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Neonatal sepsis - bacteriological profile, antibiotic susceptibility pattern in sick newborn care unit of a tertiary care hospital

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Abstract

Background: Neonatal septicaemia is a clinical syndrome characterized by systemic manifestation of infection which is accompanied by bacteraemia in first 4 weeks of life. Neonatal sepsis encompasses systemic infections including meningitis, pneumonia, arthritis, osteomyelitis, urinary tract infections and gastroenteritis.[1] Clinical suspicion, timely diagnosis and rationalize interventions is important, even a few hours of delay in initiation of treatment can result in rapid clinical deterioration of neonate.

Objective: To isolate bacteria causing neonatal septicaemia in Sick Newborn Care Unit of Tertiary care hospital and to study the antibiotic susceptibility pattern of the bacterial isolates causing neonatal septicemia.

Method: This prospective observational study included 500 neonates with probable sepsis. Their baseline information was collected in a pre-designed proforma and blood sample drawn for culture & sensitivity.

Results: Among the 500 neonates with probable sepsis, 379 (75.8%) had EOS and 121 (24.2%) had LOS. The blood culture positivity was 34.6% (n=173). Higher proportion of Gram-positive organisms were found than Gram negative. Methicillin sensitive Staphylococcus aureus and CoNS were the commonest isolates. Antimicrobial susceptibility pattern revealed 100% sensitivity to Vancomycin and Linezolid in all the Gram-positive isolates, followed by Amoxyclav and Doxycline sensitivity (80-90%). Among Gram negative isolates Klebsiella pneumoniae and Citrobacter koseri were predominant isolates. Amoxycillin-clavulanic acid (AMC) had highest sensitivity (78.9%), followed by Imipenem, Doxycycline and Amikacin. Resistance among third generation cephalosporins (cefotaxime, ceftriaxone & ceftazidime), fourth generation (Cefepime), Ciprofloxacin, Gentamicin and Piperacillin-Tazobactum were predominantly seen.

Conclusion: In spite of improvement in perinatal services, Neonatal Sepsis is still major problem in

newborns care and one of the leading causes of neonatal mortality. Changing pattern of bacteriological profile and antibiotic susceptibility pattern warrants periodic assessment of same in SNCUs.

Keyword: neonatal sepsis, sick newborn care unit, bacteriological profile, antibiotic susceptibility pattern

Introduction

Neonatal septicaemia is a clinical syndrome characterized by systemic manifestation of infection which is accompanied by bacteraemiain first 4 weeks of life. Neonatal sepsis encompasses systemic infections including meningitis, pneumonia, arthritis, osteomyelitis, urinary tract infections and gastroenteritis.[1]

Neonatal infections are also associated with significant risk of neurological abnormalities, developmental and functional delays.

"Suspected sepsis" is the commonest diagnosis in NICU. Now-a- days even after improved obstetrical management, intra-partum screening and evidence-based use of antibiotics, sepsis still remains an important contributor to mortality and morbidity in neonates.[3]

Neonatal mortality accounts for about 40% of deaths under five years of age. The global incidence of neonatal mortality caused by sepsis is only 15% but in developing countries, incidence is about 30 – 50%.[3]

There has been great progress in decreasing post neonatal causes of mortality worldwide in past few years resulting in a decrease in the proportionate contribution of neonatal mortality to under five mortality.

Despite of advances in neonatal care in recent years, sepsis still remains a life- threatening condition. UNICEF data estimated that 2.8 million neonatal deaths that occurred globally in the year 2013 were due to sepsis. Two-third of these deaths have occurred in developing countries and in India about 1.2 million.

Neonatal septicaemia can be divided into two main classes depending on the onset of symptoms;[1]

Early onset septicaemia (EOS): Signs and symptoms of sepsis present within 72 hours.[4] EOS is often associated with vertical transmission by the organisms from maternal genital tract or transplacental transmission or via passage through birth canal during labour.

