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The Significance of Clinical and Laboratory Findings in Predicting Serious Bacterial Infections in Children With Acute Fever Without a Focus

Akut Odağı Olmayan Ateş Tanısı Alan Çocuklarda Klinik ve Laboratuvar Bulguların Ciddi Bakteriyel Enfeksiyonu Öngörmedeki Değerlerinin Araştırılması

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Abstract

Objective: Fever is among most common causes of admission to hospital in childhood. In 20% of febrile infants and children, no focus can be identified by physical examination and this group is defined as "acute fever without a focus" (AFWF). Bacteremia (5%), and serious bacterial infection (15%) is determined in of children with AFWF. Clinical scales and laboratory tests are used to detect the risk of occult bacteremia and serious bacterial infection in children with AFWF This study aimed to determine relation between biochemical indicators and YALE Observation Scale, besides, rates of clinical scales and biochemical indicators predicting serious bacterial infections, in 3-36 months children with AFWF.

Material and Methods: This study was performed prospectively, in 77 cases, between 3-36 months of AFWF. Low risk criteria was evaluated by performing YALE Observation Scale in children. Complete blood count, absolute neutrophil count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin 6, procalcitonin, urine analysis, chest x-ray, cerebrospinal fluid (CSF) examination; blood, urine and CSF cultures were obtained.

Results: The mean age of the patients was 11.0 (4-36) months, 64.9% (n= 50) were boys. Most commonly AFWF recovered in patients (35.0%), and urinary tract infection was diagnosed (32.5%). Severe bacterial infection was determined in 44.2%. When patient groups with and without severe bacterial infection were compared, white blood count, ESH, CRP, and procalcitonin were significantly higher in severe bacterial infection ($p< 0.05$). Erythrocyte sedimentation rate had highest specificity (87.5%) in discriminating between groups with and without severe bacterial infection.

Öz

Giriş: Ateş, çocukluk yaş grubunda hastaneye en sık başvuru sebepleri arasındadır. Ateşli bebek ve çocukların %20'sinde fizik muayenede ateş odağı saptanamaz ve bu olgu grubu "akut odağı belli olmayan ateş" (AOA) olarak tanımlanır. Akut odağı belli olmayan ateşi olan çocukların %5'inde bakteriyemi ve %15'inde ciddi bakteriyel enfeksiyon saptanmaktadır. Akut odağı olmayan ateş varlığında gizli bakteriyemi ve ciddi bakteriyel enfeksiyon riski bulunan çocukları belirlemek amacıyla klinik ölçekler ve laboratuar tetkikleri kullanılmaktadır. Bu çalışmanın amacı, 3–36 ay arası AOA tanısı alan olgularda YALE Gözlem Ölçeği ve laboratuvar göstergelerin ciddi bakteriyel enfeksiyonu öngörmedeki değerlerini belirlemektir.

Gereç ve Yöntemler: Bu çalışma, ateş sebebiyle başvuran ve AOA tanısı alan 3-36 ay arası 77 olguda ileriye dönük olarak yapıldı. Çocuklardaki düşük risk kriterlerini değerlendirmek amacı ile YALE Gözlem Ölçeği uygulandı. Tam kan sayımı, mutlak nötrofil sayımı, eritrosit sedimantasyon hızı (ESH), C-reaktif protein (CRP), interlökin-6, prokalsitonin, tam idrar tetkiki, arka ön akciğer grafisi, beyin omurilik sıvısı (BOS) incelemesi yapıldı; kan, idrar ve BOS kültürleri incelendi.

Bulgular: Çalışmaya alınan olguların yaş ortalaması 11.0 ay (4-36), %64.9'u (n= 50) erkek idi. Olgulara en sık, düzelen akut odağı olmayan ateş (%35.0) ve idrar yolu enfeksiyonu (%32.5) tanısı konuldu; %44.2'sinde ciddi bakteriyel enfeksiyon saptandı. Ciddi bakteriyel enfeksiyonu olan olgular, olmayan grup ile karşılaştırıldığında ciddi bakteriyel enfeksiyonu olan grupta beyaz küre sayısı, ESH, CRP ve prokalsitonin anlamlı olarak yüksek bulundu ($p< 0.05$). Ciddi bakteriyel enfeksiyonu olan ve olmayan olguları ayırt etmede özgüllüğü en yüksek (%87.5) test olarak ESH saptandı. Çalışma grubunun YALE Gözlem Ölçeği puan ortancası l6 puan (6-14) olarak saptandı.

