

RESEARCH ARTICLE

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Emerging Threat of Multidrug-resistant Bacteria – An Experience from a Neonatal Intensive Care Unit of a Tertiary Care Hospital

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Abstract

Multidrug-resistant (MDR) microorganisms that cause septicemia are responsible for high morbidity and mortality rates among patients in extreme age groups and pose serious treatment challenges despite multipronged measures. This hospital-based study was conducted in the Postgraduate Department of Microbiology at a Tertiary Care Hospital of Kashmir (India) to investigate the prevalence and antimicrobial resistance patterns of bacteria that cause neonatal sepsis. As the resistance pattern of causative agents varies among hospitals, the study results suggest an appropriate empirical therapy for neonatal sepsis needs to be devised in our hospital. Neonatal sepsis, diagnosed by clinicians in the neonatal intensive care unit on the basis of clinical and laboratory findings, was categorized as early-onset sepsis (EOS) or late-onset sepsis (LOS) according to whether clinical presentation occurred at <72 h after birth or between 72 h and 28 days of life, respectively. Blood samples collected from 1200 neonates were cultured in a BacT/ALERT® 3D system (bioMérieux, Inc., Durham, NC, USA). Bacterial identification and antimicrobial susceptibility tests were performed using a VITEK 2 Compact system (bioMérieux). Of the 1200 blood cultures, 126 (10.5%) were bacteremia positive. Of these 126 cultures, 73 (58%) contained gram-positive bacteria, which occurred predominantly in the EOS group ($p < 0.001$), whereas 53 (42%) contained gram-negative bacteria, which were equally distributed in both groups. Bacteremia was more common in the EOS group ($n = 88$; 70%), with *Staphylococcus aureus* ($n = 25$; 20%) being the predominant isolate, followed by *Klebsiella pneumoniae* ($n = 20$; 15.9%). In total, 38 (30%) isolates were recovered in the LOS group, with *Klebsiella pneumoniae* ($n = 11$; 9%) being predominant, followed by *Acinetobacter baumannii* ($n = 9$; 7%). Fifty six (44.4%) and 28 (22.2%) isolates from the EOS and LOS groups, respectively, were MDR, with *Staphylococcus* spp. ($n = 49$; 38.9%), *Klebsiella pneumoniae* ($n = 17$; 13.5%), and *Acinetobacter baumannii* ($n = 14$; 11.1%) in particular showing high resistance rates. With the high prevalence of MDR infections, colistin and vancomycin can be used as initial empirical therapies in our hospital setting. This study underscores the urgent need for robust antimicrobial stewardship and infection control measures to combat the increasing threat of MDR bacterial infections in neonates.

Keywords: Neonatal Sepsis, Blood Culture, Antimicrobial Susceptibility Profile, Multidrug-resistance

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INTRODUCTION

In low- and middle-income countries, sepsis is the main cause of morbidity among neonates and responsible for 99% of the global burden of neonatal deaths. Without a significant decrease in infection-related neonatal deaths, it would be impossible to achieve Sustainable Development Goal 3, which aims to decrease the neonatal mortality rate to at least 12 per 1000 live births by 2030.¹ When sepsis is suspected in neonates, antimicrobials are administered empirically to prevent severe consequences, as the early diagnosis of neonatal septicemia is difficult.² However, the use of broad-spectrum antimicrobial agents in empirical therapy inadvertently leads to the development of multidrug-resistance among the causative agents of sepsis, resulting in a high economic burden. Organisms that acquire resistance to at least one antimicrobial agent in three or more antimicrobial classes are defined as multidrug-resistant (MDR).³ Given that antimicrobial resistance is a major public health problem, blood culture and antimicrobial sensitivity testing must be performed in all patients with suspected sepsis before initiating antimicrobials, as bacterial isolation from blood culture remains the gold standard for diagnosing bacteremia.⁴ Early recognition of the disease and the prompt administration of appropriate antimicrobials can improve the outcomes of afflicted neonates.² However, because the microbial spectrum of bacteremia and the antibiogram of the causative pathogens show interregional variation and even vary among hospitals in the same region, a single antibiotic regimen cannot be recommended in all settings. Hence, once initiated, antimicrobials should be modified according to antimicrobial susceptibility reports. Antibiotic stewardship, defined as the set of practices followed to ensure antibiotics are chosen and administered safely and appropriately, should be adopted by all healthcare settings. In this era of antibiotic-resistance, the changing microbiological patterns of bacteremia warrant an assessment of the causative agents and their patterns of susceptibility to antimicrobials. Hence, this study was conducted to identify the antimicrobial resistance patterns of bacteria isolated from neonates presenting with sepsis

within 72 h after birth (early-onset sepsis; hereinafter EOS) or between 72 h and 28 days of age (late-onset sepsis; hereinafter LOS).^{5,6}