Late onset septicaemia (LOS): Signs and symptoms of sepsis present later than 72 hours of life.[4] LOS has usually environmental origin. The most common source of infection in hospital is due to poor hand hygiene practices of health care personnel.

Blood culture remains the gold standard for diagnosis of neonatal septicaemia.[5] Clinical suspicion, timely diagnosis and rationalize interventions is important, even a few hours of delay in initiation of treatment can result in rapid clinical deterioration of neonate.

This study was conducted to know the incidence of neonatal sepsis and to identify the common isolates and their antibiotic susceptibility pattern in Sick Newborn Care Unit (SNCU) of tertiary care hospital.

Material and methods

Study Centre: Sick Newborn care Unit, Department of Paediatrics, and Department of Microbiology, Gajra Raja Medical College and J. A. Group of Hospitals, Gwalior, Madhya Pradesh.

Ethical Approval: Ethical approval was obtained from Institutional Ethical Committee.

Study Subject: Neonates with probable sepsis or neonates with PSBI (Possible serious bacterial infection) who were admitted in Sick Newborn Care Unit (SNCU) Gajra Raja Medical College and J. A. Group of Hospitals, Gwalior.

Study Design and Period: A prospective study of neonates with probable sepsis or PSBI was conducted for

a period of seven months from August 2019 – February 2020.

Sample Size: A total of 500 samples of neonates with probable sepsis or PSBI admitted in J. A. Group of Hospitals.

Inclusion Criteria: All intramural and extramural neonates with probable sepsis or PSBI during the study period whom mother or care takers gave consent to be part of the study.

Exclusion Criteria

1. Neonates with no clinical suspicion of sepsis.
2. Patient's age >28 days of life.
3. All neonates who have prior antibiotic administration.
4. Neonates with <30 weeks of gestational age.
5. Neonates with birth weight <1000gm.
6. Neonates with gross congenital malformation.
7. Neonates for whom mother or caregivers are not willing to give consent.

Data Collection: The mother's and father's name, age, sex, address, date and time of birth, mode of delivery, place of birth, date of admission, in patient number, detailed clinical history and risk factors were noted.

Sample Collection and Transportation

An area of venipuncture site was disinfected with 70% alcohol, rubbing vigorously and allowed to dry. This was followed by application of povidone-iodine in concentric circles over the site and allowed to dry for at least 1 min. About 1-2 ml of venous blood was drawn using sterile syringe, out of which 1 ml of the blood sample was inoculated aseptically into BacT/ALERT®PF Plus bottle/ conventional blood culture bottle (BHI broth) in the dilution of 1:10.

Bottles were labelled with patient's identification number and date of collection and transported along with requisition and consent form to Bacteriology and Serology sections of Department of Microbiology, Gajra Raja Medical College with minimal delay (15 minutes) for culture & sensitivity.

Statistical Analysis: The statistical analysis was performed using statistical software SPSS (2.1). The data was represented as percentages and proportions. Two or more set of variables were compared by using Chi-square test and Z-test. If the p-value was <0.05, it was considered significant.

Observation And Results

Among the 500 neonates with probable sepsis 379 (75.8%) had early onset sepsis (EOS) and 121 (24.2%) had late onset sepsis (LOS). The blood culture positivity was 34.6% (n=173).

Low birth weight, prematurity and assisted vaignal delivery (AVD) was significantly associated with culture positive sepsis (Table 1).

Table 1: Distribution According to Baseline Characteristics

Item	Probable sepsis (n=500)	Culture proven sepsis (n=173)	Chi Square	P value
Gender				
Male	265	94	0.189	0.663
Female	235	79		

Maturity				
Preterm	188	94	27.9	0.000
Term	312	79		
Birth Weight				
>2500 gm	251	76	3.79	0.05
<2500 gm	249	97		
Parity of Mother				
Primipara	241	85		0.761
Multipara	259	88		
Place of birth				
Intramural	216	65		0.064
Extramural	284	108		
Mode of delivery				
NVD	232	82	41.11	0.000
AVD	90	51		
LSCS	178	40		