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Conclusion: In conclusion, AFWF mostly recovered in children at 3-36 months, and urinary tract infection was common cause. White cell count, ESR, CRP and procalcitonin were found valuable in predicting serious bacterial infection. Further studies are needed to predict interleukin-6 value relevant to serious bacterial infection.

Keywords: Acute fever without focus, serious bacterial infections, child, YALE observation scale

Ciddi bakteriyel enfeksiyon saptanan 34 olgunun 14'ünde (%41.2) YALE Gözlem Ölçeği >6 puan olarak saptandı; CBE ile YALE Gözlem Ölçeği 6 puan ve >6 puan olma arasında istatistiksel anlamlı ilişki saptanmadı (p= 0.435).

Sonuç: Sonuç olarak, 3-36 ay arası çocuklarda, AOA'nin en sık nedenleri, düzelen akut odağı olmayan ateş ve idrar yolu enfeksiyonudur. Ciddi bakteriyel enfeksiyonu öngörmede beyaz küre sayısı, ESH, CRP ve prokalsitonin değerli testler olarak saptandı. Ciddi bakteriyel enfeksiyonu öngörmede interlökin-6'nın değeri ile ilgili çalışmalara ihtiyaç vardır. YALE Gözlem Ölçeğinin ciddi bakteriyel enfeksiyonu saptamada yararlılığı saptanmadı.

Anahtar Kelimeler: Akut odağı olmayan ateş, ciddi bakteriyel enfeksiyon, çocuk, YALE gözlem ölçeği

Introduction

Fever is among the most common causes of hospital visits in the pediatric age group, and it is a significant finding that makes families concerned. Fever is responsible for one thirds of the causes of emergency visits in children aged under 3 years (1,2).

A source that may lead to fever cannot be detected during physical examination in 20% of febrile infants and children, and thus this case group is defined as "fever without source" (FWS). Majority of the children diagnosed with fever without source have mild forms of viral diseases (3,4). The clinical picture of these cases is usually good and therefore, they are followed as outpatients; however, a couple of these cases may have bad clinical pictures and may need to be admitted to hospital and treated as inpatients. While bacteremia is detected in 5% and serious bacterial infections in 15% of the cases aged 1-2 months experiencing fever without source, it has been reported that there is 1% of bacteremia risk in cases aged 3-36 months whose *H. influenzae* type b and *S. pneumoniae* conjugated vaccines have been administered (3,5,6).

Clinical scores have been established to determine children with occult bacteremia and possible serious bacterial infection when the source of the fever cannot be identified. The most commonly used score to predict low risk groups for the group aged 1-3 months is the Modified Rochester Criteria, and the YALE Observation Score (YOS) for the group aged 3-36 months (3,7).

Many tests such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESH), procalcitonin (PCT) and interleukin-6 (IL-6) are the supporting indicators used today in detecting serious bacterial infections (8-14).

The aim of this study was to determine the predicting rate of YOS and laboratory indicators for serious bacterial infections in cases aged 3-36 months diagnosed with FWS.

Materials and Methods

This prospective study was conducted in cases aged 3-36 months presenting to the Pediatric Emergency Service due to fever between December 2011 and November 2012 and receiving FWF diagnosis as a result of history and physical examination.

The study group consisted of patients, aged 3-36 months, who were brought to the Pediatric Emergency Service with fever complaints and in whom fever was detected as ≥ 38.0°C with the tympanic method during clinical monitoring at the hospital.

Fever that lasted shorter than one week and could not be identified with a source following history, physical examination and laboratory results was accepted as FWS (3,4).

Exclusion criteria from the study were the following: those with a source for fever in history and/or physical examination (cough, nasal flow, sneeze, dysuria, otalgia, otitis, and etc.), those brought to hospital with fever complaint but could not be detected with fever during presentation and monitoring, those vaccinated in the last 2-72 hours, those having received antibiotics in the last seven days, those who had already received diagnosis with fever with unknown origin and who had had fever ongoing for seven days, those with immunodeficiency and chronic diseases, those receiving immunosuppressant medication, those with urinary catheter and ventriculoperitoneal shunt, those with distinctive viral disease findings (viral infections leading to specific skin rashes, flu-cold findings like nasal flow, sneeze, and cough).

Body temperatures of the cases were measured by the tympanic method, and fever was accepted as ≥ 38.0°C (3).

Detailed physical examination was performed by fully stripping all cases. Whether or not there were any signs of rash, swelling in the joints, redness, palpable sensitivity in the extremities, finding of meningeal irritation, celluloid, and abscess were investigated in terms of any source of infection.

