Fever without Source in Children: Six Years Experience of a Children's Hospital

Çocuklarda Odağı Olmayan Ateş: Bir Çocuk Hastanesinin Altı Yıllık Tecrübesi

Emine Polat, Hüsniye Yücel

ABSTRACT

Objective: Fever without an apparent source (FWS) in 1-36 months is challenging. An extensive evaluation is carried out, and there is a need to simplify the management of infants with FWS. In this paper, we aimed to review the follow up of the infants with FWS.
Methods: The data of 127 children admitted to the pediatric unit were analysed for six years. The age ranged from 1 to 36 months. Demographics, symptoms, history, laboratory tests, cerebrospinal fluid analysis and cultures, blood and urinalysis and cultures, chest X-rays and abdominal/transfontanel ultrasound, treatment modalities, length of stay and the requirement for pediatric intensive care unit were collected.
Results: Most of the patients were (65.4%) boys. Mean age was ≈3,2 months and fever was present for ≈1.9 days. Dehydration and signs of shock were highly significant concerning severe bacterial infections (SBIs). Two patients were diagnosed as meningitis. A chest X-ray was performed at 112 of the patients whom 17.9% had mild paracardiac infiltration. Abdominal ultrasound was performed in 18.9% of the patients, of whom 8.7% had findings related to UTI. Regarding our results, WBC value >15000x10^3/µL and CRP level > 9 mg/L could be taken as a measure to predict SBIs. However, the MPV level was not significant.
Conclusion: Approach to febrile children is still a challenge for a pediatrician although the prevalence of SBIs was low in children with FWS. In addition, WBC and CRP are valuable and informative to identify SBI, while MPV does not. The findings obtained in this review suggest that pediatricians must sufficiently focus on UTI, which is the most common cause of SBI.

Keywords: Children, fever without source, urinary tract infection, severe bacterial infection

Received: 04.24.2020 **Accepted:** 03.11.2021

ÖZET

Amaç: Odağı olmayan ateş 1-36 aylık çocuklarda zorlayıcıdır. Kapsamlı bir değerlendirme yapılır ve bu bebeklerin yönetiminin basitleştirilmesine ihtiyaç vardır. Bu yazıda odağı olmayan ateşli bebeklerin takibini gözden geçirmeyi amaçladık.
Yöntem: Pediatri ünitesine 6 yıl boyunca yatırılan 127 çocuğun verileri değerlendirildi. Yaşları 1 ile 36 ay arasında değişmekteydi. Demografik özellikler, semptomlar, öykü, laboratuvar testleri, beyin omurilik sıvısı analizi ve kültürleri, kan ve idrar tetkikleri ve kültürleri, akciğer grafileri ve karın/transfontanel ultrasonografi bulguları, tedavileri, yatış süreleri ve çocuk yoğun bakım ünitesi gereksinimleri çalışmaya alındı.
Bulgular: Hastaların çoğunluğu (%65.4) erkekti. Ortalama yaş ≈3,2 aydı ve ateş ≈1.9 gündür mevcuttu. Dehidrasyon ve şok belirtileri, ciddi bakteriyel enfeksiyonlar açısından oldukça önemliydi. İki hastaya menenjit tanısı konuldu. Akciğer grafisi çekilen 112 hastanın %17,9'unda hafif parakardiyak infiltrasyon saptandı. Abdominal ultrasonografi hastaların %18.9' unda yapıldı ve bunların % 8.7'sinde idrar yolu enfeksiyonu ile ilişkili bulgular saptandı. Sonuçlarımıza göre, ciddi bakteriyel enfeksiyonları tahmin etmek için beyaz küre değeri >15000x10^3/µL ve C- Reaktif protein seviyesi >9 mg/L bir ölçü olarak kullanılabilir. Ancak MPV düzeyi anlamlı değildi.
Sonuç: Ateşli çocuklara yaklaşım, odağı olmayan ateşli çocuklarda ciddi bakteriyel enfeksiyon prevalansı düşük olmasına rağmen, bir çocuk doktoru için hala zordur. Ayrıca beyaz küre ve C-Reaktif protein, ciddi bakteriyel enfeksiyonu tanımlamak için değerli ve bilgilendiricidir, MPV ise tanımlamaz. Bu derlemede elde edilen bulgular, çocuk doktorlarının ciddi bakteriyel enfeksiyonun en sık nedeni olan idrar yolu enfeksiyonlarına yeterince odaklanması gerektiğini düşündürmektedir.