Table 2: Distribution of Clinical Feature Among Culture Positive Cases

Clinical Features	Culture positive	Culture negative	Z test	P value
Refusal to feed	122(70.5%)	51(29.5%)	7.634	0.000
Lethargy	139(80.3%)	34(19.7%)	11.289	0.000
Hypothermia	51(29.5%)	122(70.5%)	7.634	0.000
Hyperthermia	24(13.9%)	149(86.1%)	13.440	0.000
Cyanosis	34(19.7%)	139(80.3%)	11.289	0.000
Dehydration	5(2.9%)	168(97.1%)	17.525	0.000
Tachypnoea	50(28.9%)	123(71.1%)	7.849	0.000
Apnoea	36(20.8%)	137(79.2%)	10.859	0.000
Chest retraction	47(27.2%)	126(72.8%)	8.494	0.000
Tachycardia	70(40.5%)	103(59.5%)	3.548	0.000
Diarrhoea	6(3.5%)	167(96.5%)	17.310	0.000
Abdominal distension	60(34.7%)	113(65.3%)	5.698	0.000
Jaundice	49(28.3%)	124(71.7%)	8.064	0.000

Vomiting	6(3.5%)	167(96.5%)	17.310	0.000
Poor cry	12(6.9%)	161(93.1%)	16.020	0.000
Convulsion	38(22%)	135(78%)	10.429	0.000
Bleeding manifestation	5(2.9%)	168(97.1%)	17.525	0.000

Table 3: Correlation Between Risk Factors andCulture Positive

Risk Factors	Culture positive	Culture negative	P value
Birth weight (<2.5Kg) or GA <37 wk	139 (40.9%)	201 (59.1%)	0.000
Perinatal asphyxia	129 (39.7%)	196 (60.3%)	0.001
PROM	113 (48.5%)	120 (51.5%)	0.000
Duration of labour >24hr	118 (47.8%)	129 (52.2%)	0.000
Foul smelling liquor	78 (47.3%)	87 (52.7%)	0.000
Maternal fever	20 (31.7%)	43 (68.3%)	0.61

Low birth weight, perinatal asphyxia, premature rupture of membrane, duration of labour >24 hour were significantly associated with culture positive sepsis (Table3)

Table 4: Distribution of the culture isolates

Organism	Number of isolates	LOS	EOS
MSSA	40 (23.1%)	6	34
CoNS	29 (16.8%)	4	25
K. pneumoniae	19 (11.0%)	5	14
Citrobacter koseri	18 (10.4%)	1	17
MRSA	14 (8.1%)	2	12
Enterobacter spp.	11 (6.4%)	1	10
A. baumannii	9 (5.2%)	1	8
K. oxytoca	7 (4.0%)	2	5
S. pneumoniae	6 (3.5%)	0	6
E. coli	6 (3.5%)	1	5
P. vulgaris	5 (2.9%)	1	4
C. Freundii	5 (2.9%)	1	4
P. aeruginosa	2 (1.2%)	0	2
E. faecalis	2 (1.2%)	1	1

In the present study, Gram positive organisms constituted 52.6% (n=91) culture isolates when compared to the Gram-negative isolates 47.4% (n=82). The most frequent isolate in case of both EOS and LOS was found to be MSSA. MSSA was found to be the most common 23% (n=40) Gram Positive Cocci followed by CoNS 16.8%

(n=29), MRSA 8.1% (n=14), S. pneumoniae 3.5% (n=6) and E. faecalis 1.2%(n=2). Among Gram Negative Bacilli isolates Klebsiella pneumoniae 11%(n=19), Citrobacter koseri 10.4%(n=18) and *Enterobacter spp*. 6.4%(n=11) were most frequent organisms followed by A. baumannii 5.2%(n=9), K. oxytoca 4.0%(n=7), E. coli 3.5%(n=6), whereas both P. vulgaris and C. frundii constitute only 2.9%(n=5) isolates followed by P. aeruginosa 1.2%(n=2). (Table 4)