MATERIALS AND METHODS

This prospective hospital-based study was conducted in the Postgraduate Department of Microbiology at a Tertiary Care Hospital of Kashmir (India). This hospital is equipped with a well-functioning level-III neonatal intensive care unit (ICU) where sick neonates (from birth to 28 days of life) are admitted. In total, 1200 neonates with a provisional clinical diagnosis of sepsis were admitted in the neonatal ICU during the 18-month study period, accounting for 44% of total admissions in the unit (N = 2731). After obtaining due approval by the Institutional Ethics Committee (SIMS1131/IEC/-SKIMS/2018-244), blood samples were collected aseptically from the 1200 neonates into BacT/ALERT® PF Plus (bioMérieux, Inc., Durham, NC, USA) aerobic pediatric blood culture bottles. Neonatal sepsis was diagnosed by clinicians in the neonatal ICU on the basis of clinical signs of sepsis, such as fever, lethargy, and respiratory distress, along with specific laboratory criteria, such as abnormal white blood cell counts and C-reactive protein levels.

Isolates recovered from neonates who presented with symptoms of sepsis within 72 h of birth were grouped as causative agents of EOS, whereas those recovered from patients between 72 h and 28 days of age were grouped as pathogens causing LOS.⁵

Inclusion criteria

Bacterial isolates from flagged-positive bottles of blood cultures from neonates. Flagged-positive blood culture bottles are those in which the positive growth of organisms had been detected using the BacT/ALERT® 3D Automated Microbial Detection System (bioMérieux).

Exclusion criteria

Flagged-negative blood culture bottles from neonates with a probable diagnosis of sepsis and isolates other than bacteria obtained from flagged-positive blood culture bottles.

Table 1. Incidence of bacteremia in Neonatal sepsis

		Frequency (N)	Percentage (%)
Probable sepsis (Total Samples Received)		1200	100%
Culture positive samples with significant growth (n = 178, 14.8%)	Bacteremia	126	10.5%
	Candidemia	52	4.3%
Sterile samples		1022	85.2%

Table 2. Association of various bacterial isolates with neonatal sepsis

Bacterial isolates (N = 126)		EOS	LOS	Total Frequency N%	Total (%)
		Frequency N%	Frequency N%		
Gram-positive Isolates		63 (50.0)	10 (8.0)	73	58.0
<i>Staphylococcus aureus</i>	MR	18 (14.3)	2 (1.6)	20	15.9
	MS	07 (5.6)	0	7	5.5
<i>Staphylococcus epidermidis</i>	MR	13 (10.3)	3 (2.4)	16	12.7
	MS	02 (1.6)	0	2	1.6
<i>Staphylococcus haemolyticus</i>	MR	07 (5.6)	1 (0.8)	8	6.3
	MS	06 (4.8)	0	6	4.8
<i>Staphylococcus hominis</i>	MR	04 (3.2)	1 (0.8)	5	4.0
	MS	04 (3.2)	0	4	3.2
<i>Enterococcus faecium</i>		02 (1.6)	3 (2.4)	5	4.0
Gram-negative Isolates		25 (19.8)	28 (22.0)	53	42.0
<i>Klebsiella pneumoniae</i>		09 (7.0)	11 (8.6)	20	15.8
<i>Acinetobacter baumannii</i>		05 (4.0)	9 (7.0)	14	11.1
<i>Pseudomonas aeruginosa</i>		02 (1.6)	4 (3.1)	6	4.7
<i>Escherichia coli</i>		05 (4.0)	0	5	4.0
<i>Burkholderia cepacia</i> complex		01 (0.8)	1 (0.8)	2	1.6
<i>Enterobacter cloacae</i>		3 (2.4)	1 (0.8)	4	3.2
<i>Serratia</i> spp.		0	2 (1.6)	2	1.6
TOTAL		88 (70)	38 (30)	126	100

