



Bacteremia in Febrile Children: Its Correlation with Birth Weight, Feeding Practices, Vaccination and Malnutrition

Shammi Kumar Jain^{1*}, Neeraj Gour², Jayashre Nadkarni¹ and Sneha Bhatia¹

¹Department of Pediatrics, GMC, Bhopal, India.

²Community Medicine, GGS Medical College, Faridkot, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author SKJ designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author NG managed the literature search and data analysis. Authors JN and SB proofread the manuscript and all authors approved the final manuscript.

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ABSTRACT

Background: In children under 3 years old, fever is a common presenting symptom to the physician. Fever may be an indication of a mild infectious process such as a viral upper respiratory infection or a more serious infectious process such as bacteremia, bone and joint infections, urinary tract infection, pneumonia, soft tissue infection, bacterial enteritis, meningitis, sepsis and possibly death. The evaluation of fever in this age group has great clinical importance, as any of the serious bacterial infections whose presence it may signal may have grave morbidity if not treated. However, there exists scanty data on risk of bacteraemia among febrile children of developing countries and what clinical predictors, if any, could identify those febrile infants with bacteraemia. Present study aims to determine the prevalence of bacteremia in febrile children and the effect of low birth weight, poor feeding practices & coverage of vaccination and malnutrition which are more prevalent in developing countries like India.

Objective: 1. To assess prevalence of bacteremia among hospitalized febrile children aged 3

*Corresponding author: Email: drneeraj_g04@yahoo.com;

months to 36 month.

2. To study effect of birth weight, feeding practices, vaccination and malnutrition on bacteremia in febrile children.

3. To find out different bacterial isolates.

Methods: 84 consecutive febrile children attending children emergency ward of Kamla Nehru Hospital, Bhopal, aged 3 months to 36 months with rectal temperature ≥ 38 C (100.4F) with negative H/o of antimicrobial use and who requiring hospitalization were included in the study. Exclusion criteria were current use of antimicrobial use. Children meeting eligibility criteria were studied to identify clinical predictors of bacteremia. Study subjects underwent full clinical evaluation and had blood culture done for aerobic organisms by standard method. Variable examined were age, sex, temperature, birth weight, vaccination, feeding practices, physical indices & blood culture results.

Results: 50%(42) subjects were bacteremic. *Klebsiella* (38%), *Staph aureous* (28.5%) and *E. coli* (23.80%) of positive cultures were commonly associated. 9 variables were found to be significant independent predictor of bacteremia. These were duration of fever >3 days (p=.015), birth weight <2.5 kg, no vaccination (p=.000458), low weight for age (p=.022), stunting (p=.014), presence of edema (p=.04).

Conclusion: above mentioned factors are associated with increased risk of bacteremia in febrile children. Prevention of these factors can greatly reduce the chances of bacteremia in febrile children. Clinician practicing in such a setting needs to be aware of the increased risk of bacteremia in children with these clinical features.

Keywords: Fever; young children; bacteremia; malnutrition; vaccination; feeding practices.

1. INTRODUCTION

Fever is a common presenting complaint among pediatric patients, accounting for approximately 20% of emergency department (ED) visits by children [1,2]. Hence, management of the febrile child is a challenge faced by emergency physicians on a daily basis. Despite the fact that the vast majority of children with fever have self-limited viral illnesses [3], there is a finite number who may harbor serious bacterial illnesses (SBI), and, in many cases, these patients are clinically indistinguishable from the rest. The emergency physician's challenge is to identify and treat those children who have SBIs while avoiding overtreatment with antibiotics of those without SBIs, thereby limiting the propagation of antimicrobial resistance. Making this distinction is particularly difficult early in the course of a febrile illness. Studies in developed countries show that the risk of bacteremia in vaccinated febrile child aged 3-36 months is < 2% [4,5,6]. However, there exists scanty data on risk of bacteraemia among febrile children of developing countries and what clinical feature, if any, could identify those febrile infants with bacteraemia [7].