Table 5: Antibiotic Susceptibility Pattern of Common Gram-Positive Isolates

Drug	Gram positive cocci		
	MSSA(n=40)	MRSA(n=14)	CoNS (n=29)
AMP	2 (5.00%)	2 (14.30%)	1 (3.40%)
AMC	36 (90.00%)	12 (85.70%)	28 (96.60%)
AZ	27 (67.50%)	8 (57.10%)	19 (65.50%)
CZ	28 (70.00%)	7 (50.00%)	21 (72.40%)
CIP	29 (72.50%)	7 (50.00%)	17 (58.60%)
GEN	28 (70.00%)	6 (42.90%)	18 (62.10%)
DO	36 (90.00%)	10 (71.40%)	25 (86.20%)
VA	40 (100%)	14 (100.00%)	29 (100.00%)
LZ	40 (100%)	14 (100.00%)	29 (100.00%)
CFX	40 (100%)	0 (0.00%)	NT

(AMP – Ampicillin, AMC – Amoxycillin + Clavulanic acid, AZ – Azithromycin, CZ –Cefazolin, CIP – Ciprofloxacin, GEN – Gentamicin, DO – Doxycline, VA – Vancomycin, LZ – Linezolid, CFX – Cefoxitin, NT – Not tested)

Table 6: Antibiotic Susceptibility Pattern of Common Gram-Negative Isolates

Drug	Gram negative bacilli		
	K. pneumoniae (n=19)	C. Freundii (n=5)	Citrobacter koseri (n=18)
AK	13 (68.40%)	4 (80.00%)	14 (77.80%)
AMC	15 (78.90%)	2 (40.00%)	13 (72.20%)
CTX	10 (52.60%)	3 (60.00%)	13 (72.20%)
CTR	10 (52.60%)	0 (0.00%)	12 (66.70%)
CAZ	12 (63.20%)	3 (60.00%)	13 (72.20%)
CPM	10 (52.60%)	3 (60.00%)	11 (61.10%)
CIP	9 (47.40%)	1 (20.00%)	11 (61.10%)
GEN	9 (47.40%)	2 (40.00%)	12 (66.70%)

DO	14 (73.70%)	4 (80.00%)	16 (88.90%)
PIT	9 (47.40%)	2 (40.00%)	11 (61.10%)
IPM	14 (73.70%)	5 (100.00%)	(88.90%)

(AK – Amikacin, AMC – Amoxycillin + Clavulanic acid, CTX – Cefotaxime, CTR – Ceftriaxone, CAZ – Ceftazime, CPM – Cefipime, CIP – Ciprofloxacin, GEN – Gentamicin, DO – Doxycyclin, PIT – Piperacillin + Tazobactum, IPM – Imipenem)

Antimicrobial susceptibility pattern revealed 100% sensitivity to Vancomycin and Linezolid in all the Gram-positive isolates, followed by Amoxyclav and Doxycline (80-90%). Gentamycin and cefazolin showed moderate sensitivity (50%-70%). Resistance against Ampicillin was seen (Table 5).

Among Gram negative isolates Klebsiella pneumoniae was found more predominantly. Amoxycillin -clavulanic acid was found to had highest sensitivity (78.9%), followed by Imipenam and Doxycyclin (73.7%), Amikacin (68.4%). Out of 82 Gram negative isolates, resistance to third generation cephalosporins (cefotaxime, ceftriaxone & ceftazidime), fourth generation (Cefepime), Cipro ofloxacin, Gentamicin and Piperacillin-Tazobactum were predominantly seen. (Table 6)

