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Etiology and Causative Pathogens of Febrile Neonates

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Abstract

Background: Evaluation and treatment of febrile neonates varied widely among the different centers. The prevalence of serious bacterial infection (SBI) is high in neonates; thus, most experts would support the approach of a full sepsis evaluation and hospitalization. We aimed to evaluate the clinical and laboratory characteristics of febrile neonate less than 28 days of age and describe the incidence of SBI in febrile neonates.

Methods: This prospective observational cohort study was include neonates with a rectal temperature of $\geq 38^{\circ}\text{C}$ who admitted to NICU between 2011 and 2015. Demographic information, physical examination findings, laboratory test results, and final diagnosis were recorded and compared to identifiedas serious bacterial infection (SBI) or no-SBI. For determination of SBI; CRP and WBC cut-off values were calculated by receiver operating characteristic curve analysis.

Results: 328 infants were included the study. The overall rate of SBI was 38.4%. The common final diagnosis were found unknown reason (43.6%), urinary tract infection (15.5%), dehydration (14%), and bacteremia (5.8%). The most common bacterial growth in culture *Escherichia coli* in 19 cases and Methicillin-Resistant Coagulase-Negative *Staphylococci* in 16 cases detected. A significant cut-off value could not be determined for CRP (AUC: 0.664) 95% CI: 0.604-0.723 and WBC (AUC: 0.535) 95% CI: 0.472-0.597.

Conclusion: Gram positive pathogens were more common in febrile neonates than older febrile infants. A reliable cut-off value for CRP and WBC for detection SBI in neonatal period could not be determined.

Keywords: Fever; Newborn; Pathogen; Urinary tract infection

Introduction

Fever is not uncommon in neonatal period, and the incidence rate of fever was documented as 14.4/1000 full term births [1]. Although such fevers are typically self-limiting, it has been reported that 7.1-19.7% of affected neonate also have serious bacterial infection (SBI) [2-5]. Febrileinfants younger than ≤ 28 days are at higher risk of serious bacterial infections (SBI), traditionally, so they need to go through laboratory investigation and hospitalization due to increased susceptibilityto infections.

But in some cases origin of fever is not an infection or other serious diseases. Therefore large numbers of febrile neonates continue to receive unnecessary treatment that generates emotional stress to parents, costsand may be associated with iatrogenic complications and antibiotic resistance [2-6]. Rochester and Philadelphia protocols can be used for identification of Serious bacterial infections in older infants, but in neonatal period sensitivity of these protocols are low [7]. For this reason, it is reported that C-reactive protein (CRP), absolute neutrophil count and procalcitonin levels can be used in SBI determination in the first month of life [6-9]. Some studies reported that the contribution of White blood cells count (WBC) in the identification of SBI is very low; thus,importance should be givenon CRP level over absolute neutrophil count and absolute band counts and WBC [4-10].

Firstly the objective of present study was to evaluate clinical and laboratory characteristics of febrile neonates and describe the etiology and causative organisms in febrile neonates. Secondary find out the cutoff value of the serum levels of CRP and WBC for predicting SBI.

Method

The study was a prospective observational cohort study conducted at a tertiary care university-affiliated medical center in Istanbul. The study protocol was approved by the local ethic committee. Written informed consent was obtainedfrom the parents of all infants enrolled in thestudy before inclusion.

Study population

Between January 2011 and December 2015 (5 years), all neonates who were admitted to the neonatal intensive care unit with a rectal temperature of $\geq 38^{\circ}\text{C}$ (documented at the time of medical evaluation) were eligible for the participation in this study. Gestational age ≤ 35 weeks, who refused to participate in the study, chromosome abnormality, the presence of a chronic disease, congenital malformations, admission to pediatric surgery, and incomplete records were excluded from study. A complete history was obtained from the parents of infants, and a specialist in neonatology carried out a physical examination for localizing the source of the fever in all infants.