Anahtar Sözcükler: Çocuklar, odağı olmayan ateş, idrar yolu enfeksiyonu, ciddi bakteriyel enfeksiyon

Geliş Tarihi: 28.04.2020 **Kabul Tarihi:** 11.03.2021

ORCID IDs: E.P. 0000-0003-3034-5037, H.Y. 0000-0002-7477-0302

Address for Correspondence / Yazışma Adresi: Emine Polat, MD Department of Pediatrics, Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital, Ankara, Turkey. E-mail:emine227@yahoo.com

doi:http://dx.doi.org/10.12996/gmj.2022.08

INTRODUCTION

Fever without an apparent source (FWS) occurs at approximately 7-20% of febrile children after history and physical examination in which only a small percentage possibly have a bacterial infection, such as sepsis, urinary tract infection (UTI), occult pneumonia or bacterial meningitis (1-3). Various management strategies are assigned to febrile infants by age groups of neonates (first 28 days), young infants (1 to 3 months), and older infants (3 to 36 months). Infants are often managed by the Rochester or Philadelphia Criteria to reduce unnecessary hospitalization of the infants and identify the infants who may be managed at the outpatient clinic using clinical and laboratory criteria (1, 4). However, vaccination policies of the 13-valent pneumococcal conjugate made this controversy in recent years and exactly what parameters may be useful still remains unclear. Among the children with an FWS, 10–15% of infants fewer than three months of age and 5–7% of the children between 3 and 36 months old have a severe bacterial infection (SBI), such as pneumonia, urinary tract infection, bacteremia or meningitis (5). An extensive evaluation is carried out even though the child is appearing non–toxic. Thus, there is a need for advice to simplify the management of these febrile infants (4, 6). We aimed to review the scientific evidence on decision making for the therapeutic strategies of infants and children younger than 36 months with FWS to prevent overdiagnosis and exposure to antibiotics provoking multidrug-resistant bacteria.

METHODS

After obtaining ethical approval from the Institutional Ethics Committee(the number 2019-222), we analysed the data of 127 children admitted to the pediatric unit of a Children's Hospital consecutively over some time from January 2013 to November 2018. The unit is a 26-bed tertiary clinic in which nearly 900-1200 patients are followed up in a year. The unit accepts all kinds of diseases that require multidisciplinary approach referred for diagnosis and treatment all across the country. From January 2013 to November 2018, totally 4993 children were admitted to our unit. The age group of the children ranged from 1 month to 36 months who presented with FWS ≥38°C referred from the pediatric emergency department (PED) or outpatient clinic of the hospital for further investigations. All patients were subjected to medical history, vital signs, state of hydration, behavioral state, pulse oxymetry, physical examination and routine laboratory tests and chest X-ray investigations. Demographic data like age, gender, weight, duration and degree of fever, symptoms like vomiting, runny nose, cough, diarrhea, convulsions, travel history, any diseases/any drugs used for prophylaxis or treatment, operation history, intrauterine and neonatal history, results of the laboratory tests, lomber puncture and cerebrospinal fluid (CSF) analysis and cultures, blood and urine analysis for cultures, need for chest X-rays and abdominal/transfontanel ultrasound, treatment modalities, such as antibiotics and antiviral drugs which were initiated, length of stay, the requirement for a referral to pediatric intensive care unit (PICU) were collected and documented retrospectively for statistical evaluation. Vaccination status was also recorded. The child who misses at least one of the vaccines was defined as incomplete vaccination. The patients who were admitted with shock and hypotension followed at PICU and diagnosed as sepsis, meningitis and urosepsis, and severe bacterial infections with positive cultures were recorded.

