ORIGINAL RESEARCH

Bacteremia In Febrile Young Children: Clinical Predictors

Shammi Kumar Jain[1], Jayashree Nadkarni[2], Neeraj Gour[3]

ABSTRACT

Background: Febrile young children often present to the emergency department. Some of them are at a risk for developing serious bacterial illness. There exists scanty data on risk of bacteraemia among febrile infants of developing countries and what clinical predictors, if any, could identify febrile children with bacteraemia. To assess prevalence of bacteremia among hospitalized febrile children aged 3 months to 36 month, to study risk factors for bacteremia in them and to find out the bacterial isolates.
Material and Method: 84 consecutive febrile hospitalized children attending the Paediatric Unit, Kamla Nehru Hospital, Bhopal, aged 3 to 36 months with rectal temperature ≥ 38 C(100.4F), with negative H/o of parenteral antimicrobial use were included in the study. Study subjects underwent full clinical evaluation and lab investigations including blood culture for aerobic organisms. Variables examined were age, sex, temperature, duration of fever, WBC count, Absolute Neutrophil count, Yale score, previous h/o hospitalization, birth weight and vaccination status. We tried to identify clinical predictors of bacteremia in the culture positive cases.
Results: 50% (42) subjects were bacteremic. Klebsiella (38%), Staph aureus (28.5%) and E.coli (23.80%) were the major isolates. The variables found to be significant independent predictors of bacteremia were duration of fever >3 days,birth weight <2.5 kg, no vaccination, low weight for age, stunting, presence of edema, not accepting feed, palpable organomegaly (and neutrophil count >7000.
Conclusion: A clinical diagnostic model could improve decision making by increasing sensitivity for detecting serious bacterial infection in young children. It would specially benefit clinicians practicing in low resource settings.

Keywords: Fever, Young Children, Bacteremia, Clinical Predictors

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INTRODUCTION

Fever is common complaint in infancy and childhood and bacteremia is one of the more serious causes of such fever. Some of these children are at risk for developing serious bacterial illness and may have an early stage of an infection, including bacteremia, occult pneum- onia, UTI or rarely meningitis. Bacteremia is the circulation of bacteria in blood.[1] Bacteremia is often associated with severe morbidity and mortality in children.[2] It may presents as illness with fever or it is symptomless sometimes. When bacteremia is associated with systemic inflammatory response syndrome is called sepsis. Sepsis may lead to septic shock, multiorgan dysfunction syndrome and death. By hematogenous spread bacteria can cause infection away from the original site of infection e.g. endocarditic, ostomyelitis. The source of fever may not be readily apparent on initial assessment. The evaluation of fever in young children has great clinical importance, as any of the serious bacterial infections whose presence it may signal may have grave morbidity if not treated on time. However, there exists scanty data on risk of bacteraemia among febrile infants of developing countries and what clinical predictors, if any, could identify those febrile infants with bacteraemia.[3]

Various studies show that some features might predict bacteremia singly or in combination[4,5,6] for example, Mc Gowen et al reported that age between 7 and 24 month temperature between 39.4°C and 40.6°C & WBC count >20,000 /mm^3 were criteria with high specificity for of bacteremia.[7] In another study of febrile children aged less than 2 years, Teele et al found that for WBC of > 15000/mm^3, age between 7 and 18 month, temp more than 38.8°C, and a diagnosis of pneumonia, Upper respiratory infection, or fever of unknown origin had an increased likelihood for bacteremia.[3,8] While these studies show that simple criteria can predict bacteremia, their findings may not extrapolate to children in other settings as in developing countries where children have associated co morbidities and undernutrition. And also in the countries where the PCV 7 and HIB

vaccination is not a routine vaccination[9] and even the complete vaccination coverage is 61%[10] in india and 42% in our state.[11] The prevalence of occult bacteremia in this age group would be different.

In the present study we have tried to investigate how simple clinical features and lab parameters could predict bacteremia in young febrile children seen in a tertiary care hospital setting.

MATERIALS AND METHODS

Study type: Prospective hospital based observational study.

Study location: Children's Emergency Ward of Department of Pediatrics, Gandhi Medical College and associated Kamla Nehru Hospital, Bhopal.

Study duration: November 2012 to October 2013.

Ethical consideration: Ethical approval was obtained from the Medical College Hospital Ethical Committee.

