

Neonatal Sepsis: The Alarm Bell is Ringing Loud!

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ABSTRACT

Introduction: Neonatal sepsis remains an important cause of neonatal mortality and morbidity despite the tremendous advances in the field of neonatology over the last two decades. Current research aimed to study the profile of neonatal sepsis & its antimicrobial sensitivity pattern.

Material and methods Two year prospective observational study was conducted at NICU of NMCH Patna from May 2018 to April 2020. Neonates with clinical diagnosis of neonatal sepsis as per IMCI and WHO clinical criteria for neonatal sepsis and/or >2 risk factors associated with EONS were enrolled in study.

Results: Out of the 341 cases enrolled, blood culture was positive in only 130(38%). Incidence of EONS was 67% and that of LONS was 33%. Majority of the septic neonates were preterm (64%). 55% of such neonates were of male sex. Gram negative bacteria accounted for 55% of all cases, 61% of EONS and 44% of LONS cases. The most common isolate was *Staph. aureus* closely followed by *Klebsiella sp.* Gram negative bacteria, esp. *Klebsiella* had a high incidence of resistance to the empirical antibiotic used and to most of the commonly used antibiotics. Culture positive group had a significantly higher mortality as compared to culture negative group(p<0.001).

Conclusion: Blood culture though gold standard was not positive in majority of the cases. Neonatal sepsis was more commonly associated with prematurity. Gram negative organisms were the commonest etiologic agents. Emergence of strains resistant to even the newest antibiotics poses a great concern.

Keywords: Antibiotic Resistance, Blood Culture, Early Onset Neonatal Sepsis, Late Onset Neonatal Sepsis.

INTRODUCTION

Neonatal period constitutes only the first 30 days of life and yet it accounts for 40% of all deaths in children under five years of age.¹ The three major contributors to the global burden of neonatal deaths are (in order of magnitude) prematurity, birth asphyxia, and neonatal infections.^{2,3} The toll is higher in developing countries where neonatal sepsis is responsible for about 30-50% of the total neonatal deaths.^{4,5} Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. Neonatal sepsis is classified based on the time of onset of symptoms: Early onset neonatal sepsis (EONS) presenting within 72 hours of age and Late onset neonatal sepsis (LONS) that presents after 72 hours of age.

Diagnosis of sepsis in neonates is difficult as clinical signs and laboratory markers are often nonspecific and indistinguishable from other.⁶ Even with the few diagnostic

tools that exist, pathogenic organisms remain difficult to identify.⁷ In addition, the results of these tests may take 3-5 days, which is often too long to wait as the condition of a neonate with neonatal sepsis can deteriorate rapidly. Hence, a large proportion of neonates are treated for sepsis even though their blood cultures subsequently show no growth.⁸ Meanwhile, the lack of rapid diagnostic tests often results in inappropriate use of antibiotics, thereby increasing the risk of the development of antimicrobial resistance. There is need to find out the organisms causing neonatal septicemia in each center and their antibiotic sensitivity pattern to guide effective and rational use of antimicrobials as both the etiology and the susceptibility is never uniformly the same. This would suggest the best empirical choice of antibiotics when treatment of the septic infant has to be initiated before the result of the blood culture is known.

MATERIAL AND METHODS

This prospective observational study was conducted at NICU of N.M.C.H, Patna, Bihar over 2 years from May 2018 to April 2020.

Inclusion criteria: neonates admitted with clinical diagnosis of neonatal sepsis as per IMCI or WHO clinical criteria for neonatal sepsis and/or >2 of following risk factors associated with EONS: LBW or prematurity, febrile illness in mother with evidence of bacteremia within 2 weeks preceding delivery, MSAF/foul smelling liquor, rupture of membranes for 24 hours, single unclean or >3 clean PV exams, prolonged labour (>24 hours), perinatal asphyxia (APGAR <4 at 1 min of age)

Exclusion criteria

1. Neonates already on antibiotics.
2. Major congenital malformation (as they were referred & thus couldn't be followed up)
3. Those who presented with features suggestive of sepsis but later on their features were fully explained by other

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conditions like hypoglycemia, hypocalcaemia, other metabolic causes and there was no evidence of sepsis & negative blood culture, were excluded from final analysis.

