Bacteriological Profile and Antibiogram of Blood Culture Isolates from Septicaemic Neonates and Children up to 10 Years of Age, in a Tertiary Care Centre of Eastern Bihar in India

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ABSTRACT

BACKGROUND

This study was an attempt to find the association of physical parameters, risk factors, common signs & symptoms of septicaemia, analyse the distribution of microorganisms isolated from clinically suspected cases of septicaemia, and collect their antibiogram. We also wanted to evaluate the haematological findings in conventional culture, correlate them to the sensitivity and specificity, and quantitatively identify the relevance of these haematological tests through their positive and negative predictive values.

METHODS

A total of 350 blood samples were received from patients with clinically suspected cases of blood stream infections (BSI) at the Department of Microbiology for routine culture & sensitivity and were processed using standard microbiological techniques to determine the percentage distribution of bacterial pathogens causing BSI and their antibiotic susceptibility patterns. Mueller-Hinton agar (MHA) with 4 % NaCl was used to detect methicillin resistance.

RESULTS

Of the 350 septicaemic cases, 58.8 % were from neonatal ICU and 41.2 % were from paediatric wards. Maximum culture positivity (45.3 %) was seen in < 28 days age group. Bacterial growth was seen in 62.0 % preterm babies. Probability of sepsis was more with leukopenia (85.4 %) as compared to leucocytosis (68.9 %); positive C-reactive protein (CRP) findings (63.8 %) were more likely to be associated with sepsis as compared to negative CRP findings (2.1 %). Leukopenia (97.5 %) and leucocytosis (96.3 %) had the highest specificity values.

CONCLUSIONS

Low birth weight (LBW) neonates, preterm birth and Caesarean section deliveries are risk factors that predispose neonates to septicaemia. Meropenem can be used in septaemia, but it should be reserved for critical cases, particularly those with multidrug resistant (MDR) bacteria, rather than on routine basis to prevent inadvertent promotion of bacterial resistance. This study showed that leukopenia and CRP are good indicators of sepsis, when used in combination.

KEYWORDS

Blood Stream Infection, Early Onset Septicemia, Late Onset Septicemia

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BACKGROUND

Risk factors predisposing to neonatal septicemia in developing countries include prolonged rupture of membranes, prematurity, birth asphyxia, length of hospital stay, invasive procedures, delivery location, material used in cutting & dressing cord and maternal infections during pregnancy.[1,2]

The present study was conducted to find out the association of physical parameters & risk factors to clinically suspected septicemia cases; and to see the distribution of microorganisms isolated from cases of sepsis among preadolescent children including newborns, and to collect their antibiogram.

The study also reports the haematological findings in conventional culture and tries to correlate them to the level of accuracy (sensitivity and specificity) with which they were seen to be associated with sepsis.

METHODS

This cross-sectional study was carried out in the Department of Microbiology of a tertiary care centre in Eastern Bihar, in India from May 2019 to November 2020. All patients admitted to the Pediatrics Department of the tertiary centre, with signs of sepsis were included in the study. Clearance was obtained before conducting the study vide IEC / Dept. Res. / 005 / 2019 - 2022 (Microbiology) dated 20.04.2019.

Study Population

Study population was calculated based on a total number of 840 samples received during the study period and calculated on the basis of confidence level of 95 %, and a confidence interval of 4.0. Based on the calculations, a total of 350 blood samples from clinically suspected cases of blood stream infection (BSI) were chosen by simple random sampling and processed for routine blood culture and antibiotic sensitivity, preferably during fever spikes before beginning empirical antibiotic therapy. The study population included all neonates, with age < 28 days to children up to 10 years of age.