Meningitis was defined as growth in the cerebrospinal fluid (CSF) and as >5/mm white blood cell count in CSF (3). Presence of infiltration on chest X-ray and/or fever, respiratory symptoms, and physical examination findings of parenchymal involvement were determined as pneumonia (15). A positive urine culture in a patient clinically suspected of having urinary

tract infection (UTI) was accepted as urinary tract infection (16). Detecting pathogenic bacteria in the blood culture of a child whose general condition was good to be followed as an outpatient was defined as occult bacteremia (3).

Infections threatening life or leaving sequalae in febrile children were identified as serious bacterial infections (SBI). Occult bacteremia, sepsis, meningitis, and UTI were accepted as serious bacterial infections. Sepsis was accepted as systemic inflammatory response related to infection (3).

Although two cases had growth in their urine cultures, one was accepted as sepsis due to showing sepsis presentations and the other was accepted as bacteremia due to the fact that there was growth in both urinary and blood cultures.

Upon detecting rashes and having fever ongoing for more than 5 days in a case included into the study, echocardiography was performed on the patient with a diagnosis of Kawasaki syndrome, and the case was excluded from the study due to the detection of minimal ectasia on the left coronary artery.

Two cases were excluded since the families of the cases refused to be included into the study.

The families were informed on the purpose and methods of the study, and oral consent of the parents were obtained.

Patients' age, sex, season of presentation, vaccination status, body temperature at the time of presentation (°C), other concomitant symptoms, physical examination findings (respiratory rate, respiratory findings, heart apex beat, blood pressure, hepatomegaly and splenomegaly), laboratory findings (complete blood count, absolute neutrophil count (ANC), peripheral smear, ESR, CRP, IL-6, PCT, complete urinalysis, anteroposterior chest X-ray, CSF investigation, blood, urine and CSF cultures), and definitive diagnoses were recorded. Temperature of the cases measured at home and at the time of presentation, in how many minutes the fever decreased during hospital monitoring, and how long the fever continued were also recorded.

YOS containing 6 items was used (Table 1) (17). The cases were given a value from 1-3 for each item and received the lowest 6 and the highest 18 points. Risk was accepted as increased with the increase in total points. The cases were divided into two groups as '6 points' and 'higher than 6 points' according to the median point of YALE Observation Scale.

Laboratory Investigations

Complete blood count, ANC, peripheral smear, ESR, CRP, IL-6, PCT, complete urinalysis, anteroposterior chest X-ray, CSF investigation, blood, urine and CSF cultures were examined.

Complete blood count: Complete blood count was performed on American made Beckman Coulter LH 780 with electronic cell counters. Reference range of the device for white blood cell is 4-10.5 x1000/µL and for hemoglobin, it is 12-15g/dL.

Erythrocyte sedimentation rate: Analyzed on ALİFAX. Reference range of the device is 0-20 mm/h.

Peripheral smear: Evaluated by a Pediatrician blind to the clinical and laboratory status of the patient after being stained with May-Grünwald and Giemsa and counting 100 cells. Cases whose bacilli percentage was over 5% were recorded as shift to the left (3).

Complete urinalysis: Necessary urine for complete urinalysis and urine sediment was collected by bag. Standard urinalysis was assessed using LabUMat & Urised - Complete Urine Analyzer System k (77 ELEKTRONIKA). Urine sediment was performed by centrifuging the urine put in a tube at 2000 rpm, then the fluid at the top of the tube was discarded and the fluid remaining on the bottom was examined under the microscope. Urine culture was sent accepting that the presence of more than 10 leucocytes at each microscopic field was pathogenic (3).

C-Reactive protein: Analyzed by the nephelometric method (BN™ II System Siemens, on C-reactive protein reagents). The reference range of the device is 0.0-0.4 mg/dL.

Table 1. Evaluation scale of acute disease status (YALE Observation Scale) (17)

Evaluation Criteria	1 (normal)	3 (mild-moderate deterioration)	5 (severe deteriota-ration)
Quality of cry	Strong cry, calm, happy, no cry	Whimper or sob	Weak cry, moan or high-pitched cry
Reaction to parents	Brief cry or content, calm and happy	Cries off and on	Persistent cry, harsh reactions
State variation	Awakens quickly	Difficult to awaken	No arousal or falls asleep
Color	Pink	Pale extremities or acrocyanosis	Pale, cyanotic or mottled
Hydration	Eyes, skin and mucus membranes moist	Mouth slightly dry, eyes and skin normal	Mucus membranes dry, eyes sunken
Social response	Alert or smiles	Alert or brief smile	No smile, anxious or dull

Procalcitonin: Analyzed on COBAS E 411 ANALYZER', ECL technology device. The reference range of the device is 0.0-0.05 ng/mL.

