Ad-din Medical Journal
January 2024, 2(2):27-33

# Original article

# A Retrospective Analysis of Antimicrobial Resistance Patterns of Predominant Pathogens Causing Neonatal Bloodstream Infection in Tertiary Care Hospitals of Dhaka City

Received: 27.02.2024 Accepted: 23.06.2024.

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**Abstract**

***Background:*** Neonatal bloodstream infections (BSIs) kill most poor country babies. Effective therapy requires time. A retrospective research in two tertiary hospitals in Dhaka, Bangladesh, examined the incidence of bacterial pathogens causing newborn BSIs and their antibiotic resistance patterns. ***Methodology:*** A total of 1825 blood samples were obtained from patients who were admitted at the Neonatal Intensive care unit of Ad-din Women's Medical College & Hospital, Dhaka & Rushmono specialized Hospital, Dhaka, Bangladesh from July 2020 to December 2021. All the blood samples were processed for culture using a BACT/Alert blood culture machine. Further identification & antimicrobial susceptibility tests were performed using standard microbiological procedure. ***Result:*** The incidence of bloodstream infection (BSI) in 1825 newborn intensive care facility blood samples was 17.2%. Acinetobacter spp. (23.9%) and coagulase-negative Staphylococci (CoNS) (52.7%) were the most common isolates. Staphylococcus species were resistant to ampicillin, cephradine, and erythromycin but sensitive to imipenem, vancomycin, and linezolid. 31.5% of Staphylococcus aureus and 47% of CoNS are methicillin-resistant. Staphylococcus epidermidis resists methicillin better than MRSA. One-tenth of isolated Staphylococcus species are vancomycin-resistant. Acinetobacter spp. was responsive to colistin, meropenem, piperacillin-tazobactum, and amikacin but resistant to ampicillin, cephradine, cefuroxime, and cefixime. 48% of identified Acinetobacter species are cephalosporin, fluoroquinolone, and aminoglycoside resistant, 14% are meropenem resistant, and 2.7% are Colistin resistant. ***Conclusion:*** The study emphasizes the importance of antibiotic stewardship for emerging resistance patterns and improves neonatal outcomes. Judicial use of antimicrobial agents in NICU is mandatory. These may provide valuable insights for healthcare professionals and researchers to develop effective antibiotic policies to combat neonatal sepsis and reduce associated morbidity and mortality.

***Keywords:*** BSI: blood stream infection, ARO: antimicrobial-resistant organisms, NICU: neonatal intensive care unit, Coagulase-negative staphylococci (CONS), Acinetobacter

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***How to cite this article:*** Saha R, Saha S, Mahmuda H, Fariha RSH, Lutfor AB. A Retrospective Analysis of Antimicrobial Resistance Patterns of Predominant Pathogens Causing Neonatal Bloodstream Infection in Tertiary Care Hospitals of Dhaka City. Ad-din Med J. 2024 Jul;2(2):27-33

**Introduction:**

One of the main causes of newborn death in underdeveloped nations is bloodstream infection. Nearly 50% of patients in neonatal critical care units in certain towns get bloodstream infections.[1,2] About ten million newborns are thought to pass away in the first five days of life, according to estimates from the World Health Organization. One in five newborns in certain poor nations is said to be affected by septicemia.[3] Neonatal infections can be obtained through vertical transmission from microbes in the birth canal or through environmental exposure due to inadequate health facilities. Neonatal septicemia is a clinical syndrome characterized by bacteremia, symptoms, and clinical indications that manifest during the first months of life. The delay in its diagnosis and treatment results in mortality.[4]

The compromised immune systems of neonates render them highly susceptible to infection. Neonatal sepsis is challenging to diagnose at the time of presentation and is associated with substantial morbidity and mortality. For this reason, individuals who are suspected of having sepsis are initiated on empiric antibiotic therapy until sepsis is definitively ruled out. Antimicrobial-resistant organisms (ARO) are the consequence of antibiotic overuse. ARO infection leads to a delay in the commencement of effective antibiotic therapy, a reduction in the number of treatment options, and an increase in morbidity and mortality. This is accompanied by a protracted hospital stay and increased hospitalization costs.[5]

