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Original Research Article

A study of predictors of occult bacteremia in febrile children 3 months to 36 months of age groups

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ABSTRACT

Background: The objective of the present study was to find out predictors of occult bacteremia in children, 3 months to 36 months of age group, with fever without focus and to find out most common bacteria causing occult bacteremia in the same group of children.
Methods: A cross sectional study was done between January 2017 to January 2018 on hundered children between 3 months and 36 months of age group in Deccan College of Medical Sciences, Hyderabad Telangana State in all eligible children admitted in pediatric ward. A detailed history and physical examination completed as per Performa. Various blood samples were obtained for TLC, DLC including band form%, CRP, Micro –ESR and culture by standard methods. Urine sample taken in all cases for urine culture. LP and CSF analysis done in all cases.
Results: Total 100 children enrolled in the study and 9 children excluded from the study. Out of 100 children included in study 25 (26%) found bacteremia positive. The study population included 60 male (60%) and 40 female (40%) children their mean and +SD age was 1997 +1.99 months. There were 20 male and 5 female and their children in bacteremia positive group compared to 40 male and 20 females in bacteremia negative group.
Conclusions: The study evaluated both clinical and laboratory predictors for the detection of occult bacteremia Total 8 laboratory parameters evaluated for their significance to detect occult bacteremia.

Keywords: CRP, Fever, Micro ESR, Occult bacteria,

INTRODUCTION

Fever is the most commonly presenting complaint in children below 3 years of age group, which has both infectious and non-infectious etiology, on the other hand, the most common manifestation of infection in children is the fever.[1] Among all the infections in children, viruses are the most common cause, followed by bacteria and parasites. Viral fever is a self-limiting disease, which needs only symptomatic medications, but the bacterial infections are not self-limiting, and if left untreated, may result in to serious morbidity and mortality of the child. Bacterial illness usually suspected by presence of any focus of infection, but presence of bacteremia can occur without any apparent focus of infection, or the source of infection may not be readily apparent on initial assessment of child. Without therapy bacteremia may resolve spontaneously, may persist, or may lead to localized infections, such as meningitis, pneumonia, cellulites, or supportive arthritis.[2] The pattern of sequelae may be related to both host factor and offending organism. So the detection of such children with occult bacteremia is a diagnostic challenge, and is crucial for the favorable outcome of the Childs.[3] Incidence and clinical

manifestations of bacteremia in children below 3 months is quite, because immune system of child remain immature before 3 months and incidence of bacteremia with a typical and other gram negative organism is higher.[4] This study focuses towards identification of predictors of occult bacteremia in children, who present with acute onset of fever and have no identifiable focus of infection in history or clinical examination. So that risk of occult bacteremia can be assessed before culture reports, which usually takes time and decision to treat the child with appropriate antibiotics can be taken at proper time.[5] Thus morbidity and mortality risk associated with occult bacteremia can be reduced.

METHODS

The present study entitled predictors of occult bacteremia in febrile childrens3 months to 3 years of age group is cross sectional study and has been carried out in Deccan College of Medical Sciences during the period of Jan 2017 to Jan 2018.

Total 100 children enroll during the study after excluding 6 children due to development of signs, suggestive of focus of infections. 4 children developed crepitation in lungs and 2 children have got seizure and developed altered sensorium.

The design of the study was cross sectional at a tertiary care hospital, high resource setting referral centre. Patients admitted at Deccan College of Medical science formed the population of the study. The duration of study was one year.

Inclusion criteria

- Age group 3 months to 36 months. History of fever 1 to 7-day duration.
- No focus of infection, after detailed history and examination.
- Normal skiagram of chest.
- Blood smear negative for malarial parasite.

Exclusion criteria

- Children with known neoplastic disease.
- Children with immunosuppressive disease or state.
- Children with known chronic diseases like nephrotic syndrome, liver disease tuberculosis, HIV infection etc.
- Children with congenital heart defect, like VSD, PDA etc.
- Any acutely ill child with indwelling catheters, and ventilator support.
- Children who received any antibiotic therapy within last 7 days.

