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Fever without source in infants and young children: dilemma in diagnosis and management

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Background: There is controversy surrounding the management of young children who have a fever without a source (FWS). Several strategies have been designed with the purpose of managing children with FWS.

Aims: To assess the applicability of a standardized guideline for children up to 36 months of age with FWS.

Setting: Pediatric emergency unit, Al-Adan Hospital, Kuwait City, Kuwait, from May 2011 to October 2011.

Design: Prospective, cross-sectional study.

Methods and materials: The study involved children with FWS up to 36 months of age. The guideline classifies the risk of serious bacterial infection (SBI) according to the age of the child, the presence or absence of toxemia, clinical presentation, and laboratory screening tests.

Results: A total of 481 children were included in the present study, but only 385 cases completed the study; 3.9% of patients had toxemia at the initial evaluation. We found 26 children with SBI (6.8%); 12 patients with SBI did not present with toxemia. In all, 40.4% of studied newborns were diagnosed as having a urinary tract infection, and 42.7% of patients as self-limited probable viral etiology. Of the 109 young infants without toxemia, 53.2% were classified as being at high risk of SBI. Of the 163 toddlers without toxemia, 72.4% were treated with antibiotics; 48.4% of patients received therapeutic treatment and 25.8% received empirical treatment.

Conclusion: The guideline followed in our pediatric emergency unit seemed to be appropriate in following up with these children using simple laboratory tests. The most frequent SBI in this sample was urinary tract infection.

Keywords: fever without source, serious bacterial infection, young children, sepsis, infants

Introduction

Fever is one of the most common chief complaints of children seeking medical attention. Most of these children have identifiable causes of fevers, but many have fevers without an apparent source (FWS), following conclusions made by the history and physical examination of the child.[1] Despite the frequency of fevers as a chief complaint, there is considerable controversy in the management of the young child who has FWS. The challenge in the evaluation of the febrile young child lies in balancing the minimization of risk to the patient with the costs of testing and treatment.[2]

Few children with FWS have a serious bacterial infection (SBI). Occult bacteremia (OB), urinary tract infection (UTI), and meningitis are among the causes of SBIs. The risk of SBI has been studied by categorizing infants and young children based on age, appearance, temperature, and laboratory criteria. Numerous studies found that 2%–15%

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of febrile infants younger than 3 months had bacteremia, whereas the risk of SBI in children aged 3–36 months with FWS was 2.5%–11%.[3] This changed after the introduction of the conjugate *Haemophilus influenzae* type b vaccine, as the risk of SBI was 1.5%–2.3% in children aged 3–36 months with FWS, 1.2%–2% in infants less than 3 months who were not toxic, (ie, not showing signs of toxemia irritability, changes in degree of consciousness, hypoactivity, hypotonia, lethargy, hyper- or hypoventilation, hypotension, tachycardia, signs of poor peripheral perfusion, or cyanosis), and 10%–11% in infants who were toxic.[4]

The guideline developed by Baraff[5] was based on the meta-analysis of 85 studies and on specialists' opinions. This document stratifies children according to age group and risk of SBI (low and high) using clinical and laboratory criteria. Several strategies have been designed based on this guideline with the purpose of standardizing the management of children with FWS.[6]

At the pediatric emergency department of Al-Adan hospital, Kuwait, the children were evaluated and followed-up using the guideline that stratifies the risk of SBI according to the presence or absence of toxemia, age, temperature, and laboratory findings. This guideline, which is based on guidelines published in previous literature and on the experience of our medical staff, was developed and adapted to the local context.

The controversies in the literature and the absence of local studies assessing the treatment and follow-up of children with FWS are the reasons for the present study. The objective of this study is to evaluate the applicability of a standardized guideline for children up to 36 months old who were seen at the Al-Adan hospital with FWS.

