

Etiology, Treatment, and Outcome of Children Aged 3 to 36 Months With Fever Without a Source at a Community Hospital in Southern Thailand

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Abstract

Background: Fever without a source (FWS) in young children can result from occult bacteremia, urinary tract infection (UTI), meningitis, or certain viral infections. In rural areas of Thailand, where bacterial cultures are not available in some community hospitals, the appropriate examination and management of FWS remain controversial. **Methods:** We retrospectively searched electronic medical records for medical diagnoses associated with FWS and evaluated the characteristics and clinical courses of children aged 3 to 36 months with FWS who were admitted to a community hospital in southern Thailand between January 2015 and December 2016. **Results:** Sixty-seven children aged 3 to 36 months with an initial diagnosis of FWS were enrolled. The median age was 11 months (interquartile range [IQR] 8–21 months). Complete blood counts, blood cultures, urine analysis results and urinary cultures were obtained from 67 (100.0%), 31 (46.3%), 47 (70.1%), and 7 (10.5%) patients, respectively. The most common empirical antibiotic administered to these patients was ceftriaxone (71.6%); however, 4 patients recovered without antibiotic administration. The median duration of intravenous antibiotic administration was 4 days (IQR 2–4 days). Intravenous antibiotics were replaced by oral antibiotics in 38 patients (62.3%). The median time to fever subsidence was 30 hours (IQR 12–60 hours). Regarding final diagnoses, 5 patients (7.5%) were diagnosed with culture-confirmed UTI, and 2 (3.0%) had bacteremia (due to contamination). The majority of the children (60, 89.6%) retained the diagnosis of FWS. Presentation at the hospital was significantly earlier in children with culture-confirmed UTI (median 1 day) than in those with culture-negative FWS (median 3 days) ($P = .019$). **Discussion:** We evaluated the characteristics and clinical courses of young children with FWS presenting at a community hospital and the treatment approaches utilized by physicians. Although all patients had good prognoses during the study period, we identified several areas for improvement in conducting proper examinations (especially assessments for UTI in children presenting within the first day of fever onset).

Keywords

fever without a source, children, 3 to 36 months old, community hospital, Thailand

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Introduction

Fever is one of the most commonly presented symptoms in pediatric clinics and pediatric emergency departments. As most febrile children show apparent sources of infection on presentation, the diagnosis and management of these patients are usually straightforward for clinicians. However, some children present with fever without a source (FWS). In these patients, especially children younger than 36 months, a medical history and physical examination cannot identify any source of infection. Although the majority of

these children have self-limiting viral infections, some of them might have serious bacterial infections, including urinary tract infection (UTI), occult bacteremia, or bacterial meningitis. It is therefore a challenge for physicians and

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pediatricians to identify patients who are at risk of serious bacterial infection.

The management of children aged 3 to 36 months with FWS is highly troublesome for pediatricians in terms of conducting appropriate examinations and selecting appropriate antibiotics. Prior to the introduction of the pneumococcal conjugated vaccine (PCV), the prevalence of bacteremia in seemingly healthy, young, febrile children was as high as 2.8% to 11.6%.¹ At that time, most of the guidelines recommended conducting blood and urine tests, including white blood cell counts with or without blood culture and urinalysis with or without urine culture, for all febrile (body temperature >39°C) children aged 3 to 36 months. Currently, many countries around the world have incorporated multiple vaccines into their national immunization programs, resulting in a significant reduction in the rate of bacteremia among febrile children (0.25%-1.1%).²⁻⁵ The introduction of the *Haemophilus influenzae* type B (Hib) vaccine and PCV in many countries has led to a decrease in the practice of performing blood tests in seemingly healthy children with FWS.^{6,7}

In Thailand, although the Hib vaccine was recently included in the National Expanded Programme on Immunization (EPI) in 2019, the PCV has not yet been incorporated into the EPI; thus, young children are still at risk of pneumococcal diseases. A previous study in northeastern Thailand between January 2004 and December 2010 revealed that the incidence of community-acquired bacteremia was 83.5 per 100 000 people per year in infants younger than 1 year. The isolated pathogens in these infants were *Staphylococcus aureus* (15.1%), *Escherichia coli* (10.9%), and *Acinetobacter* spp (8.9%);⁸ interestingly, neither *Streptococcus pneumoniae* nor *H influenzae* type B were identified. In contrast, another study in Thailand between 2007 and 2014 revealed that the causes of bloodstream infections among 1- to 4-year-old children were *Salmonella* nontyphi spp. (15%), *S pneumoniae* (13%), *E coli* (10%), and *H influenzae* (7.6%).⁹ This information raised a question regarding the most appropriate approach to FWS in young children, especially those aged 3 to 36 months. The situation is complicated in rural Thailand, where the majority of community hospitals are not able to perform bacterial cultures. In this study, we aimed to retrospectively review the characteristics and clinical courses of 3- to 36-month-old children with FWS who were admitted to a community hospital in southern Thailand to make recommendations regarding the management of FWS in limited settings where blood cultures are not available.