Gram-positive organisms are responsible for up to 70% of nosocomial infections in neonates in numerous hospitals, with coagulase-negative staphylococci (CoNS) causing up more than half of this total.[6,7] Conversely, in certain developing nations, neonatal pathogens may be significantly more prevalent in gram-negative organisms, which are associated with a higher prevalence of antimicrobial resistance.[3] For instance, A. baumannii described the first outbreak of multiple-drug-resistant in particularly low birth weight neonates in the United States in 2004. Pathogens also exhibit variability over time.[8] But now a days, Acinetobacter is one of the most important microorganism responsible for neonatal blood stream infection in our country.[9]

Coagulase-negative staphylococci (CoNS) are common colonizers of human skin; but now adays it has become true pathogens, rather than simply culture contaminants, causing cardiovascular, joint, and bloodstream infections. Several authors have demonstrated CoNS as the most frequent cause of blood stream infection.[10–12]

The incidence, risk factors, pattern, antimicrobial sensitivities of pathogens, and mortality of neonatal sepsis vary across various regions and countries due to epidemiological differences.[13] Empiric antibiotic therapies are predicated upon the monitoring of antimicrobial sensitivity patterns in culture isolates. To expedite the prevention of neonatal morbidity and mortality, it is necessary to implement particular strategies customized to each country's specific circumstances. This may include the prevention and treatment of neonatal sepsis. To prevent the development of resistant microorganisms and limit inappropriate antibiotic use, it is recommended that antibiotic stewardship be implemented, which includes the appropriate selection and administration of antibiotics, de-escalation of therapy, and a multidisciplinary team approach to neonatal sepsis management. In addition, neonatal survival can be enhanced by the identification of risk factors, early diagnosis, and the implementation of therapy following local epidemiology and antimicrobial resistance patterns.

The objective of this investigation was to determine the most frequently encountered bacterial pathogens that contribute to neonatal BSI in two tertiary health care hospitals in Dhaka city that have NICU facilities. Additionally, we identified the antibiotic resistance patterns of the most prevalent pathogens and analyzed the pattern to ascertain the emergence of multidrug resistance in this region.

## Materials and Methods

In this retrospective study, blood samples were obtained from patients who were admitted at the Neonatal Intensive care unit of Ad-din Women's Medical College & Hospital, Dhaka & Rushmono specialized Hospital, Dhaka, Bangladesh. A total of 1825 blood samples were processed from July 2020 to December 2021. All the blood samples were processed for culture the use of a BACT/Alert blood culture device to find out the presence of bacterial pathogens. Manual method has been utilized as well. Antimicrobial susceptibility tests were performed on the isolated pathogens using Kirby-Bauer disk diffusion method.

Bacterial isolation: Collected blood samples were directly inoculated into pediatric FAN blood culture bottle. Bottles were incubated in the BACT/Alert machine for 5 days. One drop of blood from growth positive culture bottles were directly inoculated onto MacConkey (MC) agar and blood agar (5% sheep blood) plates. Blood agar plates and MacConkey plates were then incubated at 37 °C in aerobic condition. The bacterial isolates were identified and confirmed by using standard microbiological and biochemical tests like Gram staining, growth on selective media, colony morphology on culture media, lactose fermentation, indole, and citrate utilization, H2S production, catalase, coagulase, oxidase, and urease test.All Staphylococci isolates were identified using colony morphologic analyses on Blood agar, Gram staining, and catalase and coagulase testing. Coagulase positive strains are considered as Staphylococcus aureus. Coagulase Negative Staphylococcus are further tested for Novobiocin susceptibility. Novobiocin sensitive strains ae considered as Staphylococcus epider-

midis. And remaining other species are classified as other CoNS. All tests are performed according to guidelines of World Health Organization.[14]