Isolation & Identification

The blood culture bottles containing specimens were transported within half an hour to the bacteriology laboratory, incubated at 35^0 C for 7 days and examined macroscopically for appearance of turbidity as evidence of growth during the first 12 - 18 hours after collection. Subcultures were examined for growth on next day. If there was any growth, the isolates were identified as per standard protocol based on standard protocol. If there was no growth, further subculture was done on the 2nd, 4th and the 6th day. Cultures were reported negative, if subcultures showed no growth by then.[3]

Antimicrobial Susceptibility Testing

Antibiotic susceptibility testing was done by Kirby-Bauer disc diffusion method on Muller-Hinton agar, using antibiotic discs obtained from HiMedia Laboratories, Mumbai, India. Blood agar was used for *Streptococcus pneumoniae*.[4]

Data Analysis

Performance indices were calculated for haematological parameters like (leukopenia, leukocytosis and CRP). Variables measured were the number of true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN). Sensitivity was calculated as TP / (TP + FN), specificity was calculated as TN / (TN + FP), the PPV was calculated as TP / (TP + FP) and NPV was calculated as TN / (TN + FN).

Statistical Analysis

Statistical analysis of data was done using the online application available at the website link http://www.physics.csbsju.edu/stats/contingency_NROW_NCOLUMN_form.html.

RESULTS

A total of 350 blood cultures were performed during the study period, out of which, 206 (58.8 %) were from neonatal ICU and the remaining 144 (41.2 %) were from the pediatric ward. Majority (145 / 350; 41.4 %) of the children belonged to the age group < 28 days (Table 1). Of the clinically suspected septicaemic cases of neonates, 58.5 % (205 / 350) were males and 41.4 % (145 / 350) were females. The overall male to female ratio was 1: 0.71 (Table 1).

Out of all the culture positive septicaemic cases, maximum culture positivity was seen in low birth weight (LBW) neonates (49.1 %; 53 / 108). Culture positivity in normal birth weight (NBW) neonates was lower (26.8 %; 29 / 108). Maximum bacterial growth was seen in preterm babies (62.0 %; 67 / 108) as compared to the term babies (37.9 %; 41 / 108) (Table 2).

Place of delivery seemed to be the major risk factor and majority of cases (50.9 %; 55 / 108) suffered from sepsis among children whose records showed that they were born in other institutions. It was much lesser when the delivery was in our hospital (31.5 %; 34 / 108), and the least during planned and attended home deliveries (17.5 %; 19 / 108) (Table 2).

Children born of Caesarian sections appeared to be more at risk of BSI (78.7 %; 85 / 108), as compared to those born through normal deliveries (21.3 %; 23 / 108) (Table 2).

The observed values in relation to birth weight ($P < 0.001$), gestational age ($P < 0.001$) and place of delivery ($P < 0.001$) were all statistically significant, while the P-value for the mode of delivery ($P > 0.05$) was statistically insignificant (Table 2).

Of the total 350 blood samples cultured, 184 (52.6 %) were sterile, 108 (30.9 %) showed growth of various bacteria, 20 (5.7 %) were candida species positive and 38 (10.9 %) showed growth of contaminants. Among positive

blood culture isolates, the gram-positive bacterial isolates (47.2 %; 51 / 108) marginally exceeded the gram-negative isolates (45.3 %; 49 / 108).

Isolation of gram-positive cocci (GPC) (64.4 %; 38 / 59) and fungi (8.4 %; 5 / 59) were more (26.5 %; 13 / 49) from late onset septicaemia cases (LOS) and lower (67.3 %; 33 / 49) in early onset septicemia (EOS) (Table 3).

The predominant signs and symptoms were poor activity / poor feeding (53.1 %; 186 / 350), followed by fever (21.7 %; 76 / 350), vomiting (8.2 %; 29 / 350) and convulsions (6.5 %; 23 / 350).

Gram negative bacilli (GNB) showed maximum resistance to cefuroxime, cotrimoxazole & piperacillin-tazobactam, being 76.3 % (29 / 38) each. Most of the GNB were found to be sensitive to colistin (65.7 %; 25 / 38), followed by meropenem (42.1 %; 16 / 38), amikacin (39.4 %; 15 / 38) and netilmicin (34.2 %; 13 / 38); (Table 4).