Materials and Methods

Study Design and Setting

We carried out this retrospective observational study at Thasala Hospital, a 120-bed community hospital located in

Tha Sala District, Nakhon Si Thammarat Province, Thailand, between January 2015 and December 2016. This hospital served as the local public hospital serving a regional population of 160 000 in Tha Sala District, with approximately 390 000 hospital visits per year. Tha Sala District is located approximately 780 km south of the Thai capital of Bangkok and 80 km north of the city of Nakhon Si Thammarat. For pediatric outpatient and inpatient services, both pediatricians and rotating general practitioners are responsible for pediatric patients.

Participants

We included previously healthy children 3 to 36 months of age with FWS admitted to the pediatric wards at Thasala Hospital between January 2015 and December 2016. Patients within this age group were included if they presented with a history of fever without obvious sources of infection identified by their medical history and physical examination. Patients who presented with febrile seizures were also included if there were no obvious identifiable causes of fever. Patients were excluded if they had underlying conditions, including immunodeficiency, or if they were receiving immunosuppressive therapy. During the study period, neither the Hib vaccine nor the PCV had yet been incorporated into the national immunization program.^{10,11}

Definitions

Fever: temporal temperature greater than 38°C

Time to defervescence: the duration from the time that the child's recorded temperature was >38.0°C to the last evaluation at which the temperature was >38.0°C.

Duration of intravenous antibiotics: the number of days from the day that antibiotics were initiated to the last day that antibiotics were administered.

Data Collection

In the hospital database, the final diagnoses were coded according to the International Classification of Diseases 10th Revision (ICD-10), and this information was stored in electronic medical records. We searched for eligible children 3 to 36 months of age with the following ICD-10 codes relevant to diagnoses associated with FWS:

A40 Streptococcal sepsis

A41 Other sepsis

A48 Other bacterial diseases, not elsewhere classified

A49 Bacterial infection of an unspecified site

B96 Other bacterial agents as the cause of diseases classified elsewhere

N39.0 Urinary tract infection, site not specified

G00 Bacterial meningitis, not elsewhere classified
 G01 Meningitis due to bacterial diseases classified elsewhere
 G03 Meningitis due to other and unspecified causes

Patient data regarding their medical history, underlying conditions, physical findings, laboratory findings and treatments were thoroughly examined. Patients were selected if they met our inclusion criteria.

Statistical Analysis

The data were analyzed using SPSS software V 23.0 for Windows (IBM Corp, Armonk, NY). The Kolmogorov-Smirnov test revealed that the data in this study were not normally distributed. The continuous variables were described as medians and interquartile ranges (IQRs), and the qualitative variables were described as frequencies (percentages). The Mann-Whitney *U* test was used to compare clinical characteristics and outcomes between children with culture-confirmed UTI and those with culture-negative FWS. *P* values of less than .05 were considered statistically significant.

Results

Between January 1, 2015, and December 31, 2016, a total of 82 seemingly healthy febrile children who were 3 to 36 months of age were identified by the specified ICD-10 codes. After the exclusion of the presence of localizing sources, 67 children with a presumptive diagnosis of occult bacteremia, FWS or UTI were enrolled.

The median age of the 67 children was 11 months (IQR, 8-21 months), and 33 (49.3%) patients were male. The median time of fever onset was 2 days (IQR, 1-3 days). An immunization history was found for 60 (90%) children, and all 60 of these children had completed Thailand's EPI, including immunization against diphtheria, pertussis, tetanus, poliomyelitis, measles, Japanese encephalitis, and tuberculosis, according to their ages. The median body temperature at presentation was 39°C (IQR, 38.7°C-39.7°C) (Table 1). Thirteen children (19.4%) had febrile seizures at presentation.