Fever without a source (FWS) is identified with a fever duration of fewer than five days when the history and physical examination cannot recognize a specific source in an acutely ill, nontoxic-appearing child under three years of age (7). Severe bacterial infection (SBI) is considered when signs of potentially severe infection (A:decreased alert or activity, B: breath; signs of respiratory distress, C: circulation or color (tachycardia, pallor, poor perfusion, petechiae), D: decrease in urine output or dehydration) was present; indicating severe pneumonia, urinary tract infection/pyelonephritis, bacteremia/sepsis or meningitis. Non-SBI was defined when mild infections, such as acute gastroenteritis, upper respiratory tract infection, probable viral rush or a self-limited disease with probable viral etiology was present (5,7). Most children with fever and pneumonia have respiratory signs on physical examination. The absence of respiratory signs in febrile children with leukocytosis makes the diagnosis of occult pneumonia likely, and a chest x-ray should be considered (7).

The patients who were neonates, who had hydrocephalus/ventriculoperitoneal shunt, prolonged fever for more than five days, patients who had immunodeficiency/who had used corticosteroids for more than five days, underlying chronic diseases, patients who had tracheostomy/percutaneous gastroenterostomy and incomplete medical records were excluded from this study.

The data were analyzed using software, SPSS for Windows 20 (Statistical Package For Social Sciences Inc, Chicago, IL). Distribution of continuous variables was investigated by Shapiro Wilk and Kolmogorov-Smirnov normality tests. The collected data were analyzed using the Student t-test, Chi-Square test and Mann-Whitney *U* Test. For the significance of more than two independent groups, the Kruskal-Wallis test was used. A receiver operating characteristic (ROC) curve analysis was carried out to determine the sensitivity and specificity of elevated WBC, CRP and MPV levels in patients. Multivariate analysis of independent variables was performed using Logistic Regression analysis. P-values <0.05 were considered statistically significant.

RESULTS

The patients were distributed as girls 44 (34.6%) and 83 (65.4%) boys. Mean age was 3,2±4,6 (median=2, min=1, max=36) months. Fever was present for 1.9±1.1 (median=2, min=1, max=5) days. Demographics of the patients and the relationship between variables and SBI are detailed in Table 1.

Table 1. Demographics of the patients and the relationship between variables and SBI.

Variables	SBI (n=27)	Non-SBI (n=100)	P Value
Age, Mean±SD (median)	2.5±2.5 (2)	3.4±5 (2)	p>0.05
0-3 months	23 (85.2)	87 (87)	
4-36 months	4 (14.8)	13 (13)	
Gender, Male, n (%)	22 (81.5)	61 (61)	p>0.05
Female, n (%)	5 (18.5)	39 (39)	
Weight(kg) Mean±SD (median)	5.6±1.9 (5.3)	5.5±1.7 (5.2)	
Duration of fever (Days) Mean±SD (median)	2.1±1.2 (2)	1.8±1.1 (2)	p>0.05
Degree of fever (°C) , n (%)			p>0.05
38-38.5	19 (70.4)	77 (77)	
38.5-39	7 (25.9)	20 (20)	
> 39	1 (3.7)	3 (3)	
Primary symptom/admittance, n (%)			p>0.05
Vomiting	7 (25.9)	16 (16)	
Rinorrhea	6 (22.2)	22 (22)	
Cough	7 (25.9)	23 (23)	
Diarrhea	6 (22.2)	12 (12)	
Convulsion	-----	4 (4)	
Contact with a person who had URTI, n (%)	10 (37)	38(38)	p>0.05
Parental smoking, n (%)	8 (29.6)	37 (37)	p>0.05
History of travel, n (%)	-----	4 (4)	p>0.05
Incomplete vaccination, n (%)	1 (3.7)	5 (5)	p>0.05
Physical examination, n (%)			
Dehydration	4 (14.8)	2 (2)	**p=0.004**
Prolonged capillary refill/Hypotension	8 (29.6)	3 (3)	**p<0.001**
Rush	-----	1 (1)	p>0.05
Respiratory findings	2 (7.4)	7 (7)	p>0.05
Hepatomegaly	-----	1 (1)	p>0.05
Lymphadenopathy	1 (3.7)	-----	p>0.05
Jaundice	1 (3.7)	1 (1)	p>0.05
Anemia, n (%)	13 (48.1)	55 (55)	p>0.05
Antibiotics, n (%)			p>0.05
Cefotaxime-Ampicillin	20 (74)	67 (67)	
Cefotaxime	2 (7.4)	4 (4)	
Ceftriaxone	5 (18.5)	27 (27)	
Sulbactam Ampicillin	------	3 (3)	
Meropenem	1 (3.7)	1 (1)	
Vankomycin	2 (7.4)	2 (2)	
Claritromycin	1 (3.7)	1 (1)	
Clindamycin	------	1 (1)	
Antivirals, n (%)			p>0.05
Acyclovir	1 (3.7)	1 (1)	
Gancyclovir	1 (3.7)	------	
Oseltamivir	3 (11.1)	1 (1)	
Need For PICU, n (%)	5 (18.5)	------	**p<0.001**
Length of stay (days), Mean±SD (median)	7.9±5 (6)	5.2±1.8 (5)	**p<0.001**

