DOI: 10.7860/IJNMR/2022/55647.2351

Original Article

Paediatrics Section

Aetiological Agents in Neonatal Nosocomial Sepsis and their Sensitivity Pattern from a Tertiary Care Hospital, Odisha, India: A Cross-sectional Study

RK SHWETABH[1], MANAS RANJAN UPADHYAY[2], RAJLAXMI UPADHYAY[3]

ABSTRACT

Introduction: Nosocomial infections are a major problem for hospitalised neonates due to increase in morbidity, mortality, duration of hospitalisation and costs of treatment. The magnitude of this problem varies from place to place and is unique to each place as per the organisms and their resistance pattern is concerned. There is need to develop local level surveillance data on incidence of nosocomial sepsis, causative organisms, their sensitivity pattern and periodically review antibiotic policy based on this information.

Aim: To determine the aetiological agents of neonatal nosocomial sepsis and their antibiotic sensitivity and resistance pattern.

Materials and Methods: This was a cross-sectional study in which the cases of nosocomial infections in neonates of >35 weeks were studied from November 2018-October 2019 at Sriram Chandra Bhanja Medical College and Hospital (S.C.B.M.C.H) and Sardar Vallabh Bhai Patel Postgraduate Institute of Paediatrics (S.V.P.P.G.I.P) based on clinical findings, sepsis screen and blood culture. Blood culture is considered as gold standard for diagnosis of sepsis. Blood sample (1 mL) was collected under strict asepsis in Becton Dickinson and Company (BACTEC) and was sent for performing blood culture. The data was processed and arranged into distribution tables and cross tables using Statistical Package for the Social Sciences (SPSS) version 21.0.

Results: Out of total 100 suspected cases of nosocomial sepsis, blood culture was positive in 46 (46%) of cases. *Candida* spp. was the most common obtained organism 9 (19.5%) followed by *Klebsiella pneumoniae* 8 (17.3%) and *Staphylococcus aureus* 8 (17.3%), respectively. There was increased incidence of bacterial resistance to commonly used antibiotics and combinations of it, like ampicillin, gentamicin, cefotaxime, amikacin and piperacillin+tazobactam among these bacterial isolates. Among the possible new combinations deduced from the observation, the combination of vancomycin+amikacin had sensitivity of 67.6% and can be considered as initial antibiotic combination of choice while combination with colistin and tigecycline should be reserved only for culture proven resistant cases or babies who continue to be deteriorating and critically sick while on previous combination.

Conclusion: *Candida* spp. was found to be the leading cause of nosocomial sepsis. Among bacterial organisms, *Klebsiella pneumoniae* and *Staphylococcus aureus* were the most common. Most isolates were resistant to traditional antibiotics, hence new combination like vancomycin+amikacin were more appropriate empiric choice in present context and combination with colistin and tigecycline were reserved only for culture proven resistant sepsis.

Keywords: Antibiotic combination, Blood culture, Nosocomial sepsis

INTRODUCTION

Neonatal sepsis represents a significant cause of neonatal mortality and long-term morbidity. There are an estimated 1.3-3.9 million annual neonatal sepsis cases and 4,00,000-7,00,000 annual deaths worldwide due to sepsis [1]. Severe neonatal infections (including sepsis, meningitis and pneumonia) represent a significant cause of neonatal mortality (24%) and cause short-term and long-term complications, such as preterm birth and neonatal encephalopathy. An estimated 84% of neonatal deaths due to infections could be prevented through measures such as early diagnosis and timely appropriate clinical management. Among hospital born infants, nosocomial infections account for an estimated 4%-56% of all deaths in the neonatal period, depending on the study and geographical area [1].

Neonatal sepsis is a clinical syndrome characterised by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. It encompasses various systemic infections of newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infections. Sepsis in neonates has been broadly classified in two groups-early onset sepsis (onset of sepsis within 72 hours of birth) and late onset sepsis (onset of sepsis after 72 hours of birth). Late onset sepsis has been again divided into two groups-community acquired and nosocomial sepsis [2].

Nosocomial sepsis is defined as any infection causing illness that was not present, or in its incubation period during the time of admission, and which occurs 48 hours after admission to hospital. The risk of nosocomial infection in neonates is the direct consequence of the severity of illness, prematurity, congenital defects, systemic diseases, level of invasive monitoring, indiscriminate use of antibiotics, lapses in sterilisation and disinfection techniques and the nature of diagnostic procedures. The profile of these infections keeps on changing and varies from place to place [3]. Blood culture is considered as gold standard for diagnosis of sepsis. The antibiotic susceptibility pattern obtained from blood culture can guide us about appropriate antibiotics which are to be administered. New techniques like BACTEC (Becton Dickinson and Company and BACT/ALERT (bioMerieux) blood culture systems can detect bacterial growth even within 12-24 hours [2].