All children had complete blood count data, which revealed a median white blood cell count of 21 780 cells/ μ L (IQR, 17 060-29 560 cells/ μ L), and the median neutrophil count (%) was 61.0% (IQR, 45.0%-76.0%) (Table 1). Urinalysis and urine cultures were performed in 47 (70.1%) and 7 (10.5%) children, respectively. Urinalysis and urine culture results are shown in Table 2. There were no records regarding the circumcision status of patients. Urine cultures yielded positive results in 5 of 7 specimens, identifying *E coli* and *Citrobacter diversus* in 4 and 1 specimen(s), respectively. Blood cultures were conducted for 31 (46.3%) children. All blood cultures were obtained

Table 1. Clinical Characteristics of Children Aged 3 to 36 Months With FWS (N = 67).

Clinical Characteristics	Median (IQR)
Age, months	11 (8-21)
Male, n (%)	33 (49.3)
Onset of fever, days	2 (1-3)
Immunization history, n (%)	60 (90)
Temperature, °C	39.0 (38.7-39.7)
White blood cell counts	21 780 (17 060-29 560)
Neutrophils, %	61 (45-76)

Abbreviations: FWS, fever without a source; IQR, interquartile range.

prior to antibiotic administration. Two blood cultures yielded *Micrococcus* spp and *Bacillus* spp, which were considered contaminants. No true pathogens were recovered from the blood cultures. Lumbar puncture was performed in two children aged 6 and 9 months, respectively, with febrile seizures; their cerebrospinal fluid profiles were within the normal ranges for their ages.

Of the 67 children, 63 (94.0%) received empirical antibiotics, which consisted of oral antibiotics for 2 (3.0%) and intravenous antibiotics for 61 (91.0%). Amoxicillin was the only oral antibiotic used in the two children who received oral antibiotics as an empirical treatment. Of the 61 children who received empirical intravenous antibiotics, ceftriaxone accounted for 71.6% of all the intravenous prescriptions, followed by ampicillin (11.9%), cefotaxime (4.5%), and cloxacillin (3.0%). The median duration of intravenous antibiotics was 4 days (IQR, 2-4 days). Intravenous antibiotics were replaced by oral antibiotics in 38/61 cases (62.3%). Cefixime was the most common antibiotic prescribed to replace intravenous therapy in 21/38 (55.3%) patients, followed by amoxicillin (10/38, 26.3%), erythromycin (2/38, 5.3%), cefdinir (1/38, 2.6%), norfloxacin (1/38, 2.6%), cephalexin (1/38, 2.6%), amoxicillin-clavulanate (1/38, 2.6%), and cotrimoxazole (1/38, 2.6%) (Figure 1). The median time to defervescence was 30 hours (IQR 12-60 hours), and the median duration of admission was 4 days (IQR 3-5 days) (Table 3).

Regarding the final diagnoses of these 67 children, 5 (7.5%) were diagnosed with culture-confirmed UTI, and 2 (3.0%) were diagnosed with bacteremia (due to contamination). The majority of the children (60, 89.6%) retained the diagnosis of FWS, including 27 (40.3%) who were classified as culture-negative FWS and 33 (49.3%) with no blood culture results. None of the patients were found to have true bacteremia or meningitis during the study period.

We compared clinical characteristics and outcomes between children with culture-confirmed UTI (n = 5) and those with culture-negative FWS (n = 27). While there was a significant difference in the onset of fever (*P* = .019), there were no differences between the groups in terms of

Table 2. White Blood Cells (WBCs) According to Urinalysis and the Results of Urine Cultures.

WBC From Urinalysis/ High-Power Field (HPF)	Number of Patients			Total
	Without Urine Culture	No Bacterial Growth in Urine Culture	Bacterial Growth in Urine Culture	
Not performed	20	0	0	20
WBC 0-1/HPF	36	0	0	36
WBC 3-5/HPF	4	0	1	5
WBC 10-20/HPF	0	1	1	2
WBC 30-50/HPF	0	0	2	2
WBC >50/HPF	0	1	1	2
Total	60	2	5	67

age, sex, temperature, white blood cell counts, neutrophil counts, duration of intravenous antibiotics, time to defervescence or duration of admission (Table 4). All enrolled patients were discharged to home with afebrile status, and there were no hospital readmissions.

Discussion

This retrospective study is the first to describe the characteristics and outcomes of children aged 3 to 36 months with FWS in a community hospital setting in Thailand. The clinical characteristics of these patients, including age, sex, onset of fever, temperature, and white blood cell counts, were comparable to those of patients in other studies reporting FWS among children aged 3 to 36 months in Asia¹² and Europe.¹³⁻¹⁵ One major issue in this study was the immunization status of the enrolled children. We obtained an immunization history for 60 patients (90%); all of them had received only the basic immunizations included in Thailand's national immunization schedule according to their ages, except the PCV and Hib vaccine. Although both vaccines are available in the private sector and some tertiary hospitals in Thailand, their coverage was low in the study area, which might be due to the cost and accessibility of these vaccines in highly rural areas.