Pseudomonas aeruginosa showed maximum resistance to cefotaxime (100.0 %; 11 / 11) followed by netilmicin, nalidixic acid & piperacillin-tazobactam (90.9 %; 10 / 11, each) and aztreonam & gentamicin (81.8 %; 9 / 11, each) (Table 4).

GPC showed maximum resistance to aztreonam (68.6 %; 35 / 51), followed by meropenem & cotrimoxazole (64.7 %; 33 / 51, each), and erythromycin (58.8 %; 30 / 51). Resistance to vancomycin was shown by 33.3 % (17 / 51) isolates. Only 39.2 % (20 / 51) isolates showed resistance to cefoxitin (Table 4).

Routine haematological investigation profile was recorded and analysed as shown in (Table 5), which depicts that probability of sepsis is more with leukopenia (85.4 %; 35 / 41), as compared to leucocytosis (68.9 %; 20 / 29). Also, positive C-reactive protein (CRP) finding (63.8 %; 104 / 163) was more likely to be associated with sepsis as compared to negative CRP finding (2.1 %; 4 / 187).

Comparison of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of various haematological parameters showed, CRP had the highest sensitivity (96.3 %) and negative predictive value (NPV) (97.9 %), leucopenia (97.5 %) and leucocytosis (96.3 %) had the highest specificity values (Table 5).

Physical Parameters		Sepsis Culture Positive N	%	Culture Negative N	%	Total Cases N	%	Chi-Square X^2	'P' Value
Gender	Male	63	58.3	142	58.6	205	58.5	0.365	0.952
	Female	45	41.6	100	41.6	145	41.4		
	Total	108	100	242	100.0	350	100.0		
Age	< 28 days	49	45.3	96	39.6	145	41.4	10.7	0.014
	28 days to 1 yr.	27	25.0	56	23.1	83	23.7		
	1 yr. to 5 yrs.	19	17.5	77	31.8	96	27.4		
	5 yrs. to 10 yrs.	13	12.1	13	5.3	26	7.4		
	Total	**108**	**100.0**	**242**	**100.0**	**350**	**100**		
	Age (Mean + SE)	1.583 + 0.235		1.498 + 0.124		--	--	--	--

Table 1. Association between Physical Parameters and Sepsis

Risk Factors	Parameters	Sepsis Culture Positive No.	%	Culture Negative No.	%	Total Cases No.	%	Chi-Square X^2	'P' Value
Birth weight	VLBW#	26	24.1	5	2.1	31	8.9	67.5	0.000*
	LBW##	53	49.1	78	32.2	131	37.4		
	Normal	29	26.8	159	65.7	188	53.7		
	Total	108	30.8	242	69.1	350	100.0		
Gestation	Term	41	37.9	202	83.5	244	69.7	73.3	0.000*
	Pre term	67	62.0	40	16.5	107	30.5		
	Total	108	30.8	242	69.1	350	100.0		
Place of delivery	Other institution	55	50.9	74	30.5	129	36.8	25.1	0.000*
	Own institution	34	31.5	146	60.3	180	51.4		
	Home delivery	19	17.5	22	9.1	41	11.7		
	Total	108	30.8	242	69.1	350	100.0		
Mode of delivery	CS###	85	78.7	176	72.7	261	74.5	1.41	0.236
	ND####	23	21.3	66	27.3	89	25.4		
	Total	**108**	**30.8**	**242**	**69.1**	**350**	**100.0**		

Table 2. Association of Clinically Suspected Cases by Risk Factor

#VLBW = Very Low Birth Weight, ## LBW = Low Birth Weight, ###CS = Caesarian Section, ####ND = Normal Delivery, *indicates significant statistical association at P < 0.05

