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RESEARCH ARTICLE

BACTERIOLOGICAL PROFILE OF NEONATAL SEPTICEMIA, THE ASSOCIATED RISK FACTORS AND ANTIBIOTIC SUSCEPTIBILITY PATTERN OF THE ISOLATES: A RETROSPECTIVE STUDY

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ABSTRACT

In present study, aim was to determine the bacteriological profile in Neonatal Sepsis and antimicrobial sensitivity of the organisms in the Neonatal Intensive Care Unit (NICU) of Tertiary care Hospital and to identify risk factors for neonatal sepsis. This study included records of all cases of clinically suspected septicemia in neonates admitted to the NICU from September 2015 to August 2016 (n=101).

Result: The risk of sepsis in birth asphyxia and gestational age was about 2 times higher as compared to the control group and p- value was significant at 0.05 levels. Out of the total 95 cases having perinatal fever (n = 95, 94%), 34 (34%) were culture positive and 61 (60%) were culture negative, which was statistically significant.

Conclusion: Klebseilla (Gm – ve) (23%) and Staphylococcus aureus (Gm + ve) (15.3%) were the most common organisms causing neonatal sepsis in our settings. Ampicillin and Gentamicin for 1st line, Ciprofloxacin and Piperacillin and Tazobactam for 2nd line, Meropenum and Vancomycin for 3rd line drugs for empirical antibiotic therapy.

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INTRODUCTION

In 2010 worldwide, 7.6 million children less than 5 years old died, predominantly due to infectious causes including sepsis; neonatal deaths (in the first 28 days of life), accounted for 40% of the total lives lost (Liu *et al*., 2012). In 1990, both the United Nations (UN) and World Health Organization (WHO) prioritized a 2/3rd reduction in the unacceptable child mortality rateby 2015. However, in 2013, 44% of deaths in children under the age of five occurred during the neonatal period, up from 37% in 1990. Despite major advances in neonatal care and increasing research, in developed countries, four of every ten infants with sepsis die or experience major disability including significant permanent neurodevelopmental impairment (Brocklehurst *et al*., 2011). Neonatal sepsis is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first month of life.Septicemia is a common cause of morbidity and mortality in neonates and children. According to the data from "The National Neonatal Perinatal Database" (NNPD, 2002 – 2003), the incidence of neonatal sepsis was 30 per 1000 live births. The NNPD network, comprising of 18 tertiary care neonatal units across India, found sepsis to be one of the commonest causes of neonatal mortality contributing to 19% of all neonatal deaths. (Network, 2005) The World Health Organization (WHO) estimates that 1 million deaths per year (10% of all under-five mortality) are due to neonatal sepsis and that 42% of these deaths occur in the first week of life (4). In particular, neonates with low birth weight show relatively higher morbidity and mortality (Fanaroff *et al*., 2007). The bacteria that cause neonatal sepsis are acquired shortly before, during, or after delivery. They can be obtained directly from mother's blood, skin, or vaginal tract before or during delivery, or from the environment during and after delivery. Streptococcus agalactiae (Group B streptococcus, GBS) is the most common cause of neonatal sepsis in many countries; gram negative bacilli (Escherichia coli, Klebsiella spp., Pseudomonas spp., Acinetobacter spp.) and gram-positive cocci (such as Staphylococcus aureus and Staphylococcus epidermidis) are other important causes (Monjur *et al*., 2010). A fast and correct diagnosis, followed by rapid treatment, plays an important role in the reduction of infant mortality resulting from sepsis (Muley *et al*., 2015). However, diagnosing neonatal sepsis is difficult since being exposed to known risk factors for sepsis is not a necessity, clinical signs are often vague, and laboratory parameters are nonspecific (Shamahy *et al*., 2012). Neonatal sepsis is broadly divided into two types according to the age of onset:

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- Early onset sepsis (<72 hours) - is acquired during fetal life, delivery, or at the nursery.
- Late onsetsepsis (>72 hours – 8 days) - is generally caused by microorganisms acquired from the environment rather than from the mother. (Jyothi *et al*., 2013)

Maternal, environmental, and neonatal factors determine which neonates exposed to a potentially pathogenic organism will develop sepsis.