M.V. Nielsen [8] pointed out that poor socio-economic status and chronic malnutrition could impair the immune response and predispose to invasive infection. Some studies found that parameters for underweight and wasting,

indicators for acute malnutrition were significantly associated with bacteremia [7,8]. Feeding practices are invariably associated with nutritional status. Poor feeding or faulty feeding technique causes poor nutritional status and ultimately make the child more prone to bacteremia. Similarly low birth weight babies are more prone to poor growth, increase rate of childhood illness and readmission to hospital [9]. It is also found that vaccination has a positive effect upon fever prevalence and related bacteremia [10]. These all factors appear to be interlinked with each other. Present study aims to find out the prevalence of bacteremia in febrile children and its correlation with feeding practices, birth weight and vaccination.

2. MATERIALS AND METHODS

This prospective hospital based observational study was carried out in the Children's Emergency Ward of Department of Pediatrics, Gandhi Medical College and associated Kamla Nehru Hospital, Bhopal. This hospital is a major referral center of Central India.

Ethical approval was obtained from the Medical College Hospital Ethical Committee. 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°C and above and (ii) no antibiotics received within seven days before presentation.

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:

$$\text{Sample size (N)} = Z^2 PQ/e^2 = 1.96 \times 1.96 \times 5 \times 95/5 \times 5 = 73$$

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 more than calculated sample size.

All eligible cases were 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 and durations, drug history, and history of past illnesses, feeding practices and vaccination. A clinical examination was then carried out, and temperature, weight, length, vitals recorded in a predesigned pro forma.

Conventional method of blood culture (not automated) has been employed. 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 subcultured daily onto chocolate agar, blood agar, and MacConkey 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. The operational definition of bacteraemia in this study was simply the growth of a known pathogen from the aseptically-drawn blood sample of a subject. Prediction of bacteraemia by clinical features was assessed. Association between categorical

variables and bacteraemia was assessed by means of chi square test and p value employing univariate analysis. Risk was estimated by odds ratio (OR). Significance of results was assessed at 95% confidence level, setting alpha error at 5% and probability 5%.

3. RESULTS

During the study period 88 febrile children who were admitted in children ward and who fulfilled the study criterion were enrolled in study. In 4 children, Blood culture isolates were considered as contaminants so were excluded. Pathogens were isolated in 42(50%) patients. The maximum no. of cases belonged to 3-12 month of age (Fig. 1). 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 M:F-2.6:1.

Pathogens were isolated in 42(50%) patients. Gram -ve pathogen were more common and constituted 71% of all positive cultures, with *Klebsiella* being the commonest single isolate found in 38% of isolates (Fig. 2). Out of 12 *staphylococcus aureus* there were 1 MRSA, 1 Coagulase Negative *Staphylococcus aureus* and rest were coagulase positive *staphylococcus aureus*.

Various clinical features were compared between bacteremic and non-bacteremic Children. After doing univariate analysis variables found to be significant predictors of bacteremia were birth weight <2.5 kg (p=0.0052), breastfeeding (p=0.029), no / partial vaccination (p=0.000458), low weight for age (p=0.022), low height for age (p=.014) & presence of edema (p=.04).

Association between bacteremia and indices of physical growth that describe the nutritional status of child were also analyzed. We found that bacteremia was significantly higher in children who were underweight, stunted or had pedal edema, as compared to non bacteremic children. (Table 1) Low birth weight is also significantly associated with risk of bacteremia. Exclusive breast feeding is 4 times protective against bacteremia. Similarly no / partial vaccination significantly associated with bacteremia (Table 2).