Vomiting was present at 23 (18.1%), diarrhea at 18 (14.2%), rhinorrhea at 28 (22%), cough at 30 (23.6%) and convulsion at 5 (4%) of the patients as symptoms at admission. Some of the patients had more than one symptom at once (e.g., had both vomiting and diarrhea). 48 (37.8%) of the patients had contact with a person who had upper respiratory tract infection, and 45 (35.4%) of the patients had a smoking parent. Six of the patients (4.7%) had incomplete vaccination, in which two of them had no vaccines. On the physical examination, 23 (18.1%) of the patients had a positive finding, 9 (7.2%) had respiratory findings like tachypnea, crackles and rhonchi, 11 (8.8%) had cutis marmoratus and prolonged capillary refill time reminding shock, 2 (1.6%) had jaundice, 3 (2.4%) had dermatitis, 1 (0.8%) had hepatomegaly, 1 (0.8%) had lymphadenopathy, 1 (0.8%) had a syndromic face, and 1 (0.8%) had a maculopapular rash. No petechial rash was present. It has been determined that vomiting, runny nose, cough, diarrhea, convulsions, which were initial complaints, had no relationship with SBI (P >0.05). Dehydration and signs of shock (capillary refill >2 seconds/hypotension) found on physical examination was highly significant concerning SBI with P=0.004 and P<0.001, respectively.

Lumbar puncture was performed at 110 (86.6%) of the patients whom only two patients were diagnosed as meningitis; one (0.8%) patient had positive CSF culture for pneumococcus, and one had–positive CSF PCR (polymerase chain reaction) for enterovirus, whereas the other patients had negative cultures/PCR. 17 (13.4%) of the parents did not give consent for their child to undergo a lumbar puncture procedure.

Chest X-ray was performed at 112 of the patients, and of them, 102 (80.2%) had normal findings and 10 (7.9%) had mild paracardiac infiltration. None had lober infiltration. It was found out that there was no statistically significant relationship between chest X-ray and SBI (P >0.05). Four (3.2%) of the patients was diagnosed as pneumonia because they developed respiratory symptoms during hospitalisation.

Abdominal ultrasound was performed in 24 (18.9%) of the patients whom 13 (10.2%) had normal findings and reminding 11 (8.7%) had findings mostly related to UTI, such as single kidney, ureteropelvic stenosis, crystaloides at bladder, hydronephrosis, the fullness of renal pelvis and mesenteric lymphadenopathy. It was found that there was a significance between the requirement of abdominal ultrasound and SBI (P=0.004).

The final diagnosis of the patients with FWS is summarized in Table 2.

Table 2. The final diagnosis of the patients with FWS

	Number	**%**
Sepsis/Bacteriemia	**4**	**3.2**
E. Coli	2	1.6
S. Warneri	1	0.8
S. Homunis	1	0.8
Pneumonia	**4**	**3.2**
Adenovirus	1	0.8
Meningitis	**2**	**1.6**
Pnemococcus	1	0.8
Enterovirus	1	0.8
UTI/Pyelonephritis	**6**	**4.8**
E. Coli	2	1.6
C. pneumoniae	1	0.8
Enterococcus faecalis	1	0.8
Enterobacter cloace	1	0.8
C. oxytoca	1	0.8
URTI	**2**	**1.6**
AGE	**6**	**4.8**
Rotavirüs	2	1.6
Giardia	1	0.8
Undetermined	3	2.4
Roseola infantum	**2**	**1.6**
Probable viral rush	**4**	**3.2**
Self limited disease/ Probable Viral etiology	**75**	**59.1**