Organism Type	Onset of Septicemia EOS* N (%)	LOS** N (%)	Total N (%)
Gram positive	13 (26.5)	38 (64.4)	51 (47.2)
Gram negative	33 (67.3)	16 (27.1)	49 (45.3)
Fungi	3 (6.2)	5 (8.4)	8 (7.4)
Total	**49**	**59**	**108**
Chi-square 'P' value	X^2 =17.88, P = < 0.0001*		

Table 3. Organism Type vs. Onset of Septicaemia

*EOS = Early Onset Septicemia, ** LO = Late Onset Septicemia, *indicates significant statistical association at P < 0.05

Antimicrobial	GNB (N = 38) Resistant (%)	GNB (N = 38) Sensitive (%)	*Pseudomonas aeruginosa* (N = 11) Resistant (%)	*Pseudomonas aeruginosa* (N = 11) Sensitive (%)	GPC (N = 51) Resistant (%)	GPC (N = 51) Sensitive (%)
Amikacin	15 (39.4)	15 (39.4)	7 (63.6)	6 (54.5)	11 (21.5)	31 (28.7)
Amoxycillin	26 (68.4)	12 (31.5)	-	-	23 (45.0)	19 (37.3)
Aztreonam	28 (73.6)	10 (26.3)	9 (81.8)	6 (54.5)	35 (68.6)	16 (31.3)
Cefazolin	-	-	-	-	15 (29.4)	31 (60.7)
Cefotaxime	23 (60.5)	7 (18.4)	11 (100.0)	2 (18.2)	-	-
Cefoxitin	-	-	-	-	20 (39.2)	31 (60.7)
Ceftazidime	-		8 (72.7)	5 (45.4)	-	-
Cefuroxime	29 (76.3)	6 (15.7)	-		-	-
Ciprofloxacin	24 (63.1)	9 (23.6)	8 (72.7)	7 (63.6)	29 (56.8)	19 (37.2)
Clindamycin	-	-	-	-	15 (29.4)	23 (45.0)
Colistin	13 (34.2)	25 (65.7)	5 (45.4)	10 (90.9)	-	-
Cotrimoxazole	29 (76.3)	16 (42.1)	5 (45.4)	5 (45.4)	33 (64.7)	12 (23.5)
Erythromycin	-	-	-	-	30 (58.8)	20 (39.2)
Gentamicin	20 (52.6)	8 (21.0)	9 (81.8)	2 (18.2)	16 (31.3)	24 (47.0)
Imipenem	22 (57.8)	11 (28.9)	7 (63.6)	5 (45.4)	-	20 (39.2)
Levofloxacin	20 (52.6)	11 (28.9)	5 (45.4)	10 (90.9)	-	-
Linezolid	-	-	-	-	9 (17.6)	34 (66.6)
Meropenem	19 (50.0)	16 (42.1)	7 (63.6)	8 (72.7)	33 (64.7)	18 (35.3)
Nalidixic acid	28 (73.6)	10 (26.3)	10 (90.9)	5 (45.4)	16 (31.3)	35 (68.6)
Netilmicin	25 (65.7)	13 (34.2)	10 (90.9)	5 (45.4)	25 (49.0)	20 (39.2)
Piperacillin-tazobactam	29 (76.3)	9 (23.6)	10 (90.9)	5 (45.4)	-	-
Vancomycin	-	-	-	-	17 (33.3)	26 (50.9)

Table 4. Antimicrobial Susceptibility Pattern of Organisms Isolated from Septicaemic Cases