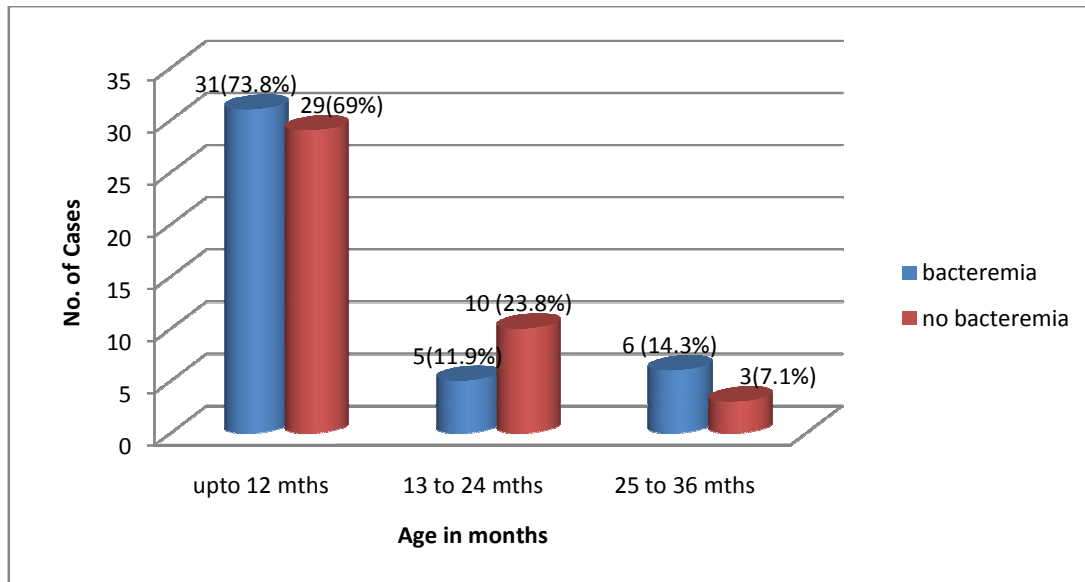


Fig. 1. Age wise distribution of children with bacteremia

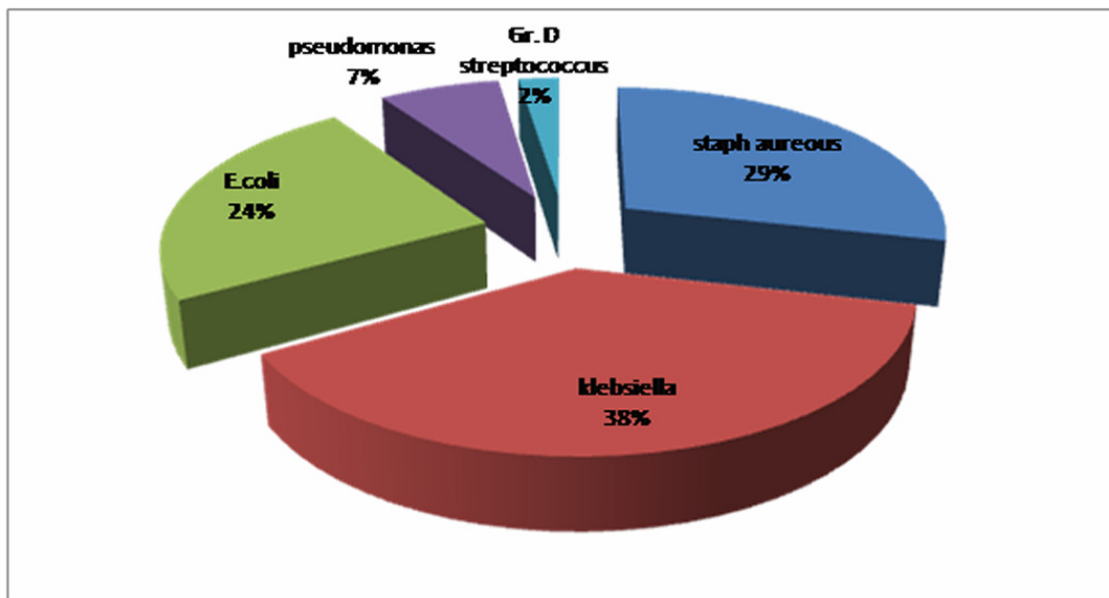


Fig. 2. Distribution of organisms isolated from bacteremic cases.

Mortality was higher in children with Bacteremia. There was a 2.5 fold increased risk of death among children with bacteremia compared to those without bacteremia (5 Vs 2, 11.9% Vs 4.76%, OR- 2.7).

4. DISCUSSION

Fever, a very common clinical complaint in childhood worldwide and accounts for

approximately 20% of emergency department visits. 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. There exist scanty data on risk of bacteremia in febrile children in developing countries. Some valuable clinical parameters can predict the likelihood of

Table 1. Association of Nutritional Status (Stunting, Wasting, Underweight and Pedal Edema) with Bacteremia

Nutritional Status	% of Bacteremic	% of Non-Bacteremic	Odds ratio (95% CI)	P value of chi-square.
Underweight (WAZ<2)	76.19	52.38	2.91 (1.14-7.40)	.022*
Stunting (HAZ <2)	54.76	28.57	3.03 (1.23-7.47)	.014*
Wasting (WHZ <2)	47.61	45.23	1.10 (0.47-2.60)	.82
B/L Pedal Edema	9.52	0	N.A.	.04*