Regarding the laboratory investigations in this study, white blood cell counts were performed in all 67 patients. However, the practice of performing blood cultures among young children with FWS varied among physicians. Despite the presence of elevated white blood cell counts (>15 000), blood cultures were performed in only 31 (46.3%) children. However, no preculture antibiotic administration was identified in this study. Urinalysis was conducted in 47 (70.1%) children, among whom 22 and 25 were male and female, respectively. All 20 children without urinalysis results were younger than 24 months of age. Urine cultures with the presence of pyuria were obtained from only 7 patients, which was beneficial in diagnosing UTI that required the presence of pyuria.¹⁶ However, white blood cell counts in urinalysis have a sensitivity and specificity of 73% to 94%

and 81% to 91%, respectively.^{17,18} As such,⁶ this practice might have underestimated the rate of UTI in this study. The management of young children with FWS varied greatly among physicians, possibly because of the following reasons. Obtaining cultures in community hospitals is not a routine practice in some rural areas of Thailand; some other community hospitals not included in this study do not have microbiology laboratories and must send blood culture specimens to provincial hospitals. The low PCV and Hib vaccine coverage contributed to the controversy regarding the management of FWS in young children. Doctors and pediatricians had to decide whether to follow the previous recommendations from the pre-PCV and pre-Hib vaccine era and obtain full workups,¹⁹ apply the new recommendations to unimmunized children,²⁰ or perform no routine blood tests on seemingly healthy febrile children aged three to 36 months.⁶ Furthermore, in Thailand, there is still a risk of bacteremia caused by other pathogens that are not preventable by vaccine, including *S aureus*, *E coli*, *Acinetobacter* spp, and nontyphoidal *Salmonella* spp,^{8,9,21-23} apart from the risk of pneumococcal bacteremia among children younger than 5 years.^{9,24} Thus, noninvasive practices might not be appropriate. During the study period, there were no national guidelines available on the diagnosis and management of infants and children with FWS.

Despite the low PCV and Hib vaccine coverage, no pneumococcal- or Hib-associated bacteremia cases were identified in this study. Furthermore, no bacteremia caused by true pathogens were reported during the study period. This might be due to the limited number of participants in this retrospective study. Moreover, blood cultures were not performed in approximately half of the enrolled patients, possibly leading to the underestimation of bacteremia, especially pneumococcal bacteremia, which can be transient and self-limiting.²⁵ These results illustrated the variability that can occur when performing different examinations among patients. The physician's clinical judgment is crucial, but it can be somewhat subjective. Thus, the use of clinical assessment tools such as the Yale Observation Scale to identify young children at risk of serious bacterial infections could be helpful in