Participant recruitment: All children aged 3-36 month, who presented with fever during November 2012 to October 2013 and who fulfilled the following eligibility criteria were enrolled into the study: (i) rectal temperature 38 ºC and above and (ii) no antibiotics received within seven days before presentation.

Sampling calculation: According to Essential Pediatrics, Ghai, 8th Edition, risk of serious bacterial infection in age group of 3 to 36 months old children is 5%. On the basis of same prevalence we have calculated our sample size using following formula:

Sample size (N) = Z^2 PQ/e^2 = 1.96x1.96 x 5 x95/5x5 = 73

Where Z = 1.96 taken value for 95% confidence level

P= prevalence taken as 5%

Q= 100-P

e= allowable error taken as 5%

Using above formula sample size was calculated as 73 and we have taken 84 participants as sample size for this study.

Data collection and processing: All eligible cases have been identified at admission, and informed consents were obtained from parents of children. A full history was obtained on each child, including name, age, sex, occupation of parents, presenting symptoms, durations, drug history, and history of past illnesses. A clinical examination then carried out, and temperature, weight, length, vitals recorded in a predesigned proforma.

Conventional method of blood culture was used. 3 to 5 mL of venous blood was obtained aseptically from a peripheral vein, of which 1-2 mL was inoculated into brain heart infusion broth and incubated at 37 ° C. Bottles were examined daily for turbidity, haemolysis, or other evidence of growth and were sub-cultured daily onto chocolate agar, blood agar, and Mac Conkey plates. Inoculated blood culture media were discarded as negative if there was no growth after continuous incubation for 72 hours. Colonies were identified morphologically by Gram stain and biochemically. Organisms were considered 'contaminants' when these were aerobic spore-bearers. An aliquot of the blood sample was used for estimating hemoglobin, total white cell count with differentials, blood film for red cell, and white cell morphology. Thick blood film for malaria parasites was also made.

Operational definition: Bacteremia in this study was simply the growth of a known pathogen from the aseptically-drawn blood sample of a subject.

STATISTICAL ANALYSIS

Prediction of bacteremia by clinical features was assessed. Association between categorical variables and bacteraemia was assessed by means of chi square test, T test and p value. Risk was estimated by odds ratio (OR).

RESULTS

Febrile children who fulfilled the study criterion and who were admitted in children ward were enrolled in study during the study period. Total 88 children were enrolled. 4 children were excluded as their blood culture isolates were considered contaminants. Pathogens were isolated in 42(50%) patients. The maximum number of cases belonged to 3-12 month of age (Fig I). No significant difference is observed between mean age of non bacteremic and bacteremic patients. (9.9 months Vs 11.26 months). Bacteremia is observed in increased frequency in infants as compared to the other age groups i.e.13-24 and 25-36 months. Though no significant relationship of bacteremia with age is shown by data analysis ($p>0.05$). Similarly no significant difference is observed in sex ratio of patients with or without bacteremia.

In 50% of patients (n=42), pathogens were isolated. Gram negative organisms were more common (71% of all positive cultures). Klebsiella is the commonest organism grown in 38% of blood cultures (table-v). It is followed by Staphyllococcus, E. coli, Pseudomonas, and Group D streptococcus. Out of 12 Staphylloccoci, 10 were Coagulase Positive and one was Coagulase Negative Staphyllococcus aureous and one was MRSA.

Signs and lab parameter were compared between bacteremic and non-bacteremic Children. The varia-

bles found to be significant independent predictors of bacteremia were duration of fever >3 days (p=.015), no vaccination (p=.00045), low weight for age (p=.02), stunting (p=.014), presence of edema (p=.04), not accepting feed (p=.039), organomegaly (p=.038) and neutrophil count >7000(p=.037).

We didn't find any association between increased WBC count and bacteremia (Table I) . Similarly Yale score >10 and chest infiltrates in X-ray were also not found to be significantly associated with bacteremia.

Association between indices of physical growth and bacteremia that describe the child's nutritional status of child were also evaluated. We found that in comparison to non bacteremic patients, children who were underweight, stunted or had pedal edema were more prone to bacteremia.

Higher mortality was observed in bacteremic children. There was a 2.5 fold increase risk of mortality among children with bacteremia.

