Diversity and Prevailing Antimicrobial Resistance in Blood Stream Pathogens at NICU of a Tertiary Care Institute in Kolkata

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ABSTRACT

BACKGROUND

Septicaemia is a leading cause of morbidity and mortality in neonates. Antimicrobial prescription for neonatal septicaemia (NS) should be wisely used depending on the regional spectra of infecting microbes and their antimicrobial resistance (AMR) patterns which vary over time, place and host factors.

METHODS

This was a descriptive cross-sectional study conducted from January 2017 to June 2017 among 102 cases of NS admitted in neonatal intensive care units (NICU). Demographic data of the concerned neonates was collected through a pre-designed checklist. Blood collected from neonates was processed for culture and sepsis screen. Antimicrobial susceptibility testing was performed for the cultured isolates and phenotypic AMR patterns were observed.

RESULTS

Most of the studied neonates had subnormal birth weight (86). Blood culture showed predominance of gram-negative bacilli (GNB) among which *Klebsiella pneumoniae* was the most common followed by Burkholderia cepacia complex. Coagulase negative staphylococcus species (CoNS) was most numerous among the cultured gram-positive cocci (GPC). Candidemia of late onset was confirmed in 25 neonates. Early onset sepsis was predominantly caused by GNB (29 / 31) predominated by *Klebsiella pneumoniae*. Multi drug resistant (MDR) pathogens viz., extended spectrum beta-lactamase (ESBL) producing GNB, carbapenem resistant-GNB (CR-GNB) and methicillin resistant staphylococcus (MRS) phenotypes were notably prevalent.

CONCLUSIONS

Multidrug resistant microorganisms are notably prevalent in neonatal septicaemia. In clinically suspected very sick septicaemic neonates not showing much improvement with guideline-led empirical antimicrobial therapy, an early antibiogram guided change over to meropenem and amikacin or even to colistin in case of reported carbapenem resistance, is highly recommended.

KEYWORDS

Antimicrobial Resistance, Blood Culture, Multi Drug Resistance, Neonatal Septicaemia

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BACKGROUND

Neonatal septicaemia (NS) is a significant cause of morbidity and mortality in the neonates and is responsible for 30 - 50 % of total neonatal deaths each year in developing countries.[1] NS is a clinical syndrome in a newborn (28 days of life or younger), manifested by systemic signs of infection and isolation of pathogen from the bloodstream.[1,2,3] Antimicrobials are the backbone of NS management. Being caused by a plethora of bacteria and by fungi like candida species, the causative spectrum exhibits dynamicity over time, even in the same location. Also, the causative agents of NS may vary according to the associated maternal, neonatal and environmental demography. Accentuating emergence of antimicrobial resistance further restricts the therapeutic choices. Hence, the antimicrobial prescription for NS should be wisely opined from the regional spectra of infecting microbes and knowledge of their antimicrobial resistance (AMR) patterns which vary over time and place.[4,5]

In this study we assessed the frequency of demographic variables viz., gestational age, birth weight, onset of septicaemia & place of delivery among the septicaemic neonates. The microbial profile of blood stream pathogens causing neonatal septicaemia and pathogen distribution within the concerned demographic variables was observed. Simultaneously, the antimicrobial susceptibility and the prevalent multi drug resistance pattern among the isolated bacterial pathogens was also characterised phenotypically.

Objectives

1. To assess the frequency of demographic variables viz., gestational age, birth weight, onset of septicaemia & place of delivery among the septicaemic neonates.
2. To observe the microbial profile of blood stream pathogens causing neonatal septicaemia and pathogen distribution within the observed demographic variables.
3. To assess the antimicrobial susceptibility and the prevalent multi drug resistance patterns in the isolated bacterial pathogens.

METHODS

This was a descriptive cross-sectional carried out on clinically suspected septicaemic neonates (0 - 28 days age) admitted in a tertiary care hospital in West Bengal, Kolkata from January 2017 to June 2017. Neonates who had congenital anomalies and birth weight less than 1000 g at the time of diagnosis were excluded from the study.

Sample Size

Considering high prevalence (50 – 80 % among various isolates) of multi drug resistant organisms isolated from septicaemic neonates as reported in a previous study from India,[6] with a 20 % relative precision and 95 % significance level for estimation of prevalence of multi drug resistant NS causing organisms, the estimated sample size was 96. Total 116 septicemic neonates were admitted in institutional NICU during the study period. On the basis of selection criteria 102 neonates were enrolled for the study.

