

Screening Tools for Bacteraemia in a Selected Population of Febrile Children

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Abstract

Introduction: This is a prospective, observational study. The aims of the study were to determine the rate of bacteraemia in febrile children in Turkey, and to evaluate the usefulness of white blood cell (WBC) count and manual differential counts of peripheral blood smears and a RISK score in predicting bacteraemia among these children. **Materials and Methods:** A total of 377 febrile children aged 3 to 36 months were included in the study. Complete blood cell (CBC) count, manual differential counts and blood cultures were performed in all patients. The main outcome measures used to evaluate the usefulness of the RISK score were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), posterior probability, areas under receiver operator characteristic curves (AUC) and miss-to-diagnosis ratio (MDR). **Results:** Among the patients, 4.4% had bacteraemia and the predominant pathogen was *Streptococcus pneumoniae*. The Yale Observation Scale scores, percentages of neutrophil and bands, band-neutrophil ratio, absolute neutrophil count and absolute band count were found to be statistically significant predictors of bacteraemia. When the RISK score was 2 or higher, sensitivity was 93.8%, false positive ratio 35.8%, PPV 10.6%, NPV 99.5%, OR 26.2 (95% CI, 3.4 to 200.8), MDR 0.066 and posterior probability value 10%. **Conclusions:** We conclude that determination of the RISK score will significantly decrease unnecessary blood culture sampling, antibiotherapy and hospitalisation among febrile patients aged 3 to 36 months without an identifiable focus of infection.

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Key words: Bacteraemia, Child, Fever, Paediatric emergency medicine, Screening

Introduction

Bacteraemia refers to the presence of bacteria in the bloodstream. The presence or absence of toxicity differentiates occult bacteraemia, which is relatively asymptomatic, from bacteraemia and sepsis, which is accompanied by findings of serious systemic illness.¹ Occult bacteraemia due to pathogenic microorganisms, without clinical evidence of an identifiable focus of infection, was first highlighted as a clinical entity in 30 of 111 children with pneumococcal bacteraemia in a study published in the early 1970s.² Since then, there have been numerous studies on the diagnosis and management of febrile children; however, the identification of any reliable predictors of bacteraemia or occult bacteraemia and its management remain controversial. In fact, most febrile children have self-limiting viral infections; however, well-appearing febrile children 3 to 36 months of age without an identifiable focus of infection are at risk for occult bacteraemia, the rates of which range between 1.6% and 10.4% in this

population.³⁻⁵ In addition, bacteraemia itself is often a self-limiting process in otherwise healthy children; however, 10% of children with bacteraemia will develop more severe illnesses such as sepsis, meningitis, pneumonia, osteomyelitis and septic arthritis unless treated. Furthermore, certain laboratory tests, and treatment with antibiotics and/or hospitalisation based on the guidelines of the management of febrile infants and children create significant inconvenience. Among these inconveniences are the discomfort and costs of blood tests,⁶ unnecessary intravenous/oral therapy and hospitalisation, complications of antibiotic therapy, increased medical intervention time,⁶ increased workload of the physician and the laboratory, possible emotional distress to parents and children.⁶ Furthermore, the physician's attitude may engender the problem of fever phobia⁷ and encourage the all-too-common practice of "treating fever" with antibiotics, which may in turn abet the abuse of antibiotics. Eventually, the emergency physician must choose one of these two approaches in

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following a febrile child with the potential for occult bacterial infection: 1) risk-minimiser approach, or 2) test-minimiser approach. However, neither approach has been shown to be better than the other.^{8,9} Hence, several studies have been conducted to determine the diagnostic power of certain laboratory tests, such as white blood cell (WBC) count, C-reactive protein, procalcitonin; and acute illness observation scores, such as Yale Observation Scale (YOS), as potential predictors of bacteraemia. Inferentially, it is suggested that the YOS, alone as a marker, is not clinically useful for identifying bacteraemia.^{6,10} The WBC count and its differentials have been evaluated as predictive features in almost all the studies of fever in children 3 to 36 months of age. The WBC count is usually elevated in children with bacteraemia. Jaffe and Fleisher found that the sensitivity of the WBC count among young children with a temperature higher than 39°C to be 65% at 15,000/mm³ or more, and 38% at 20,000/mm³ or more.^{1,11} In a study by Sur and Bukont¹² among 256 children between 3 and 36 months of age, an absolute neutrophil count (ANC) of 10,000/mm³ or more cells was as predictive of serious bacterial infection (SBI) as a WBC count of more than 15,000/mm³ with a sensitivity of 69%. It is noted that using WBC count as the sole determinant of bacteraemia and SBI is inappropriate.¹² A shift to the left in the differential count and signs of toxicity on the peripheral blood smear are seen more often in bacteraemic children than in those with viral infections. However, neither of them can be accepted as reliable in distinguishing the 2 groups.¹

To date, there have been no studies carried out in Turkey on the incidence and prevalence of bacteraemia and occult bacteraemia in young previously healthy febrile children without a focus of infection. The aims of this prospective study were: 1) to provide data on the rate of bacteraemia in children 3 to 36 months of age with rectal temperature of $\geq 39^\circ\text{C}$ living in urban areas of Turkey; and 2) to determine the diagnostic power of WBC counts and manual differential counts of peripheral blood smears, which are easy, quick, less invasive, low-cost and can be performed in any hospital setting to detect bacteraemia in febrile children.