MR: Methicillin-resistant; MS: Methicillin Sensitive

Identification and antimicrobial susceptibility testing of study isolates

Under aseptic measures, 1-5 ml of venous blood (4-4.5% of total blood volume) was drawn directly into BacT/ALERT® PF Plus (bioMérieux) aerobic pediatric blood culture bottles. Then, the bottles were checked for labeling errors regarding patient details before being loaded onto the BacT/ALERT® 3D Microbial Detection System. While maintaining aseptic measures, a 3 ml syringe was used to dispense a drop of blood from the flagged-positive blood culture bottle onto a slide for Gram staining. On the basis of the staining results, a sample from the bottle was inoculated onto

selective and differential media and incubated at 37 °C for 18-24 h. Subsequently, growth was inspected, and Gram staining of the culture was performed again to confirm the findings. Then, inocula were prepared for processing on a VITEK 2 compact system (bioMérieux) to identify the organisms to the species level and for antimicrobial susceptibility testing as per the Clinical Laboratory Standards Institute guidelines.⁷ Aside from gram-positive methicillin-resistant *Staphylococcus* spp., gram-negative isolates resistant to at least one antimicrobial agent from each of the three antimicrobial classes were defined as MDR.³

Table 3. Antibiotic susceptibility profile of Gram-positive isolates recovered from cases of neonatal sepsis

Antibiotics	Antibiotic susceptibility profile of <i>Staphylococcus</i> spp. (N = 68)		Antibiotic susceptibility profile of <i>Enterococcus</i> spp. (N = 5)	
	Sensitive N (%)	Resistant N (%)	Sensitive N (%)	Resistant N (%)
Cefoxitin	19 (28)	49 (72)	*	*
Ampicillin (Amoxicillin, Ampicillin sulbactam, Amoxicillin/clavulonic acid, Piperacillin/tazobactam)	*	*	2 (40)	3 (60)
Penicillin	0	68 (100)	1 (20)	4 (80)
Erythromycin	14 (20)	54 (80)	IR	IR
Clindamycin	24 (35)	44 (65)	*	*
Cotrimoxazole	34 (50)	34 (50)	*	*
Vancomycin	68 (100)	0	5 (100)	0
Linezolid	68 (100)	0	5 (100)	0
Teicoplanin	68 (100)	0	*	*
Tetracycline	38 (56)	30 (44)	*	*
Gentamicin	38 (56)	30 (44)	2 (40)	3 (60)
Ciprofloxacin	19 (28)	49 (72)	*	*
Levofloxacin	38 (56)	30 (44)	*	*

S: Sensitive; R: Resistant; IR: Intrinsically-resistant; *: Not tested

Statistical analysis

Data analysis was performed using SPSS v.25.0 software. Continuous variables were calculated using Student's t-test. For the 2-tailed test results, a p-value of less than 0.05 was considered statistically significant.

RESULTS

The 1200 neonates with a provisional diagnosis of sepsis made up 44% of the total admissions in the neonatal ICU during the study period (N = 2731). Among them, 126 (10.5%) had microbiologically confirmed bacteremia (Table 1). The representation of both sexes was comparable, with a male-to-female ratio of 1:0.7. As shown in Table 2, the gram-positive isolates (n = 73, 58%) comprised *Staphylococcus* spp. (n = 68) [methicillin-resistant *Staphylococcus aureus* (MRSA) (n = 20); methicillin-sensitive *Staphylococcus aureus* (n = 7); methicillin-resistant *Staphylococcus epidermidis* (n = 16); methicillin-sensitive *Staphylococcus epidermidis* (n = 2); methicillin-resistant *Staphylococcus haemolyticus* (n = 8); methicillin-

sensitive *Staphylococcus haemolyticus* (n = 6); methicillin-resistant *Staphylococcus hominis*, (n = 5); and methicillin-sensitive *Staphylococcus hominis* (n = 4) and *Enterococcus* spp. (n = 5). All 68 *Staphylococcus* isolates were resistant to penicillin, whereas 80% (n = 54) were resistant to erythromycin, 65% (n = 44) to clindamycin, and 50% (n = 34) to trimethoprim/sulfamethoxazole. Among the MDR isolates (n = 84), 58.3% (n = 49) were methicillin-resistant *Staphylococcus* spp. (Figure), with MRSA alone accounting for 23.8% (n = 20). Of the *Enterococcus faecium* isolates, 80% (n = 4) were resistant to penicillin and 60% (n = 3) to ampicillin (Table 3). However, none of the gram-positive isolates showed resistance to linezolid, teicoplanin, or vancomycin.