UTI: Urinary tract infection
URTI: Upper Respiratory tract infection
AGE: Acute Gastroenteritis

Admission to PICU of the hospital and duration of the hospital stay was highly significant regarding SBI (P<0.001).

hite blood cell (WBC) was high at 32 (25.2%), C-reactive protein (CRP) was high at 85 (66.9%) and mean platelet volume (MPV) was high at five (3.9%) of the patients. To determine the accuracy of predicting SBI, the sensitivity of 74.1% and specificity of 50% were found in receiver operating characteristic analysis when WBC value was >8900x10^3/µL, and incidentally, the sensitivity of 74.1% and specificity of 50% were found when CRP level was 9 mg/L as well.

We constructed a ROC curve to determine the accuracy of predicting SBI, and the area under the curve for WBC was 0.58 (95% confidence interval; P>0.05). We found that WBC had a positive predictive value (PPV) of 28.6% and negative predictive value (NPV) of 87.7% (Figure 1).

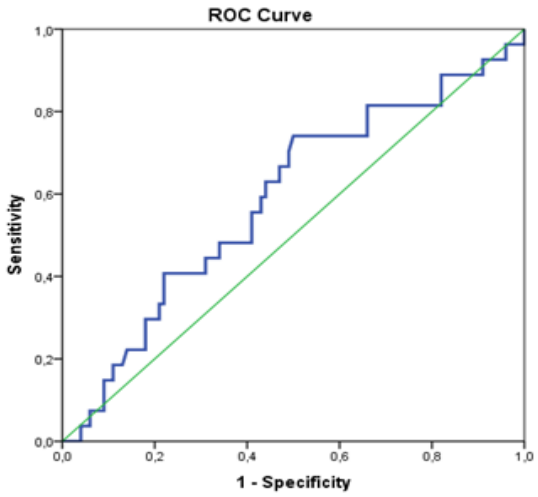

Figure 1. ROC curve for WBC

In addition, when WBC count was > 15,000/mm^3 specificity increased to 79%, but sensitivity decreased to 33% on ROC analysis. WBC count > 15,000/mm^3 had a PPV of 30% and NPV of 81.4% and WBC count was find out not to be an independent marker in determining SBI by itself at the multivariate logistic regression analysis.

We constructed a ROC curve to determine the accuracy of predicting SBI, and the area under the curve for plasma CRP was 0.62 (95% confidence interval; p=0.05). Also, we found that the CRP level had a PPV of 28.6% and NPV of 87.7% (Figure 2).

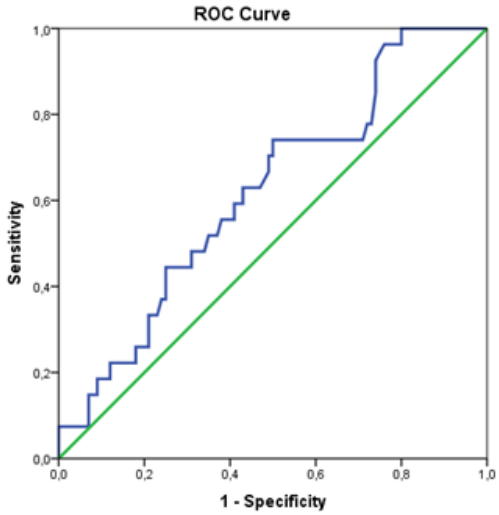

Figure 2. ROC curve for CRP

Regarding our results, a WBC value >15000x10^3/µL and CRP level > 9 mg/L could be taken as a measure to predict SBI. However, the MPV level was not significant for the prediction of the SBI (p>0.05).