Following Helsinki Declaration on research bioethics, obtaining consent & enrollment in the study, detailed history taking and thorough physical examination was done. Relevant investigations were sent and the neonates were further managed as per standard NICU protocol. The initial empirical antibiotic therapy was continued, discontinued or changed based on further clinical course and investigation reports. As per NNF 2011 guidelines, our antibiotic policy for *Culture negative sepsis* was:

- Asymptomatic neonate at risk of EONS: antibiotics stopped.
- Suspected sepsis and the neonate became completely asymptomatic: antibiotics stopped
- Suspected sepsis and the neonate improved but didn't become asymptomatic: CRP assay was repeated: If CRP positive, antibiotics continued for 7 days; If CRP negative, antibiotics stopped.

Specimens collected: 1 ml blood was collected under aseptic precautions of which 0.5 ml was immediately inoculated in a liquid blood culture bottle (nutrient broth), sent to the lab for aerobic culture and the rest 0.5 ml of blood was sent to the lab for Sepsis screen tests. Culture was done by conventional method as we don't have BACTEC or BACT/ALERT systems.

Data collection

Cases were divided into EONS if presented before 72 hrs of life and LONS if presented after 72 hrs. All positive blood cultures after excluding skin commensals and contaminants (aerobic spore bearers, mixed growth or as per Microbiologist's opinion) were analyzed. Sepsis screen was considered positive when atleast 2 of the following 5 parameters was positive: TLC<5000/ mm³, Absolute neutrophil count <1800/ mm³, Immature/total neutrophil ratio>0.2, Micro-ESR >15 mm in first hour, CRP >1mg/dl.

STATISTICAL ANALYSIS

Data was entered in Microsoft excel sheet and analysed with statistical software "SPSS version 19. Descriptive statistics tools viz mean, percentage etc were used wherever applicable. Chi-square test was used for comparison of proportions & a "P-value" <0.05 was taken as significant.

RESULTS

In our study we found statistically significantly higher proportion of preterm neonates than term neonates (64% vs 36%; p=0.0001) and more EONS cases than LONS cases (67% vs 33%; p= 0.0001) however there was no specific sex predilection (55.4% males vs 44.6% females; p=0.083) (table-1).

Isolation of gram negative bacteria (n=72, 55.4%) was higher than gram positive bacteria (n=58, 44.6%) and they caused 61% of EONS and 44% of LONS cases. There was a statistically significant higher proportion of gram negative bacteria than gram positive bacteria in EONS (61% vs 39%; p=0.004) (table-2).

Evaluation of the empirical antibiotic therapy in light of sensitivity report

Out of the 130 culture positive cases, 106 cases had been started on Ampicillin + Amikacin therapy, 24 cases with suspected meningitis had been started on Amikacin+ Cefotaxime. So, 130 cases received Amikacin, 106 received Ampicillin & 24 received Cefotaxime. Both drugs of the combination was sensitive in 22 cases (17%), only 1 was sensitive in 77 cases(59%) while none of the two was sensitive in 31 cases (24%). Only Amikacin was sensitive in 62 cases (48%), only Ampicillin was sensitive in 6 cases (5.7%) and only cefotaxim was sensitive in 9 cases (37.5%) (table-3,4,5,6).