Data collection

The data obtained for all infants included: demographic information (age at admission, gender, and birthweight), general assessment (well or sick-appearing), medical history, physical examination findings, laboratory test results, and final diagnosis. Laboratory investigations including complete blood count, CRP level, blood chemistry and culture, urine sample analysis and culture (obtained by bladder catheterization), and cerebrospinal fluid sample analysis and culture, were carried out. In the presence of respiratory symptoms or signs, chest radiography was performed. Lumbar puncture was performed according to the ward's policy, which is required for every infant if neurologic findings are positive or without the focus on fever. Stool specimens were obtained when a history of diarrhea was noted and sent for white blood cell analysis and bacterial culture. Other tests were conducted as necessary. Skin, soft tissue, and ear infections were diagnosed by physical examination.

Definition of SBI

SBI was defined as (1) the growth of a known pathogenic bacteria in one or more of cultures, (2) any disease commonly associated with bacterial pathogens including pneumonia, acute otitis media, suppurative arthritis, osteomyelitis, and soft-tissue infections (mastitis, omphalitis). Pneumonia was defined as a new discrete infiltration on the chest film, which was confirmed by an attending pediatric radiologist with the presence of typical clinical signs and symptoms.

All specimens for culture were evaluated by standard microbiological methods. No specimens were processed for viral cultures. The blood culture isolates were considered pathogenic if the organism was known to cause disease in healthy infants. UTI (urinary tract infection) was defined as the isolation of $>10^4$ CFU/mL of urine of a single pathogen by catheterization. A positive urine analysis was defined by a positive test for leucocyte esterase or nitrite by the dipstick method or leucocyte ≥ 10 cells/mm³ in uncentrifuged urine.

Methods of viral agent evaluation: in infants with viral respiratory symptoms and complaints (a runny nose, sneezing, coughing), the presence of RSV-Ag (rapid immunochromatographic test produced by Prima lab SA, Switzerland), and influenza-Ag (Immunoassay test produced by Dalian Rongbang Medical Healthy Devices, Spain) were assessed from nasopharyngeal secretions. The body weight of the subjects was taken on admission and weight loss was assessed according to the birth weight. The proportion of weight loss more than twelve percent of birth weight was considered as dehydration.

All patients were hospitalized and prophylactic antibiotic therapy was started and continued for at least 72 h (cases diagnosed only with dehydration did not receive antibiotics).

Statistical analysis

The data were analyzed by using SPSS version 15.0 (SPSS, Chicago, IL, USA). Categorical variables are reported as percentages, and normally distributed data are expressed as mean \pm SD. Statistical comparisons between positive SBI group and negative SBI group performed with Student's t-test for normally distributed data, Mann-Whitney U test for non-normally distributed data, and chi-square test for all numerical and categorical values. For predicting SBI, the serum levels of CRP and WBC count were subjected to receiver operating characteristics (ROC) curve analysis. The results were considered to be significant if analysis yielded $p < 0.05$.

Results

During the study, a total of 328 infants met the inclusion criteria. The diagram of study present in **figure 1**. **Table 1** shows the characteristics of newborns in the study.

Table 1: Demographic characteristics of 328 neonates with fever included in the study

	Mean \pm Standard deviation	Lower-upper limits
Gender, n (%) Male	184 (56.1)	
Mode of delivery, n (%) C/S	148 (45.1)	
NVD	180 (54.9)	
Gestational time, weeks	39.2 \pm 1.4	35-42
Birth weight, g	3214 \pm 492	1950-4810
Weight, at admission to the hospital, g	3368 \pm 570	2130-4960
Age, at admission to the hospital, days	12.5 \pm 8.0	1-28

Fever (°C)	38.3 ± 0.4	38-40
Length of stay in hospital, days	7.4 ± 3.7	2-22
C/S: Cesarean Section; NVD: Normal Vaginal Delivery		

Table 2: The final diagnosis of all febrile neonates

Category of Diagnosis	n (%)	
Unclassified-unknown Reason of Fever	143 (43.6)	
Urinarytractinfection	51 (15.5)	
Only dehydration	46 (14)	
Bacteremia	19 (5.8)	
Pneumonia	18 (5.5)	
Viral Respiratory Tract Infection	13 (4.0)	
Meningitis	12 (3.7)	
Complex Infection	Urinary Tract Infection +Dehydration	6
	Bacteremia+Pneumonia	4 (6.1)
	Bacteremia+Dehydration	4
	Bacteremia+Urinary Tract Infection	4