Materials and Methods

This is a prospective, observational study conducted in the Paediatric Emergency Medicine (PEM) Department of the Medical School of Cukurova University, Adana, Turkey. The hospital is a tertiary health institution that provides care for more than 12,000 child patients annually and is the primary referral centre in the south and southeast of Turkey.

The study included patients presenting from February 2001 to April 2002 to the PEM unit of our hospital. Eligible patients were 3 to 36 months of age, and had a rectal temperature of $\geq 39^\circ\text{C}$ in the PEM unit and a WBC count of

$\leq 5000/\text{mm}^3$ or $\geq 15000/\text{mm}^3$. Exclusion criteria were a clearly identifiable infection apparent on physical examination (e.g., pneumonia, urinary tract infection, meningitis, osteomyelitis, septic arthritis), immunisation within the preceding 48 hours, treatment with antibiotics within the preceding 7 days, current immunosuppressive medication, history of an immunodeficiency condition or a chronic illness that would alter the standard approach to febrile illness (e.g., haemoglobinopathy, oncologic disease, agranulocytosis, aplastic anaemia, congenital heart disease, arteritis, nephrotic syndrome, and cystic fibrosis), catheterisation (e.g., central venous catheter, and urethral catheter) and legal guardian unable to give written informed consent.

Patients with evidence of viral syndromes presenting with high fever (e.g., roseola, fifth disease and croup) were also excluded because of ethical considerations. However, patients with less apparent signs of viral illnesses (e.g., wheeze infants, and gastroenteritis) were included. Otitis media was not considered as an exclusion criterion because previous publications had documented a similar rate of bacteraemia regardless of otitis media.¹³

Informed consent was obtained from the legal guardian of each participating child, and the study was approved by the regional committee of medical research ethics.

Clinical and Laboratory Assessment and Follow-up

An attending paediatrician and/or paediatric resident examined each patient and assigned a clinical score according to the YOS.¹⁴ Body temperatures were taken by a nurse rectally, 2 to 3 cm past the anal verge where the temperature remained unchanged (2 to 4 minutes).

Routine Hib immunisation is not included in the national vaccination schedule of Turkey and is performed at will. Therefore, the patients included in the study were asked questions relating to Hib immunisation.

Complete blood cell (CBC) counts, manual differential counts, and blood cultures were performed in all patients. Total WBC was determined by an electronic cell counter (Beckman-coulter Gen-S, USA), and 100 cells of the Wright-stained peripheral blood smears were evaluated by a trained attending physician and/or paediatric resident, who was blinded to the patients' clinical and laboratory data. One to 3 mL of venous blood was drawn aseptically into vials for aerobic cultures (BACTEC™ culture vials type PEDS PLUS™/F). The vials were placed in the BACTEC 9240 fluorescent series instrument (Becton Dickinson Microbiology Systems, Sparks, USA) and incubated at 35°C for 7 days. Positive blood cultures were subcultured on 5% sheep blood agar, Mac Concey agar and chocolate agar. For isolation of *Haemophilus* species, chocolate agar and *Haemophilus* isolation agar were

incubated at 35°C to 37°C for 48 to 72 hours in an aerobic atmosphere containing 5% to 10% CO₂. In addition, when the growth of bacteria in the blood culture was evident, a gram-stained smear was performed by an attending microbiologist. Immediately afterwards, the attending paediatrician was informed about the result of the smear.

In this study, antibiotics were initiated when a patient fulfilled all 3 criteria described below: 1) WBC count lower than 5000/mm³ or higher than 15,000/mm³, 2) YOS >6, and 3) No presumed viral infection.

Ill-appearing (YOS score >10) patients were kept under supervision in the paediatric emergency observation room for 24 hours. At the end of 24 hours, children with temperatures above 39°C and no signs of improvement were admitted for investigation and further management. Patients with signs of improvement were followed up by a telephone call. Well-appearing (YOS score ≤10) patients at the initial evaluation were also followed up by a telephone call. All the patients assigned to the telephone follow-up programme were telephoned once a day for the first 3 days and on the 7th, 14th and 21st days and a standardised questionnaire was filled by the attending paediatricians. They were recalled and re-examined in the hospital when necessary. The families of children with bacteraemia were contacted as soon as possible after the results of blood cultures were known. Those with positive blood culture results were invited to the hospital for re-examination and therapy.