There was a statistically significantly higher mortality in culture positive group as compared to culture negative group(p<0.001). However, no such association existed in sepsis screen positivity. Sepsis screen positivity was not an indication for starting or continuing antibiotics, but it was

Parameter	Value
Total number of cases enrolled	341
Total number of confirmed sepsis (blood culture positive)	130 (38.1%)
Aamong culture positive cases:	
EONS	87 (66.92%)
LONS	43 (33.08%)
Term neonates	47 (36.15%)
Preterm neonates	83 (63.85%)
Males	72 (55.38%)
Females	58 (44.62%)
Sepsis screen positive	127 (37.24%)
Sepsis screen negative	214 (62.76%)
Both sepsis screen & culture positive	81 (23.75%)
Sepsis screen positive and blood culture negative	46 (13.49%)
sepsis screen negative and blood culture positive	49 (14.37%)
Both sepsis screen & culture negative	165 (48.39%)

Table-1: Overall data

Sl No.	Organism	Total (n=130)	EONS (n=87)	LONS (n=43)
01.	Staphlococcus aureus	45(34.62%)	28(32.18%)	17(39.53%)
02	Klebsiella pneumoniae	41(31.54%)	30(34.48%)	11(25.60%)
03.	Escherichia coli	21(16.15%)	17(19.54%)	4(9.30%)
04.	Pseudomonas species	7(5.38%)	5(5.75%)	2(4.65%)
05.	Coagulase negative staphylococcus	5(3.85%)	0(0.00%)	5(11.63%)
06.	Non haemolytic streptococci	4(3.08%)	3(3.45%)	1(2.33%)
07.	Beta haemolytic streptococci	4(3.08%)	3(3.45%)	1(2.33%)
08.	Acinetobacter	3(2.31%)	1(1.15%)	2(4.65%)

Table-2: Distribution of various bacteria causing neonatal sepsis

	Klebsiella (N=41)		E. coli (N=21)		Pseudomonas (N=7)		Acinetobacter (N=3)	
	S	R	S	R	S	R	S	R
Amikacin	28(68%)	13(32%)	16(76%)	5(24%)	4(57%)	3(43%)	2(67%)	1(33%)
Ampicillin	1(2.4%)	40(98%)	2(10%)	19(90%)	0(0.0%)	7(100%)	0(0.0%)	3(100%)
*Amoxyclav	2(4.9%)	39(95%)	4(19%)	17(81%)	0(0.0%)	7(100%)	0(0.0%)	3(100%)
Cefoperazone	34(83%)	7(17%)	18(86%)	3(14%)	6(86%)	1(14%)	1(33%)	2(67%)
Cefotaxime	23(56%)	18(44%)	15(71%)	6(29%)	3(43%)	4(57%)	1(33%)	2(67%)
Ceftazidime	26(63%)	15(37%)	17(81%)	4(19%)	5(71%)	2(29%)	2(67%)	1(33%)
Ceftriaxone	21(51%)	20(49%)	16(76%)	5(24%)	4(57%)	3(43%)	1(33%)	2(67%)
Cefuroxime	4(10%)	37(90%)	11(52%)	10(48%)	1(14%)	6(86%)	0(0.0%)	3(100%)
Ciprofloxacin	22(54%)	19(46%)	12(57%)	9(43%)	2(29%)	5(71%)	1(33%)	2(67%)
Gentamicin	26(63%)	15(37%)	14(67%)	7(33%)	3(43%)	4(57%)	2(67%)	1(33%)
Imipenem	38(93%)	3(7%)	20(95%)	1(5%)	6(86%)	1(14%)	3(100%)	0(0.0%)
Levofloxacin	22(54%)	19(46%)	14(67%)	7(33%)	2(29%)	5(71%)	0(0.0%)	3(100%)
Meropenem	34(83%)	7(17%)	19(90%)	2(10%)	5(71%)	2(29%)	3(100%)	0(0.0%)
Ofloxacin	21(51%)	20(49%)	12(57%)	9(43%)	1(14%)	6(86%)	1(33%)	2(67%)
Pipracillin-Tazobactam	32(78%)	9(22%)	17(81%)	4(19%)	4(57%)	3(43%)	2(67%)	1(33%)
Colistin	40(98%)	1(2%)	21(100%)	0(0%)	7(100%)	0(0%)	3(100%)	0(0%)

Table-3: Antibiotic sensitivity pattern of gram negative organisms (S=Sensitive, R=Resistant)