The Following demographic characteristics of the studied neonates were recorded through a predesigned case record form:

a. Place of delivery defined as intramural viz. in the same hospital or extramural viz. elsewhere
b. Onset of septicaemia considered as early onset (EOS) i.e., onset during the first 7 days of life or during the first 72 hours of life in the case of very low birth weight infants & late onset (LOS) i.e., onset after 7 days from delivery
c. Gestational age consisting of term neonates born at > 37 wks. or at 35 – 37 wks. of gestation & pre-term neonates born at < 35 wks. of gestation
d. Birth weight of > 2.5 k g defined as normal weight, 1.5 - 2.5 kg as low birth weight-LBW and < 1.5 kg as very low birth weight-VLBW

Blood samples for culture were collected before starting antimicrobial therapy. In patients already on antibiotic therapy (extramural neonates), blood samples were collected just before the next dose of antimicrobial agents and was processed for blood culture at the microbiology laboratory. All pure growth of gram-negative bacilli (GNB) isolates were identified by standard microbiological techniques and biochemical tests. Only pure growth of gram-positive cocci (GPC) with > 50 colony forming units per ml was selected for further processing according to the theory proposed by Craft and Finer wherein 50 cfu / ml was considered to be an indicator of true septicaemia. Candida isolates were identified using Sabouraud's media and germ tube test.

Antimicrobial susceptibility test (AST) was performed for all the bacterial isolates following Clinical and Laboratory Standards Institute (CLSI) guidelines. Surrogate antibiotic markers approved by CLSI standards were used for phenotypic screening (viz, ceftazidime – 30 µg and ceftriaxone - 30 µg) and confirmation (ceftazidime – 30 µg & ceftazidime-clavulanate - 30 / 10 µg) of extended spectrum beta lactamase (ESBL) production. GNB isolates not susceptible to imipenem or meropenem or both were defined as CR-GNB (which included both carbapenem resistant Enterobacteriaceae i.e., CRE and carbapenem resistant non-fermenting GNB) after excluding known intrinsic resistance to carbapenems among the isolates. Susceptibility to colistin was tested by broth microdilution method in Muller Hinton broth and the susceptible breakpoint was defined as MIC < = 2 mg / L. All staphylococcus species isolates were screened with cefoxitin disc (30 µg) to exclude methicillin resistance. Multi drug resistance (MDR) was defined by bacterial resistance to three or more antimicrobial classes. Every neonate was under follow-up from admission till discharge / death.

Statistical Analysis

Frequency distribution and proportion were used for descriptive statistics.

RESULTS

	Microbe; N	EOS	LOS	Intramural	Extramural	Term	Pre-term	VLBW	LBW	Norm. Wt.
GNB: Enterobacteriaceae	*E. coli*; 6	2 (7)	4 (8)	5 (9)	1 (4)	5 (17)	1 (2)	1 (3)	3 (9)	2 (18)
	Klebsiella pneumoniae.; 16	9 (29)	7 (14)	7 (12)	9 (38)	7 (24)	9 (17)	7 (19)	6 (18)	3 (27)
	Enterobacter spp.; 6	5 (16)	1 (2)	5 (9)	1 (4)	2 (7)	4 (8)	1 (3)	4 (12)	1 (9)
	Citrobacter spp..; 2	2 (7)	0	2 (4)	0	0	2 (4)	0	2 (6)	0
GNB: non-fermenters	Pseudomonas spp.; 2	1 (3)	1 (2)	2 (4)	0	0	2 (4)	1 (3)	1 (3)	0
	Acinetobacter baumannii; 4	2 (7)	2 (4)	4 (7)	0	0	4 (8)	3 (8)	1 (3)	0
	Burkholderia cepacia complex; 9	8 (26)	1 (2)	8 (14)	1 (4)	2 (7)	7 (14)	3 (8)	6 (18)	0
GPC	CoNS; 7	2 (7)	5 (10)	6 (11)	1 (4)	3 (10)	4 (8)	4 (11)	3 (9)	0
	S. aureus; 3	0	3 (6)	0	3 (13)	2 (7)	1 (2)	2 (5)	0	1 (9)
	E. faecium;1	0	1 (2)	1 (2)	0	0	1 (2)	0	1 (3)	0
Others	Candida sp.; 25	0	25 (50)	17 (30)	8 (33)	8 (28)	17 (33)	15 (41)	6 (18)	4 (36)
	Total 81	**31**	**50**	**57**	**24**	**29**	**52**	**37**	**33**	**11**