Methods

A prospective study was conducted during a 6-month period (May 1, 2011 to October 31, 2011) with children aged 0 to 36 months who presented with a fever (rectal temperature more than 38°C) without obvious focus (by history and initial clinical examination) to the pediatric emergency unit of Al-Adan hospital, Kuwait. All of the children's parents or guardians gave verbal consent after being provided with detailed information on the objectives of the study. The exclusion criteria were: children with an underlying disease that could result in immunity alterations; and children who received antibiotic therapy during the previous week. All of our patients were admitted to the observation room of the pediatric emergency unit and subjected to routine laboratory screening including complete blood count, C-reactive protein, blood culture, urinalysis (UA), urine culture, liver function tests, renal function tests, chest X-ray, and cerebrospinal fluid (CSF) examination (biochemical analysis, gram staining, cytology, latex agglutination, and culture), if indicated.

Patients were divided into three different age groups for evaluation purposes: newborns (≤ 28 days of life), young infants (from 1 to 3 months of age), and older infants or toddlers (3–36 months of age). Each group was further subdivided into patients with toxemia and patients without.

For the assessment of toxemia, the clinical evaluation was carried out when the child was not febrile (after being given 10–15 mg/kg of acetaminophen orally or rectally with and without ibuprofen 10 mg/kg, orally), since fever may cause several different degrees of prostration. Patients were determined as having toxemia when they presented with irritability, changes in their degree of consciousness, hypoactivity, hypotonia, lethargy, hyper- or hypoventilation, hypotension, tachycardia, signs of poor peripheral perfusion, or cyanosis.[1,5] According to the guideline, those children who appeared to have toxemia were evaluated by clinical and laboratory screening, given broad-spectrum parenteral antibiotics (cefotaxime, 200 mg/kg), and were then hospitalized.

According to our guidelines, any newborn who presented with a rectal temperature of greater than 38°C would be assessed clinically with laboratory investigations, would be given parenteral antibiotics (ampicillin and cefotaxime), and then would be hospitalized (due to the higher risk of SBI) for observation until the results of these tests were released and the patient was treated accordingly.

Febrile young infants without toxemia were initially clinically evaluated and then were screened in the laboratory as before. The young febrile infants were then evaluated with regard to the risk of SBI using the Rochester criteria (Table 1).[7] Infants with low-risk SBI were followed up daily in our pediatric emergency unit until the final results of all cultures were released. Those infants with any positive cultures were hospitalized, whereas those with negative cultures were followed-up until their fevers subsided. Any infants at high risk of SBI were hospitalized and received antibiotics (parenteral cefotaxime 100 mg/kg/day) until the final results of the cultures were released, the focal point of the infection was identified, and the fever subsided.

Toddlers without toxemia were clinically assessed with laboratory investigations, and were kept in our pediatric emergency observation area for 4–6 hours until results of the laboratory tests were obtained. The children were either given specific antibiotics (if the diagnosis was known),

Table 1 Rochester criteria for the assessment of bacterial infection risk in febrile young infants[7]

Clinical criteria	Laboratory criteria
Low risk criteria for serious bacterial infection	
• No prior illness	• White blood cell count between 5000 and 15,000/mm^3
• Full-term birth without complications during hospital stay after delivery	• Absolute neutrophil count < 1500/mm^3
• Well-appearing infant with no evidence of bacterial infection during physical examination	• Urine white blood cell count < 10/hpf
• No chronic illness	• Fecal leukocytes < 5/hpf in children with diarrhea

Abbreviation: hpf, high power field.

empirical antibiotics, or were followed up without antibiotics according to their initial temperature and laboratory results. We considered a temperature > 39°C and a white blood cell count > 15,000/mm^3 with absolute neutrophil count > 10,000/mm^3 to be the cut-off point in order to begin treatment with empirical antibiotics if there was no obvious diagnosis, and until the results of the cultures became available. We used oral cefpodoxime for treatment.

CSF examination was done for all newborns, high-risk young infants, and toddlers (if there was no clinical sign or symptom indicating the source of infection after the preliminary investigations, or if there were any CNS symptoms or signs).

Urine was collected from all patients by vesical catheterization for the UA, urine culture, and sensitivity test in infants less than 1 year old, and by clean catch method if the child was more than 1 year old. Urine tests showing leukocyturia (ie, the microscopic examination showed a > 10/high power field (HPF) with and without nitrite-positive findings led to the suspicion of a UTI) until the result of the urine culture was released. The urine culture was considered positive if it showed growth of ≥ 1000 unit-forming colonies (UFC)/mL if the urine was collected via vesical catheter, or of ≥ 100,000 UFC/mL if the urine was collected by the clean catch method.