İnterleucin-6: Analyzed by the MLX Luminometer Catalog Number ML1000 DYNEX TECHNOLOGIES, Inc. device. The reference range of the device is 0.0-12.7 pg/mL. IL-6 level was analyzed in 61 cases (79.2%).

Blood culture: Analyzed by BacT/ALERT® 3D Microbial Detection System. Evaluation was made according to the hemolysis status of the bacteria that grew until 7 days. Antibiogram was studied in those with growth.

Cerebrospinal fluid and urine culture: The sample was sparsely cultured in eosin methylene blue (EMB) and blood medium. It was put in an incubator at 37°C within a wax jar. The bacteria that grew the next day was evaluated according to its hemolysis status.

Statistical Analysis

Data were analyzed on SPSS (Stastistical Package For the Social Sciences) for Windows 15.0 package program. Kolmogorov Smirnov test was used to assess if the distribution of the continuous and discontinuous quantitative variables was close to normal. Descriptive statistics were shown as mean ± standard deviation or median (minimum-maximum) for continuous and discontinuous quantitative variables, and for categorical variable, they were shown as the number of cases and percentages (%).

The significance of difference in terms of mean values between the groups was investigated by the Student's t test, and the significance of difference in terms of median values was investigated by the Mann Whitney U test. Categorical variables were evaluated by Pearson's Chi-square test or Fisher's Exact Chi-Square test.

Whether or not laboratory tests were determinant in distinguishing the normal group and high-risk group according to the YALE Observation Scale scoring system was assessed by measuring the area under the curve by ROC analysis. In the event of finding the ROC curve significant, the point where the total of sensitivity and selectivity levels was maximum was accepted as the best cut-off point. Later on, the sensitivity, selectivity, positive and negative estimated values and diagnostic accuracy rate were calculated for each laboratory indicator, and $p< 0.05$ was accepted statistically significant.

This study was conducted with the approval of Local Education Planning and Coordination Council (dated: 02.11.2011 and numbered 3647).

Results

The study included 77 cases, aged 3-36 months (median 11.0 months; range 4-36 months), who presented to the Pediatric Emergency Service with fever and diagnosed with FWS during a 1-year period. Fifty-five point eight percent of the patients (n= 43) comprised patients aged 3-11 months, 40.3% (n= 31) comprised patients aged 12-23 months, and 3.9% (n= 3) comprised patients aged 24-36 months. Sixty-four point nine percent of the cases (n= 50) were males.

All cases in the study were found to have had their age-appropriate vaccines.

In the study involving a 1-year period, the patients were determined to have presented to the emergency service most commonly in spring months with a rate of 35.1% (n= 27).

The study found out that families applied to the hospital between 1-4 days after detecting fever. Seventy-five point six percent of the cases applied to hospital within the first 24 hours after the onset of fever. Median temperature measured at the time of presentation was 39°C (38.0-40.8).

Lumbar puncture was performed in 29.9% (n= 23) of the cases with suspected meningitis. Growth was observed in the SCF culture of 10.3% of the cases (n= 3) who had lumbar puncture. *S. pneumoniae* and gram-negative bacillus grew in the cerebrospinal fluid culture of two and one cases, respectively. Despite no growth in the CSF culture, one patient was accepted as having meningitis due to the fact that CSF cell count and biochemical tests suggested meningitis.

Blood culture was obtained from all cases, and growth was detected in 5.2% (n= 4). The agents growing in the cases included *S. aureus* in 2 and *Klebsiella pneumoniae* in 2 patients. Growth was detected in the urinary cultures of 33.8% of the cases (n= 26), and in all, the agent was *E. coli*.

When the cases followed with the diagnosis of FWS were evaluated in terms of discharge diagnoses, the most frequent diagnosis was spontaneously recovering fever without source (Table 2).

Evaluation of the Cases According to Risk Criteria

The cases were evaluated by YOS. YOS median score was detected as 6 (6-14).