All children of 3 to 36 months ago group, who presented with fever of less than 7 days duration, without any focus of infection after taking a through history and doing physical examination, were included in the study.

Children who found to have any focus of infection on subsequent days of examination e.g. crepitation in lungs, seizures and altered sensorium etc., and those who became actually ill due to any reason, or those who lost from follow up due to any reason, were excluded from the study.

Participants

Patients admitted in the hospital ward of age group 3 months to 36 months.

Methods

All eligible children admitted in pediatric wads. A detailed history and physical examination completed. Venous blood samples were obtained for TLC, DLC including band form %, CRP, m- ESR, serology and culture by standard methods. Urine culture. LP and CSF analysis (including culture) done in all cases below 1 year and in older children whenever indicated. Chest X-ray and peripheral blood smear examination also done in all cases to rule out any silent focus of infection in lungs and malaria as a cause of fever.

TLC analysis was done by automated cell counter, while DLC was performed by counting at least 100 WBCs on a leishmann stained peripheral blood smear. CRP was performed by most commonly used slide method or dilution method. Micro ESR (m-ESR) was determined by using pre heparinised micro hematocrit tube, with an internal diameter of one millimeter. For serological diagnosis, counter-current-immuno-eletro-phoresis (CCIEP) was performed by standard techniques using antiserum.

Outcomes

On the basis of the final diagnosis the data was divided in to two groups;

- Bacteremia positive group and
- Bacteremia negative group. Bacteremia positive group included blood culture positive, urine culture positive and serology positive cases.

The diagnosis of pyomeningitis was not apparent at the time of admission but was arrived after, CSF analysis and on follow up clinical examination. Children with nonbacterial illness were those who found to have body fluid culture or serological test negative.

Predictor variables

The study evaluated following variables for their ability to discriminate bacteremic children from non bacteremic one.

General clinical characteristics

- Age in months
- Sex
- Degree of fever in °C

Laboratory investigations

- Total leukocyte count (TLC) in /Cu mm,
- Neutrophil%
- Absolute Neutrophil Count (ANC) in /Cu mm,
- Band form neutrophils%
- Presence of toxic granules in neutrophils,
- C-Reactive protein in mg/L.
- Micro ESR in mm.

Statistical calculation

General characteristics and laboratory test results were compared between children with and without bacteremia. Chi-square analysis used for categorical variables. For continuous variables (age, temperature, TLC, neutrophil %, band form %, ANC, CRP and mESR), their means and standard deviations were calculated and compared by student T-test. Those with P-value less than 0.05 considered significant predictors. Sensitivity, specificity, PPV and NPV of significant variable were calculated by using different cut off values.

RESULTS

During the study of Jan 2017 to Jan 2018, total 100 children enrolled in the study and 9 children, excluded from study. Out of 100 children included in study 25 were found bacteremia positive (both culture and serology positive). The most common organism was *E. Coli*, which was present in 6 cases.

Table 1: Distribution of bateremia by Neutrophils with toxic granules.

			Bactermia		Total
			Negative	Positive	
Toxic granules	No	Count	68	14	82
		%	82.9%	17.1%	100%
	Yes	Count	7	11	18
		%	38.9%	61.1%	100%
$X^2 = 11.802$				P = 0.001	

The study population included 60 male and 40 female children. Their mean±SD age was 19.97±9.99 months. There were 20 male and 5 female children in bacteremia positive group, compared to 40 male and 20 females in bacteremia negative group. Both groups compared using Chi-square analysis test. The male sex found significant with p-value of 0.018. Table 1 shows that all the variable depending upon its presence and absence. The toxic granules seen in total 18 cases, out of which 11 were bacteremia positive and 7 were bacteremia negative, compared to 14 bacteremia positive and 68 bacteremia negative cases with nontoxic granules. Chis square analysis shown that toxic granules as a good significant predictor of bacteremia with P-- value of 0.001. Table -2 Shows that all continuous variables TLC, neutrophil %, band form neutrophil% ANC, and CRP found significant higher in bacteremia positive groups. The most significant continuous predictors were TLC, ANC, CRP and band form % with P-values of 0.019.0.001,0.001 and 0.002 respectively.