	Pneumonia+Urinary Tract Infection	2
Otitismedia		2 (0.6)
Gastroenteritis		2 (0.6)
Soft Tissue Infection		2 (0.6)
Total		328 (100)

The final diagnosis of the febrile neonates are presented in **table 2**. During the study period, the overall rate of SBI was 38.4% (n=126). The most common final diagnosis was febrile illness without any detectable reason, which accounted 43.6% of all cases. Urinary tract infection, dehydration, and bacteremia were the next common diagnoses, accounting for 15.5%, 14%, and 5.8%, respectively. Dehydration was detected in 56 neonates, 46 of them were diagnosed only dehydrated, whereas 10 also had SBI. The characteristics and laboratory results of neonates who had SBI or did not have SBI are compared in **table 3**.

Table 3: A comparison of the characteristics according to presence or absence of SBI (serious bacterial infection)

		SBI (+) (n=126)			SBI(-) (n=202)		p
		n	%	n	%		
Gender	Male	77	61.6	107	52.9	0.045	
Weight Loss	Yes	10	7.9	46	22.8	<0.001	
Mode of delivery	NSD	66	52.4	114	56.4	0.375	
Start to Antibiotics	Yes	126	100	140	69.3	<0.001	
		Mean ± Standard deviation					
Gestational time	weeks	39.0 ± 1.3		39.3 ± 1.4		0.012	
Birth Weight	g	3236 ± 518		3192 ± 466		0.704	
Age at Admission to the Hospital	days	13.5 ± 7.8		11.5 ± 8.1		0.017	
Weight at Admission to the Hospital	g	3443 ± 574		3294 ± 557		0.007	
Fever	°C	38.3 ± 0.4		38.3 ± 0.4		0.761	
Length of stay in hospital	days	9.8 ± 3.5		5.0 ± 2.0		<0.001	
Laboratory Results							
WBC	(cells/μL)	12 123 ± 5255		11025 ± 4204		0.279	
Platelets	(cells/mm ³)	323493 ± 113544		287237 ± 90095		0.005	
CRP	nmol/L	209.5 ± 333.3		47.6 ± 57.1		<0.001	
I/M ratio n(%)	>0.2	28 (17.1)		10 (6.1)		0.002	
ANC n(%)	>1500 cells/μL	32 (36.0)		21 (20.8)		0.02	

Urineanalysis n(%)	Leukocyte>10 cells/mm ³	38 (23.2)		2 (1.2)		<0.001
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The pathogens detected in febrile neonates with SBI are enlisted in **table 4**. Bacterial growth in culture detected at 97 patients in our study. Most common identified bacteria were

Escherichia coli (E.Coli) in 19 cases, Methicillin-Resistant Coagulase-Negative *Staphylococci* (MRCoNS) in 16 cases and *Enterococcus* in 14 cases.