Among the gram-negative isolates (n = 53; 42%), *Klebsiella pneumoniae* (n = 20) was predominant, with 90% being resistant to third- and fourth-generation cephalosporins, 85% being MDR, and 70% being carbapenem resistant. Variable resistance to aminoglycosides and fluoroquinolones was observed. The second most common gram-negative species isolated

Table 4. Antibiotic susceptibility profile of Gram-negative isolates recovered from cases of neonatal sepsis.

Antibiotics	Antibiotic susceptibility profile of Gram-negative organisms													
	Enterobacteriales (N = 31)							Non-fermenters (N = 22)						
	<i>Klebsiella pneumoniae</i> (N = 20)		<i>Escherichia coli</i> (N = 5)		<i>Enterobacter cloacae</i> complex (N = 4)		<i>Serratia</i> spp. (N = 2)	<i>Acinetobacter baumannii</i> (N = 14)		<i>Pseudomonas aeruginosa</i> (N = 6)		<i>Burkholderia cepacia</i> complex (N = 2)		
	S	R	S	R	S	R	S	R	S	R	S	R	S	R
Ampicillin	IR	IR	0	5 (100)	IR	IR	IR	IR	IR	IR	IR	IR	IR	IR
Ceftazidime	*	*	*	*	*	*	*	*	4 (29)	IR	5 (84)	1 (16)	2 (100)	0
Ampicillin/ clavulanic acid	*	*	2 (40)	3 (60)	*	*	IR	IR	IR	IR	IR	IR	IR	IR
Piperacillin/ tazobactam	6 (30)	14 (70)	4 (80)	1 (20)	2 (50)	2 (50)	0	2 (100)	4 (29)	10 (71)	3 (50)	3 (50)	IR	IR
Gentamicin	7 (35)	13 (65)	2 (40)	3 (60)	2 (50)	2 (50)	1 (50)	1 (50)	2 (15)	12 (85)	5 (84)	1 (16)	IR	IR
Amikacin	2 (10)	18 (90)	4 (80)	1 (20)	3 (75)	1 (25)	IR	IR	3 (22)	11 (78)	*	*	IR	IR
Ciprofloxacin	2 (10)	18 (90)	2 (40)	3 (60)	2 (50)	2 (50)	*	*	0	14 (100)	1 (17)	5 (83)	*	*
Levofloxacin	18 (90)	2 (10)	*	*	*	*	*	*	2 (15)	12 (85)	4 (67)	2 (33)	2 (100)	0
Ceftriaxone	2 (10)	18 (90)	3 (60)	2 (40)	2 (50)	2 (50)	1 (50)	1 (50)	1 (8)	13 (92)	IR	IR	IR	IR
Cefepime	2 (10)	18 (90)	3 (60)	2 (40)	2 (50)	2 (50)	1 (50)	1 (50)	4 (29)	10 (71)	5 (84)	1 (16)	IR	IR
Cefoperazone/ sulbactam	12 (60)	8 (40)	4 (80)	1 (20)	3 (75)	1 (25)	1 (50)	1 (50)	4 (29)	10 (71)	*	*	*	*
Imipenem	6 (30)	14 (70)	2 (40)	3 (60)	2 (50)	2 (50)	2 (100)	0	2 (15)	12 (85)	1 (16)	5 (84)	IR	IR
Meropenem	10 (50)	10 (50)	4 (80)	1 (20)	4 (100)	0	2 (100)	0	4 (29)	10 (71)	5 (84)	1 (16)	2 (100)	0
Ertapenem	2 (10)	18 (90)	2 (40)	3 (60)	2 (50)	2 (50)	1 (50)	1 (50)	IR	IR	IR	IR	IR	IR
Cotrimoxazole	109 (50)	10 (50)	3 (60)	2 (40)	29 (50)	2 (50)	0	2 (100)	4 (29)	10 (71)	IR	IR	1 (50)	1 (50)
Colistin	20 (100)	0	5 (100)	0	4 (100)	0	IR	IR	14 (100)	0	6 (100)	0	IR	IR
Minocycline	*	*	*	*	*	*	*	*	*	*	*	*	2 (100)	0