Table 2: Mean±SD of clinical and laboratory variables by status of bacteremia.

Variables	Bacteremia positive	Bacteremia negative	P-value
Age in months	19.8±11.7	20.0±9.4	0.93
Temp (c)	38.9±0.8	39.0±0.66	0.41
TLC (in cu mm)	14029±3786	12093±3415	0.02
Neutrophil (%)	60.88±8090	56.33±7.52	014
Band form (%)	3.76±1.76	2.68±1.4	002
ANC (in cu mm)	9057±2811	7180±2317	001
CRP (in mg/l)	25.44±25.59	6.32±1.36	001
mESR (in mm)	15±7	14±6	0.32

The mean age ±SD of bacteremia positive group was 19.8±11.7 months, which was not much different from bacteremia negative group 20.0±9.4 months. The p-value found insignificant (0.93) for age. The mean temperature ±SD of bacteremia positive group was 38.9±0.8°C, and mean±SD of bacteremia negative group was 39.0±0.7°C. This variable also not has shown good difference between both groups. The p-value found insignificant (0.41) for temperature.

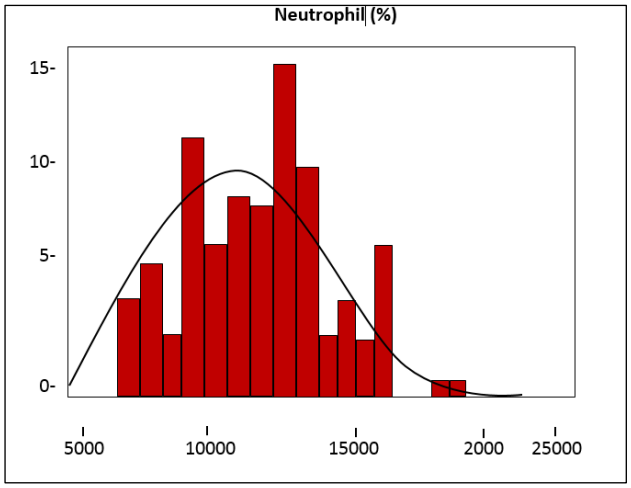

Figure 1: Frequency histogram of TLC (in /Cu mm) with its normal distribution curve TLC (in/Cu mm).

The mean±SD for TLC in bacteremia positive group was 14029±3786/cu mm, which found significantly higher than bacteremia negative group 12093±3415/cu mm. The p-value for TLC found significant (0.02). Frequency histogram of TLC is given below. Figure 1 shows that the

mean±SD for TLC in bacteremia positive group was 14029±3786/cu mm, which found significantly higher than bacteremia negative group 12093±3415/cu mm. The p-value for TLC found significant (0.02). Frequency histogram of TLC is given above. Figure 2 shows that the mean ±SD for neutrophil% in bacteremia positive group was 60.9±8.9% which was significantly higher from bacteremia negative group (56.3±7.5%). The p-value found significant for neutrophil% (0.14). Frequency histogram of neutrophil % is given above.

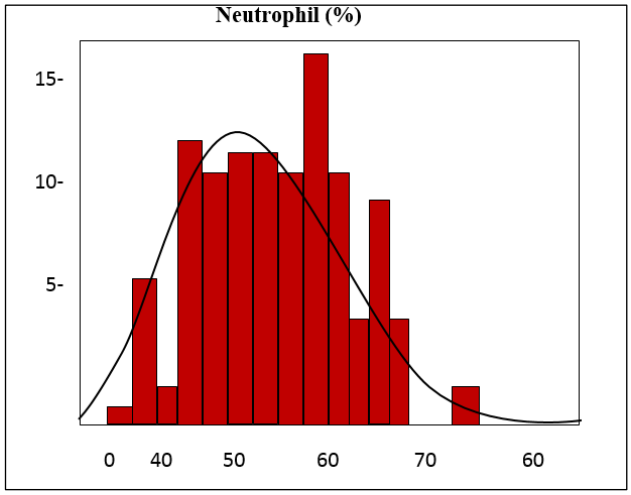

Figure 2: Frequency histogram of Neutrophil % its normal distribution curve.