Table 4: The distribution of causative bacterial pathogens in SBI

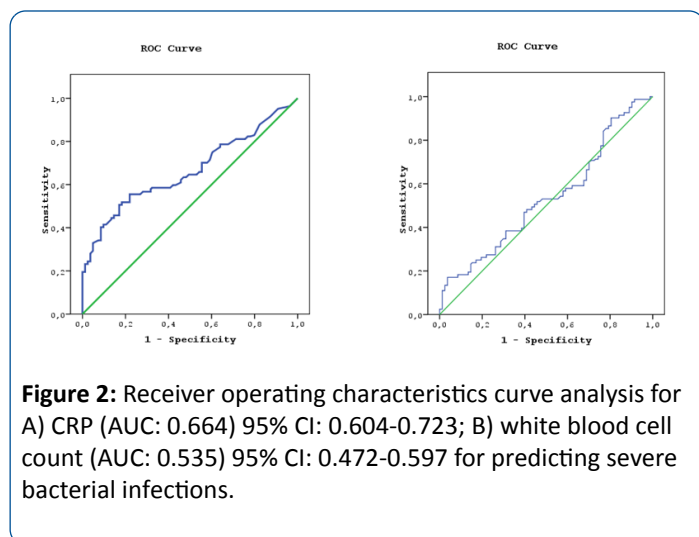
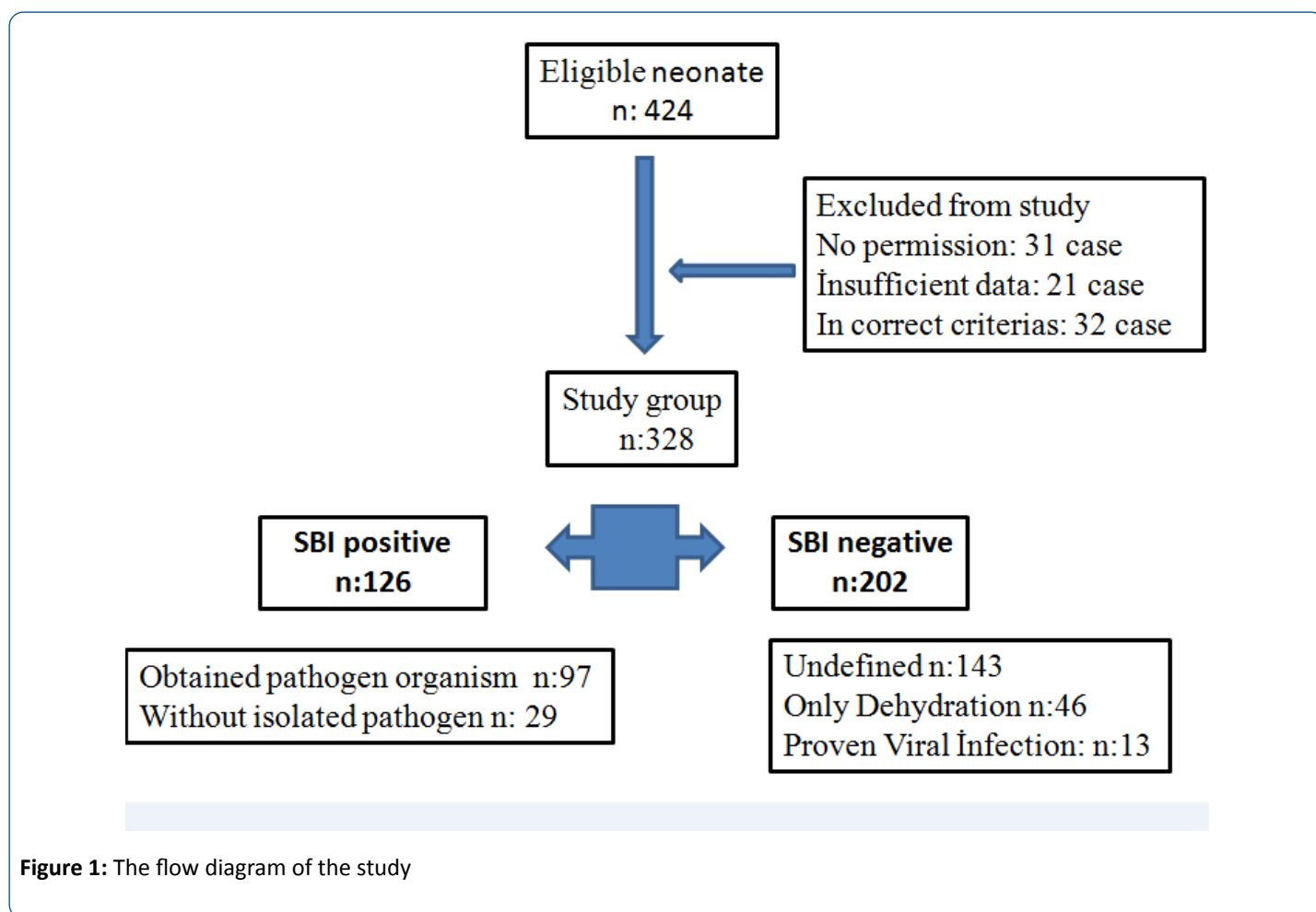
	Causative pathogen	n
Urinary tract infection n=51 (15.5)	<i>Escherichia coli</i>	15
	<i>Enterococcus</i>	10
	<i>Klebsiella species</i>	8
	<i>Enterobacter</i>	7
	CoNS	6
	<i>Proteus mirabilis</i>	2
	Undefined Gram-negative pathogen	2
	<i>Citrobacter werkmanii</i>	1
Bacteremia n=19 (5.8)	MRCoNS	7
	CoNS	3
	<i>Escherichia coli</i>	2
	<i>Enterococcus, Klebsiella species, N. Meningitidis, Enterobacter, S. warneri, S. capitis, Enteric Gram-negative rods.</i>	1*
Combined infection n=20 (6.1)	MRCoNS	6
	CoNS	5
	<i>Klebsiella species</i>	4
	<i>Escherichia coli</i>	2
	<i>Enterococcus</i>	3
Meningitis n=12 (3.7)	MRCoNS	3
	<i>K. pneumonia</i>	2
	CoNS	1
	<i>Pseudomonas</i>	1
	Undefined	5