In India very few studies like Kamath S et al., Pathak S et al., etc. have been done previously on nosocomial sepsis but no study have been done about appropriate empirical combination of antibiotics for nosocomial sepsis [3,4]. Hence the present study was done to determine the organisms causing neonatal nosocomial sepsis, their antibiotic sensitivity pattern and the best combination of antibiotics for empiric therapy in a tertiary care hospital.

MATERIALS AND METHODS

It was a cross-sectional study done in (Neonatal Intensive Care Unit (NICU) and its step down at Sriram Chandra Bhanja Medical College and Hospital and Sardar Vallabh bhai Patel Postgraduate Institute of Paediatrics (S.V.P.P.G.I.P), Cuttack from November 2018 to October 2019 after approval from Ethical Committee (Ethics committee Reg No-ECR/84/Inst/OR/2013/RR-20: application no. 22, dated 7/2/2020).

Inclusion criteria: A total of 100 neonates of ≥35 weeks who developed new infections while staying for atleast 48 hours in hospital or those neonates whose signs or symptoms persisted or worsened even after receiving atleast 72 hours of antibiotics were included in the study.

Exclusion criteria: Neonates having TORCH infection (Toxoplasomosis, Others like syphilis and hepatitis B, Rubella,Cytomegalovirus, Herpes simplex) or congenital anomaly were excluded from the study.

Sample size calculation: Sample size was calculated by the formula:

Sample size (n)=$4pq/d^2$,

Where, p=Prevalence; q=100-prevelance; d=0.005 (precision level)

Taking into account the study done by Hoseini M et al., on nosocomial sepsis, prevalence rate of nosocomial sepsis was 6.7% [5].

Hence, the calculation:

$n=4pq/d^2$

Here, p=0.066

Hence, q=1-0.066=0.934; d=0.05;

n=4*0.066*0.934/0.05*0.05

=98.6

So, minimum 98 samples were required. The present study comprised of 100 participants.

Informed consent was taken from parents. Detailed history was taken, vital signs were monitored and detailed examination was performed initially and repeated every day. Sepsis screen and blood culture were done before starting or changing antibiotics.

Blood Culture

Blood sample was collected under strict asepsis. After wearing sterile gloves a patch of skin of approximately 5 cm in diameter was disinfected, over the proposed venipuncture site with 70% isopropyl alcohol, followed by povidone iodine and again followed by alcohol. Povidone iodine was applied in concentric circles moving outward from the centre. The skin was allowed to dry for atleast one minute before sample collection. Blood sample (1 mL) of blood was collected in BACTEC and sent for culture [2].

Antibiotic Combination

Antibiotic combination was taken keeping in view covering both gram positive and gram negative organisms [6] [Table/Fig-1]. The interpretation was done in following way.

Organism	Antibiotic A	Antibiotic B	Interpretation of combination (A+B)
1	Sensitive	Sensitive	Sensitive
2	Sensitive	Resistant	Sensitive
3	Resistant	Sensitive	Sensitive
4	Resistant	Resistant	Resistant

[Table/Fig-1]: Interpretation of antibiotic combination.

Hence, if an organism was sensitive to atleast any one of the antibiotic the combination was taken to be sensitive, which was logical also as combination was given to the patient as well. On the other hand if the organism was resistant to both the antibiotics than the combination was taken to be resistant.

STATISTICAL ANALYSIS

The data were processed and arranged into distribution tables and cross tables using SPSS version 21.0.

RESULTS

Total of 100 cases were enrolled, out of which 67 (67%) were males. Positive blood culture was found in 46% cases. Among 100 cases taken in the present study 32 (32%) cases were of gestational age 35-37 weeks, 67 (67%) were between 37-42 week and 1 (1%) case was post-term (>42 weeks) [Table/Fig-2].

Age	No of cases n (%)
Preterm (35-37 weeks)	32 (32%)
Term (>37-42 weeks)	67 (67%)
Post-term (>42 weeks)	1 (1%)

[Table/Fig-2]: Age distribution of cases.

Most common sign/symptom for changing/adding antibiotic was poor feeding/lethargy 43 (43%) followed by respiratory distress 25 (25%) [Table/Fig-3].

Sign/symptoms	No. of cases n (%)
Poor feeding/lethargy	43 (43%)
Respiratory distress	25 (25%)
Abdominal distension/vomiting	7 (7%)
Seizure	6 (6%)
Fever	5 (5%)
Shock	4 (4%)
Apnoea	3 (3%)
Others (Bleeding, sclerema, etc)	7 (%)

[Table/Fig-3]: Sign/symptoms after which antibiotics were added/changed.