The mean±SD for band form neutrophil% in bacteremia positive group was 3.76±1.76, compare to 2.68±1.40 in bacteremia negative group. The p-value found significant for this variable (0.002).

The mean±SD for ANC in bacteremia positive group was 9057±`2811/ cu mm, which found significantly higher from bacteremia negative group 7180±2317/ cu mm. The p-value for ANC found 0.001and the mESR did not found significantly different between both groups. The p-value found 0.32.

DISCUSSION

The Study evaluated common clinical characteristics (age, sex and degree of fever) and common laboratory parameters for their ability to detect bacteremia in acutely febrile children without any focus of infection.

The bacteremia positive criterion used in this study were all body fluid culture positive and serology positive cases. Out of these 25% bacteremia positive cases, 9 (36%) were blood culture positive, 8 (32%) urine culture positive, 2 (8%) CSF culture positive and 6 (24%) were serology positive cases. The overall prevalence of bacteremia was 25%. The rate of prevalence was lower than one of the Indian studies done by Dr. S. Singhi et al on the other hand western studies documented a much lower prevalence of bacteremia ranging from 2.5 to 11%.[6] The most common prevalence was *E. coli* and Salmonella in this study exactly opposite to western studies, which implies *S. Pneumonae* as the most common cause of occult bacteremia.[7] In the general clinical characteristics 3 variables evaluated for their ability to discriminate between the children with and without bacteremia. These variables were age of child, sex and degree of fever.

The total study of population comprised of 60 (60%) male children, out of them were 20 found in bacteremia positive group compared to only 5 female children out of total 40 (40%) female population. The chi square analysis performed for significance of male sex to discriminate bacteremia children, showed a significant p-value of 0.018. One of the multi centered study done by Bass et al document no sex-based difference in prevalence of bacteremia.[8]

Next variable evaluation of this study was age of child. The mean + SD for age was 19.9±9.9 months. The mean±SD for age in bacteremia positive group was 19.8±11.7 months compared to 20.0±9.4 months in bacteremia negative group. The chi-square analysis showed non-significant p-value of 0.93, which showed that there is no age-based difference in prevalence of bacteremia in children. Other studies analyzing this variable have given different conclusion. Kuppermann N et al, Lee GM et al observed specifically for pneumococcal bacteremia and concluded that children's 6 months to 2 years of age group are at higher risk of developing pneumococcal bactereima.[9,10] Kuppermann also concluded that risk of salmonella is highest in children below 1 year. In this study out of 6 cases of *salmonella* 5 children were above 1 year and 4 children above 2 years. Probably this is due to developing self-eating habits of children above 1 year. *S. pneumonae* found in 3 children, 1 child was below 6 months, while 2 children were above 1 year.

The next variable of general characteristics was degree of fever. The degree of fever at the time of presentation was used for statistical calculation. The mean±SD for temperature in this study was 39.9±0.84°C. In bacteremia positive group mean±SD was 39.7±1.07°C compare to 39.0±0.66°C in bacteremia negative group which is definitely significantly higher in bacteremia positive group. Student t-test used to compare mean ±SD showed very significant p-value of <0.001. So, this study concluded that degree of fever is proportional to risk of bacteremia in children. Lee GM et al also concluded that risk of bacteremia is proportional to degree of fever. In the group of laboratory predictors of bacteremia, 8 most commonly used laboratory investigation were used. These were total leukocyte count, absolute neutrophil count, neutrophil %, granulocyte %, band form neutrophil %, presence of toxic granules in neutrophil, C-reactive protein and micro ESR. All parameters analyzed for their significance to predict bacteremia in children by used

student t-test, except one presence of toxic granules in neutrophil, which analyzed by chi-square analysis.

This study found total 18 cases with toxic granules in neutrophil, out of them 11 (61.1%) cases were distributed in bacteremia positive group, while only 7 (38.9%) cases were found in bacteremia negative group. This observation found very significant when analyzed by chi-square analysis which gave p-value of <0.001.