Table 2. Discharge diagnosis of the cases [n, (%)]

	n=77 (%)
Spontaneously recovering fever without source	27 (35.0)
Urinary tract infection	25 (32.5)
Pneumonia	10 (13.0)
Acute gastroenteritis	4 (5.2)
Meningitis	4 (5.2)
Bacteremia	4 (5.2)
Infectious mononucleosis	1 (1.3)
Measles	1 (1.3)
Sepsis	1 (1.3)

Table 3. Laboratory values of the cases according to median score of YALE Observation Scale (*)

Variables	YALE Observation Scale Score =6 (n= 49)	YALE Observation Scale Score >6 (n= 28)	Total (n= 77)	p
Hemoglobin (gr/dl) (mean ± SD)	11.0 ± 1.1	11.0 ± 0.9	11.0 ± 1.0	0.975[a]
White blood cell count ($10^3/mm^3$) [median(min-max)]	14.4 (5.6-32.5)	14.3 (3.7-34.8)	14.4 (3.7-34.8)	0.436[b]
Absolute neutrophil count ($10^3/mm^3$) [median (range)]	8.5 (1.3-22.5)	8.4 (1.4-29.3)	8.4 (1.3-29.3)	0.443[b]
Number of cases with high bacilli [n (%)]	24 (49.0)	14 (50.0)	38 (49.4)	1.000[c]
Platelet count (*$10^3/mm^3$) [median (range)]	335 (121-659)	368 (168-658)	344 (121-659)	0.120[b]
Erythrocyte sedimentation rate (mm/h) [median(range)].	20.0 (2.0-111.0)	19.5 (2.0-81.0)	20.0 (2.0-111.0)	0.945[b]
C-reactive protein (mg/dl) [median(range)].	3.1 (0.3-16.0)	1.9 (0.3-27.0)	2.3 (0.3-27.0)	0.391[b]
Procalcitonin (ng/mL) [median(range)].	0.4 (0.1-30.2)	1.8 (0.1-25.0)	0.6 (0.1-30.2)	0.227[b]
Interleucin-6 (n= 74) (pg/mL) [median(range)]	23.3 (0.4-235.0)	45.1 (5.0-235.3)	32.0 (0.4-235.0)	**0.020[b]**
Pathology on Chest X-ray (+)[n (%)]	6 (12.2)	4 (14.3)	10 (13.0)	1.000[d]
Pathology in Urinalysis (+) [n (%)]	22 (44.9)	11 (39.3)	33 (42.9)	0.811[d]

a: Student's t test, b: Mann Whitney U test, c: Pearson's Chi-Square test; d: Fisher's Exact test Chi Square test.
*: Column percentage.

When the cases were divided into two groups according to the median score of YALE Observation Scale as 6 points and >6 points, a statistical difference was not established in terms of mean age and season of presentation, but female cases were found to rank more in the >6 points group compared to male patients (0.697; 0.271; 0.038, respectively).

The number of febrile days of the cases in the >6 points group of YOS was determined higher than the other group (p= 0.034). A statistical relation was not established between the YOS median scores and the temperature of the case measured at home and at the time of presentation, in how many minutes the fever decreased in the hospital and the length of hospital stay (p= 0.052; 0.292; 0.426; 0.111, respectively).

Although procalcitonin values in cases in the >6 points group of YOS were found higher than the other group, there was no statistically significant difference (p= 0.227). In cases in the >6 points group of YOS, IL-6 value was found higher (p= 0.029) (Table 3).

When the cases were divided into two groups according to the median score of YALE Observation Scale as 6 points and >6 points, a statistical difference was not established between those with growth in the blood and urine cultures (p= 0.134; 0.437, respectively).

ROC analysis was used to distinguish 'normal-high' risk groups for cases whose median score of YOS was 6 and >6. Only the area of IL-6 under the curve was found statistically significant among the values of white blood cell count, ANC, ESR, CRP, PCT and IL-6 (AUC= 0.668; %95 confidence interval: 0.527-0.809 and p= 0.029) (Figure 1).

The best cut-off point for IL-6 in distinguishing cases in the normal and high-risk groups according to YOS was detected as 38.25 mg/dl. Sensitivity, specifity, positive estimated value and negative estimated value of IL-6 at this point were found respectively as 65.2%, 65.8%, 53.6%, and 75.8%.

YOS was calculated as >6 points in 3 (75%) of the 4 cases with meningitis, in 1 sepsis case (100%), in 3 (75%) of the 4 cases with bacteremia, and in 7 (28%) of the 25 cases with UTI (p= 0.070).

Evaluation of the Cases With Serious Bacterial Infection

Serious bacterial infection was detected in 44.2% (n= 34) of the cases.