Out of 46 isolates 9 (19.5%) were fungal (*Candida* spp.) and 37 (80.5%) were bacterial, out of which 20 (54.1%) were gram positive and 17 (45.9%) were gram negative. Out of total 37 bacterial isolates, *Staphylococcus aureus* 8 (21.6%), *Klebsiella pneumoniae* 8 (21.6%), *Acinetobacter baumannii* 7 (18.9%) followed by *Staphylococcus haemolyticus* with 6 (16.2%) were important bacterial isolates. *Klebsiella pneumoniae* was the most common gram negative isolate followed by *Acinetobacter baumannii* while *Staphylococcus aureus* and Staphylococcal haemolyticus lead in gram positive isolates [Table/Fig-4].

Candida species obtained in the present study were 100% sensitive to voriconazole, flucytosine and amphotericin B. The sensitivity with capsofungin and micafungin was 88.8% while sensitivity to fluconazole was 66.7% [Table/Fig-5].

Organism obtained	Number of cases	Percentage
Candida spp.	9	19.5%
Klebsiella pneumoniae	8	17.3%
Staphylococcus aureus	8	17.3%
Acinetobacter baumannii	7	15.3%
Staphylococcus haemolyticus	6	13.1%
Staphylococcus hominis	3	6.6%
Staphylococcus epidermidis	2	4.3%
Enterobacter cloacae	1	2.2%
Escherichia coli	1	2.2%
Enteorococcus durans	1	2.2%

[Table/Fig-4]: Organisms isolated in blood culture (N=46).

Antifungal drug	Number of cases sensitive	Number of cases resistant	Percentage sensitivity
Voriconazole	9	0	100%
Flucytosine	9	0	100%
Amphotericin B	9	0	100%
Capsofungin	8	1	88.8%
Micafungin	8	1	88.8%
Fluconazole	6	3	66.7%

[Table/Fig-5]: Sensitivity of candida to various antifungals (n=9).

Antibiotic sensitivity among gram positive organisms was tigecycline (100%) followed by vancomycin (89.5%), cotrimoxazole (87.5%), colistin and amikacin (80%) each, linezolid (77.7%), teicoplanin (65%), ciprofloxacin (30.7%) and for gram negative organisms was colistin (87.5%) followed by tigecycline (75%), amikacin (35.2%), gentamicin (18.75%) and ciprofloxacin (13.3%) [Table/Fig-6].

Overall vancomycin (89.5%) had maximum sensitivity, followed by colistin (85.7%), tigecycline (84%), linezolid (77.7%) and teicoplanin (65%) [Table/Fig-6].

Overall, the combination of teicoplanin+colistin, tigecycline+vancomycin, colistin+vancomycin, tigecycline+colistin and colistin+linezolid had sensitivity of 82.8%, 85.7%,88.8%, 90% and 93.75%, respectively.

Even when four most important bacterial isolates are taken (Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii and Staphylococcus haemolyticus), which constitute 78.3% (29/37) of all bacterial isolates then also the sensitivity to teicoplanin+colistin, tigecycline+vancomycin, colistin+vancomycin, tigecycline+colistin and colistin+linezolid were at 79.3%, 81.5%, 89.2%, 86.9% and 92%, respectively, which is comparable to the overall sensitivity to all bacterial isolates taken together [Table/Fig-7].

DISCUSSION

Nosocomial sepsis is a serious problem especially in developing countries like India. According to World Health Organisation (WHO), the estimated incidence of hospital acquired sepsis in neonates was 112.9 cases per 1000 Intensive Care Unt (ICU) treated neonates [1]. Among hospital born infants, hospital acquired infections account for an estimated 4% to 56% of all deaths in the neonatal period, depending on the study and geographical area investigated [1]. Neonatal nosocomial sepsis account for 56.6% of all the nosocomial infections among all the age groups (neonates, pediatric and adults) [1].