*One for each pathogen. MRCoNS: Methicillin-resistant coagulase-negative *Staphylococci*; CoNS :Coagulase-negative *Staphylococci*

A total of 328 urine specimens were collected by the urinary catheter of the 51 infants diagnosed with UTI, only 60.1% had pyuria. The most common pathogens isolated from urine cultures was *E.coli*. The most common pathogen was MRCoNS in bacteremia, complex infection, and meningitis (**Table 4**). Among the 124 neonates, in whom lumbar puncture was performed, 12 had leucocyte count >10 and 7 showed positive CSF (Cerebrospinal Fluid) culture. Rapid viral antigen test was

performed in 48 neonates with respiratory tract infection, and 13 were detected positive (RSV=8 cases, Influenza=5 cases).

ROC curve analysis was carried out to determine the optimal CRP cut-off values and WBC counts for detecting SBI. A significant cut-off value could not be determined for CRP (AUC: 0.664) 95% CI: 0.604-0.723 and WBC (AUC: 0.535) 95% CI: 0.472-0.597 (**Figures 2A and 2B**).



Discussion

Fever is a common symptom in neonate visiting outpatient clinics. The causes of fever in these neonates vary from dehydration, mild viral infection to serious bacterial infections which are progressive and lead to severe morbidity or mortality. Evaluation and treatment of febrile neonates varied widely among the different centers [11]. These differences demonstrate the deficiency of and highlight the necessity for national or

international guidelines for the assessment of fever in this age group.

Given this, the overall prevalence of SBI is high in neonates; thus, most experts would support the approach of a full sepsis evaluation and hospitalization [12]. Nevertheless, the studies on the treatment approaches for febrile neonate suggested a modification of management models with the addition of CRP and erythrocyte sedimentation rate, and also recommended in-hospital treatments of the neonates with low-risk factors and follow-up without an antibiotic treatment [13,14]. The current status is none of the markers alone or in combination display satisfactory sensitivity or precision for the diagnosis of SBI in well-appearing febrile neonates, and there is no consensus about the assessment and management of outpatient newborns with fever.

The prevalence of SBI in infants of <3 months of age with fever is about 7.1-19.7%. This is higher in infants aged 0-28 days (9-28%) than those 2-3 months old (7.1%) [2-9,15,16]. We found the overall rate of SBI was high (38.4%) and our findings confirmed that SBI was seen more frequent in the neonatal period.

UTI is the most common SBI in infants younger than 90 days age, which was found in 3.0-11.0% of febrile infants in various reports [17]. On the other hand, UTI was found higher and reported that 14-21.3 percent in febrile neonates that means UTI affects approximately 1 in 6 febrile neonates [2-11,18]. In our

study, UTI incidence was found similarly the most common etiology of fever in neonatal period.

In the studies evaluating low-risk criteria of febrile infants, UTI was the most frequently missed SBI [19]. The sensitivity of urinalysis and urine dipstick test for determination of UTI is low approximately 60 to 79% [18]. Similarly, in our study, only 60.1% of UTI cases were positive in standard urinalysis. Thus standard urinalysis was found to be insufficient in the identification of UTI during neonatal period.

Pathogens of UTI were *E. coli* in 81% and *K. pneumoniae* in 19% in infants less than 3 months [20]. In febrile neonates, the most common uropathogens were found *Escherichia coli* (71%), *Enterococcus* (10%) and *Klebsiella sp.* (10%) [18]. We were cultured *E.coli* (15/51) as the most common pathogen in UTI, but in our study different pathogens especially *Enterococcus*, *Enterobacter* and CoNS were found high proportion in febrile outpatient newborns. This situation was attributed to the different colonizations of different societies in community-acquired infections.