Antibiotic	Organism							
	Staph aureus (N=45)		CONS (N=5)		NHS ¹ (N=4)		BHS ² (N=4)	
	S	R	S	R	S	R	S	R
Amikacin	32(71%)	13(29%)	4(80%)	1(20%)	2(50%)	2(50%)	3(75%)	1(25%)
Ampicillin	14(31%)	31(69%)	2(40%)	3(60%)	0(0.0%)	4(100%)	2(50%)	2(50%)
*Amoxyclav	28(62%)	17(38%)	3(60%)	2(40%)	0(0.0%)	4(100%)	3(75%)	1(25%)
Cefotaxime	21(47%)	24(53%)	2(40%)	3(60%)	1(25%)	3(75%)	3(75%)	1(25%)
Ceftriaxone	23(51%)	22(49%)	3(60%)	2(40%)	1(25%)	3(75%)	3(75%)	1(25%)
Chloramphenicol	7(16%)	38(84%)	1(20%)	4(80%)	0(0%)	4(100%)	2(50%)	2(50%)
Cloxacillin	29(65%)	16(35%)	2(40%)	3(60%)	1(25%)	3(75%)	3(75%)	1(25%)
Cotrimoxazole	18(40%)	27(60%)	0(0.0%)	5(100%)	0(0%)	4(100%)	2(50%)	2(50%)
Erythromycin	21(47%)	24(53%)	2(40%)	3(60%)	0(0%)	4(100%)	3(75%)	1(25%)
Cefuroxime	21(47%)	24(53%)	3(60%)	2(40%)	1(25%)	3(75%)	3(75%)	1(25%)
Ciprofloxacin	25(56%)	20(44%)	3(60%)	2(40%)	2(50%)	2(50%)	3(75%)	1(25%)
Gentamicin	26(58%)	19(42%)	2(40%)	3(60%)	1(25%)	3(75%)	3(75%)	1(25%)
Linezolid	45(100%)	0(0.0%)	5(100%)	0(0.0%)	4(100%)	0(0.0%)	4(100%)	0(0.0%)
Piperacillin-Tazobactam	30(67%)	15(33%)	4(80%)	1(20%)	3(75%)	1(25%)	4(100%)	0(0.0%)
Vancomycin	45(100%)	0(0.0%)	5(100%)	0(0.0%)	4(100%)	0(0.0%)	4(100%)	0(0.0%)

Table-4: Antibiotic sensitivity pattern of gram positive organisms(S=sensitive, R=Resistant)

Amikacin		Ampicillin		Amoxyclav		Colistin		Cefoperazone		Ceftaidime		Cefotaxime		Ceftriaxone	
S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
69	31	4	96	8	92	98.6	1.4	82	18	69	31	58	42	58	42
Cefuroxime		Ciprofloxacin		Gentamycin		Imepenem		Levofloxacin		Meropenem		Ofloxacin		Piperacillin-tazobactam	
S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
22	78	51	49	62	38	96	4	53	47	85	15	49	51	76	24

Table-5: Overall antibiogram of Gram Negative organisms (in%)

Amikacin		Ampicillin		Amoxyclav		Cefotaxime		Ceftriaxone		Chloramphenicol		Cloxacillin		Cotrimoxazole	
S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
71	29	31	69	59	41	47	53	52	48	17	83	60	40	34	66
Erythromycin		Cefuroxime		Ciprofloxacin		Gentamycin		Linezolid		Piperacillin-tazobactam		Vancomycin			
S	R	S	R	S	R	S	R	S	R	S	R	S	R		
45	55	48	52	57	43	55	45	100	0	71	29	100	0		

Table-6: Overall antibiogram of gram positive organisms (in%):