Haematological Parameter Variants	Parameter Present (P) / Absent (A)	Conventional Culture Positive (N = 108)	Negative (N = 242)	Total N = 350	Positivity (%)	Sensitivity	Specificity	PPV	NPV
Abnormal leukocyte count	P A	43 (TP) 65 (FN)	27 (FP) 215 (TN)	70	61.4	74.1 %	88.8 %	61.4 %	93.5 %
Leucopenia (< 5000 / mm^3)	P A	35 (TP) 73 (FN)	6 (FP) 236 (TN)	41	85.4	32.4 %	97.5 %	85.4 %	32.4 %
Leucocytosis (> 20,000 / mm^3)	P A	20 (TP) 88 (FN)	9 (FP) 233 (TN)	29	68.9	18.5 %	96.3 %	68.9 %	72.6 %
Platelet count (< 100000 / dl)	P A	49 (TP) 59 (FN)	110 (FP) 132 (TN)	159	30.8	45.4 %	54.6 %	30.8 %	69.1 %
C-reactive protein (positive, > 6 mg / dl)	P A	104 (TP) 4 (FN)	59 (FP) 183 (TN)	163	63.8	96.3 %	75.6 %	63.8 %	97.9 %
C-reactive protein (negative, < 6 mg / dl)	P A	4 (TP) 104 (FN)	183 (FP) 59 (TN)	187	2.1	3.7 %	24.4 %	2.1 %	36.2 %

Table 5. Evaluation of Haematological Parameters with Conventional Culture Positivity

DISCUSSION

The present study was an attempt to find out the association of physical parameters & risk factors to clinically suspected cases of septicaemia; the common signs & symptoms associated with clinical suspicion of septicaemia; and to analyse distribution of microorganisms isolated from cases of neonatal sepsis and collect their antibiogram. The study also reports the haematological findings in conventional culture and to correlate them to the level of accuracy (sensitivity and specificity) with which they were seen to be associated with sepsis and to quantitatively identify the relevance of these haematological tests through their PPV and NPV.

Out of the total clinically suspected cases of neonates, 58.5 % (205 / 350) were males and 41.4 % (145 / 350) were females. Among the males, culture positivity was 58.3 % (63 / 108) and for females it was 41.6 % (45 / 108). This was comparable to the other studies.[5] The reason for male preponderance is unknown, but could be due to gender-dependent factors.

In the present study, the total number of LBW babies were 37.4 % (131 / 350) clinically suspected neonates, amongst which culture positivity was seen in 49.1 % (53 / 131) cases. This finding was close to the outcome of the study conducted by other workers, where clinical sepsis was more commonly associated with LBW newborns (60 %).[6]

Our study shows that out of the total of 350 blood samples that were cultured, around half the samples (52.6 %; 184 / 350) were sterile. 30.9 % (108 / 350) samples showed growth of various pathogenic bacteria, while 5.7 % (20 / 350) were candida species positive**.** Other studies have reported similar findings earlier, where the growth of pathogenic bacteria was seen in 29.5 % samples, while 63.8 % showed no growth after 7 days of incubation.[7] Contrasting findings of both bacteraemia (88.9 %) and fungemia (11.1 %) in higher percentages of infected individuals have also been reported.[8] Low blood culture isolation rate in the current study might be due to prior treatment through antibiotics before blood collection either to the mother or to the baby ; or the possible infection of neonates with viruses, other fungi or anaerobes, which cannot be ruled out, but were not detected in the present study.[9,10,11]

The present study results showed 9.7 % (34 / 350) growth of contaminants in the cultures. The common contaminants were bacillus species, micrococcus species, and diphtheroids. In contrast, other studies have reported bacillus species and micrococcus species (37.0 % each), *Staphylococcus epidermidis* (14.8 %) and diphtheroids (11.1 %) as contaminants.[12]

Findings of other studies reported predominance of gram-negative isolates like acinetobacter species, enterobacter species and salmonella species In BSI.[13] Among the gram positive pathogens, coagulase-negative staphylococci (CoNS) and *Staphylococcus aureus* were the most common isolates in our study. A higher prevalence rate of septicaemia was recorded by other workers, due to GNB (67.5 %), than due to gram-positive bacteria (32.5 %).