DISCUSSION

In this study, we aimed to review the scientific evidence on decision making for the therapeutic strategies of infants and children between 1-36 months with FWS. This study demonstrated that the patients were distributed as boys predominantly. This was consistent with the literature (8). Mean age was ≈3.2 months and fever was present for ≈1.9 days. The findings showed that life-threatening conditions like dehydration, shock and prolonged capillary refill were more frequent in children with SBIs consistent with the literature, whereas vomiting, runny nose, cough, diarrhea, convulsions, which were initial complaints, had no relationship with SBI (8). According to our results, there were no symptoms at admission significantly associated with SBI, whereas the findings at physical examinations, such as dehydration and prolonged capillary refill time/hypotension, were highly indicative of SBI.

Observation scale scores trying to detect SBI in febrile infants might be inadequate to identify SBI (9) so that a 'step-by-step' approach was validated for the management of febrile infants (10) and scoring systems were searched for this difficult identification. However, these models do not seem to demonstrate any influence on clinical practice in the PED (11). Overall, clinicians may prefer a stepwise diagnostic and therapeutic approach instead of an arithmetic predictive model (12). Thus, the management of these children can sometimes be a dilemma. We found that 21.3% of the children who had FWS developed SBI. A prospective study with 1060 children reported that 12.9% of the FWS had severe/invasive bacteriel infections (8); however, a study reported a lower prevalence of 7.2% (2), which can be explained by their high vaccination status nationwide leading to herd immunity. Although recent novel approaches using biosignatures have stated that we are close to demonstrating the performance of Procalcitonin (PCT) and CRP versus genomic-based reference standards, probably it will take a long time before the evidence for genomics is recognized and can be utilized in clinical practice (13). Right now, these novel techniques are expensive and may cause too much delay. In addition, clinical, biological markers with the common predictors must be discovered while considering the critical requirement for better targeting of antibiotics (14, 15). Also, a recent prospective study determined that a host-protein signature showed superior diagnostic performance in the differentiation of viral from bacterial infections in case of FWS (16). However, future studies are necessary for the validation to reduce the overuse of antibiotics.

Two of our FWS patients were diagnosed as meningitis; one patient had pneumococcus, and one patient had enteroviral meningitis. Also, 13.4% of the parents did not provide consent for their child to undergo a lumbar puncture procedure. A recent study found out that approximately 5% of the parents do not give informed consent for this procedure because they had inadequate knowledge about it, and their most frequent concern was paralysis (17). There is also a controversy to perform LP routinely on infants over one month of age in case of FWS. Some authors think that it is unnecessary and must be individualized by an experienced pediatric emergency physician to prevent under-diagnosing nonbacterial meningitis (18).

Among the UTIs, Escherichia coli was the most common pathogen with 42.8%, and the others were Klebsiella pneumoniae, Enterococcus faecalis, Enterobacter cloacae and Klebsiella oxytoca, respectively, which was parallel to a similar study (8). Two children with both UTI and bacteraemia were infected with Escherichia coli. Sepsis/bacteraemia was diagnosed in four children, and the bacteria isolated in blood cultures were Escherichia Coli in two, Stafilococcus warneri and Staphylococcus hominins were positive one by one (8). After the pneumococcal conjugate vaccine, the outcomes of the children with FWS were detected to represent a 94.6% decrease overall and a 100% decrease in Streptococcus pneumoniae, while rates of UTIs were the most prevalent bacterial infection hereafter (19). Recent studies report that the emphasis on managing children with FWS should be on diagnosing, especially UTI (19-22). A study validated the UK guidelines which concentrate on diagnosing UTI for the management of children with FWS and suggested that US guidelines should be changed, which still focus on the detection and treatment of occult bacteraemia because SBI is uncommon from now on (19). In addition, in a recent study, a risk score called Lab-score (based on CRP, PCT and urinary dipstick) is refined to maximize the prediction ability for SBI, which promised wider applicability. However, these results need validation with larger samples (23). As authors, we also think that UTI must be focused on when FWS is present.

The profit of chest X-ray in children with FWS is low, but in children with respiratory signs, high fever, or marked leukocytosis (>20,000/mm^3), it is mostly appropriate in detecting clinically occult pneumonia. Therefore, the routine use of chest X-rays in FWS is a controversial issue (24). In our study, the findings demonstrated that X-ray was performed in 112 patient and of whom 80.2% had normal findings and 7.9% of them had mild paracardiac infiltration. None of the patients had lober infiltration. It was found that there was no statistically significant relationship between chest X-ray and SBI, which was consistent with the literature (24). Therefore, we only advise X-Ray in case of clinically suspected pneumonia.