Table 1. Distribution of Blood Stream Pathogens among Various Study Groups

*Figures within parenthesis indicate % of summation of individual column data

	E. coli	*Klebsiella pneumoniae*	Enterobacter sp.	Citrobacter sp.	Pseudomonas sp.	Burkholderia sp.	Acinetobacter sp.
Amoxycillin	0	0	0	0	-	-	-
Amoxycillin-clavulanate	0	0	0	0	-	-	--
Piperacillin-tazobactam	1 (17 %)	5 (31 %)	6 (100 %)	2 (100 %)	2 (100 %)	-	1 (25 %)
Cefuroxime	0	0	5 (83 %)	2 (100 %)	-	-	-
Cefixime	0	0	5 (83 %)	2 (100 %)	-	-	0
Ceftriaxone	0	0	5 (83 %)	2 (100 %)	1 (50 %)	-	0
Ceftazidime	0	0	5 (83 %)	2 (100 %)	1 (50 %)	7 (78 %)	0
Cefepime	1 (17 %)	5 (31 %)	5 (83 %)	2 (100 %)	1 (50 %)	-	0
Cefoperazone-sulbactam	1 (17 %)	5 (31 %)	6 (100 %)	2 (100 %)	-	-	-
Meropenem	1 (17 %)	11 (69 %)	6 (100 %)	2 (100 %)	2 (100 %)	9 (100 %)	1 (25 %)
Imipenem	1 (17 %)	11 (69 %)	6 (100 %)	2 (100 %)	2 (100 %)	-	1 (25 %)
Ertapenem	1 (17 %)	11 (69 %)	6 (100 %)	2 (100 %)	-	-	-
Amikacin	2 (33 %)	10 (63 %)	4 (67 %)	2 (100 %)	2 (100 %)	-	1 (25 %)
Gentamicin	0	3 (19 %)	4 (67 %)	2 (100 %)	2 (100 %)	-	1 (25 %)
Ciprofloxacin	5 (83 %)	8 (50 %)	6 (100 %)	2 (100 %)	0	-	1 (25 %)
Levofloxacin	5 (83 %)	8 (50 %)	6 (100 %)	2 (100 %)	0	2 (22 %)	1 (25 %)
Colistin	6 (100 %)	16 (100 %)	6 (100 %)	2 (100 %)	2 (100 %)	-	-
Cotrimoxazole	0	4 (25 %)	2 (33 %)	1 (50 %)	0	0	1 (25 %)
Minocycline	-	-	-	-	-	8 (89 %)	3 (75 %)
Tigecycline	4 (67 %)	12 (75 %)	6 (100 %)	2 (100 %)	-	-	-
Chloramphenicol	-	-	-	-	-	9 (100 %)	-

Table 2. Antimicrobial Susceptibility of Gram Negative Bacilli

Hyphen (-) denotes the antimicrobials not recommended for susceptibility testing in the respective bacteria[23]

Antimicrobial	CoNS *	*S. aureus**	*E. faecium*
Penicillin	0	0	0
Amoxicillin	0	0	0
Cefoxitin	1 (14 %)	3 (100 %)	-
Gentamicin	3 (43 %)	2 (67 %)	0
Amikacin	5 (71 %)	3 (100 %)	-
Ciprofloxacin	1 (14 %)	2 (67 %)	0
Levofloxacin	2 (28 %)	2 (67 %)	0
Cotrimoxazole	4 (57 %)	2 (67 %)	-
Doxycycline	6 (86 %)	3 (100 %)	-
Tigecycline	6 (86 %)	3 (100 %)	-
Clindamycin	2 (29 %)	2 (67 %)	0
Erythromycin	0	1 (33 %)	0
Linezolid	7 (100 %)	3 (100 %)	1 (100 %)