Definitions of Terms

Bacteraemia was defined as the presence of pathogenic bacteria in the blood of a patient. Occult bacteraemia was defined as the presence of pathogenic bacteria in the blood of a well-appearing febrile child in the absence of an identifiable focus of infection. Contamination was ruled out when more than 2 organisms were present in the same culture (3 cases).

At follow-up examinations, focal infections and sepsis were defined on the basis of physical examination, leukocyte counts, antigen detection, cultures of blood or other body fluids, and ancillary studies. These definitions were made at the beginning of the study and staff were informed through written and oral means.

ANC was calculated by multiplying the total WBC by the sum of the percentage of mature neutrophils and percentage of band forms seen on the peripheral blood smear. Absolute band count (ABC) was computed by multiplying the total WBC count by the percentage of band forms. Band-neutrophil ratio (BNR) was calculated by dividing the percentage band count by the percentage of total neutrophil count.

Statistical Analysis

Receiver operating characteristic (ROC) curves and the areas under the ROC curves (AUC) were computed to measure the predictive power of the diagnostic tests. We also calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio (OR), posterior probability, and miss-to-diagnosis ratio (MDR) at various thresholds of these tests. MDR was defined as the ratio of false-negative results to true-positive results among patients with bacteraemia. It is represented by the following equation: “(1/Sensitivity) – 1”. MDR is valuable only when used to compare the relative number of cases missed by 2 or more tests in the same patients and at test thresholds previously established to be optimal for a particular disease.¹⁵ Posterior probability was calculated as follows: First, the rate of bacteraemia (ROB) in the study population was calculated. Second, the likelihood ratio (LR) for each given parameter was calculated. Third, the pretest odds (preodds) were calculated using the “ROB/(1-ROB)” formula. Fourth, post-test odds (postodds) were calculated using the “preodds x LR” formula. Finally, posterior probability was calculated using the “postodds/(1 + postodds)” formula.¹⁶

The risk score (RISK) was based on the significant relationships of YOS, percentage of neutrophils in the peripheral blood smear [neut (%)], percentage of bands in the peripheral blood smear [band (%)], ANC, ABC, and BNR in the peripheral blood smear evident by the ROC curves. The RISK score of a patient was defined as the number of clinical and laboratory findings that exceeded the optimal cut-off values given in Table 1.

$P < 0.05$ was considered statistically significant. Statistical analyses were performed with the SPSS (SPSS Inc, Chicago, IL) software.

Results

Of 377 eligible patients, 12 were excluded from the current analysis (Fig. 1). These included 5 patients whose blood culture specimens were lost, 3 patients whose data on the manual differential count were not recorded, 2 patients whose caregivers wanted to quit the study although they had given written informed consent, 1 patient who was inadvertently enrolled despite being younger than 3 months, and 1 patient who was given a diphtheria-tetanus-pertussis (DPT) vaccine 1 day prior to the study. The clinical and laboratory data from the remaining 365 patients were subjected to analysis. Out of 365 patients, 16 (4.4%) had bacteraemia, 32 (8.8%) had growth of contaminant bacteria and 314 (86%) had sterile blood cultures.

Data about demographic and clinical features of 365 patients with and without bacteraemia are shown in Table

Table 1. The Results of the Posterior Probability Tests, Sensitivity, False Positivity, Positive Predictive Value, Negative Predictive Value and Odds Ratio for the RISK Parameters, which are Equal to or Higher than the Stipulated Cut-off Value in Identifying Bacteraemia

	No. of patients	Sensitivity	False positivity	PPV	NPV	Odds ratio (95% CI)	Posterior probability
YOS ≥ 11	116	75%	29.8%	10.3%	98.4%	7.1 (2.2-22.4)	10.0%
Neutr (%) $\geq 67\%$	121	75%	31.2%	9.9%	98.4%	6.6 (2.1-22.4)	9.9%
Band (%) $\geq 3\%$	71	68.8%	17.2%	15.5%	98.3%	10.6 (3.5-31.6)	15.6%
ANC $\geq 11484/\text{mm}^3$	113	75%	28.9%	10.6%	98.4%	7.4 (2.3-23.4)	10.7%
ABC $\geq 194/\text{mm}^3$	71	75%	16.9%	16.9%	98.6%	14.7 (4.6-47.3)	16.6%
BNR ≥ 0.0293	87	75%	18.1%	16%	98.6%	13.6 (4.2-43.6)	14.1%

95% CI: 95% confidence interval; ABC: absolute band count; ANC: absolute neutrophil count; Band (%): the percentage of band forms in the peripheral blood smear; BNR: The band-neutrophil ratio; Neutr (%): the percentage of neutrophils in the peripheral blood smear; NPV: negative predictive value; PPV: positive predictive value; YOS: Yale Observation Scale score

