PREDICTORS OF SERIOUS BACTERIAL INFECTION IN INFANTS UPTO 8 WEEKS OF AGE

Virendra Kumar
Sunit Singhi

ABSTRACT

During a period of 2 years we prospectively studied 116 infants upto 8 weeks of age with suspected sepsis. Each infant was assessed clinically before laboratory evaluation for sepsis. Depending upon impression of sepsis, temperature abnormality, micro ESR (mESR), WBC counts and toxic granulations infants were assigned to either high (n = 74) or low (n =31) risk group for serious bacterial infection (SBI). All infants were kept under observation till the final decision for hpspitalization was made. Eighty six per cent of cases in high risk group and 26% of cases in low risk group were hospitalized and treated with antibiotics. SBI was present in 55% of the high risk group infants compared to one (3%) in the low risk group. Culture for bacterial infections were positive in 22 (19%) cases; bacteremia was found in 15 (13%) infants. None of the variables individually predicted the presence of bacteremia or SBI satisfactorily. Presence of two or more criteria out of the three criteria namely impression of sepsis, raised mESR and toxic granulation could identify 93% of infants with bacteremia and 95% of those with SBI and excluded 89% of cases without SBI.

Key words: *Infants, Bacterial infection, Predictors, Bacteremia.*

Various parameters have been analyzed to predict bacteremia and serious bacterial infection (SBI) in infants under 2 months of age but none has been found fool proof (1-3). However, individual studies have shown that physicians impression of ill appearance (1-4), abnormal WBC count(2,4,5), elevated ESR(l) and hyperpyrexia are significantly more common in those with SBI. In absence of reasonably sensitive criteria to pick up SBI many more infants may get hospitalized just on suspicion and exposed to hospital related complications(6). Having faced these problems we planned this study to find out: (i) the prevalence of SBI and bacteremia in infants upto 8 weeks of age attending our pediatric emergency services; and (ii) to evaluate a set of risk criteria which individually or in combination, may predict infants who are likely to have SBI. The criteria were: (i) impression of sepsis; (ii) temperature abnormality (rectal temperature >38°C or <36°C); *(iii)* micro ESR >10 mm/first hour; (iv) abnormal white blood cell counts (WBC > 15,000 or <5,000/mm^3); and (v) presence of toxic granules (TG) on peripheral blood smeer.

Material and Methods

Infants upto 8 weeks of age with suspected sepsis who were evaluated at Pediatric Emergency Services of Nehru Hospital, PGIMER, Chandigarh during a two year period formed the study population. The

From the Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012.

Reprint requests: Dr. Sunit Singhi, Additional Professor, Emergency and Intensive Care Department of Pediatrics, PGIMER, Chandigaih 160 012.

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infants either had fever or one or more of the following symptoms: poor activity and feeding, breathing problem, abnormal cry, seizures, loose stools, abdominal distension or skin and soft tissue infection. Each infant was assessed clinically on arrival, a complete history and physical examination was done. Impression of sepsis was recorded as strong, ambivalent or negative based on: *(i)* appearance, *(ii)* level of activity, *(iii)* responsiveness, *(iv)* feeding pattern, and *(v)* consolability. After clinical assessment venous blood sample was obtained for blood counts, mESR, hematocrit, culture and blood sugar estimation. Lumbar puncture for CSF cell count, biochemical analysis and culture, and chest X-ray were done routinely for all babies upto 4 weeks of age and thereafter whenever indicated by history or physical examination. Stool culture was done only in those who had diarrhea. We could not screen all the infants for urinary tract infection due to the practical difficulties in collecting a clean, uncontaminated urine for urinalysis and culture in a busy emergency area. An earlier study(7) had shown that only one half of the patients with UTI have abnormal urinalysis and an unacceptably large number of cases yield indeterminant results from culture of a bag specimen. Micro ESR was done by capillary method(8) and if hematocrit was <30 or >60% the result was excluded from the analysis. For toxic granulations blood smears were stained with Leishman's stain and examined under oil immersion. Abnormal granules were characterized as deep blue, coarse granules with irregular distribution in the cytoplasm. If >15% of neutrophils showed presence of TG then it was considered as abnormal. Diagnosis of meningitis was based on the criteria used by Dagan *et al.(2)*. Bacteremia, meningitis, pneumonia, empyema, cellulitis, osteomyelitis, septic arthritis, necrotizing enterocolitis (NEC) and bacterial gastroenteritis were grouped as SBI. This arbitary designation has the utility in grouping together the diseases with potentially serious consequences(9). The infants were considered to be at low risk for SBI if they had normal temperature on admission, negative impression of sepsis, normal blood count (WBC count 5000-15000/mm^3), absence of TG and mESR of < 10 mm in the first hour.