Antimicrobial Susceptibility Testing: According to Clinical and Laboratory Standards Institute (CLSI) guidelines of 2019 antimicrobial susceptibility testing was performed by using disc diffusion (Kirby-Bauer's) technique on Mueller Hinton agar (Merck, Germany).[15] The antibiotic discs of ampicillin (Amp), cephradine (Ceph), cotrimoxazole (Cot), ciprofloxacin (Cip), levofloxacin (Lev), nalidixic acid (NA), ceftriaxone (CTR), chloramphenicol (Clo), amoxyclav (AMC), cefixime (CXM), cefotaxime (CTX), gentamicin (Gen), amikacin (AK), azithromycin (Az), ceftazidime (CAZ), meropenem (Mero), piperacillin-tazobactam (PIT), colistin (Col) were used for Gram negative bacteria and ampicillin (Amp), cephradine (Ceph), cotrimoxazole (Cot), ciprofloxacin (Cip), levofloxacin (Lev), cefotaxime (CTX), ceftriaxone (CTR), amoxyclav (AMC), gentamicin (Gen), amikacin (AK), imepenem (Ime), cefuroxime, cefixime (CXM), oxacillin (Ox), cloxacillin (Clox), erythromycin (Ery), Novobiocin, doxycycline (Do), vancomycin (Van), linezolid (Lz) were used for Gram positive bacteria. All antibiotic discs are obtained from Oxoid Ltd, Bashingstore, Hampire, UK.

Microsoft Excel program were used for statistical analysis and figure generation.

## Results

The frequency of newborn blood stream infection from 1825 blood culture samples from neonatal intensive care unit patients is shown in Table-1. 17.2% (313/1825) had bloodstream infection. About 52.7% are coagulase negative Staphylococcus (CoNS), 23.9% are Acinetobacter, 6.1% are Staphylococcus aureus and rests are others. No Salmonella Typhi or paratyphi was found. These data indicate that Coagulase-negative Staphylococci Spp. and AcinetobacterSpp. are the main causes of newborn blood stream infection, but Salmonella speceis not (Table 1, Figure 1).

Most Neonatal blood stream infections were caused by Staphylococci, and CoNS were most often isolated. Among the CoNS 124 was identified as S.epidermidis. They were sensitive to imipenem (86.06%), vancomycin (90.30%), and linezolid (100%) but resistant to ampicillin (92.73%), cephradine (83.03%), and erythromycin (52.12%) (Figure 2).

Resistance pattern of various Staphylococcus spp is categorized in detail in Table 2(a), 2(b), and 2(c).Staphylococcus species which showed resistance to penicillin, oxacillin andcloxacillin are considered as methicillin resistance. Among the S.aureus 31% are detected MRSA and 15.8% are VRSA [Table 2(a)]. Almost 55% of S.epidermidis were found Methicillin resistant, whereas vancomycin resistance was detected in 13% S.epidermidis [Table 2(b)]. CoNS than S.epidermidis show Methicillin resistance among 22% cases; but no vancomycin resistance is found [Table 2(c)].

Gram negative pathogens most frequent in newborn blood stream infections include Acinetobacter spp. They responded better to colistin (100%), meropenem (90%), piperacillin-tazobactam (92%), and amikacin (82%). Ampicillin (90%), cephradin (80%), cefuroxime (90%) and cefixime (80%) are more resistant (Figure 3). The identified Acinetobacter species are 48% cephalosporin, fluoroquinolone, and aminoglycoside resistant, 14% meropenem resistant, and 2.7% Colistin (Polymixin E)