2. Bacteria that were considered pathogenic included *Streptococcus pneumoniae* (11 cases), *Klebsiella pneumoniae* (2 cases), *Streptococcus agalactiae B* (group B streptococcus) (1 case), *Staphylococcus aureus* (1 case) and *Stenotrophomonas maltophilia* (1 cases). The following species were considered as contaminants: *Staphylococcus epidermitis* (13 cases), *Staphylococcus warnerii* (9 cases), *Staphylococcus hominis* (4 cases), *Pseudomonas vesicularis*

(2 cases), *Staphylococcus sciuri* (1 case), *Staphylococcus capitis* (1 case), *Staphylococcus xylosus* (1 case) and *Streptococcus anginosus* (1 case). Of all the patients with bacteraemia, 5.2% had fever without an identifiable focus of infection, 2% had presumptive viral infections and 2.1% with acute otitis media (AOM) had bacteraemia (Fig. 1).

In this study, since Hib immunisation was either completed or at least its first dosage was given to only 248 patients

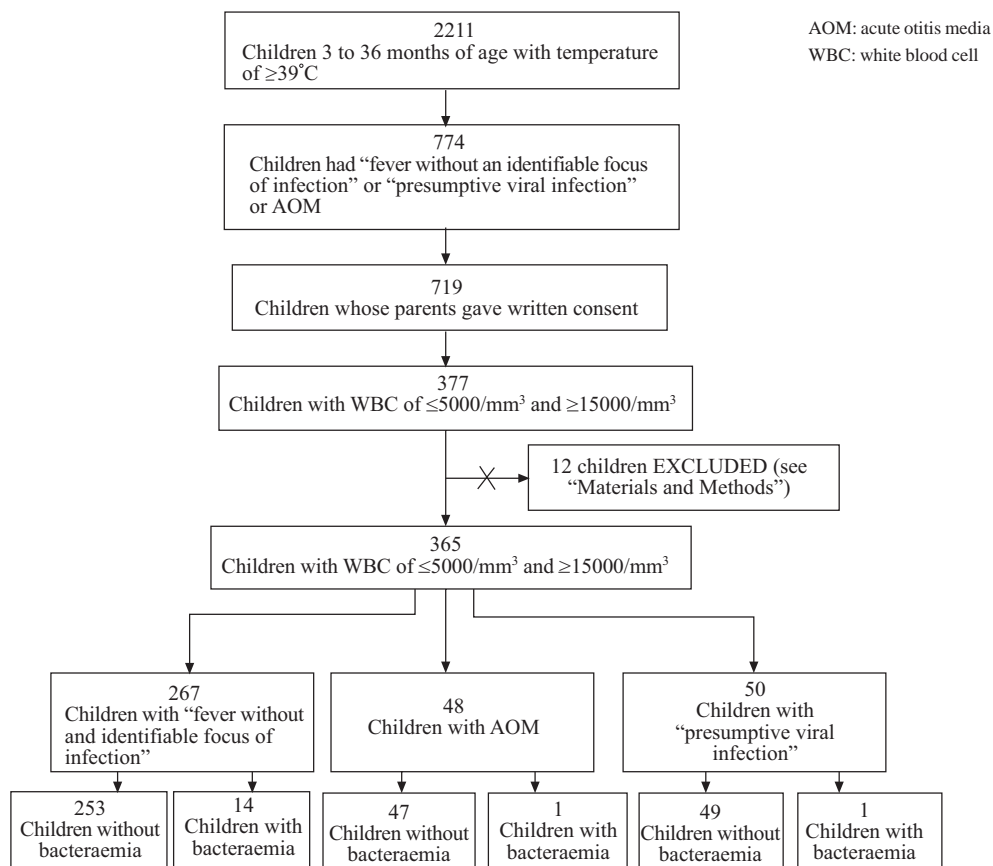


Fig. 1. The selection and diagnosis flow chart of the cases.

Table 2. Demographics and Clinical Features of the Patients with and without Bacteraemia