DISCUSSION

Fever, a very common clinical complaint in childhood worldwide is a common reason for seeking health care. Bacteremia is an important cause of fever and can be associated with severe morbidity and even mortality if not diagnosed on time. The gold standard for the diagnosis of bacteremia is blood culture. However it may take up to 48 hrs for the result of blood culture to be known. In a busy setting, the physician requires a rapid and effective strategy to assess the risk of bacteremia in a child with fever. Some valuable clinical parameters can predict the likelihood of bacteremia in a febrile child just presenting for health care, long before culture results are obtained. The present study sought to identify such predictors in children between 3-36 month age group seen in a tertiary care hospital setting.

A total of 84 Blood samples were collected among which 42(50%) blood cultures grew pathogenic organisms. The results of our study are similar to Omola et al.[3] Hasson et al. [12] and Huda et al [13] that prevalence of bacteremia in febrile children is much higher in developing countries as compared to developed countries. A recent study done by A. Bang, and P. Chaturvedi [14] (2009) in India also found 28% prevalence of bacteremia in febrile children.

Overall gram negative organisms (71%) are the most common organisms to grow.

A study conducted by Levy et al (1996) found that gram negative organism are isolated in >50% of pediatric patient with bacteremia. He found that Klebsiella, Pseudomonas and E.coli (26, 20 & 19%) were the predominant organisms. He concluded that Klebsiella is currently the most common organism causing gram negative bacteremia in children. No wonder Klebsiella (38%) is the commonest organism to grow in our study also followed by Staph, E. coli, Pseudomonas and Group D streptococcus (29, 24, 7 & 2% respectively).

Typhoidal/non typhoidal salmonellae were not grown. Plausible reason may be that for non typhoidal salmonella, bacteremia is present only in 1-5% of cases, further stool culture is more appropriate than blood culture. For typhoidal salmonella, Result of Blood cultures are positive in 40-60% of the patient seen early in the course [Nelson]. As our most patients (63 out of 84), presented within 4 days of fever this may be one of the reason. Secondly Typhoidal salmonella is better grown in bile broth which we did not use. Similarly Pneumococci were not grown. Recovery of Pneumococcus from positive blood culture may be difficult due to autolysis of Pneumococci such autolysis may distort the appearance of Pneumococci on gram stain or prevent growth on sub subculture or broth.

Both of these groups of Bacteria can be better picked up by automated Blood Culture system & we used conventional method of Blood Culture this may be the reason.

4 in the non bacteremic group and 3 in bacteremic group have UTI. Klebsiella, E. coli and CoNS were recovered from their blood cultures in bacteremic group. Out of 29, 2 patients with gram negative bacteremia had UTI.

Out of 29, 15 patients with gram negative bacteremia have pneumonia. 12 were having klebsiella and 3 were having Ecoli.

Age was not a predictor of bacteremia in our study. There was no significant difference between mean age of bacteremic and non bacteremic patients. (11.26 months Vs 9.9 months). Bacteremia was higher in infants as compared to the other age groups i.e.13-24 and 25-36 months. The data analysis though, did not show any significant relation of bacteremia with age (p>0.05). Similarly there was no significant difference in sex ratio of patients with or without bacteremia.

This is in accordance with finding of Tina stathakis et al. (2007) [15], who studied febrile patient aged 3 months - 36 months in Australia. This is also in accordance with finding with Grace M. Lee et al [16] who found 6-12 months (OR 1.06, 95% C.I.: 0.73-1.55) and 24 to 36 months old (OR 0.75 95% CI : 0.46-1.23) age group showed no significant differences in the odds ratio when compared with 12-24 months old group for occult bacteremia.

However Mc Gowan et al & Teele et al found that an age of 24 months or less was the epidemiological factor with the highest sensitivity for bacteremia. Omola (2002) working in Nigeria also documented

Table I : Association of presenting complaints with bacteraemia

Clinical feature	% of bacteraemic (n=42)	% of non-bacteraemic (n=42)	Odds ratio (95% CI)	p value
Fever > 3 days	40.47	16.66	3.40(1.23-9.42)	0.015*
↑ rate of breathing	28.57	45.23	0.48(0.20-1.20)	0.11
Diarrhoea	16.66	21.42	0.73(0.25-2.19)	0.57
Vomiting	9.52	21.42	0.39(0.11-1.37)	0.13
Not accepting feed	23.80	7.14	4.06(1.03-16.02)	0.034*
convulsion	35.71	33.33	1.11(0.45-2.73)	0.81
unconsciousness	11.9	7.14	1.76(0.39-7.88)	0.45
Excessive crying	9.52	4.76	2.11(0.36-12.17)	0.39
(* p value < .05)				

Table II. Association of physical findings and chest X-ray with bacteremia.