Infants less than 3 months with bacteremia, 54% were caused by group B *Streptococcus*, 23% by *E. coli* [20]. There are not a sufficient source for pathogens causing bacterial infections in only febrile newborns. Gram positive pathogens MRCoNs and CoNS, near to 50% percent causative bacteremia in our study.

Bacterial pathogens were not detected mostly in babies apply with fever and this situation was identified as viral syndrome by many authors and fever attributed to viral syndrome in their studies with a rate of 60.2% and 72% respectively [2,21]. Viral culture or rapid viral antigen analysis were not done in both studies.

Recent meta-analysis about RSV and SBI demonstrated that rates of positive SBI are not different between febrile neonates with or without positive RSV and respiratory viral infection status is not an accurate clinical determinant in distinguishing SBI risk in febrile neonates [22]. On the contrary, concomitant confirmed viral infections reduce the probability of SBI from 12.3% to 4.2% and bacteremia from 2.7% to 1% [23].

It is suggested that full septic evaluations are not necessary in nontoxic appearing infants with a positive RSV test [24]. In our study, we could not detect any reason for the fever in about 43.6% babies. Among the 48 babies, with whom we conducted rapid antigen test, 13 were detected virus antigen (RSV +Influenza). None of the low-risk protocols include a viral testing in the evaluation of the febrile infant. However, our study suggests that viral antigen screening can be useful in guiding the management of febrile neonates similar to other age groups.

The need for lumbar puncture in infants with fever is still a debatable issue. Previous studies on <90 days old babies reported the rate of bacterial meningitis and aseptic meningitis 0.2% and 14.4%, respectively [25]. In the studies, where only neonates were included, the rate of bacterial meningitis was 0.5-4.4% [2,11-13]. Lumbar puncture and CSF analysis were not done routinely in the mentioned studies.

Certain incidences of bacteremia and meningitis were missed in neonates who were analysed according to definition of low-

risk for SBI [15,16]. In a comprehensive review on this subject, it was stated that whether a lumbar puncture is required to all febrile infants or which parameter can predict the need for lumbar puncture cannot be answered definitely [17]. Our study revealed a higher rate of meningitis in newborns than the infants between ages of 1-3 months. In our study, lumbar puncture was conducted according to the ward's policy, which suggests performing a lumbar puncture for every infant if the neurologic finding is positive or without the focus of fever. By this method, we believe that undetected cases of meningitis were reduced as much as possible.

The earlier studies proposed that, in the assessment of <90 days old febrile infants, the diagnostic data for various laboratory measures can be employed by using individual thresholds of the following tests: urinalysis (microscopy, dipstick), WBC, erythrocyte sedimentation rate (ESR), ABC, absolute neutrophil count (ANC), procalcitonin and Interleukin-6 [26]. The overall accuracy of ANC and ABC was greater than that for WBC [14]. The use of CRP showed higher overall accuracy than WBC, ANC, and procalcitonin in accurately diagnosing infants with and without SBI [9,27]. The combination of procalcitonin with urinalysis was reported as more sensitive for identifying SBI in babies between 2 and 60 days old [28]. Recently, Nosrati reported that CRP was the only parameter found to be significantly associated with SBI (odds ratio, 1.042; 95% confidence interval CI: 1.028-1.056) in febrile infants [25].

However, in this study, the cut-off value for CRP was determined as 2 mg/dl which led to higher specificity to this parameter to identify SBI. On the contrary of these information, it was notified that "no marker could be totally rule out SBI in febrile infants less than 3 months of age" [26,29,30]. In our study, which included only neonates, a reliable cut-off value could not be determined for CRP and WBC.

In this prospective observational study, which included 328 febrile newborns, determined that SBI incidence in febrile infants was encountered at pretty high rates. Most common focus detected in newborn babies with SBI was UTI and the most common pathogen was *E. Coli*. We found Gram positive pathogens were more common than in infants less than 90 days. A reliable cut-off value for CRP and WBC for detection SBI could not be determined.

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