S: Sensitive; R: Resistant; IR: Intrinsically-resistant; *: Not tested

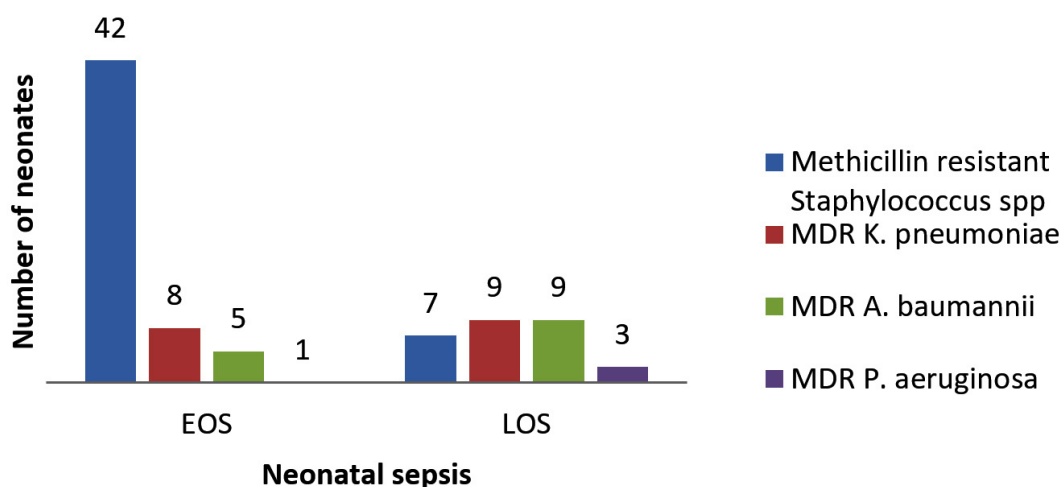


Figure. Distribution MDR isolates in neonatal sepsis (EOS and LOS)

was *Acinetobacter baumannii* (n = 14), with 100% being MDR and 80% being sensitive to colistin only (Table 4 and Figure). The remaining gram-negative isolates were sensitive to colistin, except for two isolates each of *Burkholderia cepacia* complex and *Serratia* spp., which were intrinsically resistant to colistin. However, the *Burkholderia cepacia* complex (n = 2), *Serratia* spp. (n = 2), *Enterobacter cloacae* complex (n = 4), and 80% of *Escherichia coli* and *Pseudomonas aeruginosa* isolates were sensitive to meropenem (Table 4).

DISCUSSION

MDR organisms pose a major health risk in ICUs.⁶ In this study, most of the neonates in the neonatal ICU of the tertiary care hospital had a provisional diagnosis of sepsis (44%). A similar percentage (45.9%) in Egypt was reported by Shehab *et al.*⁷ In our study, 14.8% of neonates had microbiologically confirmed sepsis, with 10.5% presenting with bacteremia, an incidence rate similar to that in Southeast Europe (18%) as reported by Segal *et al.*⁸ However, these rates were lower than those reported in Nepal (40%)⁹ and Southern India (23%).¹⁰ The low culture positivity in our study could be due to the prior use of antibiotics and an over-emphasis on blood culture, as the clinical presentation in this age group was subtle.

The majority of isolates recovered were gram-positive bacteria, with *Staphylococcus* spp. being the most common and predominant in the EOS group (p < 0.001; chi-square test, 33.49), similar to the observations made in West Africa by Fortress *et al.*¹¹ However, our findings were contrary to those observed in Delhi, India by Agarwal *et al.*¹² The predominance of *Staphylococcus* spp. in EOS was also observed in China by Li *et al.*¹³ By contrast, Moftian *et al.* observed that gram-negative isolates were the predominant causative agents of EOS in Iran.¹⁴ *Staphylococcus aureus* (22%) and *Staphylococcus epidermidis* (14%) were identified as the most common *Staphylococcus* spp. in our study, similar to the findings reported by Ansari *et al.* in Uttar Pradesh, India.¹⁵ As normal flora of the nose and skin, respectively, *Staphylococcus aureus* and *Staphylococcus epidermidis* cause bacteremia by crossing the natural defense line, especially as a result of the extensive use of invasive devices and manipulation of peripheral intravenous lines in immunologically immature neonates. Among the MDR *Staphylococcus* isolates identified, 72% were resistant to methicillin, with MRSA (16%) accounting for the highest proportion. By contrast, Tanu *et al.* observed that more than 50% of *Staphylococcus aureus* isolates recovered from neonates with sepsis in Delhi, India, were methicillin-resistant.¹⁶ However, in a multicenter

study conducted by Kim *et al.* in Korea, gram-negative MDR isolates were predominant.¹⁷ MRSA, the first known widespread superbug, is associated with a high death rate and has become a serious threat, especially in ICUs, necessitating the exploration and use of new drug regimens for its eradication.¹⁸