In the present study for nosocomial infections, fungal (*Candida* spp.) sepsis was present in significant number of cases 9 (19.5%), compared to a lower incidence noted by Hosseini M et al., at 10.1% and Lopez Sastre JB et al., at 12% [5,7]. In the present context

Organisms	Antibiotic sensitivity to various antibiotics (% age)													
	AMK	GEN	FEP	CTX	TZP	MEM	CST	TGC	SXT	AMP	CIP	LZD	TEC	VAN
Gram -ve														
Klebsiella pneumoniae	50 (4/8)	37.5 (3/8)	28.5 (2/7)	37.5 (3/8)	14.2 (1/7)	16.6 (1/6)	85.7 (6/7)	50 (4/8)	42.8 (3/7)	12.5 (1/8)	25 (2/8)	-	-	-
Acinetobacter baumannii	14.2 (1/7)	0 (0/6)	0 (0/7)	0 (0/7)	0 (0/7)	16.6 (1/6)	85.7 (6/7)	100 (6/6)	14.2 (1/7)	-	0 (0/6)	-	-	-
Escherichia cloacae	100 (1/1)	0 (0/1)	100 (1/1)	0 (0/1)	0 (0/1)	0 (0/1)	100 (1/1)	100 (1/1)	0 (0/1)	-	0 (0/1)	-	-	-
Escherichia coli	0 (0/1)	0 (0/1)	-	-	0 (0/1)	0 (0/1)	100 (1/1)	100 (1/1)	-	100 (1/1)	-	-	-	-
Gram +ve														
Staphylococcus aureus	80 (4/5)	-	-	20 (1/5)	0 (0/6)	-	80 (4/5)	-	-	-	66.7 (2/3)	33.3 (2/6)	37.5 (3/8)	85.7 (6/7)
Staphylococcus haemolyticus	-	20 (1/5)	-	-	-	-	-	100 (3/3)	100 (3/3)	-	25 (1/4)	100 (6/6)	83.3 (5/6)	100 (6/6)
Staphylococcus hominis	-	66.7 (2/3)	-	-	-	-	-	100 (3/3)	66.7 (2/3)	-	0 (0/3)	100 (3/3)	100 (3/3)	100 (3/3)
Staphylococcus epidermidis	-	100 (2/2)	-	-	-	-	-	100 (2/2)	100 (2/2)	-	50 (1/2)	100 (2/2)	100 (2/2)	100 (2/2)
Enterococcus durans	-	0 (0/1)	-	-	-	-	-	100 (1/1)	-	-	0 (0/1)	100 (1/1)	0 (0/1)	0 (0/1)
Gram positive	80 (4/5)	45.4 (5/11)	-	20 (1/5)	0 (0/6)	-	80 (4/5)	100 (9/9)	87.5 (7/8)	-	30.7 (4/13)	77.7 (14/18)	65 (13/20)	89.5 (17/19)
Gram negative	35.2 (6/17)	18.75 (3/16)	20 (3/15)	18.75 (3/16)	6.25 (1/16)	14.3 (2/14)	87.5 (14/16)	75 (12/16)	26.6 (4/15)	22.2 (2/9)	13.3 (2/15)	-	-	-
Overall	45.4 (10/22)	29.6 (8/27)	20 (3/15)	19 (4/21)	4.5 (1/22)	14.3 (2/14)	85.7 (18/21)	84 (21/25)	47.8 (11/23)	22.2 (2/9)	21.4 (6/28)	77.7 (14/18)	65 (13/20)	89.5 (17/19)

[Table/Fig-6]: Antibiotic sensitivity of bacterial isolates.
All isolates were not subjected to all antibiotics; *AMK: Amikacin; AMP: Ampicillin; FEP: Cefepime; CTX: Cefotaxime; CIP: Ciprofloxacin; CST: Colistin; SXT: Cotrimoxazole; GEN: Gentamicin; MEM: Meropenem; LZD: Linezolid; TZP: Piperacillin-tazobactam; TEC: Teicoplanin; TGC: Tigecycline; VAN: Vancomycin

Antibiotic combination	*Staphylococcus aureus+ Klebsiella pneumoniae+Acinetobacter baumannii+Staphylococcus haemolyticus* (n=29)	Total (n=37)
CST+LZD	88.4% (23/26)	91.1% (31/34)
CST+VAN	89.2% (25/28)	88.8% (32/36)
TGC+CST	86.9% (20/23)	87.1% (27/31)
TGC+VAN	81.5% (22/27)	85.7% (30/35)
TEC+CST	79.3% (23/28)	80.5% (29/36)
TEC+TGC	64.2% (18/28)	69.4% (25/36)
TGC+CIP	68.1% (15/22)	74.1% (23/31)
VAN+AMK	65.5% (19/29)	67.6% (25/37)
CST+CIP	69.2% (18/26)	64.7% (22/34)
SXT+VAN	61.5% (16/26)	63.7% (21/33)
MEM+VAN	53.8% (14/26)	55.8% (19/34)
TZP+VAN	48.1% (13/27)	50% (18/36)
MEM+AMK	45% (9/20)	45.5% (10/22)
TZP+LZD	38.4% (10/26)	45.5% (15/33)
CTX+AMK	50% (10/20)	50% (11/22)
AMP+AMK	45% (9/20)	50% (11/22)
TZP+AMK	40.9% (9/22)	41.6% (10/24)
CIP+AMK	40% (10/25)	37.5% (12/32)
CTX+GEN	28% (7/25)	31.2% (10/32)
AMP+GEN	26.3% (5/19)	28.6% (10/35)
TZP+GEN	28% (7/26)	24.2% (8/33)