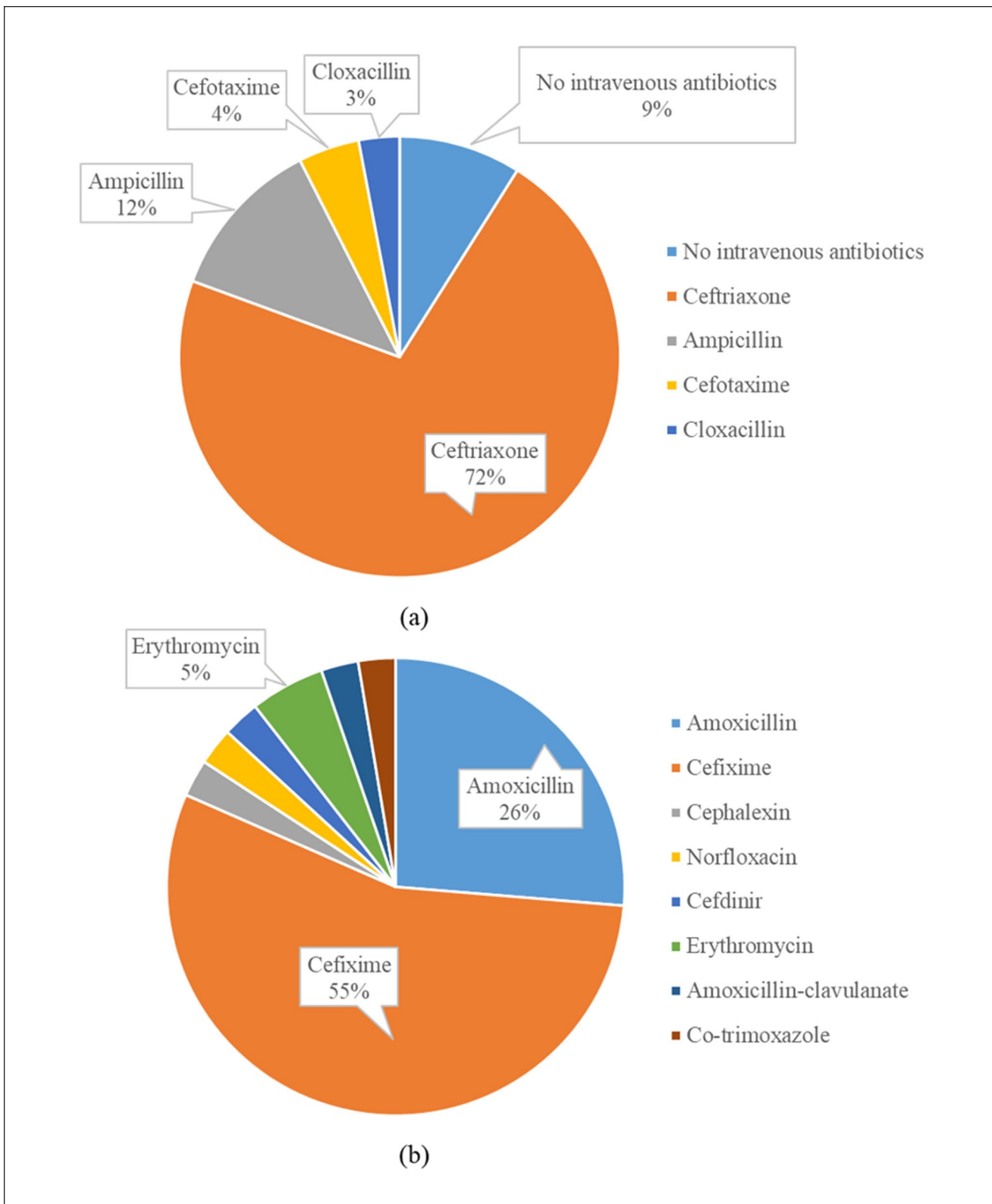


Figure 1. (a) Empirical intravenous antibiotics administered to 3- to 36-month-old children with fever without a source (FWS); (b) oral antibiotics used to replace intravenous therapy in 3- to 36-month-old children with FWS.

Table 3. Clinical Courses of Children Aged 3 to 36 Months With FWS (N = 67).

Clinical Course	Median (IQR)
Duration of IV antibiotics, days	4 (2-4)
Time to defervescence, hours	30 (12-60)
Duration of admission, days	4 (3-5)

Abbreviations: FWS, fever without a source; IQR, interquartile range; IV, intravenous.

resource-limited situations.²⁶ Future studies should focus on the effectiveness of clinical assessment tools in a rural setting in Thailand.

Regarding antibiotic use among children with FWS, ceftriaxone was the main antibiotic used in this retrospective study, which corresponded to the recommendations.^{6,20} At the time of defervescence, intravenous antibiotics were replaced by oral antibiotics in approximately two-thirds of the patients; however, the selection of oral antibiotics varied greatly and included cefixime, amoxicillin, erythromycin, cefdinir, norfloxacin, cephalexin, amoxicillin-clavulanate, and cotrimoxazole. These agents are considerably different in their effectiveness against gram-positive and gram-negative organisms. In this study, defervescence occurred within 12 to 60 hours; thus, viral infection was presumed to be the cause of fever in the majority of the enrolled patients. These patients certainly had no need for antibiotics other than the initial administration of empirical antibiotics. To develop recommendations for this condition and to strengthen antibiotic stewardship programs, further studies need to identify the epidemiological characteristics of pediatric bacteremia, as well as susceptibility patterns, in different parts of Thailand.