MATERIALS AND METHODS

Aim

To determine the bacteriological profile in Neonatal Sepsis and antimicrobial sensitivity of the organisms in the Neonatal Intensive Care Unit (NICU) of Tertiary care Hospital and to identify risk factors for neonatal sepsis.

Objectives

- To relate risk factors with bacteriological profile of neonates admitted in NICU of Tertiary care hospital.
- To evolve a protocol for empirical antibiotic therapy for newborns suspected to have neonatal sepsis.
- To identify preventable risk factors, if any.

Study population

This study includes records of all cases of clinically suspected septicemia in neonates admitted to the Neonatal Intensive Care Unit (NICU) of tertiary care hospital.

Sample size

All clinically suspected patients of neonatal septicemia, admitted to the NICU from September 2015 to August 2016 were selected.

Study place

This study was carried out in the NICU, Tertiary Care hospital in Nagpur with the cooperation from the Department of Microbiology.

Study period

This study was carried out from September 2015 to August 2016.

Inclusion criteria

Records of all neonates clinically suspected of septicemia that were admitted to the Neonatal Intensive Care Unit of tertiary care hospital.

Exclusion criteria

Neonates with inborn errors of metabolism.

Design

This was a hospital record based Retrospective study.

Method

Records of clinically suspected cases of neonatal septicemia, admitted to the NICU from September 2015 to August 2016 were selected. Detailed history regarding maternal and neonatal risk factors was evaluated.

Sepsis was clinically suspected by the following signs

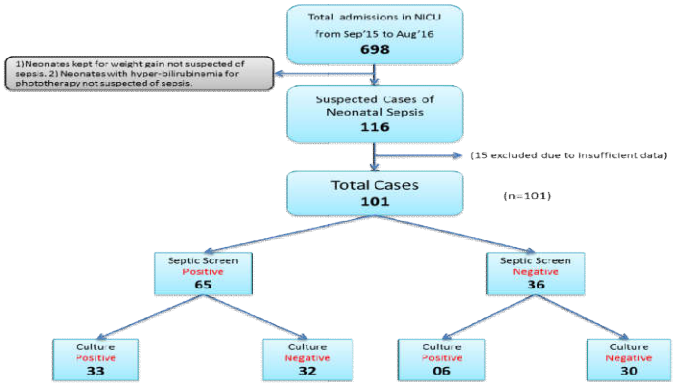
- Temperature instability
- Lethargy
- Apnea
- Poor feeding
- Abdominal distention
- Heme – positive stools

As per NICU protocols, sepsis screening for patients with clinically suspected sepsis included

- Total leucocyte count - < 5000/mm3
- Absolute neutrophil count - Low counts as per manroe chart
- Immature/total neutrophils - >0.2
- Micro – ESR - >10mm in 1st hour
- C Reactive Protein (CRP) - >1mg/dl

Blood culture

Blood samples were collected from a peripheral vein under aseptic conditions. Blood was collected in 3 bottles: EDTA (CBC, ESR), plain bottle (CRP), and 1 – 2ml blood in blood culture bottle containing brain heart infusion broth. The culture bottles were incubated at 37 deg. C. Subculture was done on blood agar and Mac Conkey's agar. On the basis of the colony morphology, gram staining and biochemical reactions, identification of the organism was done. The antibiotic sensitivity pattern was tested by Kirby Bauer Disc diffusion method as recommended by the CLSI guidelines. All blood cultures were observed for at least 7 days before they were reported as sterile.



Total 698 neonates were admitted in the NICU of tertiary care hospital from September'15 to August'16. Out of which 116 were suspected cases of neonatal sepsis as per above-mentioned signs. Total participants included in the study were 101.