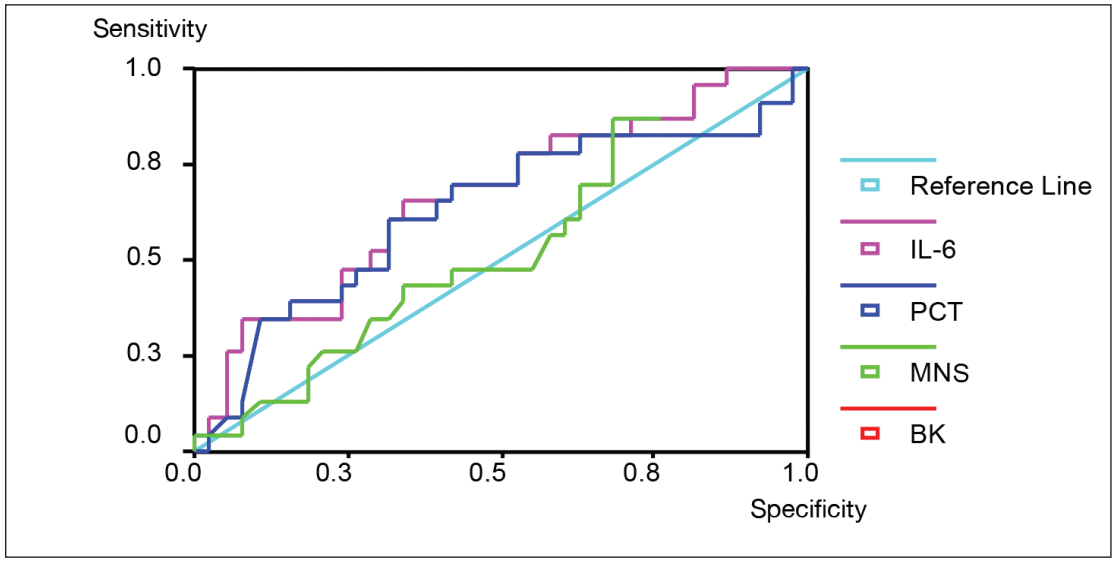

Figure 1. A. ROC Curve regarding WBC, ANC, IL-6 and PCT in distinguishing YALE Observation Scale Score of 6 and > 6

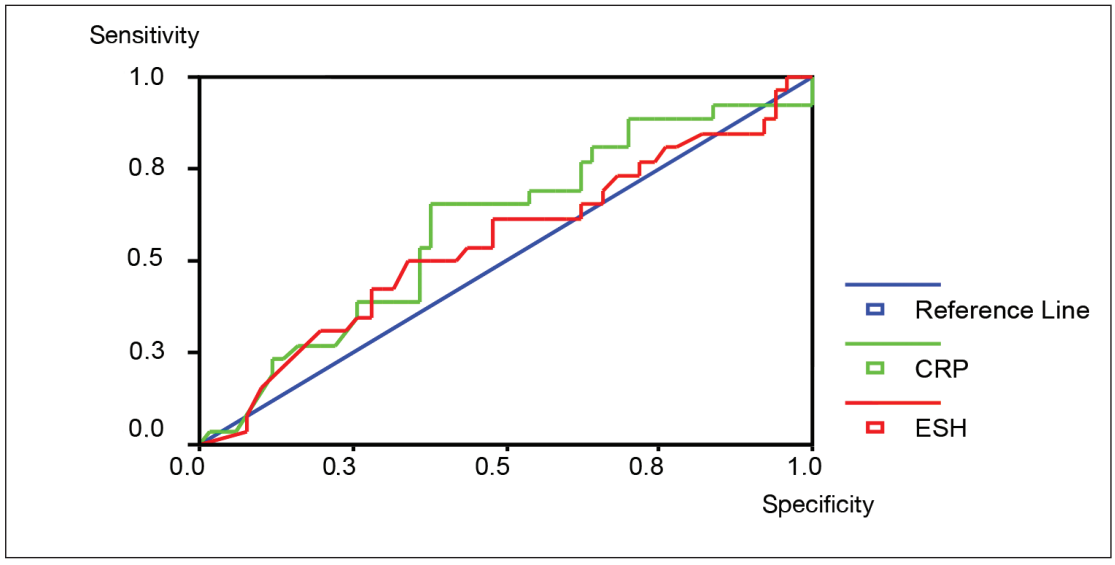

Figure 1. B. ROC Curve regarding WBC, ANC, IL-6 AND PCT in distinguishing YALE Observation Scale Score of 6 and > 6

While a statistical difference was not observed between having serious bacterial infection (SBI) and age average and sex, SBI was least detected in summer months (n= 2, 5.9%) (p= 0.531; 0.970; 0.02, respectively).