Children with UA suggestive of UTI were treated according to their age. For young infants, they were hospitalized and given intravenous cefotaxime until the results of the urine culture were obtained and the patients were treated accordingly. Conversely, toddlers were treated according to their clinical status; if their tests were suggestive of acute pyelonephritis or any abnormal ultrasound findings, patients were admitted to the hospital and treated as before, whereas other children without these criteria were treated by empiric oral cefpodoxime and followed until the result of their urine culture and sensitivity tests returned.

Clinical reassessment of patients who were not hospitalized was conducted at least every 24 hours for young infants, and at every 48 hours for children aged 3–36 months until: (1) their fevers subsided; (2) there were any positive cultures; or (3) there was a clinical sign or symptom indicating the source of infection. All children who showed signs of any positive culture growth were contacted on the telephone for reassessment and hospitalization.

Results

A total of 481 cases were included in the present study, but only 385 cases completed the study as 96 cases were excluded (22 patients either did not return for reassessment and/or contact on the telephone was not successful; 45 cases were excluded because sample collections were refused by the children's parents, particularly CSF; 13 cases were excluded because hospitalization was refused; and 16 cases were excluded because the antibiotic treatment was discontinued based on the parents' decision). The characteristics of the sample and the children's clinical evaluations are shown in Table 2.

In the present study, 3.9% of patients had toxemia at the initial evaluation. We found 26 children with SBI (6.8%), but 12 patients with SBI did not present with toxemia. Data from patients with SBI are shown in Table 3. OB was responsible for fevers observed in 19.2% of patients with SBI. OB reported in patients was due to *Klebsiella pneumoniae*, Gram-negative bacilli, *Streptococcus pneumoniae*, *Serratia marcescens,* and *Citrobacter freundii*.

Of the 104 newborns included in the study, 5.8% of patients presented with toxemia, and 8.7% of them presented with SBI. Most of the patients (79.8%) were diagnosed as having a UTI and self-limited viral infection.

Young infants without toxemia (n = 109) were classified according to the Rochester criteria.[7] A total of 58 patients were classified as being at high-risk for SBI (41 patients had a UTI) and 51 were at low risk. All low-risk groups were followed up without antibiotic use, but nine patients were given oral antibiotics (cefpodoxime) according to their general status after 2 days of follow-up before the culture reports returned, and five patients had positive urine cultures and were labeled as having a UTI. Four patients among the low-risk group (5.4%) deteriorated on follow-up and were readmitted to hospital – one patient had meningitis, two had

Table 2 Characteristics of the sample and children's clinical evaluation according to stratification into age groups

Variables	General (n = 385) (100%)	<30 days (n = 104) (27%)	1–3 months (n = 113) (29.4%)	3–36 months (n = 168) (43.6%)
Male/female	195/190	51/53	65/48	79/89
Toxemia	15 (3.9)	6 (5.8)	4 (3.5)	5 (2.97)
Without toxemia	370 (96.1)	98 (94.2)	109 (96.5)	163 (97.3)
SBI	26 (6.8)	9 (8.7)	9 (7.96)	8 (4.8)
SBI in patients without toxemia	12 (3.2)	4 (4.1)	5 (4.6)	3 (1.8)
Presenting symptoms				
Temperature > 39°C	142 (36.9)	13 (13.3)	67 (59.3)	62 (36.9)
Decreased feeding	212 (55.1)	60 (57.69)	60 (53.1)	92 (54.7)
Urinary symptoms	95 (24.9)	16 (15.3)	38 (33.6)	41 (24.4)
Final diagnosis				
UTI	150 (39)	42 (40.4)	41 (36.3)	67 (39.9)
Self-limited disease or probable viral etiology	143 (37.1)	41 (39.4)	44 (38.9)	58 (34.5)
Meningitis	13 (3.4)	5 (4.8)	5 (4.4)	3 (1.8)
Pneumonia	19 (4.9)	6 (5.8)	6 (5.3)	7 (4.2)
Bronchiolitis	15 (3.9)	5 (4.8)	4 (3.5)	6 (3.6)
OB	9 (2.3)	4 (3.8)	2 (1.8)	3 (0.6)
URTI	30 (7.8)	1 (0.96)	11 (9.7)	18 (10.7)
Viral exanthema	6 (1.7)	0 (0)	0 (0)	6 (3.6)
Total	385 (100)	104 (100)	113 (100)	168 (100)
Patients without toxemia receiving				
Empirical antibiotic		0	55 (53.4)	41 (25.8)
Specific antibiotic		96	48 (46.6)	77 (48.4)
No antibiotic		0	0	41 (25.8)
Total		96	103	159