The findings showed that there was a significance between the requirement of abdominal ultrasound and SBI. This significance might be because these patients had UTI. Thus, this procedure was performed.

WBC was high at 25.2%, CRP was high at 66.9% and MPV was high at 3.9% of the patients. According to our results, a WBC value >15000x10^3/µL and CRP level > 9 mg/L could be taken as a measure to predict SBI. Some studies reported the utility of the WBC count in evaluating febrile infants and demonstrated that patients with a WBC count >15 000/mm3 were more likely to have SBI and they suggested that including the complete blood count (CBC) as part of the evaluation of febrile infants decreased the frequency of missed SBIs (25-27). Similar to our results, several studies stated that WBC count > 15,000/mm^3 was associated with SBI, but this was not as sensitive in determining SBI as CRP (27-29). In addition, some studies reported that WBC counts in patients with SBI were significantly higher than in patients without SBI (27). In our study, specificity increased to 79% on the basis of WBC count > 15,000/mm^3 and WBC count was find out not to be an independent marker in determining SBI by itself just like similar studies (27). Although literature states that CRP and PCT tests have more sensitivity and specificity compared with the WBC count (25, 30), PCT is not used routinely in the PED/outpatient clinic of our hospital. Thus, we could not compare the efficacy of the PCT, but CRP was found out to be more useful than WBC, similar to their results. In our study, the MPV level was not significant for the prediction of the SBI. There is one study in literature investigating MPV in FWS, in which the preliminary results showed no significance (27). However, we should note that admission to the PICU of the hospital and duration of hospital stay was highly significant regarding SBI as expected.

CONCLUSION

Approach to febrile children is still a challenge for a pediatrician although the prevalence of the SBIs was low in children with FWS. WBC and CRP are still valuable and informative to identify SBI whilst MPV does not. Our findings in this review suggest that pediatricians must sufficiently focus on UTI, which was the most common cause of the SBI in febrile children. Comprehensive investigations with larger samples are required to guide for management strategies and future biosignature tests since FWS still keeps its importance.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1.Baraff LJ. Management of fever without source in infants and children. Annals of emergency medicine. 2000;36(6):602-14.

2.Craig JC, Williams GJ, Jones M, Codarini M, Macaskill P, Hayen A, et al. The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses. Bmj. 2010;340:c1594.

3.Bachur RG, Harper MB. Predictive model for serious bacterial infections among infants younger than 3 months of age. Pediatrics. 2001;108(2):311-6.

4.Jhaveri R, Byington CL, Klein JO, Shapiro ED. management of the Non–toxic-appearing Acutely Febrile Child: a 21st Century Approach. The Journal of pediatrics. 2011;159(2):181-5.

5.Galetto-Lacour A, Gervaix A. Identifying severe bacterial infection in children with fever without source. Expert review of anti-infective therapy. 2010;8(11):1231-7.

6.Irwin AD, Drew RJ, Marshall P, Nguyen K, Hoyle E, Macfarlane KA, et al. Etiology of childhood bacteremia and timely antibiotics administration in the emergency department. Pediatrics. 2015:peds. 2014-61.

7.Valcarce MÁF-C. Fever without a source in children younger than 36 months.

8.Hubert-Dibon G, Danjou L, Feildel-Fournial C, Vrignaud B, Masson D, Launay E, et al. Procalcitonin and C-reactive protein may help to detect invasive bacterial infections in children who have fever without source. Acta Paediatrica. 2018.

9.Nigrovic LE, Mahajan PV, Blumberg SM, Browne LR, Linakis JG, Ruddy RM, et al. The Yale Observation Scale Score and the risk of serious bacterial infections in febrile infants. Pediatrics. 2017:e20170695.

10. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L. Validation of the "step-by-step" approach in the management of young febrile infants. Pediatrics. 2016:e20154381.

11. Irwin AD, Grant A, Williams R, Kolamunnage-Dona R, Drew RJ, Paulus S, et al. Predicting risk of serious bacterial infections in febrile children in the emergency department. Pediatrics. 2017;140(2):e20162853.