Table 3. Antimicrobial Susceptibility of Gram Positive Cocci

*Vancomycin and teicoplanin could not be reported owing to lack of CLSI disc diffusion guidelines

Bacteria	MRS*	ESBL†	CR-GNB†	Other MDR‡
CoNS	6 / 7	-	-	-
E. *coli*	-	-	5 / 6 §	1 / 6
Klebsiella pneumoniae	-	6 / 16	5 / 16	5 / 16
Enterobacter spp.	-	1 / 6	-	-
Acinetobacter spp.	-	-	¾	-
Other bacteria	-	-	-	-

Table 4. Frequency of Antimicrobial Resistance Patterns among the Bacterial Isolates

In all the above stated numerical fractions, the numerator represents total number of resistant bacteria and the denominator represents total frequency of concerned bacterial species isolated in the study population.

* Methicillin resistant Staphylococcus sp.

† Extended spectrum beta lactamase producer

† Carbapenem resistant gram-negative bacilli

‡ Other multi drug resistant bacilli

§ includes 1 metallo beta lactamase (MBL) producer

During the study period of 6 months, total 102 blood samples of neonates suspected with sepsis were cultured. 81 blood cultures were reported culture positive (56 bacterial isolates and 25 fungal isolates). Various maternal and neonatal demographic variables concerning the study population have been represented in Figure 1. Microbial profile of the cultured blood stream pathogens and their distribution in various overlapping demographic study groups is shown in Table 1. Culture reports showed overall predominance of GNB among which *Klebsiella pneumoniae* was most commonly reported followed by *Burkholderia cepacia* complex. Among the few reported isolates of GPC (11), coagulase negative staphylococcus species (CoNS) was the commonest isolate. Culture positive fungal septicaemia (25 / 81) was caused by candida non-albicans species. Antimicrobial sensitivity pattern of the gram negative and gram-positive blood stream bacterial isolates are shown in Table 2 & Table 3 respectively. Most susceptible antimicrobial in GNB was colistin (100 % in tested isolates). Most susceptible antimicrobial in GPC was linezolid (100 %). 31 / 56 (55 %) bacterial isolates were MDR viz. ESBL producing GNB, CR-GNB and methicillin resistant staphylococcus (MRS) as shown in Table 4.

DISCUSSION

We identified a plethora of microbes causing neonatal septicaemia and noted that NS was predominantly caused by multi drug resistant (MDR) GNB similar to a cohort study from Delhi.[6]

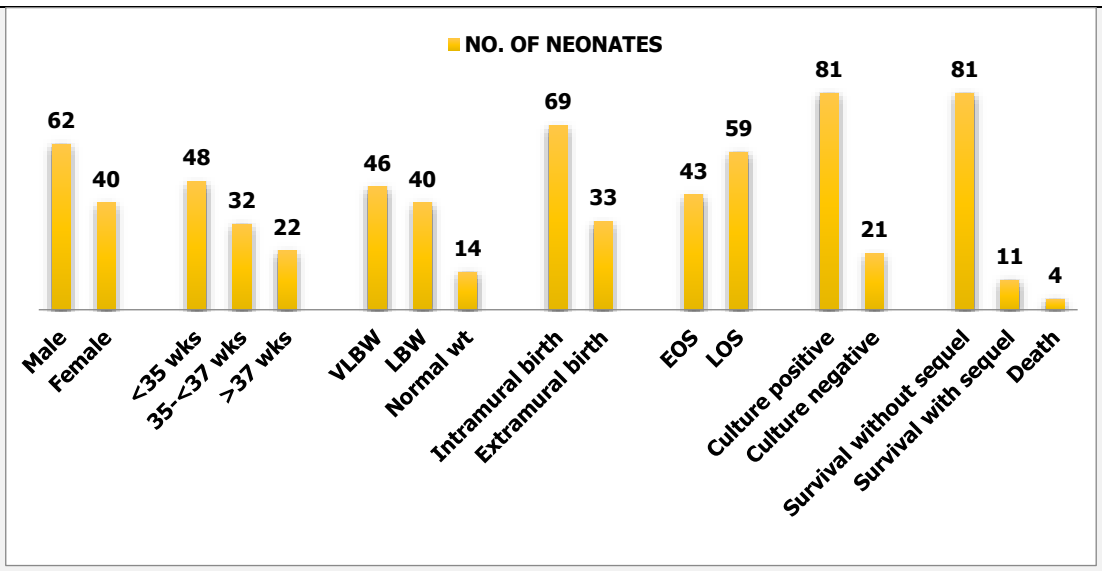

Figure 1. Demographic Variables Studied in 102 Septicaemic Neonates

#outcome could not be assessed in 6 neonates as they took leave against medical advice