Table 1: The water quality parameters of different stations of the four studied rivers

| Pathogen | Number =N |
|---|---|
| CoNS | 165 |
| Acinetobacter | 75 |
| Staphylococcus aureus | 19 |
| Klebsiella | 17 |
| Enterobacter | 18 |
| E.coli | 5 |
| Proteus | 5 |
| Pseudomonas | 4 |
| S.pneumoniae | 3 |
| Enterococci | 2 |
| Salmonella typhi | 0 |
| Salmonella paratyphi | 0 |
| Total | 313 |

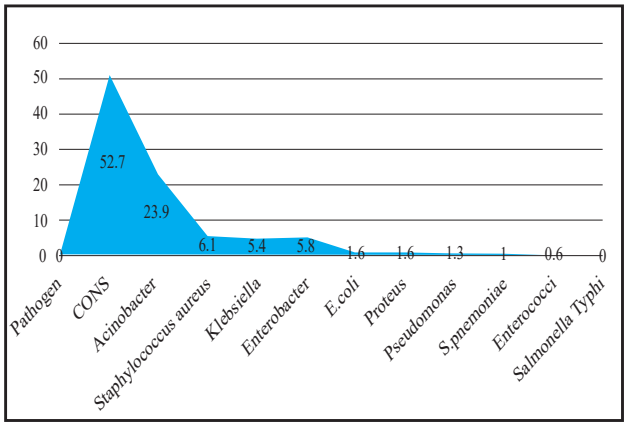


Figure 1: Distribution of bacterial pathogens causing neonatal bloodstream infection (Percentage)

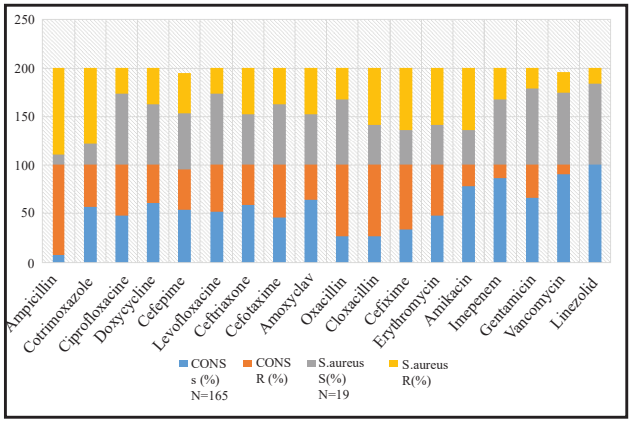


Figure 2: Susceptibility pattern of CONS spp. to different antimicrobial agents (n=165)

Table 2 (a): Categorization of Staphylococcus aureus spp. (N=19) according to their antibiotic resistance pattern:

| Definition | Number | Percentage |
|---|---|---|
| MRSA(resistance to ampicillin, oxacillin, cloxacillin) | 6 | 31.6% |
| MRSA +Resistance to Aminoglycosides, Tetracycline, Chloramphenicol, Macrolides) | 4 | 21.1% |
| VRSA (Vancomycin resistant) | 3 | 15.8% |
| Non-specific sensitivity pattern | 6 | 31.6% |

Table 2 (b): Categorization of *Staphylococcus epidermidis* spp. (N=124) according to their antibiotic resistance pattern

| Definition | Number | Percentage |
|---|---|---|
| MRSE(resistance to ampicillin, oxacillin, cloxacillin) | 68 | 54.9% |
| MRSE +Resistance to Aminoglycosides, Tetracycline, Chloramphenicol, Macrolides) | 15 | 12.1% |
| VRSE(Vancomycin resistant) | 16 | 12.9% |
| Non-specific sensitivity pattern | 25 | 20.2% |

Table 2 (c): Categorization of CONS spp. Other than *Staphylococcus epidermidis* (N=41) according to their antibiotic resistance pattern:

| Definition | Number | Percentage |
|---|---|---|
| MRCONS(resistance to ampicillin,oxacillin, cloxacillin) | 9 | 22% |
| MRCONS +Resistance to Aminoglycosides, Tetracycline,Chloramphenicol, Macrolides) | 6 | 14.6% |
| VR CONS(Vancomycin resistant) | 0 | 0 |
| Non-specific sensitivity pattern | 26 | 63.4% |