Abbreviations: n, number; SBI, serious bacterial infection; UTI, urinary tract infection; OB, occult bacteremia; URTI, upper respiratory tract infection.

a UTI, and one had bronchiolitis. Five patients were recalled due to positive blood cultures, although they were clinically well; however, all laboratory investigations were repeated for them and the second blood culture was negative among these patients.

Of the 163 toddlers who presented without toxemia, 118 patients were treated with antibiotics; 77 patients received therapeutic treatments, and 41 patients received empirical treatments. The mean time of the empirical antibiotic therapy was 72 hours, until the results of the urine cultures and preliminary blood cultures were available. The presence of SBI was evidenced in two (4.9%) of the 41 toddlers who received empirical antibiotics in agreement with the guideline. There were not any cases of SBI in the toddlers who were not treated with antibiotics.

Patients with UA suggestive of a UTI were treated as before. Four young infants (0–3 months) categorized as low-risk for SBI with normal UA were recalled due to positive urine cultures and were subsequently hospitalized. Twelve young infants with urine tests suggestive of a UTI were admitted and treated, but the urine cultures were negative.

CSF examinations were done only if there was no clinical sign or symptom indicating the source of infection after the preliminary investigations, or if there were any CNS symptoms

Table 3 Final diagnoses established for patients with toxemia

Final diagnoses	SBI			Total (n = 26) (%)
	Newborn (n = 9) (%)	Young infants (n = 9) (%)	Older infants (n = 8) (%)	
% of total number per age group	8.7	7.96	4.8	6.8
UTI	3 (33.3)	2 (22.2)	3 (37.5)	8 (28.6)
Meningitis	2 (22.2)	2 (22.2)	1 (12.5)	5 (19.2)
Pneumonia	1 (11.1)	2 (22.2)	2 (25)	5 (19.2)
Bronchiolitis	1 (11.1)	1 (11.1)	0 (0)	2 (7.7)
OB	2 (22.2)	2 (22.2)	1 (12.5)	5 (19.2)
Viral exanthema	0 (0)	0 (0)	1 (12.5)	1 (3.8)
Total	9 (100)	9 (100)	8 (100)	26 (100)

Abbreviations: SBI, serious bacterial infection; UTI, urinary tract infection; OB, occult bacteremia.

or signs. Meningitis was reported in 13 patients; five of them had SBI, and three patients presented with toxemia.

Discussion

We presented here our guidelines followed in Al-Adan Hospital, Kuwait, for patients less than 36 months who present with FWS, while trying not to miss cases with SBI.

Many strategies have been developed that are aimed at delivering medical care and following up with children who present with FWS.[2,6,8] After the introduction of the conjugated vaccine in Kuwait against *S. pneumoniae* and *H. influenzae*, many changes happened in terms of the distribution and presentation of the patients. On the other hand, the renovation of our pediatric emergency unit was conducted in 2009; a larger observation unit means that patients can remain for 24 hours and be continuously observed.