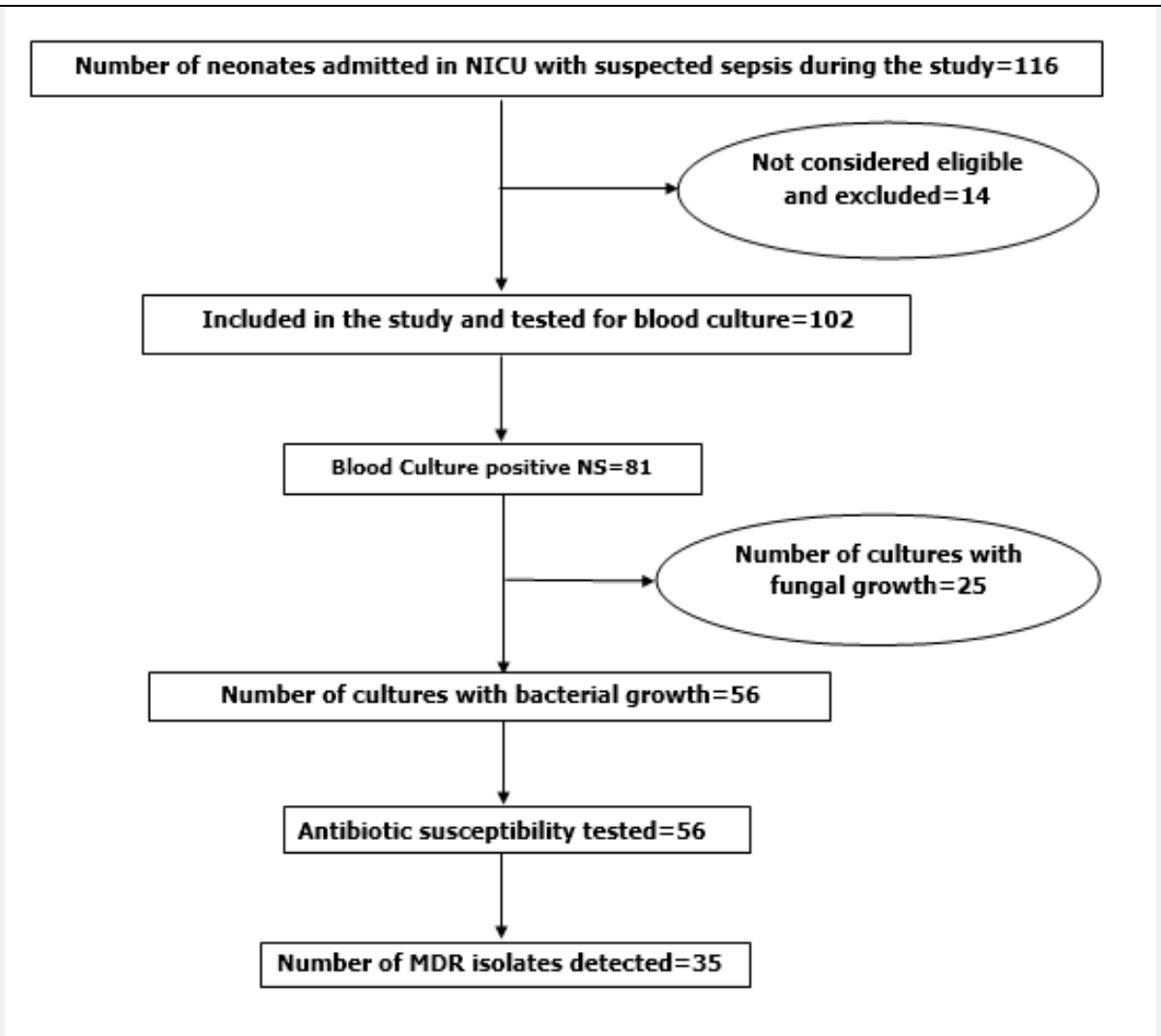

Figure 2. Study Flowchart

Postnatally, the infant may be exposed to GNB during resuscitation and on exposure to articles used in daily care.