As none of the gram-positive bacteria isolated in our study were resistant to vancomycin, linezolid, or teicoplanin, vancomycin can be used as empiric therapy for staphylococcal infections. Although the clinical effects of vancomycin and linezolid are comparable, linezolid use is associated with myelosuppression and thrombocytopenia, side effects that are leading causes of the drug being withdrawn. Similar observations were reported by Lufen *et al.* in a study conducted in China.¹⁹ Likewise, because limited data exist regarding the pharmacokinetics and pharmacodynamics of teicoplanin in neonates, the optimal dosing regimen remains questionable. However, researchers have proposed the routine use of therapeutic drug monitoring for optimal teicoplanin administration, as concluded by Ramos *et al.* in a study conducted in the United Kingdom.²⁰

In our study, gram-negative isolates were equally responsible for both EOS and LOS. *Klebsiella pneumoniae* was the predominant isolate (16%) and was responsible for 7.1% of the EOS and 8.7% of the LOS cases. Similar observations were reported by Hu *et al.*, who conducted a multicenter antimicrobial surveillance study in China.²¹ In our study, *Acinetobacter baumannii* was the most common non-fermenting gram-negative bacterium isolated (11.1%), similar to the results of Panda *et al.*, who conducted a four-year surveillance study in Odisha, India.²² MDR *Klebsiella pneumoniae* was the second most resistant pathogen (13.5%) isolated in this study. By contrast, Hu *et al.* reported other MDR Enterobacterales as being more prevalent in their study cohort.²¹ The high resistance rates to third- and fourth-generation cephalosporins (90%) and carbapenems (70%) observed in the present study could be due to the circulation of extended-spectrum beta-lactamase producing strains in our region. Additionally, as 65% of the strains were resistant to gentamicin, this drug cannot be recommended as empiric therapy for treating bacteremia in our setup.

The immune systems of neonates are immature, making them more prone to hospital-acquired infections. An upsurge in bacteremia caused by MDR *Klebsiella pneumoniae* has been observed globally, especially in neonatal ICUs. The World Health Organization (WHO), which has included MDR *Klebsiella* spp. among the most dangerous superbugs, recommends treatment using only a few therapeutic options along with the detachment of invasive devices. These benefits were also suggested in a report by Ravi *et al.* on their study in Tamil Nadu, India.²³ The success of *Klebsiella pneumoniae* as a pathogen can also be attributed to its hypervirulent pathotype and well-known capability to acquire antibiotic resistance determinants.²¹ Moreover, both of the most prevalent gram-negative organisms belonging to the ESKAPE group of pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) are categorized under the “critical group” in the WHO global priority pathogen list and are almost entirely responsible for the spread of antimicrobial resistance among the strains responsible for hospital-acquired infections.¹⁸ Non-fermenting gram-negative isolates have also emerged as a major cause of nosocomial infections, being responsible for occasional outbreaks, and are the fourth most common gram-negative bacteria responsible for bacteremia. According to the Centers for Disease Control and Prevention (Atlanta, USA) nearly 80% of all reported *Acinetobacter* infections are caused by *Acinetobacter baumannii*, which is the leading agent of infections in ICUs.³ Lob *et al.* reported that 95% of *Acinetobacter baumannii* isolates collected from different centers in the USA were MDR, similar to the observations in our study (100%).²⁴

Antimicrobial resistance is increasing to lethally high levels globally and is the most urgent public health concern worldwide.¹⁸ *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are among the six leading agents causing high mortality rates. Their resistant strains were responsible for 3.57 million deaths in 2019, and this number may increase to 10 million by 2050 if left unchecked.²⁵ Although none of the gram-positive and gram-negative strains isolated in this study were resistant to

colistin, the observed MDR pattern of the causative agents is similar to that observed in a national multicenter study conducted in Delhi, India by investigators of the Delhi Neonatal Infection Study.¹² Similar observations on neonatal sepsis in the United Kingdom were made from an international multicenter cohort study conducted by Russell *et al.*²⁶ Those authors concluded that antibiotic regimens for neonatal sepsis are diverging from the WHO guidelines; hence, trials of newer empiric regimens are urgently needed to address the surge in MDR strains.²⁶ Research on the usefulness of older antibiotics such as colistin for treating neonatal septicemia caused by MDR bacteria is warranted. Based on current data, colistin is an effective agent against MDR gram-negative bacteria, with an acceptable safety profile, indicating that it can be a useful alternative for treating MDR septicemia. However, to reduce the risk of resistance and maximize antimicrobial activity, monotherapy should be avoided, and combination therapies should be considered meticulously, as suggested by many investigators.²⁷

Limitations

This was an observational study of a single center in northern India, which restricts the generalizability of the antibiotic resistance profiles to other locations, regardless of the substantial sample size. Moreover, clinical details and other laboratory parameters were not included, as they were not the focus of this study. Additionally, blood cultures have low sensitivity, which is further affected by prior antibiotic use in patients. Future research should focus on the application of molecular diagnostics to improve pathogen detection as well as multicenter studies to generalize the findings.