Characteristic	No bacteraemia (349 children)	Bacteraemia (16 children)	Total (365 children)
Sex	183 (52.4%) male 166 (47.6%) female	7 (43.8%) male 9 (56.3%) female	190 (52%) male 175 (48%) female
Age (months)			
Mean ± standard deviation	15.07 ± 9.8	13.9 ± 7.7	15.01 ± 9.6
Median	12	12	12.0
Diagnosis			
Fever without an identifiable focus	253 (72.5%)	14 (87.5%)	267 (73.2%)
Non-specific viral illness	49 (14%)	1 (6.3%)	50 (13.7%)
AOM	47 (13.5%)	1 (6.3%)	48 (13.2%)
YOS			
Mean ± standard deviation	9.44 ± 2.8	13.7 ± 4.4	9.6 ± 3.0
Temperature (°C)			
Mean ± standard deviation	39.2 ± 0.3	39.2 ± 0.3	39.2 ± 0.3
WBC (cells x 10 ⁶ /L)			
Mean ± standard deviation	15802.9 ± 6522.4	15468.7 ± 6231.8	15788.3 ± 6502.1
Percentage of neutrophils in the peripheral blood smear (%)			
Mean ± standard deviation	57.7 ± 14.8	69.4 ± 10.6	58.2 ± 14.8
Percentage of lymphocytes in the peripheral blood smear (%)			
Mean ± standard deviation	39.0 ± 14.9	24.6 ± 10.5	38.4 ± 15.0
Percentage of neutrophils in the peripheral blood smear (%)			
Mean ± standard deviation	1.0 ± 2.4	5.1 ± 4.5	1.2 ± 2.6
Median	0.0	4.0	0.0
The absolute neutrophil count (cells x 10 ⁶ /L)			
Mean ± standard deviation	9473.3 ± 5085.2	11464.9 ± 4814.1	9560.6 ± 5083.7
Median	99884.0	12800.0	10020.0
The absolute band count (cells x 10 ⁶ /L)			
Mean ± standard deviation	170.2 ± 457.8	681.4 ± 687.6	192.6 ± 480.4
Median	0.0	619.0	0.0
Band-neutrophil ratio (BNR) in the peripheral blood smear			
Mean ± standard deviation	0.016 ± 0.037	0.075 ± 0.072	0.018 ± 0.041
Median	0.0	0.058	0.0

WBC:white blood count; YOS: Yale Observation Scale score

Table 3. AUC Values for the RISK Parameters in Identifying Bacteraemia

	AUC (95% CI)	P value
YOS	0.799 (0.671-0.927)	<0.001
Percentage of neutrophil in the peripheral blood smear	0.738 (0.634-0.842)	0.001
Percentage of band form in the peripheral blood smear	0.799 (0.670-0.928)	<0.001
The absolute neutrophil count	0.683 (0.533-0.832)	0.013
The absolute band count	0.785 (0.659-0.911)	<0.001
Band-neutrophil ratio in the peripheral blood smear	0.785 (0.658-0.911)	<0.001

95% CI: 95% confidence interval; AUC: area under curve; YOS: Yale Observation Scale score

(67.9%), the population of this study should not be considered either in the pre-Hib vaccine era or in the post-Hib vaccine era.

ROC curves for age, temperature, WBC count, and the percentage of lymphocytes in the peripheral blood smear

were not statistically significant enough to determine bacteraemia ($P > 0.05$). However, AUC values of YOS, percentage of neutrophils percentage of band forms, BNR in the peripheral blood smears, ANC and ABC as predictors of bacteraemia were statistically significant (Table 3).

Table 4. Antibiotic Therapy and Its Outcomes

	Full recovery	Bacteraemia (+)	“An identifiable focus of infection” or sepsis	Both bacteraemia (+) and “an identifiable focus infection” or sepsis
Oral antibiotics (Sultamicillin or Amoxicillin-Clavulanate)	163	4	10	1
Intramuscular antibiotics (Ceftriaxone)	84	9	2	1
No antibiotics	88	1	2	-

Table 5. The Relationship Between RISK Score and Bacteraemia

	RISK score of ≥2	RISK score of <2
Bacteraemia (-)	127	222
Bacteraemia (+)	15	1
Total	142	223

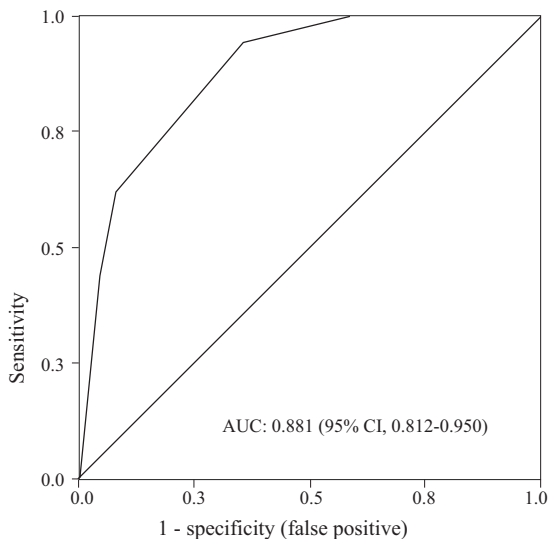


Fig. 2. Receiver operating curve (ROC) and area under curve (AUC) values for the RISK score in identifying bacteraemia.

Posterior probability, sensitivity, false positivity, PPV and NPV calculated according to the cut-off values are shown in Table 1. ROC curves, AUC and 95% CI values of the RISK score based on the cut-off values are shown in Figure 2. When the RISK score was 2 or above, sensitivity was 93.8%, false positive ratio 35.8%, positive predictive value 10.6%, NPV 99.5%, OR 26.2 (95% CI, 3.4 to 200.8), MDR 0.066 and posterior probability value 10%.

Detection of toxic granulation in the peripheral blood smear was not significant enough to determine bacteraemia ($P > 0.05$, Chi-square test).

