.	n.p.	n.p.	

P1 interval from onset to admission (days)

P2 febrile period (days)

P3 duration of intravenous antibiotic treatment (days)

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

age (months)	sex	pathogen	P2*	Ultrasound	VCUG	eCT
14	f	E. coli	3	high echoic SOL	VUR rt. 3°	rt. Wedge-shaped defect
2	f	E. coli	3	high echoic SOL	n.p.	bil. tumor-like defects
3	m	E. faecalis	3	hydronephrosis rt. SFU 3° lt. SFU 1°	VUR lt. 3° rt. 5°	bil. tumor-like defects
20	f	E. coli	4	bil. renal enlargement reduced blood flow lesion	bladder diverticulm	bil. renal enlargement bil. tumor-like defects
54	f	E. coli	2	reduced blood flow lesion	VUR lt. 2°	lt. wedge-shaped defect
3	m	E. coli	3	n.p.	VUR rt. 2°	rt. wedge-shaped defect
4	m	E. coli, E. faecalis	2	n.p.	n.p.	lt. wedge-shaped defect
52	f	Klebsiella pneumoniae	3	n.p.	VUR lt. 4° rt. 3°	bil. tumor-like defects
56	f	E. coli	4	n.p.	VUR lt. 4°	lt. tumor-like defects

Table 3 Characteristics of patients with AFBN

P2, febrile period (days)

\* There was no significant difference between the tumor-like group and wedge-shaped group (P = 0.078)

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

Ultrasound examinations were performed on all patients, and 43 patients who consented to participate underwent voiding cystourethrography (VCG). In the PN group, one patient had Society for Fatal Urology (SFU) grade 4 hydronephrosis, one had SFU grade 3 hydronephrosis, and one had SFU grade 2 hydronephrosis. The patient with SFU grade 3 hydronephrosis had ipsilateral 4th-degree vesicoureteral reflux (VUR). Dwarf kidneys were observed in two patients; one had ipsilateral 3rd-degree VUR and the other had no reflux but had 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. Ultrasound and VCG findings are summarized in **Table 3**. The AFBN group had a higher rate of complications (77.8%), namely, severe VUR, obstructive urinary tract abnormalities, and other congenital anomalies of the kidney and urinary tract (CAKUT); however, the rates did not significantly differ between the PN and AFBN groups (p= 0.064). In addition, the febrile period was shorter for the wedge-shaped group than for the tumor-like group, but

the difference was not significant (P=0.078).

#### Discussion

Using 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 treatment duration of 3 weeks. The PN group had four cases of relapse, which could be attributable to underlying CAKUT or initiation of drug resistance rather than to the short treatment period. Therefore, it may not be necessary to perform eCT at admission, as recommended in a systematic review<sup>14</sup>, or to administer antibiotics for a total duration longer than 3 weeks to a child with AFBN, as previously reported<sup>4</sup>. Although the number of cases was small and there was no significant difference between patients with tumor-like defects and those with wedge-shaped defects (P=0.078), the time to resolution tended to be shorter for the latter group (Table 3), suggesting that diagnosing AFBN, especially in children with wedge-shaped defects, and administering antibiotics for a total of 3 weeks might result in overtreatment.

Initial treatment of UTI is often in accordance with AAP5 and NICE6 guidelines. Children older than 2-3 months should be treated with oral antibiotics in an outpatient setting if they are able to ingest drugs orally and make frequent visits to the clinic. However, JAID/JSC guidelines state that intravenous antibiotic therapy is the standard of care because prompt antibiotic treatment is important in the initial treatment of fUTI15 and the emphasis is on providing reliable treatment intravenously rather than oral administration, which may not be possible. Although it is difficult to make a conclusive recommendation, because medical settings and insurance systems differ between countries, as do the types and doses of antibiotics that are covered by insurance, intravenous administration is probably the safest initial treatment. Although we have been shifting to providing oral medication at 72 h after resolution of fever, it may be possible to shorten this period<sup>16-18</sup>.