CONCLUSION

The high prevalence of MDR isolates in neonatal ICUs leads to difficulty in arriving at effective treatment decisions, thus highlighting the need for deeper investigations of the local epidemiology of causative agents of neonatal septicemia to establish empiric therapies. Given the high prevalence of gram-positive and gram-negative MDR organisms observed in our study, colistin and vancomycin can potentially be empiric

therapies for neonates with suspected sepsis. Measures to reduce infection rates by undertaking regular surveillance to recognize changes in the causative agents and their drug resistance patterns should be considered. This study highlights the critical need for enhanced antimicrobial stewardship and infection control strategies in neonatal care settings. Our findings contribute to the growing body of evidence regarding the global challenge posed by MDR infectious agents and underscore the importance of continued research and policy interventions to improve neonatal outcomes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by the Institutional Ethics Committee, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, J&K, India, via letter No.: SIMS1131/IEC/-SKIMS/2018-244.

REFERENCES

1. Milton R, Gillespie D, Dyer C, et al. Neonatal sepsis and mortality in low-income and middle-income countries from a facility-based birth cohort: an international multisite prospective observational study. *Lancet Glob Health*. 2022;10(5):e661-e672. doi: 10.1016/S2214-109X(22)00043-2
2. Celik IH, Hanna M, Canpolat FE, Pammi M. Diagnosis of neonatal sepsis: the past, present and future. *Pediatr*