Considering the aforementioned criteria and clinical manifestations (as indicated in the Materials and Methods section), patients were given oral or intramuscular

Table 6. The Number of Children With SBI and Their RISK Scores

RISK score	No. of patients	Final diagnosis
0	145	UTI (1 case) Acute pharyngotonsillitis (1 case)
1	78	UTI (1 case) Acute pharyngotonsillitis (1 case) Bacteraemia (1 case)
≥2	142	Bacteraemia (13 cases) UTI (1 case) Acute otitis media (1 case) Meningitis (2 cases) Meningitis + Bacteraemia (1 case) Pneumonia (4 cases) Pneumonia + Bacteraemia (1 case) Septic arthritis (1 case) Sepsis (1 case)

SBI: serious bacterial infection; UTI: urinary tract infection

prophylactic antimicrobial treatment. Antimicrobial therapies and clinical outcomes are shown in Table 4.

If the RISK score had been employed, blood cultures and/or prophylactic antibiotic regimen would have been avoided in 223 patients since in this group the risk score was less than 2 (Table 5). The relation between the RISK score and the number of children with fever diagnosed as SBI during follow-up are shown in Table 6. The AUC value of ROC curves was used to determine the power of this relation and was found to be 0.790 (95% CI, 0.710 to 0.869, $P < 0.001$). Making the diagnosis of SBI, we found that when the RISK score was 2 or more, the sensitivity was 83.3%, false positive ratio 34.9%, PPV 17.6%, NPV 97.8%, OR 9.3 (95% CI, 3.5 to 24.9), MDR 0.2 and posterior probability value 9.9%.

After an initial evaluation, 56 patients were hospitalised in the paediatric emergency observation room and the remaining 309 patients were assigned to a telephone follow-up at home (Fig. 3). All the patients included in the study (including the patients with SBI) recovered well.

Discussion

This was the first study in Turkey to document the rate of bacteraemia and occult bacteraemia among a selected

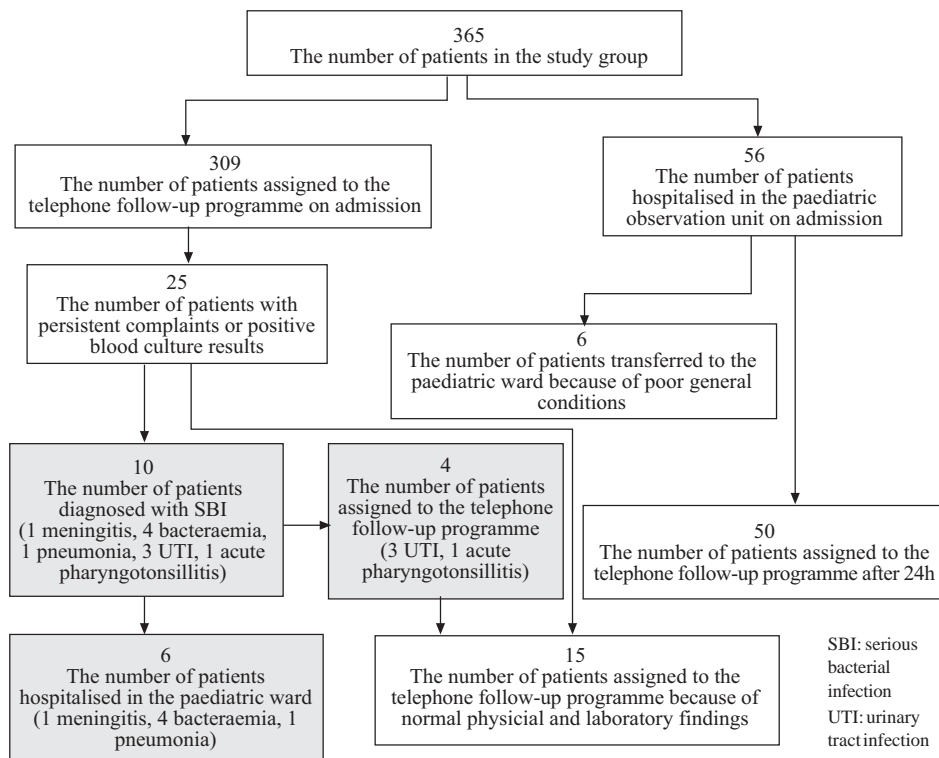


Fig. 3. The distribution of patients by hospital and home follow-ups.