AFBN was first reported and recognized by Rosenfield et al.<sup>3</sup>. Diagnosis of AFBN is generally based on eCT defects<sup>8,11,19</sup>. However, PN has also been reported to exhibit wedge-shaped defects on eCT<sup>19,20</sup>. Delayed enhancement CT is reportedly useful in detecting pathological changes in renal parenchyma<sup>11,12</sup>, and delayed eCT imaging is necessary to definitively distinguish PN from AFBN. However, because the radiation dose is naturally doubled, indications for delayed eCT should be interpreted with caution, and the examination should be avoided in infants. Ultrasonography is also useful for diagnosis of AFBN<sup>21,22</sup> because it shows renal enlargement, the 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 in PN, but no significant differences were observed in pathogens or urinary findings (**Table 1**); therefore, distinguishing between PN and AFBN is difficult.

Cheng et al.4 recommended long-term antibiotic therapy for AFBN, although definitive diagnosis of AFBN is difficult, as mentioned above. Because AFBN lesions are not revealed by contrast on delayed eCT, blood flow may be largely absent. Therefore, it is theoretically correct to increase the duration of drug administration to ensure that a sufficient antibiotic dose reaches AFBN lesions. Conversely, in patients considered to have PN, when eCT shows defects immediately after contrast administration but the defects improve with delayed eCT, blood flow is preserved to some extent, which may lead to a better response to antibiotics and less time to resolution. We believe that the effect of antibiotics reflects blood flow in the lesion; thus, duration of fever is a more pathognomonic factor than a diagnosis of PN and AFBN by eCT and is an important factor in determining optimal 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 of the present patients had renal urinary tract abnormalities: one had a unilateral double renal pelvis and ureter and an ipsilateral giant ureter and ureterocele, and the other had a buried penis and unilateral grade 3 VUR (**Table 2**). Both cases developed recurrence during follow-up after completion of initial treatment. Extended spectrum lactamase (ESBL)-producing *E. coli* was detected in one of the two patients with no renal-urinary tract abnormalities. Fever resolved after initiation of treatment but recurred while the patient was receiving intravenous antimicrobials, which were administered intravenously for 7 days. Treatment was terminated after 7 days of oral administration, and no recurrence was observed after oral administration. The other child had no complications but relapsed during follow-up, after treatment was completed. It is not clear whether these four children would have benefited from longer administration of antibiotics. It remains unclear whether a longer course of antibiotics is necessary, particularly in patients with complicated malformations.

AFBN was reported to be more common in girls<sup>14</sup>, and the present AFBN group had significantly more girls than the PN group. In addition, among adults AFBN predominantly affects women<sup>23</sup>. We believe that this sex difference is related to the incidence of fUTI, which is more common in boys among children younger than 1 year but more common in girls among children older than 1 year. This is thought to be due to anatomical differences, such as posterior loading of the penis and urethra length. Indeed, in this study, the median age of the PN group was 3 months, as compared with 14 months in the AFBN group. In addition, diagnosis of fUTI may be delayed in early childhood, even though fUTI is aggressively investigated and diagnosed in early infancy. The epidemiology of AFBN needs to be verified in a large cohort with accurate diagnosis.

Our protocol excluded severe infections such as bacteremia and renal abscesses. We also excluded patients younger than 1 month from our study because neonates with UTI should be evaluated for associated systemic infections. We further excluded older children with fUTI because they may have an underlying disease or scarring from repeated UTIs. No child in the present study had chromosomal abnormalities or multiple congenital malformations. We do not recommend the present treatment protocol for children who are at risk of infection of multiple organs or who have already developed severe bacterial complications, such as bacteremia or renal abscesses, on admission.

The fact that the children who were diagnosed with AFBN were relatively older does not exclude the possibility that they had repeated UTI and were diagnosed with AFBN on the basis of existing scarring. In addition, because eCT was not performed in all patients, we cannot exclude the possibility that AFBN was included in the PN group. However, we believe that these factors do not disprove our hypothesis that fever duration can be used to guide management.

#### Conclusion

We developed an effective protocol that uses duration of fever to determine duration of antibiotic therapy. This protocol allows patients to complete treatment with antimicrobial agents earlier than previously possible. Additionally, our protocol does not always require eCT to differentiate AFBN, which reduces the need for invasive diagnostic procedures in children.

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