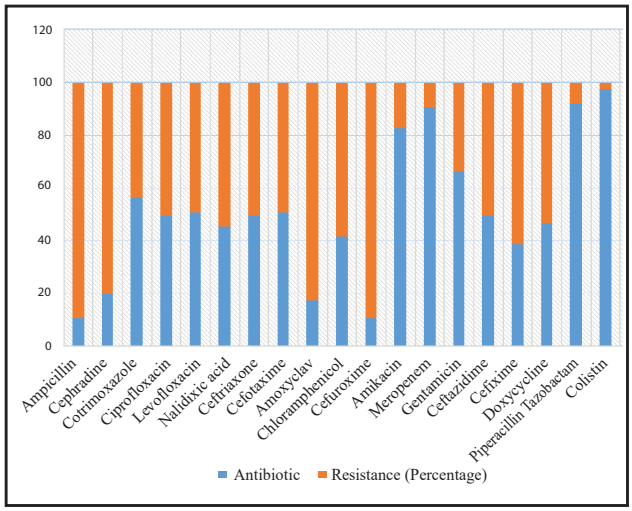


Figure 3: Susceptibility pattern of *Acinetobacterspp.* to different antimicrobial agents (n=75)

Table 3: Categorization of *Acinetobacter spp.* (N=75) according to their antibiotic resistance pattern:

| Category | Definition | Number | Percentage |
|---|---|---|---|
| MDR | Resistant to-<br>• All cephalosporin and inhibitor combination<br>• Fluoroquinolones<br>• Aminoglycoside | 36 | 48% |
| XDR | MDR+ resistant to carbapenems | 14 | 18.7% |
| PDR | XDR+ resistant to Polymixin E (Colistin) | 02 | 2.7% |
| Unclassified | Miscellaneous pattern of sensitivity | 23 | 30.6% |

## Discussion:

Neonatal bloodstream infections and antibiotic resistance are global concerns. This investigation detected 17.2% bloodstream infection without anaerobic culture. ICU patients are more likely to develop nosocomial BSIs. Due to vertical transmission from dealing, neonates are more susceptible to infection. The most common pathogens isolated from neonates were Coagulase-negative Staphylococci Spp(52.7%, 165/313) and AcinetobacterSpp (24%, 75/313) (Table 1, Figure 1).

CoNS are the main pathogen in Late-Onset Neonatal Sepsis (LONS), especially in premature babies. Several publications found that Gram-positive microorganisms cause more neonatal hospital-acquired bloodstream infections than gram-negative and yeast.[16–18] Within the first week of life, neonates become rapidly colonized by environmental pathogen.[19,20] With CoNS &Acinetobacter infection, central venous catheters (CVC), mechanical ventilation, parenteral nourishment, and other invasive skin or mucosa-breaching treatments, BSI risk increases significantly.[21,22]Thus, hospitalized newborns get most of the germs from parents, caregivers, and their surroundings.[23] Hospital workers may spread endemic strains of organisms for long durations.[24] Antibiotic resistance in skin-residing bacteria is minimal at birth but rises significantly in the first week of hospitalization. Perinatal antibiotic exposure selectively affects neonatal microorganism spectrum and antibiotic resistance.[25] CoNS &Acinetobacter spp. blood infection can occur in the babies without being under intensive care or antibiotics, mechanical ventilation or having indwelling catheters.[26]

However, we have observed an increase of susceptibility against Cotrimoxazole (50%) than the studies of previous decades.[27] If this trend continues, cheaper first-line medications for newborn blood stream infections may be attainable.