population of febrile children at risk for bacteraemia. The rate of bacteraemia and occult bacteraemia was 4.4% and 1.32% respectively, which is consistent with the results of the previous studies reporting the rates of 1.6% to 10.4%.^{4,5,10,11,17-26} The majority of studies reporting rates of bacteraemia below 4% were carried out in “the post-*H. influenzae* type b era”.^{4,5,10,11,18,26} We found that the Hib immunisation rate was 67.9% in the study population. Prior to the introduction of universal *H. influenzae* type b conjugate vaccines for infants, this organism accounted for 10% to 25% of bacteraemia in this age group and 42% of the complications identified at follow-up.^{18,27} With widespread immunisation against *H. influenzae* type b infection, bacteraemia is now almost always caused by *S. pneumoniae*.^{17,28} Similar with previous studies, we found that the most common cause of bacteraemia was *S. pneumoniae*. In this study, there were no cases of bacteraemia caused by *H. influenzae* type b. It may be that 67.9% the patients had had at least one shot of the Hib vaccine. Nevertheless, *K. pneumoniae*, a capsular bacterium which is not expected to cause bacteraemia in otherwise healthy children in the outpatient setting, was detected in 2 cases. One patient with *K. pneumoniae* bacteraemia was a 3-month-old female. She had been hospitalised for 45 days due to fever of unknown origin, negative blood culture and positive urine culture for *K. pneumoniae* and discharged following a decrease in temperature 2 days after the initiation of an

antimicrobial treatment regimen. The other patient with *K. pneumoniae* did not have any predisposing factors on history, physical examination and laboratory tests. The emergency department was notified in the 36th hour about the positive results of blood cultures in both patients.

In several studies,^{5,6,10,18,21} age, temperature and WBC were shown to be indicators for bacteraemia; but they were not statistically significant in this study. This can be explained by our selection criteria for age, temperature and WBC. Nevertheless, ROC curves show that YOS, neutr (%), ANC, ABC, band (%), and BNR in the peripheral blood smears provide diagnostic information about bacteraemia. Previous studies that acknowledge the prediction power of these tests for bacteraemia have yielded conflicting results. This may be due to low rates of bacteraemia in the previous studies, which makes demonstration of a statistical significance not possible. In the present study, when the cut-off values detected by the ROC curves of the clinical and laboratory test results which showed diagnostic values were used, prediction of bacteraemia rates increased by 6.6 to 14.7 times (Table 1).

If the RISK score had been at least 2, 15 of the 16 bacteraemia cases would have been diagnosed (Table 5). If the RISK score had been used, 223 patients whose scores were under 2 would not have needed blood cultures and 149 of them would not have needed antibiotherapy. If the parameters WBC, peripheral blood smear and YOS

evaluation were used to determine the RISK score, it would not have been necessary to take blood samples for CBC from these 223 patients. Manual WBC, which is much cheaper, could have been performed instead. Thus, using the RISK score would have resulted in significant cost reductions. In addition, the anxiety of the parents waiting for follow-up results, visits to the hospital, increased work load of the laboratory staff and the physician and, most importantly, venous sampling, which is more invasive method, would have been avoided, and instead, the latter capillary sampling could have been performed. With NPV of 99.5% and OR of 26.2, the risk score indicates high predictive power for the absence of bacteraemia in a population of children 3 to 36 months with temperatures $\geq 39^{\circ}\text{C}$.

RISK scores with NPVs of 97.8% and ORs of 9.3 have high prediction power for absence of SBI. In febrile children, the RISK score has high prediction power for the absence of both bacteraemia and SBI (NPVs: 99.5% and 97.8%, respectively). Therefore, we believe that the RISK score can be used in deciding when to take blood cultures and when to start an antibiotics regimen in suspected cases of bacteraemia. In addition, it can be easily done in any hospital setting, is low cost, reduces the need for further tests that may cause more discomfort for the child, and the results can be obtained within an hour.

The settings where one can make use of the results of this study are limited. The following conditions are required: 1) The patients must be 3 to 36 months old; 2) The patient's body temperature must be $\geq 39^{\circ}\text{C}$; 3) WBC count must be $\leq 5000/\text{mm}^3$ or $\geq 15000/\text{mm}^3$; 4) There must be no localised infection (excluding AOM) or diagnosed viral disease; 5) There must be no acute or chronic diseases that can alter the patients' overall condition; and 6) at least 67.9% of the population must be Hib-vaccinated.

In conclusion, the RISK score does not seem to be a very good diagnostic tool but it can be used as a screening tool for bacteraemia and SBI. Therefore, in children aged 3 to 36 months with fever and no focus of infection on physical and laboratory examinations, evaluating the RISK score will significantly decrease unnecessary blood culture sampling, antimicrobial therapy and hospitalisation.