Statistical Analysis

The obtained data was statistically analyzed by applying descriptive (Mean, Standard Deviation, t-value) tests of

significance of mean differences in terms of various variables. All the data was entered and further statistical analysis was done with the help of IBM- SPSS 25 software.

RESULTS

Records of 101 neonates with suspected sepsis admitted to NICU were studied. There were 53 males (52%) and 48 (48%) females. Fifty nine (58%) were full term while the remaining forty-two (42%) were preterm. Forty-six percent of neonates (**n** = 46) were delivered by spontaneous vaginal delivery and 54% (**n** = 55) were delivered by caesarean section (CS). Seventy-two neonates were low birth weight (71%); twenty-nine neonates were of normal birth weight (29%). Among these 101 neonates, 48 (48%) were diagnosed as early onset sepsis and 53(52%) as late onset sepsis as shown in table no.1:1.

Table. 1:1 Characteristic of suspected septic neonates admitted in NICU

	Characteristics		n
1	Gender	Male	53
		Female	48
2	Delivery	Preterm	48
		Full-term	53
3	Type of delivery	Normal	46
		CS	55
4	Birth weight	LBW	72
		NBW	29
5	Onset of sepsis	Early	48
		Late	53

CS = Caesarean section; LBW = Low birth weight (birth weight < 2500gm); NBW = normal birth weight; Early onset sepsis <72 h after birth;

Table .no. 1:2- Comparison between Septic Screening and Culture Positivity of clinically suspected sepsis

	Culture Growth Positive	Culture Growth Negative	Total
Septic Screening Positive	33	32	65
Septic Screening Negative	06	30	36
Total	39	62	101

late onset sepsis ⩾72 h after birth. Table no.1:2. Of the neonates suspected clinically, 39 had culture positivity. Of these 39 culture positive septic neonates, 33 (84.6%) were positive using lab parameters for sepsis screening, 6 (15.4%) were septic screen negative. Out of 62 culture negative neonates, 32 (51.6%) were septic screen positive and 30 (48.4%) were septic screen negative. Similarly out of 65 neonates that were septic screen positive, 33 (50.7%) were culture positive and 32 (49.3%) were culture negative. Of the 36 septic screen negative cases, 6 (16.6%) were culture positive and 30 (83.4 %) were culture negative.

Table 1:3- Comparison between Birth weight and Culture Positivity of clinically suspected septic neonates

Gram	Culture positive	Culture negative	p Value
Above 2500 gm	10	19	p< 0.75
1501 gm – 2499 gm	15	33	p <0.37
Below 1500 gm	14	10	p >0.04*
Total	39	62	

p <0.05*, gm-gram

The above table compares the culture growth with birth weight of the studied neonates.

It was seen that positive culture growth was statistically significant in participants with birth weight < 1500 gm.All cases were assessed for various risk factors of neonatal sepsis. The significant maternal factors included premature onset of labor, premature rupture of membrane (PROM) >18 hours, prolonged labor (>24 hours both stages) and difficult delivery with instrumentation, febrile illness in the mother during or within two weeks of delivery, foul smelling and/ or meconium stained liquor amnii. Notable neonatal factors included birth asphyxia, prematurity, low birth weight infants, and difficult resuscitation.