Parameter	Value
1. Cases initially started on antibiotics	341(100%)
1.a. Cases with culture positive and antibiotics continued	130(38%)
1.b. Negative culture & clinical course compatible with sepsis: Antibiotic continued.	119(35%)
1.c. Negative culture & clinical course incompatible with sepsis: Antibiotic stopped	92(27%)
2. Mortality data in:	
2.a. Overall	51(14.9%)
2.b. Blood culture positive cases(n=130)	29(22.3%)
2.c. Blood culture negative cases (n=211)	22(10.4%)
2.d. Both Culture & sepsis screen positive (n=81)	24(29.6%)
2.e. Culture positive and sepsis screen negative(n=49)	12(24.5%)
2.f. Culture negative and sepsis screen positive (n=46)	6(13%)
2.g. Both culture and sepsis screen negative (n=165)	9(5.5%)

Table-7: Treatment and mortality data

decided based on the culture report and the clinical condition of the baby (table-7).

DISCUSSION

Blood culture is the gold standard for confirmation of neonatal sepsis but culture positivity varies from 6.7% to 55.4%. In this study we had culture positivity rate of 38.12% which is comparable with the study of Kumhar et al⁹ (42%). However, higher culture positivity rate (56%) had been reported by Sharma et al.¹⁰ Chow et al¹¹ reported growth of anaerobes in 26% cases. Since a sizeable no. (62%) of our aerobic culture had no growth, the possibility of infection by anaerobes and fastidious bacteria can be suspected. However, feasibility, logistics & cost of such approach needs to be explored further.

Out of the 130 cases with positive blood culture, 83(63.8%) were preterm and this was statistically significant (P <0.005). This is comparable to many studies including the study of Kamble et al.¹² Preterm infants are at an increased risk of infection because of their inherent compromised immunity, vulnerable skin and mucosal barrier, prolonged hospital stay and extensive interventions. In our study, EONS (66.92%) was commoner than LONS (33.08%) and this is comparable to the findings of researchers of developing countries including India (Chug et al¹³) This underlines the importance of timely recognition and management of perinatally acquired infections causing EONS.

Overall the isolation of gram negative bacteria (55.38%) was higher than gram positive bacteria (44.62%). Various studies have shown that in the last two decades, the isolation of Gram positive organisms has increased significantly. Nevertheless the predominance of gram negative corroborates with the findings of other studies done in the Indian context (Kaistha et al¹⁴). In India, the Gram-negative organisms are

mainly represented by *Klebsiella*, *E. coli*, *Pseudomonas*, and *Acinetobacter*. Among Gram-positive organisms, *Staphylococcus aureus*, CONS and *Streptococcus species* are most commonly isolated, which is very similar to our study. However, we found that whereas Gram negative bacteria are predominant in EONS with *Klebsiella pneumoniae* (35% of cases) being the commonest isolate, in LONS it's the Gram positive bacterias (56% of the cases), esp. *Staph aureus* (40% of cases) which outnumber other bacteria in this group. This underscores the relative higher occurrence of gram positive bacteria in horizontal transmission unlike gram negative bacteria which tend to be more common in vertical transmission¹⁵. In this study, low isolation rates of beta hemolytic streptococcus can be attributed to their infrequent colonization of pregnant women or possibly, to the presence of strains with low virulence.¹⁶ Antibiotic resistance is a global problem and reports of multidrug-resistant bacteria in developing countries are increasing. In our study, older Beta lactam antibiotics (ampicillin, amoxicillin-clavulanate) were sensitive in less than 8% of gram negative isolates. Of particular concern is the occurrence of resistance in about 50% of gram negative isolates to ciprofloxacin, ofloxacin, cefotaxime, ceftriaxone. The only good choices included amikacin, ceftazidime, cefoperazone, imipenem, meropenem and piperacillin-tazobactam combination. Gram negative bacteria here were *Klebsiella* and *E coli*, both of which were highly resistant to ampicillin (upto 95%) and the common cephalosporins like ceftriaxone and cefotaxime (upto 45%). Overall, the most sensitive antibiotic against gram negative isolates was colistin (98%) imipenem (96%) followed by meropenem (85%), piperacillin-tazobactam (76%). Of utmost concern was high level of resistance seen in *Klebsiella* with no single antibiotic sensitive in all cases with few isolates resistant to