Discussion

Mortality and morbidity due to neonatal sepsis is high despite the use of higher antibiotics and advanced supportive care. Neonatal sepsis still remains a diagnostic and treatment challenge to the health care providers. An early and prompt diagnosis helps in the institution of therapy at the earliest and also prevents the unnecessary use of antibiotics thereby keeping the emergence of drug resistance in check. In the present study 500 neonates with probable sepsis were investigated and 173 (34.6%) were found to be culture positive. Different studies depict culture positivity from 7.8% to 57.50%[6-7]. The variation in the rate of isolation can be attributed to the fact that the incidence of neonatal sepsis varies from place to place under the influence of various predisposing factors like gestational age, birth weight of the neonate, maternal nutrition, perinatal care, health care facilities etc. It also varies due to different infection control practices and with prior administration of antibiotics to the mother before delivery or to the neonate before collecting blood sample. Infection by anaerobic microorganisms also contribute to this disparity. In the present study, the incidence of early onset sepsis (EOS) was 85% which is more when compared to the late onset sepsis (LOS) 15%. It is consistent with the studies conducted by Movahedian AH et al (2006), Rasul C.H et al (2007), Waseem R et al (1996), Aletayab et al (2011), Al-Shamahy et al (2012)[8-12], Muley et al (2015)[13], Samaga et al (2016)[14], Samaga et al (2017)[15], Kumar et al (2018)[16] and Galhotra et al (2018)[7]. In the present study 233 mothers have history of PROM which may be the reason for EOS to be more than LOS. However inverse pattern of higher LOS has been reported in the studies done by Kayange N et al (2010), Aftab R & Iqbal I (2006), Karambin MM et al (2011) and Shrestha NJ et al (2011) [17-20] .The lower incidence of LOS in present study cannot be explained by a single factor. Various changes that have occurred in the recent years in addition to the increased awareness in prevention of sepsis like better hand hygiene practices, maintaining standard protocols in

handling intravenous catheters and shorter duration of invasive ventilation due to the use of surfactants could have contributed to the decreased incidence of LOS. Gram positive organisms constituted 52.6%(n=91) culture isolates when compared to the Gram-negative isolates 47.4%(n=82). In the present study MSSA 23.1% (n=40), CoNS 16.8%(n=29), Klebsiella pneumoniae 11%(n=19), Citrobacter koseri 10.8%(n=18) and MRSA 8.1%(n=14) were the predominant organisms causing septicemia. Karthikeyan et al reported that Staphylococcus aureus was the predominant pathogen followed by Klebsiella pneumoniae which correlates well with present study[21]. Renuka Mohanty et al reported that Staphylococcus aureus is a major cause of neonatal septicemia[22]

Roy et al observed that the most frequent offender in neonatal sepsis were Klebsiella species followed by Enterobacter species, Coagulase - negative staphylococci, Staphylococcus aureus and Escherichia coli.[23] Chaudhury et al reported that the ratio of gram positive to gram negative bacteremia was 1:1[24]. Muley et al (2015)[13] reported that gram negative organisms were predominant than gram positive organisms, Klebsiella pneumoniae found to be predominant pathogen followed by Staphylococcus aureus. Samaga et al (2016)[14] reported gram-negative bacilli more than gram positive bacilli. The most predominant organisms observed were Klebsiella pneumonia, Staphylococcus aureus and Citrobacter spp. Yadav et al (2017)[6] reported majority of culture positive cases were gram negative (78.3%) while gram positive was 16.25% and the predominant organisms were Klebsiella pneumonia and Enterobacter spp. Kumar et al (2018)[16] reported Staphylococcus aureus as more predominant culture isolate followed by Klebsiella pneumonia. Similar to the findings reported in the studies conducted in developed countries by Karlowicz et al (2000) and Awoniyi et al (2009) where predominant cause of sepsis were GBS and CoNS.[25-26] Sanghvi TP et al (1996) and Stoll BJ et al (2002) also reported the variation in the etiology of neonatal sepsis between developing and developed countries.[27-28] The pathogens most often implicated to cause neonatal sepsis not only differ in geographical distribution but also change with respect to time even in the same area which can be attributed to the difference in living conditions according to Shrestha P et al (2007).[17] Long term epidemiological studies performed have revealed an increasing trend in incidence of CoNS in the recent years. Both K. pneumoniae and S. aureus are nosocomial pathogens as they tend to colonize the hospital environment as well as health care personnel, making these organisms the predominant cause of sepsis. Higher rates of E. coli isolation has been demonsrated in the studies done by Agarwal A et al (2015), Naher HS & Khamael AB (2013) and Mustafa et al (2014).[29-31] MN Shah and PB Desai (2011) reported that E.coli was the predominant cause of neonatal sepsis.[32] But in studies done by Rahul Kamble & Rajesh Ovhal (2015) , Sanjay D Rathod et al (2012) and Amare Gebrehiwot et al (2012) lower E. coli isolation rates of <10% were reported which is similar to this study in which E. coli was isolated from only 6 neonates (3.5%).[33-35] Isolation of Enterococcus species has been occasionally reported from various studies. In the present study E. faecalis (n=2) accounting for 1.2% of culture positivity was isolated. Similarly lower isolation rates were also seen in the studies conducted by Rao Pooja et al (2015) and Sanjay D Rathod et al (2012).[34,36] Antimicrobial susceptibility pattern plays an essential role in effective management of sepsis in neonates and it varies from