HAZ = Height-for-age <2 SD. WAZ= Weight-for-age <2 SD. WHZ= Weight-for-height <2 SD

(* p value < .05)

bacteremia in a febrile child just presenting for health care. Identification of such risk factors and appropriate preventive measurement to reduce them can reduce the burden of bacteremia and help in identifying the bacteremic febrile children early long before culture results are obtained. The present study sought to identify such risk factors 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. [7] Hasson et al. [11] and Huda et al. [12] 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, 2009 [13] in India also found 28% prevalence of bacteremia in febrile children.

Age was not a predictor of bacteremia in our study. The maximum no. of cases belonged to 3-12 month of age. 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 M:F -2.6:1.

In our study we found that vaccination have a protective role against risk of developing bacteremia ($p=0.000458$). Among bacteremic patients 50% of patients were immunized as per age and 50% had partial / no vaccination. Among non bacteremic patients 85.71% (n=36) have vaccination as per age. To conclude 78% of non /

partially vaccinated febrile children had bacteremia.

This is in concordance with Lee GM et al. (1998 USA) [4]. In his study all children seen through 1993 to 1996, 3 month to 36 months of age with temperature of $\geq 39^{\circ}\text{C}$, with no identified source of infection and discharged to home were considered to be at risk for occult bacteremia and included in study. He 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%.

Subsequently Alpern ER et al.,2000 [5] also reported the lower prevalence of occult bacteremia i.e. 1.9%(95%CI: 1.5%-2.3%) in post HIB vaccine era. *Pneumococcus* accounted for 82.9% of all pathogen and *H influenzae* was not a causative organism in that cohort.

Similar results are also shown by Herz AM & Greenhow TL, 2005 [6] 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. They conclude that since the release & wide spread use of pneumococcal vaccine, cases of Pneumococcal bacteremia have fallen.

Novignon & Nonvignon [10] in their study "Prevalence of fever in children under 5 yrs in 4 sub Sahara African countries" found that children vaccinated against fever related disease were less likely to report fever. This relationship does not come as a much surprise as vaccination against these diseases has been

Table 2. Showing distribution, P value, sensitivity, specificity, PPV, and NPV of various clinical features

Parameter	Bacteremic children (n=42) %	Non-bacteremic children (n=42) %	Sensitivity (%)	Specificity (%)	PPV	NPV	Odd's ratio (95%C.I.)	P value of chi-square.
Age _≤ 12 months	73.80	69.04	48	86	52	67	<u>2.14</u>	0.20
Vs 13-24 months	11.90	23.80					(0.65-7.01)	
Vs 25-36 month	14.29	7.15	84	9	52	33	<u>0.53</u>	0.40
							(0.12-2.34)	
Low birth weight (n=67)	48	16.66	48	82	71	65	<u>4.61</u>	.0052*
							(1.52-14.43)	
No/Partial vaccination	50%	14.28	50	86	78	63	<u>6</u>	.000458*
							(2.09-17.23)	
Inadequate/Faulty feeding technique	42.85	30.95	43	69	58	55	<u>1.67</u>	0.25
							(0.68-4.1)	
EBF (n=43)	47.82	80	48	20	41	25	<u>0.23</u>	0.029*
							(0.06-0.9)	

*p value < .05, EBF exclusive breast feeding.

well embraced and practice across several health systems in developing countries. This also shows consistency with literature that effective vaccination has positive effect on fever prevalence.

We also studied feeding pattern in our study. In our study 36.9% of patient had inadequate feeding or faulty feeding technique (FFT) was present. F.F.T. / inadequate feeding was said to be present when –

1. Below 6 months: If bottle feeding is present.
2. After 6 months: Exclusive breast feeding is present / Top + Breast feeding is predominant mode of feeding / bottle feeding is present / weaning not established and milk is predominant food.

Feeding bottles are liable to bacterial contamination and infant is more prone to develop bacteremia. Similarly after 6 month of life predominant milk feeding without weaning being started leads to poor nutrition. In our study patients who were in bacteremic group shown increased frequency of faulty feeding pattern (42.85% Vs 30.95%, OR-1.67) however this association is statistically not significant (P value > .05).