[Table/Fig-7]: Combined antibiotic sensitivity pattern of important and all isolates.
*AMK: Amikacin; AMP: Ampicillin; FEP: Cefepime; CTX: Cefotaxime; CIP: Ciprofloxacin; CST: Colistin; SXT: Cotrimoxazole; GEN: Gentamicin; MEM: Meropenem; LZD: Linezolid; TZP: Piperacillin-tazobactam; TEC: Teicoplanin; TGC: Tigecycline; VAN: Vancomycin

fungal sepsis should be an important etiology of nosocomial sepsis in hospital setting like ours. Among the fungal isolates no resistance was found against Amphotericin B but one-third of isolates were resistant to Fluconazole, which is in contrast to the observation made by Caggiano G et al., where sensitivity to both the antifungal stand at 100% [8]. Fluconazole was the 1st line antifungal and mostly used in Very Low Birth Weight (VLBW) infants, as a prophylactic and many cases as empiric choice as antifungal, so the present observation emphasises the need to avoid empiric use of antifungals and restrict use of antifungal drugs in culture positive fungal sepsis.

Among bacterial isolates (37) *Staphylococcus aureus* (21.6%), Klebsiella pneumonia (21.6%), *Acinetobacter baumannii* (18.9%) and *Staphylococcus haemolyticus* (16.2%) were common.Similar observation was made by Kamath S et al., [3] where *Staphylococcus aureus* (12.3%) and *Klebsiella pneumoniae* (16.4%) were commonly isolated [3]. In a similar study Pathak S et al., also observed *Staphylococcus aureus* (26%) and Klebsiella pneumonia (33.3%) followed by *Acinetobacter baumannii* (13.3%) to be common gram positive and gram negative isolates [4].

The sensitivity of *Klebsiella pneumoniae* to colistin was 85.7% and similar to observation in all type of neonatal sepsis i.e 88.8% and 91.67% by Pokhrel B et al., and Hashmi MA et al., respectively [9,10]. Sensitivity to amikacin, gentamicin, meropenem and piperacillin+tazobactam was just 50%, 37.5%, 16.4% and 14.2% in the present study, suggesting increasing resistance to the commonly used antibiotics. The study done by Saritha Kamath S et al., and Pathak S et al., suggested sensitivity of *Klebsiella pneumoniae* to amikacin 55.6% and 70%, respectively while that to gentamicin was found to be 16.7% and 10%, respectively [3,4] [Table/Fig-8a].

Acinetobacter baumannii was sensitive to tigecycline in 100% cases, followed by Colistin in 85.7%. The study conducted by Pokhrel B et al., and Hashmi MA et al., found the sensitivity of *Acinetobacter baumannii* to colistin as 80% and 100%, respectively [9,10]. Pokhrel B et al., also found the sensitivity to tigecycline as 66.7% while Abdelhamiod SM, found it to be 75% [11]. All these difference is due to different levels of use and misuse of these antibiotics. In study done by Kamath S et al., the sensitivity was observed to be 100% with amikacin and 95.5% with cotrimoxazole while that to gentamicin was 22.7% [3]. However in the present study the sensitivity to amikacin and cotrimoxazole was just 14.2% each and there was 100% resistance to gentamicin [Table/Fig-8b].

For gram negative organisms sensitivity was maximum with colistin (87.5%) followed by tigecycline (75%) in the present study. Comparing it with other studies, Pokherl B et al., and Abdelhamid SM, found sensitivity of gram negative organism against tigecycline to be 85.7% and 86.7% respectively [9,11]. Pokhrel B et al., also found sensitivity of gram negative organisms against colistin to be 82.4% [9].