We classified our patients into three age groups: newborns, (0–28 days old), the young infant (between 1 and 3 months of age; however, some authors define this group as including children between 1 and 2 months of age); and the older infant or toddler (3–36 months of age), although some studies include only patients up to 24 months old in this group. Although the use of chronologic age distinctions are somewhat artificial (as the risk of SBI is likely to be inconsequentially different between a 28-day-old child and a 29-day-old child), there is some rationale behind this age distinction given that younger children often have decreased immunologic function and are more commonly infected with virulent organisms.[9]

SBI was reported in 6.8% of our studied population: nine newborns (8.7%), nine young infants (7.96%), and eight older infants (4.8%). Twelve patients presented without toxemia (3.2%). Our rate is very close to what was reported by Machado et al,[10] who presented a study of 251 febrile children with FWS and SBI; the authors reported that SBI presented in 9.1% of children. However, in the Machado et al study, the sample size was smaller; there were 251 patients, in comparison with our sample of 385 patients. In addition, not all investigations were done. On the other hand, other studies reported higher incidence rates of SBI; for instance, Lacour et al[11] conducted a study with 124 children aged up to 36 months old who presented with FWS. The authors identified 23% of cases were associated with SBI, 10% of cases were associated with focal bacterial infections, and 67% of cases presented with probable viral infections. Similarly, Gervaix et al[12] reported a study that involved the follow-up of febrile children up to 2 years of age; the findings demonstrated that 20.2% of children presented with FWS, and of these 17.3% had SBI. All of our patients were vaccinated against *H. influenzae* and *S. pneumoniae*. This difference in rates can therefore be explained by the number of vaccinated children, as well as by the early search for and availability of medical services in Kuwait.

All of our patients had a final diagnosis, and laboratory investigations were completed on all of our patients (including CSF examinations), given that we excluded those patients whose parents refused CSF examinations at the beginning of the study. Compared with other studies,[10–12] prior researchers had not defined the final diagnoses in detail, except for cases of SBI while paying special attention to OB.

As in most of the previous studies, UTI was the most common bacterial infection observed in children with FWS (39%). The general prevalence of UTI ranges from 2% to 5% in febrile children younger than 2 years old;[13] fever is often the only symptom of UTI in this age group.[14] This was also the same in our study, although some patients presented with urinary tract symptoms (24.9% of patients). UTI was the most frequent cause of SBI.

For the newborn and young infant groups, SBIs were most common.[3,6,9,15] Therefore, our guidelines were appropriate in managing febrile infants in a more aggressive way for the identification of SBI, and treating them in the most successful manner. Some studies have shown that the occurrence of SBI is present in approximately 10% of febrile infants between 1–2 months old, and in up to 13% of newborns;[9,15] however, in our study, SBI was only present in 8.7% of children during the neonatal period, and in 7.96% of young infants. This can be explained by the early search for medical advice, and the availability of medical services in Kuwait.

Older infants (3–36 months of age) without toxemia were the most controversial group in terms of determining the most appropriate form of management. All of the febrile older infants were put under observation in our observational area for at least 4 hours until all of the laboratory results were available; these children were also followed up every 48 hours after returning home. Some authors concluded that the observation period of 24 hours was sufficient enough in evaluating the patients, but in our study we recommend that 4–6 hours of observation, the availability of all test results, and a follow-up period is enough to detect the risk for SBI.

Empirical antibiotic therapy is another very controversial aspect of many treatment strategies used for children with FWS. The initiation of empirical antibiotic therapy may reduce the occurrence of SBIs and their complications.[14,16–18] In our study, we used the total white blood cell count $> 15{,}000/mm^3$ or an

absolute neutrophil count > 10,000/mm^3 as the cut-off point for deciding whether to use empiric antibiotic therapy in children more than 3 months old.[19] This was done only after all initial investigations (including CSF examination) were completed, and only if the focus of the fever or infection could not be specified. This strategy was intended to increase the specificity for identifying SBI and reducing the use of empiric antibiotic therapy; however, clinical follow-up is very important. On the other hand, the excessive use of antibiotics may have an impact on the increase in rates of bacterial resistance.

The most important limitations in our study were the loss of follow-up of 36 children (14.34%), and parents' refusal to permit laboratory investigations, especially CSF examinations. Families' decisions to not admit their sick children to the hospital, and choosing to take them home instead were other limitations. All of these children were excluded from the study.