Regarding the final diagnoses, most patients (89.6%) retained the diagnosis of FWS at discharge. Serious bacterial infections might have been underestimated due to a lack of proper examinations, especially urinalysis and urine culture, which were performed in only 47 (70.1%) and 7 (10.5%) children, respectively, as previously discussed. UTI was diagnosed according to the presence of pyuria and positive culture results in 5 cases in this study. However, the UTI rate of 7.5% in this study corresponded to the rates of UTI in other studies on patients in the same age group (6.8%-9.9%).^{2,14} No occult pneumonia was identified in this study, as chest radiographs are not routinely performed in febrile young children who have normal lung signs on examination, even if white blood cell counts were greater than 20,000, as suggested by some recommendations.^{6,20}

We performed a comparison of clinical characteristics and outcomes between children with culture-confirmed UTI and those with culture-negative FWS to differentiate children with and without invasive bacterial infections. Children with culture-confirmed UTI presented at the hospital significantly earlier (median, 1 day) than those with culture-negative FWS (median, 3 days). We strongly

recommend that in such a limited setting, physicians obtain urinalysis and urine culture data in children with FWS who present early, especially within the first day of fever.

Our study highlights the characteristics and clinical courses of young children with FWS admitted to community hospitals as well as the several different approaches utilized by physicians working in the community hospital setting. The advantage of studying patients in this community hospital was the availability of the microbiology laboratory; however, there were differences in the management of young children with FWS among physicians. The following issues were identified: (1) There was a low rate of blood culture analyses for children with high fever and white blood cell counts greater than 15 000. (2) There was a low rate of urinalysis, especially among children younger than 24 months.⁶ (3) There was a low rate of urine culture in children with pyuria. However, performing bacterial cultures in every case may be time consuming. In our opinion, applying clinical observation scales²⁶ and obtaining inflammatory marker data, such as procalcitonin levels,²⁷⁻²⁹ can help identify patients at risk for serious bacterial infections. Nevertheless, the procalcitonin test is still quite expensive and unavailable in most community hospitals in Thailand. Regarding the implications for primary care, the results our study highlight that we needed to educate primary physicians and interns regarding the possibility of serious bacterial infections among young children presenting with FWS, especially UTIs. Furthermore, there is a need for evidence-based guidelines regarding the management of young children with FWS presenting in primary care settings, where resources are limited.

This study had several limitations. First, due to insufficient clinical data and a lack of patient follow-up among children treated by outpatient services, we included only febrile children admitted to the hospital. Hence, our results might not be representative of the entire population of children with FWS during the study period. Second, this study was carried out in a single community hospital, which resulted in a small sample size, and thus, the results might not be applicable in other settings. Third, the study period was 2 years, which might not be effectively representative. Finally, because of the retrospective study design, the quality and the completion of clinical information relied on the attending physicians, leading to the possibility of selection bias toward cases with complete data and correct ICD-10 diagnosis codes.

Conclusions

Our study highlighted the characteristics and clinical courses of young children with FWS who were admitted to a community hospital, as well as several different approaches utilized by the treating physicians. Children with culture-confirmed UTI presented to the hospital

Table 4. Comparison of Clinical Characteristics and Outcomes in Children Aged 3 to 36 Months With Culture-Confirmed UTI and Culture-Negative FWS.

Clinical Characteristics	Culture-Negative FWS (n = 27), Median (IQR)	Culture-Confirmed UTI (n = 5), Median (IQR)	P
Age, months	12 (9-21)	11 (4-18)	.285
Onset of fever, days	3 (1-4)	1 (0.8-1.0)	.019
Temperature, °C	39.0 (38.7-39.7)	39.0 (38.6-39.5)	.841
White blood cell count	21 780 (16 990-30 760)	20 440 (18 425-24 200)	.725
Neutrophil count, %	63.0 (47.0-78.0)	59.0 (53.0-75.5)	1.000
Duration of intravenous antibiotics, days	4.0 (4.0-5.0)	3.0 (3.0-6.0)	.579
Time to defervescence, hours	36.0 (12.0-64.0)	30.0 (17.0-48.0)	.579
Duration of admission, days	4.0 (4.0-5.0)	4.0 (4.0-6.5)	1.000

Abbreviations: FWS, fever without a source; IQR, interquartile range; UTI, urinary tract infection.

significantly earlier than those without invasive bacterial infection. No true bacteremia cases were identified during the two-year study period, and all the enrolled patients had a good prognosis without hospital readmission. However, we identified several areas for improvement in choosing proper examinations and the appropriate selection of antibiotics for children with FWS in the community hospital setting.

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Declaration of Conflicting Interests

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Ethical Approval

The study was reviewed and approved by the Ethics Committee on Human Rights Related to Research Involving Human Subjects, Walailak University, prior to the recruitment of participants (WUEC-18-007-01).

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