Amikacin, gentamicin, cefotaxime, meropenem and ciprofloxacin were only 35.2%, 18.75%,18.75%,14.3% and 13.3% sensitive, respectively in the present study. Hosseini M et al., concluded from their study that ciprofloxacin (85.7%) and chloramphenicol (84.6%)

Parameters	Name of study (Sensitivity in % age)					
	Kamath S et al, Mangalore (2010), [3]	Hoseini M et al, Iran (2014), [5]	Pathak S et al, Agra (2018), [4]	Pokhrel B et al., Nepal (2018), [8]	Hashmi MA et al., Pakistan (2020), [10]	Present study
Population characteristic	Nosocomial sepsis	Nosocomial sepsis	Nosocomial sepsis	Sepsis	Sepsis	Nosocomial sepsis
Antibiotic						
Amikacin	55.6	36.4	70	43	-	50
Ampicillin	38.9	-	-	-	-	12.5
Cefepime	-	-	-	-	-	28.5
Cefotaxime	13.9	9.1	50	9.5	-	37.5
Ciprofloxacin	-	100	50	23.8	16.7	25
Colistin	-	-	-	88.8	91.67	85.7
Cotrimoxazole	50	54.5	-	-	-	42.8
Gentamicin	16.7	9.1	10	25	16.7	37.5
Meropenem	-	-	60	100	25	16.6
Tigecycline	-	-	-	81.8	81.8	50

[Table/Fig-8a]: Comparison of sensitivity of *Klebsiella pneumoniae* in various studies [3-5,8,10].

Parameters	Name of study (Sensitivity in % age)				
	Kamath S et al., Mangalore (2010), [3]	Hoseini M et al., Iran (2014), [5]	Pokhrel B et al., Nepal (2018), [8]	Hashmi MA et al., Pakistan (2020), [10]	Present study
Population characteristic	Nosocomial sepsis	Nosocomial sepsis	Sepsis	Sepsis	Nosocomial sepsis
Antibiotic					
Amikacin	100	0	0	-	14.2
Cefotaxime	63.6	0	14.3	-	0
Ciprofloxacin	81.8	100	81.25	-	0
Colistin	-	-	80	100	85.7
Cotrimoxazole	95.5	-	-	-	14.2
Gentamicin	22.7	100	28.6	-	0
Tigecycline	-	-	66.7	-	100

[Table/Fig-8b]: Comparison of sensitivity of *Acinetobacter baumannii* in various studies [3,5,8,10].

are more sensitive against gram negative bacteria while sensitivity for gentamicin was just 18.1% [5]. Hashmi MA et al., found sensitivity of gram negative organisms to Colistin and Meropenem to be 96.55% and 28.6%, respectively [10].

The sensitivity of *Staphylococcus aureus* to vancomycin is 85.7% in the present study while in other studies done by Kamath S et al., Hosseini M et al., and Pathak S et al., it was 100% each [3-5] [Table/Fig-8c].Two-third of *staphylococcus aureus* were resistant to linezolid while sensitivity to amikacin was 80%.Comparing it to study done by Dalal P et al., and Hashmi MA et al., the sensitivity of *staphylococcus aureus* to linezolid was 87% and 88.8%, respectively [10,12]. Though in the current hospital teicoplanin is not commonly used still we observed high degree of resistance to teicoplanin (62.5% resistance) as compared to Kamath S et al., and Dalal P et al., where they found no resistance to Teicoplanin at all [3,12] [Table/Fig-8c].

It was observed that the sensitivity of *stahylococcus* haemolyticus to be 100% against cotrimoxazole, linezolid, tigecycline and vancomycin, while it was 83.3% against teicoplanin. Tessema B et al., in their study of neonatal sepsis observed sensitivity of *staphylococcus haemolyticus* to be 100% against vancomycin and 93.3% against linezolid and 73.3% against teicoplanin [13] [Table/Fig-8d].

Sensitivity among gram positive organisms was tigecycline (100%), followed by vancomycin (89.5%), cotrimoxazole (87.5%), colistin and amikacin (80%) each, linezolid (77.7%), teicoplanin (65%) but ciprofloxacin and cefotaxime has just 30.7% and 20% sensitivity. Similarly, Hosseini M et al., observed that most sensitive antibiotics against gram positive bacteria was vancomycin (94.1%). Pokhrel B et al., observed sensitivity of vancomycin and linezolid against gram positive bacteria to be 100% each [5,8]. Hashmi MA et al., [11] also observed sensitivity of gram positive bacteria against vancomycin and linezolid to be 83.78% and 81.08% respectively [10]. Dalal P et al., and Li X et al., found sensitivity to teicoplanin as 100% and 98.9%, respectively while Li X et al., also found sensitivity to tigecycline be 100% against gram positive organisms [14].