- Res. 2022;91(2):337-350. doi: 10.1038/s41390-021-01696-z.
3. Glossary of terms related to antibiotic resistance. <https://www.cdc.gov/narms/resources/glossary.html>, Accessed 01 april, 2024.
4. Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: 2021. <https://www.who.int/publications-detail-redirect/9789240027336>, Accessed 01 april, 2024.
5. Miranda S, Harahap A, Husada D, Faramarisa FN. Risk factors of multidrug-resistant organisms neonatal sepsis in Surabaya tertiary referral hospital: a single-center study. *BMC Pediatr*. 2024;24(1):1–8. doi: 10.1186/s12887-024-04639-9
6. Ren Z, Yang S, Han J, et al. Reduction of antibiotic use and multi-drug resistance bacteria infection in neonates after improvement of antibiotics use strategy in a level 4 neonatal intensive care unit in southern China. *Eur J Clin Microbiol Infect Dis*. 2023;42(1):87–98. doi: 10.1007/s10096-022-04522-4
7. Shehab El-Din EMR, El-Sokkary MMA, Bassiouny MR, Hassan R. Epidemiology of Neonatal Sepsis and Implicated Pathogens: A Study from Egypt. *Biomed Res Int*. 2015;2015(1):509484. doi: 10.1155/2015/509484
8. Segal J, Hoxha M, Wien S, et al. The bacterial profile of neonatal sepsis and antibiotic use in the tertiary care NICU of Kosovo. *J Pediatr Neonatal Care*. 2018;8(2):105–108. doi: 10.1506/jpnc.2018.08.00319
9. Yadav NS, Sharma S, Chaudhary DK, et al. Bacteriological profile of neonatal sepsis and antibiotic susceptibility pattern of isolates admitted at Kanti Children's Hospital, Kathmandu, Nepal. *BMC Res Notes*. 2018;11(1):301. doi: 10.1186/s13104-18-3394-6
10. Pavan Kumar DV, Mohan J, Rakesh PS, Prasad J, Joseph L. Bacteriological profile of neonatal sepsis in a secondary care hospital in rural Tamil Nadu, Southern India. *J Family Med Prim Care*. 2017;6(4):735–738. doi: 10.4103/jfmpc.jfmpc_66_17
11. Aku FY, Akweongo P, Nyarko K, et al. Bacteriological profile and antibiotic susceptibility pattern of common isolates of neonatal sepsis, Ho Municipality, Ghana-2016. *Matern Health Neonatol Perinatol*. 2018;4:2. doi: 10.1186/s40748-017-0071-z
12. Agarwal, Ramesh & Sankar, Jeeva, Chaurasia, Suman. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study. *Lancet Glob Health*. 2016;752-760. doi: 10.1016/S2214-109X(16)30148-6
13. Li Z, Xiao Z, Li Z, Zhong Q, Zhang Y, Xu F. 116 cases of neonatal early-onset or late-onset sepsis: a single center retrospective analysis on pathogenic bacteria species distribution and antimicrobial susceptibility. *Int J Clin Exp Med* 2013;6(8):693-699.
14. Moftian N, Rezaei-Hachesu P, Arab-Zozani M, et al. Prevalence of gram-negative bacteria and their antibiotic resistance in neonatal sepsis in Iran: a systematic review and meta-analysis. *BMC Infect Dis*. 2023;23(1):534. doi: 10.1186/s12879-023-08508-1
15. Ansari F, Banerjee T, Kumar A, Anupurba S. Coagulase-Negative Staphylococci in Neonatal Blood: How Concerning? *J Lab Physicians*. 2023;15(1):126-130. doi: 10.1055/s-0042-1757411
16. Singhal T, Rodrigues C, Soman R, et al. Treatment of MRSA infections in India: Clinical insights from a Delphi analysis. *Indian J Med Microbiol*. 2022;40(1):35-45. doi: 10.1016/j.ijmm.2021.11.005
17. Kim HJ, Oh DK, Lim SY, et al. Antibigram of multidrug-resistant bacteria based on sepsis onset location in Korea: a multicenter cohort study. *J Korean Med Sci*. 2023;38(10):e75. doi: 10.3346/jkms.2023.38.e75.
18. WHO Antimicrobial Resistance. Available online: <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance>. Accessed 01 april, 2024.
19. Duan L, Zhou Q, Feng Z, et al. A Regression Model to Predict Linezolid Induced Thrombocytopenia in Neonatal Sepsis Patients: A Ten-Year Retrospective Cohort Study. *Front. Pharmacol*. 2022;13:710099. doi: 10.3389/fphar.2022.710099
20. Ramos-Martin V, Neely MN, McGowan P, et al. Population pharmacokinetics and pharmacodynamics of teicoplanin in neonates: making better use of C-reactive protein to deliver individualized therapy. *J Antimicrob Chemother*. 2016;71(11):3168-3178. doi: 10.1093/jac/dkw295
21. Hu F, Yuan L, Yang Y, et al. A multicenter investigation of 2773 cases of bloodstream infections based on China antimicrobial surveillance network (CHINET). *Front Cell Infect Microbiol*. 2022;12:1075185. doi: 10.3389/fcimb.2022.1075185
22. Panda SK, Nayak MK, Jena P, et al. Nonfermenting, Gram-Negative Bacilli Causing Neonatal Sepsis in Odisha, India: Four-Year Surveillance. *Cureus*. 2022;14(2):e22219. doi: 10.7759/cureus.22219
23. Ravi V, Vijay DD, Sujithra A, Jayanthi S, Subramanian TK, Harish N. Neonatal Sepsis: The impact of Hypervirulent *Klebsiella pneumoniae* in a Tertiary Care Hospital. *J Pure Appl Microbiol*. 2022;16(3):2035-2044. doi: 10.22207/JPAM.16.3.56
24. LobSH, Hoban DJ, Sahm DF, et al. Regional differences and trends in antimicrobial susceptibility of acinetobacter baumannii. *Int J Antimicrob Agents*. 2016;47:317–23. doi: 10.1016/j.ijantimicag.2016.01.015
25. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet* 2022;399(10325):629–655. doi: 10.1016/S0140-6736(21)02724-0
26. Russell NJ, Stohr W, Plakkal N, et al. Patterns of antibiotic use, pathogens, and prediction of mortality in hospitalized neonates and young infants with sepsis: A global neonatal sepsis observational cohort study (NeoOBS). *PLOS Med*. 2023;20(6):e1004179. doi: 10.1371/journal.pmed.1004179
27. Baltogianni M, Dermitzaki N, Kosmeri C, Serbis A, Balomenou F, Giapros V. Reintroduction of Legacy Antibiotics in Neonatal Sepsis: The Special Role of Fosfomycin and Colistin. *Antibiotics* 2024;13(4):333. doi.org/10.3390/antibiotics13040333