even colistin or imipenem. High prevalence of resistance to commonly used antibiotics has also been reported by studies done by Shaw et al¹⁷ and Tsering et al.¹⁸ The gram positive isolates were also mostly resistant to the older antibiotics like ampicillin, cotrimoxazole, chloramphenicol, erythromycin and cefuroxime. Ampicillin resistance was seen in about 70% of the *S. aureus* strains and about half of CONS and BHS strain. Similar high rate of ampicillin resistance against *S.aureus* (upto 95%) and CONS (upto 90%) was seen in many studies done in our country. However, all *Staphylococcal* isolates were sensitive to Vancomycin and linezolid. Because of the rising resistance, newer drugs (carbapenems, Vancomycin, Linezolid) should be kept as reserve drugs for MDR isolates especially ESBL producers and over prescription of vancomycin and linezolid should be strongly discouraged to prevent the development of resistant strains such as enterococci.

As per our NICU protocol, all cases with clinical sepsis were started on Ampicillin + Amikacin combination, except for suspected meningitis cases which were started on Cefotaxime + Amikacin. When we evaluated the resistance pattern to this empirical treatment, we were surprised to find that almost 25% cases were resistant to both drugs of the combination, both drugs sensitive in only 17% cases and a single agent of the two was sensitive in nearly 60% cases. Whereas, almost 70% of gram positive as well as gram negative isolates were individually sensitive to either piperacillin-tazobactam or amikacin & at least one drug of this combination was sensitive in nearly 93% of all cases. Hence a co-prescription of these 2 drugs may appear prudent as the initial choice while awaiting blood culture reports. However, it has to be kept in mind that a resistant report isn't the sole criteria for changing an antibiotic regimen which has to take into account the organism & the clinical improvement at the same time as per NNF guidelines 2011.

We also studied mortality in different groups who received antibiotic therapy. The group with culture positive sepsis had a statistically significant higher mortality as compared to those with negative blood culture (22.3% vs 10.4%; $p < 0.001$). This was similar to the study by Kamble et al¹² but the lower mortality rates in our study may be attributed to earlier suspicion and prompt treatment of neonatal sepsis.

Limitations of the study

Ours was a single center study and hence our findings can't be universally generalized. Also, we didn't perform cultures for anaerobes, fastidious bacteria and fungi.

CONCLUSION

Blood culture though traditionally regarded as gold standard, wasn't positive in many of the cases (62%) with clinical sepsis. Neonatal sepsis was more commonly associated with prematurity and EONS was more common than LONS. Gram negative organisms were the commonest etiologic agents of neonatal sepsis. But, whereas EONS was most commonly caused by gram negative organisms, LONS was caused more commonly by gram positive organisms. The most common isolate was *Staph. aureus*, but this was closely followed by

Klebsiella. Together these 2 organisms were responsible for nearly 2/3 rd cases of neonatal sepsis. There was a high occurrence of resistance to the commonly used antibiotics, more so in gram negative bacterias esp. *Klebsiella*. Almost 70% of gram positive as well as gram negative isolates were individually sensitive to either piperacillin-tazobactam or amikacin and hence a co-prescription of these two antibiotics appear prudent as the initial choice while awaiting for the blood culture reports. A positive blood culture carries higher risk of mortality.

There is a pressing need for development of rapid diagnostic tests for neonatal sepsis to prevent late or unnecessary antibiotics therapy. As the sensitivity pattern changes over time with emergence of resistance to the drugs being used in a particular setting, it is important to monitor trends in changing sensitivity pattern to consider an alternate empirical antibiotic regimen. It is also important to follow all infection prevention measures given the emergence of multi drug resistant strains which is a never ending process.

Abbreviations

BHS: Beta haemolytic streptococci; EONS: Early onset neonatal sepsis; GA: Gestational age; GBS: Group B streptococcus; NHS: Non haemolytic streptococcus; LONS: late onset neonatal sepsis; LBW: Low birth weight; PT: Preterm; ROM: rupture of membranes;

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