Parameters	% of Bacterimic	% of Non- Bacterimic	Odds Ratio (95% CI)	p Value
	54.05	58.53	0.60 0.25-1.48	0.26
Chest infiltrate	52.38	54.76	1.10 0.47-2.60	0.82
Palpable Organomegaly	42.85	14.28	4.5 1.56-12.97	0.0037*
(* p value < 0.05)				

Table III. Association of Temperature, WBC and Neutrophil Count with bacteremia.

Paramer	Bacteremic Pt.	Non bacteremic Pt.	p value
Temperature	Mean 101.61 S.D. .874	Mean 101.55 S.D. .864	0.792
WBC Count	Mean 11045 S.D. 5153	Mean 10751 S.D. 3963	0.771
Neutrophil Count	Mean 6686 S.D. 5183	Mean 4692 S.D. 3050	0.037*
(* p value < 0.05)			

that age below six months is associated with significantly higher risk with bacteremia (OR 3.2 p value 0.013). This may be due to inclusion of patient having age below 3 months as in our study we don't include the patient having age below 3 months.

Our study we found that vaccination have a protective role against risk of developing bacteremia (P value -.000458). Among bacteremic patients 50% of patients were immunized as per age and 50% had partial / no vaccination. Among non bacterimic patients 85.71% (n=36) have vaccination as per age. This is in accordance with Lee GM[16] who found that the wide spread introduction of a conjugated vaccine against HIB was followed by a decline in the overall prevalence in 3-36 month age group of the occult bacteremia from all pathogens to less than 2%.

Similar results are also shown by Herz AM & Greenhow TL[17] that implementation of routine vaccination with conjugated pneumococcal vaccination resulted in 84% reduction of pneumococcal bacteremia (0.2-1.3%) and 67% reduction in overall bacteremia (0.7-1.6%) in study population.

In our study fever of more than 3 days were associated with significant risk of bacteremia. Hsiao AL et al.[18] (57-180 days old infant) and Issacman DJ et al[19] (3 month to 36 months) also showed significant association of duration of fever with occult bacteremia in univariate and multivariate model. Study done by Guen CG et al[20] (2007) provides an overall median prior duration of fever of 24 (range 0.25-192) hours Vs. 4.6 (±3.13) hours in children with occult bacteremia. However studies done by Pratt A. et al[21], Trautner BW et al[22] and Fernadez Lopez A[23] did not found any association between duration of fever and risk of bacteremia. According to Elshout G.[24] the plausible explanation of this inconclusive result is that meningitis and sepsis are serious bacterial infection that can develop relatively quickly; whereas bacterial pneumonia and UTI take a relatively longer period of time to manifest. Another explanation is that these studies were performed in developed countries where coverage of vaccination is very high and HIB Vaccination is given.

Table IV: Association of Age, Vaccination & Nutritional Status (Wasting, Stunting, Underweight and Pedal Edema) with Bacteremia.

Nutritional Status	% of Bacteremic	% of Non - Bacteremic	Odds Ratio (95% CI)	p. Value
Age≤ 12 Months	73.81	69.03	2.1/ 0.6-7.0	0.20
Vs 13-24 Months	11.91	23.79	0.52/0.12 -2.33	0.40
Vs 25-36 Month	14.28	7.14		
No/Partial Vaccination	50	14.2	6/2.09-17.23	0.00045*
Underweight (weight for age <-2SD)	76.1	52.3	2.9/1.1-7.4	0.02*
Stunting (height for age <-2SD)	54.7	28.5	3.03/1.2-7.4	0.014*
Wasting (weight for height <-2SD)	47.6	45.2	1.1/.47-2.6	0.8
Pedal Edema (B/L)	9.5	0	N.A.	0.04*
(* p value < .05)				