This research found high ampicillin, cephradine, and erythromycin resistance in Staphylococci spp., the main pathogen of newborn BSI. (Table 3). CONS were sensitive to amikacin (78%), imipenem (86%), vancomycin (90%) and linezolid (100%). S. epidermidis (55%), Staphylococcus aureus (31.5%) are methicillin-resistant.
MR Staphylococcus strains introduced into healthcare settings are transmitted and persistent-based on the availability of vulnerable patients, selective pressure from antimicrobial use, colonization pressure from larger numbers of colonized or infected patients, and hospital device implementation.[28]

Methicillin-resistant S. epidermidis far exceeds MRSA. S. epidermidis is linked to methicillin resistance more than S. aureus.[29] Since many S.aureus, S. epidermidis, and other CONS isolates are methicillin-resistant (MR), then glycopeptides are indicated for therapy.[30] However, about 10% of isolated Staphylococcus species are vancomycin-resistant. Other developing country research found similar results.[18,31]Currently, vancomycin and linezolid are effective treatments for CONS and S. aureus. The rise of Vancomycin-resistant staphylococcus (10%) worries medical professionals. hence CoNS infections must be properly diagnosed and treated.

We have found CoNS spp. are 46-67% more Cephalosporin-resistant. Previous investigations have demonstrated that antimicrobial resistance patterns resemble antibiotic usage in a hospital unit, and our NICU's substantial use of Beta-lactams and aminoglycosides may have selectively pressured commensal CoNS.[32]

Acinetobacter spp. is the second-most prevalent newborn blood stream pathogen (23.9%). In Bangladesh, Acinetobacterwas the most prevalent neonatal BSI isolate for decades. We found increased sensitivity to colistin (98%), meropenem (97%), piperacillin-tazobactum (80%), and amikacin (77.8%) (Figure 3). Many Bangladeshi and Indian investigations found similar susceptibility patterns.[9,33]Acinetobacter species in isolation are 48% MDR (cephalosporin, fluoroquinolone, and aminoglycoside), 14% meropenem (XDR), and 2.7% PDR (Colistin or Polymixin E) (Table 3)

Cefepime, ceftazidime, aztreonam, ciprofloxacin, gentamicin, and tobramycin were considered MDR, whereas amikacin, ampicillin sulbactam, imipenem meropenem, and pipeacillinTazobactum were sensitive.[34] Several reports showed that the normal flora are affected byusage of broad spectrum antibiotics and induced MDR A. baumannii.[35]

Carbapenem resistance in Acinetobacter spp. isolated from clinical samples ranged from 14-35% in Bangladesh and India.[9,35,36]The imipenem resistance of Acinetobacter spp. varied from 0 to 40% in the last decade, according to regional antibiogam data.[37] First-line carbapenem treatment for sepsis or suspected sepsis is currently given to many Bangladeshi newborns. Additionally, community-wide antibiotic usage complicates newborn sepsis treatment. As new antimicrobials become ineffective, Acinetobacter sp. are spreading fast. They gain resistance faster than Gram-negative organisms.[38] At present, the therapeutic options for infections caused by antibiotic resistant strains are limited. This suggests using antibiotics sparingly to treat Acinetobacter infections.

## Limitation of the Study

Resource restrictions prevented us from distinguishing indoor and outdoor patient samples. So we couldn't identify nosocomial from community-acquired BSI. We couldn't get patient data on clinical symptoms or any infant BSI risk variables.

## Conclusion

Our investigation identifies leading bacterial pathogens causing newborn bloodstream infections (BSI) in Dhaka city across various age groups and their antibiotic susceptibility patterns. Our data shows that CoNS are the main neonatal pathogen. CoNS strains were resistant to ampicillin, cephradine, erythromycin, or sensitive to imipenem, vancomycin, and linezolid. More Staphylococcus spp. are now resistant to methicillin and vancomycin, while Acinetobacter is resistant to third-generation cephalosporins and carbapenems, compared to a decade ago. Clinicians and policymakers should focus on this. Our results could assist healthcare personnel give better treatment to their patients and researchers and policymakers establish suitable antibiotic policies to tackle future infectious disease concerns.

## Conflict of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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