Table 1:4. Maternal and neonatal risk factors associated with neonatal sepsis

Risk Factor		Culture Positive	Culture Negative	p-Value
Perinatal Fever	Present	34	61	p >0.05*
	Absent	5	1	
PROM	Present	4	11	p <0.458
	Absent	35	51	
Prolonged Labor	Present	6	2	p <0.06
	Absent	33	60	
Foul smelling	Present	22	28	p <0.37
Liquor	Absent	17	34	
Gestational Age	< 37 weeks	13	35	p >0.04*
	> 37 weeks	26	27	
Birth Asphyxia	Present	9	3	p >0.01*
	Absent	30	59	
Neonatal	Present	9	9	p <0.40
Resuscitation	Absent	30	53	
RDS	Present	14	25	p <0.29
	Absent	15	47	

* Significant at p < 0.05 level

Table 1:4- depicts the various maternal and foetal risk factors in neonates with sepsis. The maternal factor having a significant risk for the development of sepsis was perinatal fever. The risk of sepsis in birth asphyxia and gestational age was about 2 times higher as compared to the control group and p- value is significant at 0.05 levels. Out of the total 95 cases having perinatal fever (n = 95, 94%),34 (34%) were culture positive and 61 (60%) were culture negative, which was statistically significant. The significant risk factors were perinatal maternal fever, prolonged rupture of membranes (>12 hours), Neonatal Resuscitation, Low Birth Weight

Table 1:5. Causative organisms in culture proven septic participants

Gram Positive (6)		Gram Negative (27)		Fungi (6)	
Organisms	No.	Organisms	No.	Organisms	No.
MSSA	3	Klebsiella	9	Candida	4
MRCONS	1	Pseudomonas	5	Yeast	2
MSCONS	1	Burkholderiacepacia	8		
MRSA	1	Enterobacteriaceae	1		
		E-Coli	3		
		Citrobacter	1		

[MSSA: Methicillin sensitive S. aureus, MRCONS: Methicillin resistant coagulase negative S. aureus, MSCONS: Methicillin sensitive coagulase negative S. aureus, MRSA: Methicillin resistant S. aureus]

(Gupta and Date, 2015) The frequency of Gram-positive, Gram-negative and fungi of all clinically significant isolates was (n = 6, 15%), (n = 27, 70%) and (n = 6, 15%) respectively.Blood cultures report for 101 neonates and 39% were culture positive. Gram-positive isolates were (n =6), Methicillin sensitive S. aureus (MSSA) - 3 (50%), Methicillin resistant coagulase negative S aureus (MRCONS) - 1 (17%), Methicillin sensitive coagulase negative S aureus (MSCONS) -

1 (17%), Methicillin resistant S. aureus (MRSA) - 1 (17%). Whereas Gram-negative isolates were (n =27),Klebsiella - 9 (33%), Pseudomonas - 5 (19%), Burkholderiacepacia - 8 (30%), Enterobacteriaceae - 1 (4%), E-Coli - 3 (11%), Citrobacter - 1 (4%). Fungal sepsis was seen in 6 cases (n = 6), Candida - 4 (67%), and Yeast - 2 (33%). Overall Klebseilla (23%) and S. aureus (15.3%) are the commonest organisms causing neonatal sepsis.

Table 1:6. Antibiotic sensitivity respective to organisms (gram-positive and gram-negative bacteria, and fungi)

ORGANISMS	P	COT	CTR	CTX	LF	IMP	MRP	CIP	GEN	L7	PI	PIT	VA	CD	E	AK	NT	CAZ	AZ	CL	FLC	KT	IT	A
MSSA	Y			Y		Y				Y	Y	Y	Y											
MRCONS								Y		Y		Y	Y	Y										
MSCONS	Y							Y	Y	Y		Y	Y	Y	Y									
MRSA										Y			Y											
ECOLI					Y		Y					Y				Y								
ENTEROBACTERCIAE	Y	Y	Y					Y	Y									Y						
CITROBACTER					Y		Y		Y		Y	Y				Y								
KLEBSEILLA		Y		Y		Y		Y	Y			Y					Y		Y	Y				
PEUDOMONAS								Y			Y	Y				Y	Y							
BURKHOLDERIA		Y	Y		Y	Y	Y		Y															
CANDIDA																					Y	Y	Y	Y
YEAST																					Y			