Temperature was not a predictor of bacteraemia in our study, which contrasts with the previous findings by workers, who found higher temperatures to be associated with risk of bacteraemia. For example, Teele et al.[8] found no positive blood cultures in children with temperature of <38.9 ºC, while 4.1% of those with temperature of >38.9 ºC had positive blood cultures. In another study, McCarthy et al [6] documented positive blood cultures in 7.3% of children with temperature of 40 ºC. Their findings suggest that risk of having bacteraemia increases with increasing temperature, and bacteraemia was uncommon in children with temperature of <38.9 ºC. Recent study done by Omola et al.[3](2002, Nigeria) and Tina Stathakis et al.[15](2007, Australia)also documented that higher temperature is not significantly associated with bacteremia. Akpede et al. [25] (1993, Nigeria) concluded that prevalence of bacteremia was not influenced by temperature.

Bacteria	No.	%
Staphyloccocal Aureous	12	28.57
Klebsiella	16	38.09
E.Coli	10	23.80
Pseudomonas Aeroginosa	3	7.14
Gr. D. Streptococus	1	2.38
Total	42	100

Table V: Showing type and number of bacterial isolates among bacteremic patients.

In our study the symptom of "not accepting feed" was significantly associated with risk of bacteremia.

In our study we found that indices of physical growth do influence the prevalence of bacteremia. Weight-for-age is a useful tool for continuous assessment of nutritional progress and growth. Children whose weight-for-age is below -2SD from the median of reference population are classified as underweight. There was a higher rate of bacteraemia in those who were underweight. This agrees with Omola et al. ($p=0.025, \chi^2=4.98$) and Nielsen et al.[26](OR=1.8, 95%CI =1.3-2.5) who found similar results. Similarly pedal edema (pitting) is an indicator of severe acute malnutrition. It was found to be significantly associated with risk of bacteremia. Stunting is an indicator of chronic malnutrition. Children whose Height-for-age is below -2SD from the median are classified as stunted. It was also significantly associated with bacteremia in our study. This is in contrast with study of Omola et al.[3] and Nielsen et al.[26] who did not find any association between bacteremia and stunting.

We found that neutrophil count is better predictor of bacteremia than total WBC count. Herz A.M. et al.[17] (2005) also concluded that given the increasing relative incidence of bacteremia with organisms other than S. pneumoniae, WBC count > 15,000 becomes a less useful screening tool. In our study we found that mean neutrophil count in bacteremic patients was significantly higher than non bacteremic patients (6686 Vs 4692, p=0.034). This agrees with Winchester et al.[2] and Todd[27] who found that if the

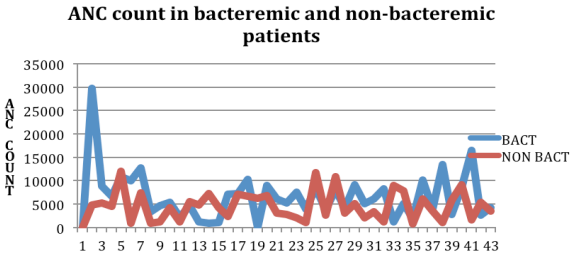

Figure I: Distribution of Absolute Neutrophil Count in bacteremic and non bactremic cases.

absolute number of neutrophils was >10,000/mm3, or if the absolute number of non-segmented neutrophils was >500/mm3, or both, the patient had an 80% chance of having a severe bacterial infection. Isaacman[19] et al. demonstrated an increased risk of bacteraemia was associated with neutrophil count exceeding 9.46 X 10^9/L. Data from Kupperman et al.[28] showed that a neutrophil count ≥10000/mm3 was a better predictor of bacteraemia than a WBC ≥ 15000/mm3.

Abnormally palpable organomegaly was significantly associated with risk bacteremia in our study ((p value - 0.0037).These organs may be pushed down due to respiratory distress or may be enlarged due to bacterial sepsis. Spleen may also be palpable due to malaria. In our study we found that abnormal palpable organomegaly is significantly associated with risk of bacteremia .

CONCLUSION

Bacteraemia often represents a diagnostic challenge in developing countries, since most healthcare centers lack adequate laboratory facilities to do the necessary bacterial cultures or are unable to do so on time. Besides, physicians tend to underestimate the likelihood of serious bacterial infection in young children with fever. A simple prediction tool can be used to risk stratify this population and assist in clinical decision making. Thus, a practical utility of this study for our environment is that the findings can be used for developing clinical guidelines.

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