It is found that exclusive breast feeding have 4 times protective role against bacteremia. ($p=0.029$, O.R.-0.23). In our study there were total 43 patients who were aged between 3-6 months. In this age group exclusive breast feeding were present in 80% of non bacteremic patients whereas in bacteremic group it is present only in 47% of patients. Breast milk fully meets the nutritional requirement of infants in the first few months of life. It contains antimicrobial factors such as macrophages, lymphocytes, secretory IgA, anti-streptococcal factor, lysozyme and lactoferrin which provide considerable protection not only against diarrheal diseases and necrotizing enterocolitis, but also against respiratory infections in the first of life. It is easily digested and utilized the normal and premature babies. Moreover it prevents malnutrition and reduces infant mortality [14].

In our study we found that low birth weight was significantly associated with risk of bacteremia in febrile patients (p value = .0052, OR=4.69, 95% CI; 1.52-14.43). In our study out of total patients ($n=84$), we knew the birth weight of 67 patients. Rate of bacteremia was higher in LBW patients as

compared to non LBW patients (48% Vs 16.6%). Most L.B.W infants are preterm, some are term but S.G.A. Preterm infants are vulnerable to wide spectrum of morbidity like developmental disability, chronic lung disease, poor growth, increase rate of childhood illness and readmission to hospital [9]. Nutritional management is critical for immediate survival as well as subsequent growth & development of LBW babies. Immaturity & poor Neonatal reflexes often precludes the breast feeding at birth. Use of alternative method of feeding often delays breast feeding or breast feeding not established at all. This leads to faulty feeding technique & often results in poor growth which makes the child more vulnerable to infection in later life.

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. [7] ($p=0.025$, $\chi^2=4.98$) and Nielsen et al. [8] (OR=1.8, 95%CI =1.3-2.5) who found similar results. Wasting is an indicator of acute malnutrition. Wasting is defined as weight for height < - 2SD from the median. We couldn't find any association between wasting and risk of bacteremia (P value > 0.05). This agrees with Omola et al. [7] who also didn't find significant association between wasting & risk of bacteremia (P value -0.893 χ^2 - 0.043). However Nielsen in his study among 1196 children in Rural Ghana, found that wasting is significantly associated with bacteremia (OR -1.9, 95% CI: 1.2-2.8). Similarly pedal edema (pitting) is an indicator of severe acute malnutrition. It was found to be significantly associated with risk of bacteremia ($p=0.04$). According to bulletin of WHO [15], there is high prevalence of pneumonia, bacteremia and UTI in children with malnutrition. According to Bhambal S et al. [16]. "Despite the absence of clinical signs children with SAM are nearly all infected, particularly if they have poor appetite." 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. [7] and Nielsen et al. [8] who did not find any association between bacteremia and stunting.

5. CONCLUSION

The incidence of bacteremia in febrile children in our country is higher than developed countries. Gram negative bacteria are the most common pathogens in febrile children. In the context of large population, the absolute number of febrile children and the burden of fever remain enormous in India. Bacteraemia, a major cause of fever in children, 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. Bacteremia is associated with significant morbidity and mortality in children. Efforts to reduce bacteremia and its consequences should start right from the antenatal period by improving the maternal nutrition, vaccination, health hygiene thus reducing the chances of having LBW babies. Similarly breastfeeding should be well promoted. Its nutritional superiority to any other food in first 6 months of life, its anti infective property and readily availability make breast feeding the most cost effective tool to prevent bacteremia and malnutrition particularly in first 6 months. Higher rate of bacteremia in our setup may be attributed to lower vaccination coverage i.e. 61% in India and 42% in our state (M.P.) [17,18]. Vaccination appears to be most cost effective tool in developed countries in reducing bacteremia. Robust vaccination coverage can decrease the rate of bacteremia in febrile children comparable to developed countries. Also we must include pneumococcal and Hib vaccine in our routine vaccination schedule. Maintaining good nutritional status is the key to prevent malnutrition and bacteremia. Counseling of mother about nutrition and feeding practices is equally important. Bacteremia related mortality is still high in our country so the treating physician must be well aware of such risk factors to identify and manage bacteremia early.

ETHICAL APPROVAL

Permission of institutional ethical committee was sought and informed consent was also obtained from all study participants.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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