REFERENCES

- Fleisher GR. Infectious disease emergencies. In: Fleisher GR, Ludwig S, Henretig FM, editors. Textbook of Pediatric Emergency Medicine. 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2006: 783-852.
- Burke JP, Klein JO, Gezon HM, Finland M. Pneumococcal bacteremia. Review of 111 cases, 1957-1969, with special reference to cases with undetermined focus. *Am J Dis Child* 1971;121:353-9.
- Greenes DS, Harper MB. Low risk of bacteremia in febrile children with recognizable viral syndromes. *Pediatr Infect Dis J* 1999;18:258-61.
- Alpern ER, Alessandrini EA, Bell LM, Shaw KN, McGowan KL. Occult bacteremia from a pediatric emergency department: Current prevalence, time to detection, and outcome. *Pediatrics* 2000;106:505-11.
- Isaacman DJ, Shults J, Gross TK, Davis PH, Harper M. Predictors of bacteremia in febrile children 3 to 36 months of age. *Paediatrics* 2000; 106:977-82.
- Kuppermann N, Fleisher GR, Jaffe DM. Predictors of occult pneumococcal bacteraemia in young febrile children. *Ann Emerg Med* 1998;31: 679-87.
- Akpede GO, Akenzua GI. Aetiology and management of children with acute fever of unknown origin. *Paediatr Drugs* 2001;3:169-93.
- Smith N. Infectious diseases. In: Cameron J, Jelinek G, Everitt I, Browne G, Raftos J, editors. Textbook of Paediatric Emergency Medicine. 1st ed. Edinburgh: Churchill Livingstone-Elsevier, 2006:261-72.
- Green SM, Rothrock SG. Evaluation styles for well-appearing febrile children: Are you a "risk minimizer" or a "test-minimizer"? *Ann Emerg Med* 1999;33:221-4
- Teach SJ, Fleisher GR. Efficacy of an observation scale in detecting bacteremia in febrile children 3 to 36 months of age, treated as outpatients. Occult Bacteremia Study Group. *J Pediatr* 1995;126:877-81
- Jaffe DM, Fleisher GR. Temperature and total white blood cell count as indicators of bacteremia. *Pediatrics* 1991;87:670-4.
- Sur DK, Bukont EL. Evaluating fever of unidentifiable source in young children. *Am Fam Physician* 2007;75:1805-11
- Schutzman SA, Petrycki S, Fleisher GR. Bacteremia with otitis media. *Pediatrics* 1991;87:48-53.
- McCarthy PL, Sharpe ML, Spiesel SZ, Dolan TF, Forsyth BW, DeWitt TG, et al. Observation scales to identify serious illness in febrile children. *Pediatrics* 1982;70:802-9.
- Bonsu BK, Harper MB. Utility of the peripheral blood white blood cell count for identifying sick young infants who need lumbar puncture. *Ann Emerg Med* 2003;41:206-14.
- Shochet S, Newman T. White blood cell count likelihood ratios for bacteremia in febrile young children. *Arch Pediatr Adolesc Med* 2000;154:963-4.
- Browne GJ, Ryan JM, McIntyre P. Evaluation of a protocol for selective empiric treatment of fever without localising signs. *Arch Dis Child* 1997;76:129-33.
- Lee GM, Harper MB. Risk of bacteremia for febrile young children in the post-Haemophilus influenzae type b era. *Arch Pediatr Adolesc Med* 1998;152:624-8.
- McGowan JE, Bratton L, Klein JO, Finland M. Bacteremia in febrile children seen in a "walk-in" pediatric clinic. *N Engl J Med* 1973;288:1309-12.
- Teele DW, Pelton SI, Grant MJ, Herskowitz J, Rosen DJ, Allen CE, et al. Bacteremia in febrile children under 2 years of age: results of blood cultures of 600 consecutive children seen in a walk-in clinic. *J Pediatr* 1975;87:227-30.
- McCarthy PL, Jekel JF, Dolan TF. Temperature greater than or equal to 40°C in children less than 24 months of age: A prospective study. *Pediatrics* 1977;59:663-8.
- Dershewitz RA, Wigder HN, Wigder CM, Nadelman DH. A comparative study of the prevalence, outcome, and prediction of bacteremia in children. *J Pediatr* 1983;3:352-8.
- Waskerwitz S, Berkelhamer JE. Outpatient bacteremia: clinical findings in children under two years with initial temperature of 39.5°C or higher. *J Pediatr* 1981;99:231-3.
- Carroll WL, Farrell MK, Singer JI, Jackson MA, Lobel JS, Lewis ED. Treatment of occult bacteremia: a prospective randomized clinical trial. *Pediatrics* 1983;72:608-12.
- Bennish M, Beem MD, Ormiste V. C-reactive protein and zeta sedimentation ratio as indicators of bacteremia in pediatric patients. *J Pediatr* 1984;104:729-32.
- Bandyopadhyay S, Bergholte J, Blackwell CD, Friedlander JR, Hennes H. Risk of serious bacterial infection in children with fever without a source in the post-Haemophilus influenzae era when antibiotics are reserved for culture-proven bacteremia. *Arch Pediatr Adolesc Med* 2002;156:512-7. Erratum in: *Arch Pediatr Adolesc Med* 2002;156:749.
- Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Management of the febrile one- to 36-month-old child with no focus of infection. *Paediatr Child Health* 1996;1:41-5.
- Luszczak M. Evaluation and management of infants and young children with fever. *Am Fam Physician* 2001;64:1219-26.