Data was analysed for statistical significance by Chi square test with Yates correction (whenever needed) for contingency table and 't' test for continuous variables. Sensitivity, specificity, and positive and negative predictive value were calculated for each of the risk criteria and their combinations.

Results

During a period of about 2 years we studied 116 infants with suspected sepsis. Their age ranged from 1-60 days with a mean of 27 days. Thirty six were <2 weeks of age, 28 were between 2-4 weeks and 52 were older than 4 weeks of age. The male/female ratio was 2.9:1. Rectal temperature was recorded in 106 infants at the time of admission. Though, 80% (93/116) of the infants had a positive history of fever before hospitalization, on examination only 35 infants were febrile (temperature >38.0°C) and 5 had hypothermia (temperature <36°C). High fever (>39.5°C) was noted in six infants, of which three had sepsis, two malaria and one intracranial bleed as a complication of hemorrhagic disease of newborn.

Table I shows final diagnosis of the study infants. A diagnosis could be made in 25 (22%) infants with a thorough clinical examination while in another 32 (28%) infants with some localizing signs, a diagnosis could be arrived at after relevant investigation(s). Fifty (43%) infants were labelled as having

TABLE I-*Final Diagnosis in 116 Infants upto* 8 *Weeks of Age Evaluated for Suspected Sepsis*

Variables	No. of cases	Cases with positive culture	Treated with anti-biotics	Mortality
Diagnosis apparent on initial assessment				
Abscess/cellulitis	8	6(B_2)*	8-	3
Gastroenteritis	3	-	3	2
Bronchiolitis	14	-	3	-
Diagnosis established following investigations				
Pneumonia	15	l(B_1)	13	2
Meningitis	11	2(B_1)	11	3
Aseptic meningitis	1	-	-	-
Empyema	1	1	1	-
Septic arthritis	2	1	1	-
NNEC	2	2(B_2)	2	1
Possible sepsis without localization	50	9(B_2)	33	3
Miscellaneous				
Congenital heart diseases	3	-	1	-
Intracranial bleed	1	-	1	1
Birth asphyxia	1	-	-	-
Malaria	4	-	-	-
Total	116	22(B_{22})	77	15

*Number of cases with positive blood culture

possible sepsis without localization; 9 (18%) of them had bacteremia. Remaining 9 had unrelated problems; four of them had malaria and came with history of fever.

A positive culture for micro-organisms was obtained in 22 infants, blood culture - was positive in 15 while in others body fluid from the affected site grew micro-organism *(Table II).* Out of the 15 infants with a positive blood culture, 14 were below 28 days of age (mean age 14 days), while out of 7 infants with culture positive from other sites, six were 30 days or above. There was a male dominance (M:F—4:1). The com monest organism isolated w*as Klebsiella pneumoniae* in 12. This was followed by *Staph. aureus* - 5 cases, *Pseudotnonas aeruginosa* - 3, *E. coli* - 1 and Acinetobacter - 1. An overall mortality of 13% (15 cases) was noted, out of which two cases died probably of a cause unrelated to infection, one died of intracranial hemorrhage and other due to peritoneal bleed during dialysis.