Wack RP et al and Bachur RG et al have evaluated and concluded same result that presence of toxic granules in neutrophil is a significant predictor for bacteremia in children.[10,11]

TLC or WBCs count is the most widely studied laboratory investigation for prediction of bactermia in children. The mean±SD of TLC in this study was 12577±3592/cu mm. In bacteremia positive group mean±SD of TLC was 14029±3786/cu mm, which found significantly higher than 12093±3415/ Cu mm in bacteremia negative group. The t-test calculated p-value of 0.019. Overwhelming studies are there which support this finding of the study. Though different studies have used different inclusion and exclusion criteria, age ranges, fever cut offs and statistical analysis to conclude their results. One widely accepted meta-analysis performed by Braff et al shows that children <3 months, have the risk of bacteremia increases with increase in TLC. Though different studies used different cut-off values for their results, but most commonly used cut-off value is >15,000/cu mm or >15/HPF.[12]

Mean±SD of Absolute Neutrophil Count (ANC) in the study of population was 7650±2568/ Cu mm. In bacteremia positive group it was 9057±2811/cu mm compared to 7180±2317 in bacteremia negative group. This Significantly higher value in bacteremia positive group confirmed statistically with p-value of <0.001 by t-test.

The mean±SD for neutrophil% in bacteremia positive group was 60.9±8.9% which was significantly higher from bacteremia negative group (56.3±7.5%). The p-value found significant for neutrophil% (0.014). This predictor could not be compared with other studies because of paucity of literature available for this predictor. Neutrophil% found significant, so neutrophil% (Neutrophils±Band form) 33 would definitely be significant predictors. The mean±SD of band form neutrophil % was 2.95±1.56. In bacteremia positive group it was 2.76±1.76, compare to 2.68±1.4 in bacteremia negative group. This significantly higher value in bacteremia positive group analyzed by t-test. T-test gave significant p-value of 0.002. Total 3 cut off values assessed for best balance of sensitivity and NPV. Band form % more than 2 % gave best sensitivity and NPV of 0.88 and 0.87 respectively. The mean±SD of CRP in this study was 10.08±16.56. Mean±SD in bacteremia positive group was significantly higher 25.44±25.59 mg/L. compare to 5.20±6.86 mg/L in bacteremia negative group. P-value found very significant, <0.001. CRP is a widely accepted laboratory marker of sepsis in children less than 3 months and particular in neonates.

Baraff et al do not consider CRP as a good screening tool when compared it with TLC or WBCs cont.[12] On the other hand, many recent studies are accepting it as a good screening tool for prediction of bacteremia in children. though screening goals of these newer studies were slightly different. Only one recent study by Issacmann et al. recommended it as screening tool of occult bacteremia. This study found CRP as a good screening tool for occult bacteremia in children >3 months. The study used 3 cutt-off values of CRP to achieve good balance of sensitivity and NPV and CRP of >12 mg/L gave sensitivity of 0.76 and NPV of 0.92. The cut –off values of CRP used by this study are different than what used by other studies.[12,13]

The mean + SD of mESR in this study was 14.13±6.22 mm. In bacteremia positive group it was 15.20±7.06 which was not much different form 13.77±5.94 in bacteremia negative group. The p-value found 0.323. When including all focal and non-focal infections, benign and serious infection, then it is a better screening tool. But so far discrimination of occult bacteremia is concern, it's not a good predictor. Through Indian study by D S. Singhi et al concluded that mESR >25 mm is highly specific for predicting bacteremia in children.[2,8,14]

CONCLUSION

Among 100 children included in the study, 25 (25%) found bacteremia positive and 75 (75%) bacteremia negative. The study evaluated both clinical and laboratory predictors for the detection of occult bacteremia. In the general characteristics male sex and degree of fever found to be the good predictor with a p-value of 0.018 and <0.001 respectively. *E. coli* and *Salmonella* were the two most common organisations responsible for occult bacteremia, each of them were present in 6(24%) cases.

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