It was found in our study that, while gram positive bacterial pathogens contributed more to LOS (64.4 %), gram negative pathogens contributed more to EOS (67.3 %). This finding was close to findings of some other studies where LOS was most common, with CoNS as the predominant gram-positive pathogen (67.6 %), while gram negative isolates were predominant in EOS.[14]

Regarding the physical status of neonates at the time of presentation, our study showed that slightly more than half the neonates (53.1 %; 186 / 350) presented with poor activity / poor feeding, fever (21.7 %; 76 / 350), vomiting (8.3 %; 29 / 350) and convulsions (6.6 %; 23 / 350). A study in South India reported 72 % cases with poor activity / poor cry, followed by 10.67 % with respiratory distress and 8 % with convulsions in their study.[15]

In our study, gram negative isolates showed maximum sensitivity to colistin (65.7 %), followed by meropenem (42.1 %), amikacin (39.4 %) and netilmicin (34.2 %). On the other hand, *Pseudomonas aeruginosa*, though a gram-negative bacteria, showed maximum sensitivity to levofloxacin and colistin (90.9 %, each), followed by meropenem (72.7 %) and ciprofloxacin (63.6 %). In a different study, all the gram-positive pathogenic isolates were sensitive to linezolid, tigecycline and vancomycin. Isolates were also sensitive to cotrimoxazole (78.8 %), ceftriaxone (77 %), azithromycin (76.9 %), cefepime (60 %), erythromycin (59.6 %) & clindamycin (53.9 %).[16]

Sensitivity to isolates appears to vary greatly from one place to another and is likely to be a result of local antibiotic pressure which, in turn, is influenced by local prescription practices. An Italian study reported varied isolate specific drugs to treat neonatal BSI, wherein *Escherichia coli* was highly sensitive (100 %) to amikacin, klebsiella to ciprofloxacin (100 %), enterobacter to cotrimoxazole (90 %)

& ciprofloxacin (88.9 %) and group B streptococci to ampicillin.

In our study leukopenia was associated with a greater probability of sepsis (85.4 %). This is in concordance with studies which showed a 42 % blood culture positivity rate with leukopenia and only a 29 % culture positivity rate in cases with total leucocyte count (TLC) > 5000 / cu mm.[17]

Abnormal TLC was seen in 61.4 % cases, while thrombocytopenia was seen in 69.1 % cases in the present study. These findings were not concordant with reports of some authors, who showed a higher percentage of abnormal TLC, and much lower percentage of thrombocytopenia.[18] This wide difference in the haematological findings can be attributed to the methodologies while performing the tests.

In our study, leucocytosis had a high specificity (96.3 %) and low sensitivity (18.5 %) which means that it is more accurate in excluding sepsis. Its PPV was high (68.9 %) indicating that the probability of sepsis in subjects with leucocytosis was high. CRP also had the highest sensitivity (96.3 %) amongst all tests, meaning that in comparison to leucocytosis and leukopenia, CRP can identify those with sepsis more accurately.

Our study showed that WBC count < 5000 / cu mm was found to have a specificity of 97.5 %, but sensitivity of 32.4 %. Other findings showed that leucocytosis had an NPV of 72.6 %. CRP had a high NPV (97.9 %) and the lowest PPV (63.8 %). In a different study, a WBC count < 5000 / cu mm was found to have a specificity of 94 % but a sensitivity of only 50 %.[19] In yet another study, sensitivity, specificity, NPV and PPV for leucopoenia were 22 %, 68 %, 29 % and 59 % respectively.[20]

CONCLUSIONS

LBW neonates, preterm birth, and Cesarean section deliveries are risk factors that predispose neonates to septicaemia. Meropenem can be used in septicaemia, but it should best be reserved for critical cases when patient does not respond to other antibiotics particularly in case of MDR bacteria, rather than on routine basis to prevent inadvertent promotion of bacterial resistance. This study showed that leukopenia and CRP are good indicators of sepsis, when used in combination.

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