Risk Criteria and SBI

Out of 116 cases, 11 were excluded due

TABLE II-*Details of Infants with Positive Cultures*

Pts No.	Age (days)	Sex	Temporary (OC)	Impression of sepsis	WBC (/mm^3)	TG	mESR (mm/h)	Organism.	Discharge diagnosis
With clinical localization									
1	60	M	39.0	S	13000	NR	20	Sa(P)	Chest wall abscess
7	08	M	38.6	S	38000	+	20	Sa	SP/pustules
13	30	M	37.8	AM	30000	+	-	Sa(P)	Empyema
46	20	M	37.5	N	5800	+	15	Kp	SP/pn
71	30	M	-	N	18200	+	15	Kp(P)	Septic arthritis
72	05	F	<36	S	16000	-	12	Acb(c)	SP/MN/Pn
73	20	M	37.8	AM	10200	+	30	Kp	SP/MN
76	45	M	38.5	AM	36000	+	20	Ps(F)	SP/cellulitis nose
81	15	F	39.6	AM	2600	+	15	Kp	SP /NBC
95	14	F	38.2	AM	16000	+	20	Ps	SP/cellulitis
98	36	F	38.0	AM	7000	NR	18	Kp(P)	SP/ abscess
105	60	F	39	S	3000	+	20	Ps(F)	SP/cellulitis
110	02	F	37	N	8600	-	2	Kp	SP /NBC
Without clinical localization									
24	22	M	37.8	N	9800	+	20	Kp	SP
25	30	M	39.0	S	5000	+	20	Sa	SP
64	03	M	40.0	S	20000	+	17	*E coli*	SP
70	04	M	36.8	AM	8400	+	14	Kp	SP
75	15	M	39.0	AM	18000	+	18	Kp	SP
77	25	M	38.6	AM	160000	+	10	Sa.	SP
99	16	M	-	AM	18000	+	16	Kp	SP
113	12	M	<36.0	AM	24000	+	17	Kp	SP
114	11	M	<36.0	AM	8400	+	16	Kp	SP

Abbreviations:

S-Strong, AM-Ambivalent, N-negative, NR-Not recorded,
Sa-Staphylococcus aureus, Kp-Klebsiella pneumoniae, Ps-Pseudomonas species, Acb-Acinetobacter, SP-Septicemia, Pn-Pneumonia, MN-Meningitis, NECecrotizing enterocolitis.

'All culture positive from blood unless specified in parentheses (P)-Pus, (C)-CSF,(F)-l1uid from local site.

to inadequate data to define a risk group. Rest of the 105 cases were grouped under high (74 cases) or low risk (31 cases) category. Any infant who had at least one risk criteria positive was placed into high risk group. Thus, in the high risk group 48 (66%) infants had raised mESR, 47 (64%) positive impression of sepsis, 41 (54%) toxic granulation, 38 (51%) temperature abnormality and 33 (45%) abnormal WBC counts. Two or more risk criteria were present in 56 (75%) infants in the high risk group. There was no significant difference in the high and low risk groups with respect to the age and sex distribution.

The overall prevalence of SBI and bacteremia in the study population was 36% (42/116) and 13% (15/116), respectively. In the high risk group it was 55% (41/74) and 19% (14/74), respectively, and in the low risk group only one infant had bacteremia ($p<0.01$). This infant probably had a nosocomial infection. His initial blood culture was sterile. After about 36 hours of observation in hospital for poor feeding and activity, he developed abdominal distension and feed intolerance and a repeat blood culture at this time grew *Klebsiella pneumoniae.* Though the study protocol for low- risk infants was to withhold antibiotics and observe till culture report became available, the final decision to start antibiotics and hospitalization was on the treating physician. Eighty six per cent of the high risk and 26% of the low risk infants were treated with antibiotics. Remaining 14% of high risk infant had a non-infective pathology, therefore antibiotics were not required and were stopped after the first dose.

We analysed all the 5 criteria for then-relationship with bacteremia and SBI *(Tables III & IV).* Positive impression of sepsis and temperature abnormality respectively could identify about 79% and 74% of cases with SBI and bacteremia. Hypothermia was a very sensitive indicator of SBI; all the five infants with a temperature <36°C at admission had SBI, three also had bacteremia ($p<0.001$). Among the laboratory criteria presence of toxic granulation was the most sensitive and specific followed by raised mESR. Abnormal WBC counts had a low sensitivity.