12.de Vos-Kerkhof E, Gomez B, Milcent K, Steyerberg EW, Nijman RG, Smit FJ, et al. Clinical prediction models for young febrile infants at the emergency department: an international validation study. Archives of Disease in Childhood. 2018:archdischild-2017-314011.

13. Kuppermann N, Mahajan P. Role of serum procalcitonin in identifying young febrile infants with invasive bacterial infections: one step closer to the holy grail? JAMA pediatrics. 2016;170(1):17-8.

14. Kaforou M, Herberg JA, Wright VJ, Coin LJ, Levin M. Diagnosis of bacterial infection using a 2-transcript host RNA signature in febrile infants 60 days or younger. Jama. 2017;317(15):1577-8.

15. Lubell Y, Althaus T. Biomarker tests for bacterial infection—a costly wait for the holy grail. The Lancet Infectious Diseases. 2017;17(4):369-70.

16. Ashkenazi-Hoffnung L, Oved K, Navon R, Friedman T, Boico O, Paz M, et al. A host-protein signature is superior to other biomarkers for differentiating between bacterial and viral disease in patients with respiratory infection and fever without source: a prospective observational study. European Journal of Clinical Microbiology & Infectious Diseases. 2018:1-11.

17. Acoglu EA, Oguz MM, Sari E, Yucel H, Akcaboy M, Zorlu P, et al. Parental Attitudes and Knowledge About Lumbar Puncture in Children. Pediatric emergency care. 2018.

18. Mintegi S, Benito J, Astobiza E, Capape S, Gomez B, Eguireun A. Well appearing young infants with fever without known source in the emergency department: are lumbar punctures always necessary? European Journal of Emergency Medicine. 2010;17(3):167-9.

19. Waddle E, Jhaveri R. Outcomes of febrile children without localising signs after pneumococcal conjugate vaccine. Archives of disease in childhood. 2009;94(2):144-7.

20. Bass III PF. Fever without a source, think UTI first. Contemporary Pediatrics. 2017;34(7):24.

21. McNulty TA. There's much to read between the covers, so get started! Contemporary Pediatrics. 2017;34(7):4-6.

22. Elhassanien AF, Hesham A-AA, Alrefaee F. Fever without source in infants and young children: dilemma in diagnosis and management. Risk management and healthcare policy. 2013;6:7.

23. Leroy S, Bressan S, Lacroix L, Andreola B, Zamora S, Bailey B, et al. Refined Lab-score, a Risk Score Predicting Serious Bacterial Infection in Febrile Children Less Than 3 Years of Age. The Pediatric infectious disease journal. 2018;37(5):387-93.

24. Westra SJ, Karmazyn BK, Alazraki AL, Dempsey ME, Dillman JR, Garber M, et al. ACR Appropriateness Criteria Fever Without Source or Unknown Origin—Child. Journal of the American College of Radiology. 2016;13(8):922-30.

25. Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. Procalcitonin and C-reactive protein as diagnostic markers of severe bacterial infections in febrile infants and children in the emergency department. The Pediatric infectious disease journal. 2007;26(8):672-7.

26. Bilavsky E, Yarden-Bilavsky H, Amir J, Ashkenazi S. Should complete blood count be part of the evaluation of febrile infants aged≤ 2 months? Acta Paediatrica. 2010;99(9):1380-4.

27. Gunduz A, Tekin M, Konca C, Turgut M. Effectiveness of Laboratory Markers in Determining Serious Bacterial Infection in Children with Fever without Source. Journal of Pediatric Infectious Diseases. 2018;13(04):287-92.

28. Mahajan P, Stanley R. Fever in the toddler-aged child: old concerns replaced with new ones. Clinical Pediatric Emergency Medicine. 2008;9(4):221-7.

29. Ishimine P. Fever without source in children 0 to 36 months of age. Pediatric Clinics. 2006;53(2):167-94.

30. Lopez AF, Cubells CL, García JG, Pou JF. Procalcitonin in pediatric emergency departments for the early diagnosis of invasive bacterial infections in febrile infants: results of a multicenter study and utility of a rapid qualitative test for this marker. The Pediatric infectious disease journal. 2003;22(10):895-904.