Conclusion

Countless studies, use of new SBI markers, fast identification of virus, and the production of new vaccines has modified the ways in which FWS is managed in children. Of importance are the reassessment of children, and providing instructions to the children's guardians that the children should return for medical assessment if they present with any signs of worsening. Our guideline seemed to be appropriate for the follow-up of children with FWS up to 36 months old, but only after the initial laboratory tests were conducted, which should be performed by any health care provider. All of the children who presented with SBI were identified in the initial evaluation or during follow-up.

Disclosure

The authors report no conflicts of interest in this work.

References

1. McCaig LF, Burt CW. National Hospital Ambulatory Medical Care Survey: 2002 emergency department summary. *Adv Data*. 2004;340:1–34.
2. Belfer RA, Gittelman MA, Muñiz AE. Management of febrile infants and children by pediatric emergency medicine and emergency medicine: comparison with practice guidelines. *Pediatr Emerg Care*. 2001;17(2):83–87.
3. Mahajan P, Stanley R. Fever in the toddler-aged child: old concerns replaced with new ones. *Clin Pediatr Emerg Med*. 2008;9(4):221–227.
4. Akintemi OB, Roberts KB. Evaluation and management of the febrile child in the conjugated vaccine era. *Adv Pediatr*. 2006;53:255–278.
5. Baraff LJ. Management of infants and children 3 to 36 months of age with fever without source. *Pediatr Ann*. 1993;22(8):497–498, 501–504.
6. Baraff LJ. Editorial: Clinical policy for children younger than three years presenting to the emergency department with fever. *Ann Emerg Med*. 2003;42(4):546–549.
7. American College of Emergency Physicians Clinical Policies Committee, American College of Emergency Physicians Clinical Policies Subcommittee on Pediatric Fever. Clinical policy for children younger than three years presenting to the emergency department with fever. *Ann Emerg Med*. 2003;42(4):530–545.
8. Klein JO. Management of the febrile child without a focus of infection in the era of universal pneumococcal immunization. *Pediatr Infect Dis J*. 2002;21(6):584–588; discussion 613–614.
9. Baker MD, Avner JR, Bell LM. Failure of infant observation scales in detecting serious illness in febrile, 4- to 8-week-old infants. *Pediatrics*. 1990;85(6):1040–1043.
10. Machado BM, Cardoso DM, de Paulis M, Escobar AM, Gilio AE. Fever without source: evaluation of a guideline. *J Pediatr (Rio J)*. 2009;85(5):426–432.
11. Lacour AG, Gervaix A, Zamora SA, et al. Procalcitonin, IL-6, IL-8, IL-1 receptor antagonist and C-reactive protein as identificators of serious bacterial infections in children with fever without localising signs. *Eur J Pediatr*. 2001;160(2):95–100.
12. Gervaix A, Caflisch M, Suter S. Management of children with fever without localizing signs of an infection. *Arch Pediatr*. 2001;8(3):324–330. French.
13. Practice parameter: the diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. American Academy of Pediatrics. Committee on Quality Improvement. Subcommittee on Urinary Tract Infection. *Pediatrics*. 1999;103(4 Pt 1):843–852.
14. Bass JW, Steele RW, Wittler RR, et al. Antimicrobial treatment of occult bacteremia: a multicenter cooperative study. *Pediatr Infect Dis J*. 1993;12(6):466–473.
15. Baker MD, Avner JR. The febrile infant: What's new? *Clin Pediatr Emerg Med*. 2008;9:213–220.
16. Baraff LJ, Oslund S, Prather M. Effect of antibiotic therapy and etiologic microorganism on the risk of bacterial meningitis in children with occult bacteremia. *Pediatrics*. 1993;92(1):140–143.
17. Harper MB, Bachur R, Fleisher GR. Effect of antibiotic therapy on the outcome of outpatients with unsuspected bacteremia. *Pediatr Infect Dis J*. 1995;14(9):760–767.
18. Bulloch B, Craig WR, Klassen TP. The use of antibiotics to prevent serious sequelae in children at risk for occult bacteremia: a meta-analysis. *Acad Emerg Med*. 1997;4(7):679–683.
19. Kuppermann N, Fleisher GR, Jaffe DM. Predictors of occult pneumococcal bacteremia in young febrile children. *Ann Emerg Med*. 1998;31(6):679–687.