Lack of normal flora and serum bactericidins against gram-negative bacilli in neonates allows for rapid colonisation with virulent microbes.[3] Early onset sepsis

(EOS) is caused by maternal intrapartum transmission of invasive organisms and late-onset sepsis (LOS) is caused by a postnatal acquisition (nosocomial or community sources) of the pathogen.[7] In contrast to the cohort study from Delhi, our study showed predominance of LOS over EOS, which is in coherence with similar studies from other Asian countries.[6] In our study EOS was predominantly caused by GNB (29 / 31) wherein *Klebsiella pneumoniae* was the most common (9 / 31) isolate, similar to the findings from Tanzania.[8] *Burkholderia cepacia* complex (8 / 31) was the second most common isolate. Two out of 31 EOS cases were attributed to CoNS which is also the most common GPC isolated in our study. No fungal infection was detected in this group. Corroborating with our findings, Ansari S et al. documented CoNS as the most common cause of both EOS and LOS among gram-positive group of organisms. Likewise, they also recovered burkholderia species from EOS cases.[9] However, the metacentric study from Delhi has reported acinetobacter species as the most common pathogen even in EOS.[6] Cortese F et al. have reported Group B streptococci (GBS) and *E. coli* as the most commonly oetiology.[7] In our study population no early-onset GBS sepsis was noted because antenatal screening and intrapartum prophylaxis was well assured. Among neonates with LOS, predominance of candidemia (25 / 50) was reported, followed by GNB (16 / 50) among which *Klebsiella pneumoniae* was the most common isolate. According to Stoll BJ et al. gram-positive bacteria cause 70 % of the first episodes of LOS; gram-negative organisms were responsible for 18 % of LOS and remaining 12 % were caused by fungi, whereas, Ansari et al. documented GNB as most common causative agent of LOS.[9,10] Candida species were considered the third most common cause of late-onset sepsis in the NICU.[11] We noted that candidemia cases were clustered during the initial two months of our study thereby suggesting a possibility of nosocomial fungal NS outbreak caused by candida non-albicans species, *Acinetobacter baumannii* was isolated in our study from 5 % culture positive cases of septicaemic neonates accounting for 7 % and 4 % cases in EOS and LOS, respectively similar to an Egyptian study.[2]

We observed that in preterm neonates candida species (17 / 52) septicaemia out-numbered that of Enterobacteriaceae whereas, in term neonates, septicaemia was mostly caused by Enterobacteriaceae, viz, *Klebsiella pneumoniae* (7 / 29), E. *coli* (5 / 29). GPC caused 17 % (5 / 29) infections in term neonates and only 12 % (6 / 52) infections in pre-term group. Premature / preterm neonates are at much higher risk of sepsis (both early-onset and late-onset) than infants born at full term because of their immature immune system. Premature newborns lack specific humoral immunity because antibodies do not cross the placental barrier until late in pregnancy.[12] Prematurity is a known cause of candidemia and invasive fungal infection, predominantly due to candida species (*C. albicans, C. krusei* and *C. parapsilosis*), and an increasingly common cause of mortality and morbidity in preterm babies.[11]

Most of our studied neonates belonged to VLBW (46) followed by LBW (40) study groups. GNB was most common in all three groups. However, in VLBW neonates, prevalence of candida species 15 / 37 (41 %) was also quite high and close to that of GNB. Also, among the three birth weight groups, candida species was most commonly isolated from VLBW. In the last two decades candida septicaemia incidence is increasing may be due to the increased survival rates of preterm LBW or VLBW and sick neonates. Incidence rates of candida septicaemia has ranged from 2.6 % to 16.7 % among the VLBW infants and from 5.5 % to 20 % among extremely low birth weight infants, with a mortality rate of around 30 %. The immature immune system predisposes VLBW infants to skin and mucosal fungal colonisation, dissemination and overwhelming infection.[11]

According to National neonatal perinatal database (NNPD); report 2002 - 2003, *Klebsiella pneumoniae* is the most common isolate in both inborn or intramural (32 %) and extramural / out born neonatal sepsis (27 %).[13] Our findings of extramural septicemic neonates was closer to NNPD report (38 % *Klebsiella pneumoniae*), though, in our study population, among 57 culture confirmed cases of intramural neonatal septicaemia, 17 (30 %) neonates suffered from candidemia.