place to place. Sound knowledge of the pattern of antibiotic sensitivity in the region guides in the right choice of prophylactic antibiotics. In the present study, the antimicrobial susceptibility pattern revealed 100% sensitivity to Vancomycin and Linezolid in all the Gram positive isolates which correlates with the studies conducted by Mane AK et al (2010), Sanjay D Rathod et al (2012), Mustafa et al (2014), Rahul Kamble & Rajesh Ovhal (2015),[31,34,37] Samaga et al (2016)[14], Yadav et al (2017)[6], Samaga et al (2017)[15], Khante SV et al (2017)[38] and Galhotra et al (2018).[7] Present study depicts Amoxyclav and Doxycline highly sensitive (80-90%), Gentamicin and cefazolin moderately sensitivite (50%-70%) and ampicillin resistance among the Gram positive isolates. Yadav et al (2018)[6], Mustafa M et al (2014), Aletayeb SMH et al, Rao Pooja et al (2015) [11,31,36,] Muley et al (2015)[13], Samaga et al (2016)[14] and Kumar et al (2018)[16] also reported poor sensitivity of Ampicillin and Cefotaxime. In present study Klebsiella pneumoniae was found more predominantly among Gram negative isolates, Amoxycillin-clauvulanic acid (AMC) was found to had highest sensitivity (78.9%), followed by Imipenam and Doxycyclin (73.7%), Amikacin (68.4%). These observations were similar to the findings of Waseem R et al (2005)[12], Mustafa M et al (2014)[31], Samaga et at (2016)[14] and Samaga et al (2017).[15] Yadav et al (2018)[6] reported Amikacin, Gentamicin, Meropenem and Imipenem were 100% sensitive. Kumar et al (2018)[16] reported resistance for Amikacin. In present study out of 82 Gram negative isolates, resistance to third generation cephalosporins (cefotaxime, ceftriaxone & ceftazidime), fourth generation (Cefepime), Ciprofloxacin, Gentamicin and Piperacillin- Tazobactum were predominantly seen. Mutlu M et al (2011)[39]. Couto RC et al (2007)[40], Iregbu et al (2006)[41] and Sanjay D Rathod et al (2012)[34], Muley et al (2015)[13], reported similar degree of resistance among third generation cephalosporins. While high sensitivity to third generation to Cephalosporins was observed by Samaga et al (2016)[14], 100% sensitivity to PIT observed by Samaga et al (2017)[15]. Galhotra et al (2018)[7] observed resistance to Ciprofloxacin, Cephalosporins and Aminoglycoside.

Conclusion

Neonatal sepsis is one of the leading causes of neonatal mortality. Early institution of appropriate antibiotic improves the outcome. There is no universal cocktail of antibiotics effective against every bacterium and which is suitable to every septic newborn. Unless there is regular surveillance of bacteriological profile of neonatal care units/ sick newborn care units, the appropriate management and better outcome is like daydream as bacteriological profile as well as sensitivity pattern is ever changing process. Battle can be won only if the enemies (bugs) are identified and appropriate weapons (antibiotics) are used.

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