Considering lack of isolation of causative agents in a significant number of patients and the inherent delay in getting the culture report, sick patients were to be started empiric antibiotic. With the present resistant pattern observed in both gram positive and gram negative organisms its necessary to go for more appropriate antibiotic combination to improve survival. For empiric antibiotic combination traditional antibiotic combination are losing their importance with combinations like piperacillin+tazobactam+gentamicin, ampicillin+gentamicin, cefotaxime+gentamicin and cefotaxime+amikacin having sensitivity of 24.2%, 28.6% ,31.2% and 50% only. The new empiric combination which can be used in desperately sick neonates are teicoplanin+colistin, tigecycline+vancomycin, tigecycline+colistin, colistin+ vancomycin, and colistin+linezolid having sensitivity of 80.5%, 85.7%, 87.1%, 88.8% and 91.1%, respectively. Comparing it to other studies, Al-Mouqdad MM et al., found a combination of amikacin+cloxacillin to be a better empiric combination for late onset sepsis [15]. Sivanandan S et al., had suggested a combination of cloxacillin+gentamicin as

Parameters	Name of study (Sensitivity in % age)					
	Kamath S et al., Mangalore (2010), [3]	Hoseini M et al., Iran (2014), [5]	Dalal P et al., Rohtak (2017), [12]	Pathak S et al., Agra (2018), [4]	Hashmi MA et al., Pakistan (2020), [10]	Present study
Population characteristic	Nosocomial sepsis	Nosocomial sepsis	Late onset sepsis	Nosocomial sepsis	Sepsis	Nosocomial sepsis
Antibiotic						
Amikacin	-	50	-	-	-	80
Ampicillin	-		-	12.5	-	-
Cefotaxime	-	0	-	-	-	20
Chloramphenicol	-	50	-		70.4	-
Ciprofloxacin	-	0	-	62.5	37.0	66.7
Colistin	-	-	-	-	-	80
Doxycycline	-		35	25	70.4	-
Linezolid	-	-	87	-	88.8	33.3
Teicoplanin	100	-	100	-	-	37.5
Vancomycin	100	100	77	100	92.6	85.7

[Table/Fig-8c]: Comparison of sensitivity of *Staphylococcus aureus* in various studies [3-5,10,12].

Parameters	Name of study (Sensitivity in % age)	
	Tessema B et al., Germany, (2021), [13]	Present study
Population characteristic	Sepsis	Nosocomial sepsis
Antibiotic		
Ciprofloxacin	13.3%	25%
Cotrimoxazole	26.7%	100%
Gentamicin	20%	20%
Linezolid	93.3%	100%
Tigecycline	-	100%
Teicoplanin	73.3%	83.3%
Vancomycin	100%	100%

[Table/Fig-8d]: Comparison of sensitivity of *Staphylococcus haemolyticus* in various studies [13].

empiric antibiotic combination for late onset sepsis, but has also recommended a combination of vancomycin+cefotaxime to be given empirically to neonates with cardio-respiratory instability and in the areas where MRSA (Methicillin Resistant *Staphylococcus Aureus*) is prevalent [6].

Even if four most common bacterial isolates are taken (*Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Staphylococcus haemolyticus*), then the sensitivity to teicoplanin+colistin, tigecycline+vancomycin, colistin+vancomycin, tigecycline+colistin and colistin+linezolid is 79.3%, 81.5%, 89.2%, 86.9% and 88.4%, respectively, which is comparable to the overall sensitivity. And, finally the combination of vancomycin+amikacin has sensitivity of 67.6% and hence can be considered as 1st line empiric therapy.

Resistance is a continuous phenomenon however antibiotic stewardship is also necessary to be taken care of, so it is important to follow a fixed infection preventive strategy and use the appropriate combination of antibiotics with minimum side effects for the treatment of nosocomial sepsis and de-escalate or change the antibiotics after getting culture report.

Limitation(s)

The present study had the limitation that extremely preterm neonates were not taken into account and long-term follow-up was not done.

CONCLUSION(S)

The present study shows increased fungal sepsis which is important consideration as evident by resistance to fluconazole in one-third of cases. *Staphylococcus aureus* is one of the important gram positive isolate and showed an increased resistance to front line anti-staphylococcal antibiotics like teicoplanin, linezolid and vancomycin. Similarly, gram negative organism like *Klebsiella pneumoniae* and *Acinetobacter baumannii* also showed an increased resistance to amikacin, gentamicin, meropenem and colistin. So, more emphasis should be given for infection prevention and antibiotic stewardship. Periodic evaluation of antibiotic resistance and appropriate selection of antibiotic combination with maximum sensitivity will help saving life.

REFERENCES

[1] World Health Organization. Global report on the epidemiology and burden of sepsis: Current evidence, identifying gaps and future directions. Last assessed: May 1, 2022.

[2] Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. Indian J Pediatr. 2008;75(3):261-66. https://doi.org/10.1007/s12098-008-0056-z.