Temperature measured at the time of presentation was found higher in cases with SBI (p= 0.033). A statistical relation was not detected between SBI and the temperature of the case measured at home, in how many minutes the fever decreased in the hospital, the number of febrile days in hospital, and the length of hospital stay (p= 0.553; 0.457; 0.923; 0.271, respectively).

A statistically significant difference was not detected between having a serious bacterial infection and hemoglobin, white blood cell count, absolute neutrophil count, the number of cases with high bacillus count, platelet count, ESR, CRP, procalcitonin, and IL-6 (p= 0.411; 0.232; 0.712; 0.516; 0.375; 0.232; 0.348; 0.151; 0.262, respectively).

YOS was detected as >6 points in 14 (41.2%) of the 34 cases with serious bacterial infection, and no statistically significant relation was established between SBI and having YOS 6 and >6 points (p= 0.435).

Discussion

Fever in childhood causes suspense in both the families and the physicians since it is one of the most frequent complaints of hospital presentations. Children under the age of 3 years constitute the majority of the cases brought to the hospital due to fever, and approximately 20% of these cases have no definitive source of infection with history and physical ex-

amination (1,3,18). The most crucial issue in evaluating cases diagnosed with fever without source is detecting cases with serious disease risk and thus preventing the implementation of unnecessary tests and treatments to other cases (3,19,20). Therefore, guidelines regarding the evaluation of febrile infants and children have been published to help physicians decide (3,7,19).

It has been reported that bacteremia detected in cases diagnosed with FWS is usually seen in infants aged under 2 years. Both occult bacteremia and risk of serious bacterial infection are higher in febrile infants aged younger than 3 months (1-4).

This study evaluated 77 cases, aged 3-36 months, who presented to the Pediatric Emergency Service with fever and was diagnosed and admitted to hospital with fever without source.

The study found out that families applied to the hospital between 1-4 days after detecting fever. Seventy-five point six percent of the cases applied to hospital within the first 24 hours after the onset of fever. In a study conducted on children aged 2-24 months in Ankara in the year 1995, it was reported that only 17.4% of the families brought their children to a healthcare institution within the first day after the onset of fever (21). In a study conducted in Elazığ in 2005, it was reported that 70.6% of the children were brought to a healthcare institution within the first day after the onset of fever (22). These studies established that febrile cases had been brought to hospital earlier by their families within the years. It is thought that this is a result of the fact that families can now reach healthcare services more easily and are now more conscious about health.

When the discharge diagnoses of the cases were evaluated, the most frequently made diagnosis was spontaneously recovering fever without source (35%). Parallel to our study, vast majority of the cases followed for fever without source comprises spontaneously recovering, possibly viral infections (3). In a study by Machado and colleagues (23), the authors have reported that this diagnosis group constitutes a vast majority of the cases (48.9%). This rate has been found as 60% in a study by Lacour and colleagues (24). In our study, this rate was found lower, which was attributed to the fact that suspected viral cases were excluded from the study and the number of cases was lower.

Urinary tract infection is the most frequently encountered bacterial infection in cases with FWS diagnosis. UTI prevalence in cases aged under 2 years has been reported as 2-5% (25). UTI prevalence has been put forth as 7.4% in the study by Machado and colleagues (23). In a study conducted on febrile cases aged 1-24 months in Istanbul, growth has been established in 39% of the cases (26). UTI was detected in 32.5% of the cases diagnosed with FWS in our study. Lower respiratory tract infection was detected as 13% in the cases diagnosed with FWS in our study. Similar to our study, Isaacman and colleagues (27) have reported pneumonia in 17% of the 256 cases followed with the diagnoses of FWS. In the study by Luszczak (28), 26% of the cases who presented with fever and admitted to hospital hreceived bronchopneumonia diagnosis. This rate has been reported as 1.9% and the prevalence of suspected viral infections as 40.9% in the study by Machado and colleagues (23) conducted on 215 cases. The authors have, therefore stated that pneumonia prevalence was low. In our study, the exclusion of suspected viral cases resulted in a higher detection of pneumonia rate.

Bacterial meningitis in our study was found as 3.8%. Machado and colleagues (23) have not reported any case of meningitis. In a study conducted in Istanbul, bacterial meningitis has been diagnosed in 5.4% of the cases admitted to hospital due to fever (26).

Evaluation of the Cases According to Toxicity Criteria

Bacteremia and serious bacterial infection are detected in 5% and 15% of the cases with fever without source, respectively (4). If the source cannot be detected in the event of acute fever, clinical scorings have been developed as regards age groups in order to determine occult bacteremia and possible serious bacterial infection (2,4,6).