Klebsiella pneumoniae isolates (comprised of 6 ESBL producers, 5 CR-GNB and 5 other MDR strains) were all susceptible to colistin followed by tigecycline (75 %), imipenem and meropenem (69 % each), amikacin (63 %), ciprofloxacin and levofloxacin (50 % each) and piperacillin-tazobactam (31 %). Our finding of colistin sensitivity is similar to several other past studies, but we detected higher resistance to rest of the tested drugs.[14,15] Similar resistance to imipenem and meropenem among *Klebsiella pneumoniae* has also been reported by Amin AJ et al.[16] All penicillins and extended-spectrum cephalosporins except cefepime were reported highly resistant similar to Khan SN et al.[15] E. *coli* isolates (predominantly CRE) were 100 % susceptible to colistin followed by fluoroquinolones (83 %) and tigecycline (67 %) and highly resistant to rest of the antimicrobials tested. Amin AJ et al. has also reported low sensitivity for most antimicrobials tested with E. *coli* except meropenem and piperacillin-tazobactum.[13,14] Studies from Tanzania have reported high prevalence of ESBL producing Enterobacteriaceae among NS pathogens.[17,18] Except E. *coli* and acinetobacter species most of the other tested GNB were well susceptible to amikacin in addition to fluoroquinolones and colistin.

Among the non-fermenting GNB, burkholderia species (intrinsically resistant to multiple antimicrobials) was the predominant isolate (8 / 57, 14 %) and was well susceptible to almost all tested antimicrobials except fluoroquinolones. Patra S et al. have reported *Burkholderia cepacia* blood stream infections in 12 out born neonates (5 preterm and 7 term). They observed highest bacterial susceptibility for meropenem (100 %), followed by cefoperazone-sulbactam, piperacillin-tazobactam, cotrimoxazole (83 %), ceftazidime (75 %) and ciprofloxacin (42 %).[19] Pseudomonas species isolates reported in our study were found susceptible to all the tested antimicrobials, and 3 / 4 (75 %) *Acinetobacter baumannii* isolates were tested resistant to the carbapenems in addition to all other tested antimicrobials. Carbapenem resistance in *Acinetobacter baumannii* has been previously reported by Chatterjee S et al.[20] On the contrary, Shehab El-Din EM et al. have mentioned that acinetobacter species

isolates were resistant to all antimicrobial agents except imipenem and amikacin on a small number.[2] High degree of resistance to both extended spectrum cephalosporins and carbapenems has been documented among both Enterobacteriaceae and non-fermenting GNB pathogens in a recent study from Delhi.[6]

Among GPC, CoNS was most commonly isolated and it was quite alarming to note that 6 out of 7 CoNS isolates were MRS. Indian studies from Delhi and Kolkata have reported occurrence of MRS among CoNS isolates from bacteraemic neonates.[6,21] However, methicillin resistance was not detected in any of the three *S. aureus* isolates in our study in contrary to other studies.[6,17,18] Similar to past reports, we also concluded that rising AMR is threatening the return of pre-antibiotic era in Indian NICUs.[6,22]

CONCLUSIONS

Susceptibility of preterm and subnormal birth weight neonates to both bacterial and fungal sepsis mandates high index of suspicion for appropriate diagnosis and management. Though *Klebsiella pneumoniae* commonly causes neonatal septicaemia in all studied demographic groups, non-fermenting gram-negative bacilli have remarkable role in early onset sepsis. Most of these bacteria are multi drug resistant with high degree of resistance to extended-spectrum cephalosporins. So, in clinically suspected very sick septicaemic neonates not showing much improvement with guideline led empirical antimicrobial therapy, an early antibiogram guided change over to meropenem and amikacin or even to colistin in case of reported carbapenem resistance, is highly recommended. Further studies on colonisation pattern of maternal genital tract and hospital environment are needed for source tracing. Geographical, regional and inter-institutional dynamicity of NS pathogens and their variable AMR profiles emphasize the need of similar continuous surveys to ensure proper management of neonatal septicaemia.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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