[P – penicillin, Cot – cotrimoxaxole, CTR- ceftriaxone, Le -levofloxacin, ctx – cefotaxim, Imp –imipenum, Cip –ciprofloxacin, MRP- meropenum, Gen –gentamicin, Lz- linezolid, Pi- piperacillin, Pit- piperacillin tazobactum, VA –vancomycin, CD –clindamycin, E –erythromycin, Ak –amikacin, Net –netilmycin, Caz- ceftazidime, Az- azithromycin, Cl- colistin, Flc –flucanazole, Kt- ketoconazole, It –itroconazole.
A -amphotericin b]

In gram positive organisms, all of them were sensitive to Vancomycin, Linezolid, followed by Piperacillin and Tazobactam, Clindamycin, Ciprofloxacin and Penicillin. In gram negative organisms, sensitivity was seen to Piperacillin and Tazobactam, followed by Meropenum, Ciprofloxacin, Gentamycin, Amikacin, followed by Netilmycin, and Levofloxacin. Candida and Yeast were sensitive to all antifungal medications.

DISCUSSION

Septicemia in neonates refers to generalized bacterial infection documented by positive blood culture in the first four weeks of life (Agnihotri *et al*., 2004) and is one of the four leading causes of neonatal mortality and morbidity in India (Tsering *et al*., 2011; Jain *et al*., 2007; Kumhar *et al*., 2002). Neonatal septicemia continues to be a major problem for neonates in neonatal intensive care units around the world. (Gomaa *et al*., 2001). The infection can be contracted from the mother via trans placental route, ascending infection, during passage through an infected birth canal, or exposure to infected blood at delivery (Mayuga and Isleta, 2005). The newborn infants are more prone to bacterial invasion than the older children or adults, due to their weaker immune system, premature babies being even more susceptible (Ghosh *et al*., 2001). Our study showed perinatal fever, prematurity, birth asphyxia to be statistically significant factors for neonatal sepsis. The sex wise distribution was males (52.4%) and females (47.6%). In two separate studies by Schuchat A *et al*. and Yancey MK showed similar maternal and neonatal risk factors responsible for neonatal sepsis. (30,31) whereas in a study by Ansari S *et al*. 61.4% were males and 38.6% were female neonates (Ansari *et al*., 2015).

The report of the National Neonatal-Perinatal database showed Klebsiella as the predominant (29%) pathogen. (18) Klebsiella spp.(23%) was the predominant Gram-negative species isolated in this study, which agrees with previous reports.(Tsering *et al*., 2011; Shrestha *et al*., 2008; Begue, 1991) In our study, the most frequent isolate was Klebsiella (23%) and this was in accordance with other Indian studies. (Das *et al*., 1999), (Kapoor *et al*., 2000), (Khaneja *et al*., 1999) Gram negative organisms (Klebsiella species, Citrobacter species), Streptococcus, Staphylococcus are leading cause of neonatal sepsis. (Ram Sunder Sharma *et al*., 2016) Our study showed gram positive organisms were sensitive to Piperacillin &Tazobactam, Penicillin, Vancomycin and Linezolid, and gram negative organisms were sensitive to Piperacillin & Tazobactam, Gentamycin, Ciprofloxacin and Meropenum. In a study by Gupta *et al*. showed highest sensitivity to Imipenem and Cefotaxime (Gupta, 2015). A studyby Khaneja M *et al*. also found quinolones to be effective in the treatment of multidrug resistant gram-negative infections in patients including premature and extremely low birth weight infants (Khaneja, 1999)

Conclusion

- Risk factors which were statistically significant: Birth asphyxia, Prematurity and Perinatal fever.
- Klebseilla (Gm – ve) (23%) and Staphylococcus aureus (Gm + ve) (15.3%) were the most common organisms causing neonatal sepsis in our settings.
- Ampicillin and Gentamicin for 1st line, Ciprofloxacin and Piperacillin &Tazobactam for 2nd line, Meropenum and Vancomycin for 3rd line drugs for empirical antibiotic therapy.

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