In our study, cases, aged 3-36 months, diagnosed with FWS were evaluated and YALE Observation Scale was implemented on all cases. Median value of YALE Observation Scale was detected as 6, and YOS was found >6 in 36.4% of the cases. The number of male patients with high YOS scores was found higher.

It has been reported that YALE Observation Score has a sensitivity of 92% for the diagnosis of serious disease when combined with history and physical examination (20,27,29). It has been established that serious disease is present only in 2.7% and 92.3% of the patients with a YALE Observation Score of '10' and '16', respectively (17). In another study, serious disease has been confirmed in 88 cases out of 186 with a YOS score of ≥ 10, and a statistically significant relation has been established between the severity of the disease and YOS (30). An evaluation as such could not be performed in this study since the number of patients with a YOS score of ≥ 10 was low. In our study, a significant relation was not found between YOS score and serious bacterial infection.

When ROC analysis was used to distinguish 'normal-high' risk groups according to YOS, only the area under the curve for IL-6 was found statistically significant among the laboratory parameters. The best cut-off point for IL-6 in distinguishing cases, aged 3-36 months, in the normal and high-risk groups according to YOS was detected as 38.25 mg/dl. Sensitivity,

specifity, positive estimated value and negative estimated value of IL-6 at this point were found respectively as 65.2%, 65.8%, 53.6%, and 75.8%. No study was found in the literature regarding the relation between IL-6 and YOS in children diagnosed with acute fever without source. Further studies are needed in this respect with more number of cases.

Evaluation of Cases With Serious Bacterial Infection

Serious bacterial infection was detected in 37.3% of the cases diagnosed with FWS. Gervaix and colleagues (31) have reported in their study that FWS is diagnosed in 20.2% of the cases aged 0-36 months presenting with fever, and they have classified 17.3% of these cases as serious bacterial infection. Lacour and colleagues (24) have reported serious bacterial infection in 23% of 124 cases aged 0-36 months and diagnosed with FWS. Machado and colleagues (23) have confirmed this rate in their study as 9.3%. Isaacman and colleagues (32) have detected serious bacterial infection in 11% of 256 cases aged 3-36 months presenting with fever. In our study, serious bacterial infection was confirmed in 37.3% of the cases. The high rate of serious bacterial infection in our study is attributed to the fact that the region our hospital is located in has a low socioeconomic and literacy rate, the number of cases included was low, and the study was conducted in a tertiary hospital.

Several laboratory methods were used to detect serious bacterial infection. White blood cell, neutrophil, and bacilli count are commonly used in detecting serious bacterial infection (3). However, it is known that white blood cell indicators are less valuable in detecting serious infection and insufficient to exclude serious infection (9). CRP and procalcitonin that have been started to be used in the last decade are accepted as better indicators (33).

In a study by Maniaci and colleagues (13) conducted on 234 cases aged 1-3 months, it has been reported that PCT is a useful test in detecting serious bacterial infection. In another study, it has been confirmed that CRP and procalcitonin are helpful in detecting serious bacterial infection (14). According to a meta-analysis, the sensitivity and specifity of PCT levels have been found higher compared to CRP (88% vs 75% and 81% vs 67%, respectively) in detecting bacterial infection in children admitted to hospital and in differentiating non-infectious inflammation (12). While the sensitivity of PCT levels have been found higher compared to CRP in the differential diagnosis of bacterial and viral infection in the same study (92% vs 86%, respectively), no distinctive difference has been reported between their specificities (73% vs 70%, respectively). The authors have indicated that PCT is a relatively new test requiring more studies for its reliability.

In our study, laboratory indicators were not useful in estimating serious bacterial infection. However, this was considered to be the result of the fewness of the cases included into the study.

The limitations of the study include not having gathered information on the sociocultural level of the cases and evaluating the cases in terms of malnutrition.

To conclude, the most common causes of FWS in children aged 3-36 months are spontaneously recovering fever without source and urinary tract infection. Laboratory tests were not found useful in predicting serious bacterial infection. Usefulness of YALE Observation Scale in detecting serious bacterial infection was not confirmed. There are further studies needed regarding the scales to be used in predicting serious bacterial infections.

Ethics Committe Approval: The ethical approval for this study was obtained from T.C. Sağlık Bakanlığı Ankara Training and Research Hospital EPPK (Decision no: 0439-3647 Date: 02.11.2011).

Informed Consent: Patient consent was obtained.

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