On looking at combination of different criteria we found that only 6% of the infants in non SBI group fulfilled 3 criteria compared to 88% in SBI group ($p<0.001$); none had >3 criteria in non SBI group *(Table III).* Presence of any two of the following three criteria positive impression of sepsis, presence of TG and raised mESR, predicted all the cases of bacteremia and SBI (excepting one with probable nosocomial infection) and excluded 89% of cases without SBI *(Tables III & IV).*

Discussion

The oases we studied were of the kind that one might see in a busy emergency area and needs to decide whether a given infant is to be treated with antibiotics or not. Our data favors the previous observations(2-4) that being male and < 1 month of age is more frequently associated with bacterial infections *(Table II).* In our study population about 60% of the infants had a focus of localization of their infection which is much higher than those reported by others(l). This is possibly contributed by infants with respiratory focus, a number of them might have had viral infection as noted by Dagan *et al.(2).* However, in developing countries the incidence of bacterial respiratory infections is much high than the developed ones.

We used somewhat different criteria to define risk group than other authors. The

TABLE III- *Sensitivity, Specificity and Predictive Value of Various Criteria to Diagnose SBI in Infants Evaluated for Sepsis*

Criteria	SBI (n=42)	No SBI (n=63)	Sensitivity (%)	Specificity (%)	Predictive value	
					+ve (%)	-ve (%)
Impression of sepsis						
Positive*	33	14	79	78	70	84
Negative	9	49				
WBC count.						
Abnormal	23	10	55	84	70	74
Normal	19	53				
TG						
Present	36	5	95	89	88	95
Absent	2	41				
Micro ESR						
> 10 mm/h	35	13	90	73	73	91
≤10 mm/h	4	38				
Temperature						
Abnormal	28	10	74	82	74	82
Normal	10	47				
No. of criteria present						
None	01	30	-	-	-	-
One or more	41	33	98	48	55	96
Two or more	40	16	95	75	71	97
Three or more	37	04	88	94	73	92
Four or more	26	-	62	100	100	80
Five	10	-	24	100	100	66

*Includes strong and ambivalent impression of sepsis.

main differences were inclusion of TG, mESR, and temperature abnormality rather than fever, in addition to the impression of sepsis and abnormal WBC counts. These criteria used by us were selected not only because of their simplicity and cost effectiveness but also for their reasonable sensitivity and specificity in previous studies. Some of these criteria have been evaluated in past but there is limited experience with toxic granulations as a screening criteria.

Clinical impression of sepsis undoubtedly plays an important role in identifying infants with SBI and bacteremia. However, as an isolated criteria it tended to over-diagnose or miss the cases with SBI. Similar

TABLE IV- *Sensitivity, Specificity and Predictive Value of Various Criteria to Diagnose Bacteremia in Infants without Clinical Localization of Infection*

Criteria	Blood culture		Sensitivity (%)	Specificity (%)	Predictive value	
	+ve (n=9)	-ve (n=39)			+ve (%)	-ve (%)
Impression or sepsis						
Positive.	7	7	78	82	50	94
Negative	2	32				
WBC count						
Abnormal		7	56	82	42	89
Normal	4	32				
TG						
Present	9	4	100	86	69	100
Absent	0	25				
Micro ESR						
> 10 mm/h	8	14	89	53	36	94
10 mm/h	1	16				
Temperature						
Abnormal	6	2	75	94	75	94
Normal	2	31				
No. or criteria present						
None	-	18	-	-	-	-
One or more	-	21	-	-	-	-
Two or more	9	10	100	74	47	100
Three or more	8	3	89	92	73	97
Four or more	7	-	78	-	100	-
Five	2	-	22	-	100	-

.Includes strong and ambivalent impression of sepsis.

observation has been made by Baraff *et al.* (10) from a meta-analysis of five prospective studies, which had data on 415 nontoxic and 247 toxic appearing febrile infants under 60 days of age. Toxic appearance (impression of sepsis) identified only 56% of all SBI and 84% of 32 bacteremic infants in these studies, while among nontoxic appearing *(i.e.,* negative impression of sepsis), 7.5% infants had SBI; half of them had UTI. Baker *et al.* (11) also noted inability of an acute observation scale (based on social smile, activity, playfulness *etc.)* to discriminate between febrile infants aged 4 to 8 weeks with and without serious infection.