[3] Kamath S, Mallaya S, Shenoy S. Nosocomial infections in neonatal intensive care units: Profile, risk factor assessment and antibiogram. Indian J Pediatr. 2010;77(1):37-39. https://doi.org/10.1007/s12098-010-0005-5.

[4] Pathak S, Agarwal D, Singh P, Pathak M, Narayan S. Late-onset neonatal sepsis: Overview of risk factors and bacterial etiology in a tertiary care hospital in North India. J Mahatma Gandhi Inst Med Sci. 2018;23:69-72. Doi: 10.4103/jmgims.jmgims_33_16.

[5] Hosseini M, Abdinia B, Ahangarzadeh Rezaee M, Abdoli Oskouie S. The study of nosocomial infections in neonatal intensive care unit, A prospective study in Northwest Iran. International Journal of Pediatrics. 2014;2(3.2):25-33. Doi: 10.14196/mjiri.32.48.

[6] Sivanandan S, Soraisham AS, Swarnam K. Choice and duration of antimicrobial therapy for neonatal sepsis and meningitis. International Journal of Pediatrics. 2011;2011:712150. Doi.org/10.1155/2011/712150.

[7] López Sastre JB, Coto Cotallo D, Fernández Colomer B; Grupo de Hospitales Castrillo. Neonatal sepsis of nosocomial origin: An epidemiological study from the "Grupo de Hospitales Castrillo". J Perinat Med. 2002;30(2):149-57. Doi: 10.1515/jpm.2002.019.

[8] Caggiano G, Lovero G, De Giglio O, Barbuti G, Montagna O, Laforgia N, et al. Candidemia in the neonatal intensive care unit: A retrospective, observational survey and analysis of literature data. Biomed Res Int. 2017;2017:7901763. https://doi.org/10.1155/2017/7901763.

[9] Pokhrel B, Koirala T, Shah G, Joshi S, Baral P. Bacteriological profile and antibiotic susceptibility of neonatal sepsis in neonatal intensive care unit of a tertiary hospital in Nepal. BMC Pediatrics. 2018;18(1):01-08. https://doi.org/10.1186/s12887-018-1176-x.

[10] Hashmi MA, Lodhi MA, Toor KM, Tahir A, Khan HS, Aziz R. Emerging antimicrobial resistance in neonatal sepsis. J Coll Physicians Surg Pak. 2020;30(12):1312-15. Doi: https://doi.org/10.29271/jcpsp.2020.12.1312.

[11] Abdelhamid SM. Time to positivity and antibiotic sensitivity of neonatal blood cultures. J Glob Infect Dis. 2017;9(3):102-07. Doi: 10.4103/jgid.jgid_1_17.

[12] Dalal P, Gathwala G, Gupta M, Singh J. Bacteriological profile and antimicrobial sensitivity pattern in neonatal sepsis: A study from North India. Int J Res Med Sci. 2017;5(4):1541-45. Doi: http://dx.doi.org/10.18203/2320-6012.ijrms20171261.

[13] Tessema B, Lippmann N, Knüpfer M, Sack U, König B. Antibiotic resistance patterns of bacterial isolates from neonatal sepsis patients at University Hospital of Leipzig, Germany. Antibiotics. 2021;10(3):323. https://doi.org/10.3390/antibiotics10030323.

[14] Li X, Ding X, Shi P, Zhu Y, Huang Y, Li Q, et al. Clinical features and antimicrobial susceptibility profiles of culture-proven neonatal sepsis in a tertiary children's hospital, 2013 to 2017. Medicine (Baltimore). 2019;98(12):e14686. Doi: 10.1097/MD.0000000000014686.

[15] Al-Mouqdad MM, Egunsola O, Ali S, Asfour SS. A neonatal unit experience with empiric antibiotics for late-onset neonatal sepsis: A retrospective study. Pediatr Qual Saf. 2019;4(6):e239. Doi: 10.1097/pq9.0000000000000239.

PARTICULARS OF CONTRIBUTORS:

1. Senior Resident, Department of Paediatrics, SCB Medical College and Hospital, Cuttack, Odisha, India.
2. Associate Professor, Department of Paediatrics, FM Medical College, Balasore, Odisha, India.
3. Associate Professor, Department of Pharmacology, Shri Jagannath Medical College, Puri, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
RK Shwetabh,
Flat No. 105, Siba Plaza, Gajpati Nagar, Bhubaneswar, Odisha, India.
E-mail: rk.shwetabh@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Feb 18, 2022
- Manual Googling: May 30, 2022
- iThenticate Software: Jun 08, 2022 (21%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Feb 13, 2022**
Date of Peer Review: **Mar 22, 2022**
Date of Acceptance: **May 30, 2022**
Date of Publishing: **Sep 30, 2022**