Contrary to the previous report our data

does not support the observed association between high fever and bacteremia in young infants in our population. High fever (>39.5°C) was noted in only 6 cases and only three had SBI (two culture positive). In our setting where malaria still remains a major health problem it is an equally important cause of high fever in young infants as we observed in two cases. On the other hand absence of fever cannot rule out a possibility of sepsis. In a large series of consecutive infants young than 8 weeks old evaluated for sepsis, 30% with SBI were afebrile (<37.8°C) at the time of admission(12). In our study, 3 (20%) infants with bacteremia had normal temperature (36-37.8°C) while 2 (12.5%) cases had <36°C. Two of these children had no history of fever as well. Some of the difference could be due to more frequent use of antipyretics and differences in the ability of the material perception of fever at home.

WBC counts are often used for discriminating bacterial and nonbacterial illnesses and have found a place in criteria proposed for predicting SBI by some authors(l,2). However, our data does not support use of this criteria in isolation in infants' under 2 months. Only 50% of bacteremic infants had high WBC counts, and none had low counts.

Toxic granulations represent the cytoplasmic alterations in peripheral blood neutrophils in response to bacterial infection(14) and has been found to be of greater use in differentiating localized from generalized infection or the development of complications. We found presence of toxic granules as the most sensitive and specific single criteria with a negative predictive value of 95%.

Micro ESR correlates well with conventional ESR measurement(8) and has been well established for screening of neonatal sepsis(15-17). We found mESR as a sensitive screening criteria in infants under 8 weeks of age. This is in agreement with previous observations(15-17). However, therapeutic decision-making based on mESR may be difficult because of its low specificity (75%).

We found a combination of three criteria most useful namely a positive impression of sepsis, TG and mESR. Presence of a combination of any two of these identified all the cases of SBI and bacteremia and excluded 89% of cases without SBI in this study. Apparently, sepcific variables used in combinations by different authors have varied but use of physical findings (physician impression of sick look, focal infection) and result of septic workup (WBC abnormality, ESR, pyuria) has been found effective in several studies to predict absence or presence of SBI and bacteremia(12,13). Crain and Shelov(l) found a combination of physician's impression of sepsis, WBC count < 15000/mm^3 and ESR >30 mm/hour highly sensitive (100%) in identifying bacteremia in infants under 8 weeks, while Avner *et al.* (13) found 100% sensitivity for either a combination of physician's impression of ill appearance of focal infection, and abnormal WBC counts (including increased band forms) or pyuria.

In our study the proportion of cases in low risk group was just the half in comparison to the other studies. It was because of a liberal definition of the high risk, presence of a single risk factor was good enough for inclusion in the high risk and to exclude the low risk category. Studies from the West have generally defined high risk group when two or three risk factors were present. It is for the same reason that prevalence of SBI

in our high risk group was 36% while in those analysed by Baraff *et al.* (10) was 21.2%. In the low risk group, there was only one infant who had bacteremia, even this was acquired during hospital stay. We feel that infants identified as at low risk using the criteria adopted by us are unlikely to have serious bacterial infection or bacteremia. However, the risk of UTI is not ruled out. An analysis of previous studies has shown a 3.5% rate of UTI in febrile infants younger than 8 weeks and 1% risk of SBI in 'low risk' febrile infants under 60 days(10).

Since 26% of low risk and 70% of non SBI high risk group infants were treated with antibiotics, it is not possible to comment about the value of the risk criteria in deciding the need for antibiotic therapy. However, this data does suggest that infants in whom the impression of sepsis is negative, TG are absent on blood smear and mESR is < 10 mm during first hour are very unlikely to have SBI or bacteremia and hence can be observed without antibiotics. On the other hand, those who are assessed as having positive impression of sepsis or abnormal temperature with either mESR > 10 mm in first hour, or toxic granules on peripheral smear are likely to have SBI/bacteremia and should be admitted and treated for sepsis till the results of more specific[1] investigations and culture are available. An independent evaluation of these criteria may be done in a given population, as one patient population may not be a true representative of other patient population(18).

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