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Prevalence and Antimicrobial Resistance Pattern with Associated Gens of Extended Spectrum β- lactamase, Carbapenemases and Methicillin Resistant *Staphylococcus aureus* Producing Organisms isolated from Neonatal Sepsis in Dhaka City of Bangladesh

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Abstract

Background: Extended spectrum β-lactamase (ESBL), carbapenemases and MRSA producing organisms led to serious concern about septicaemic neonates in neonatal intensive care units (NICU) due to high resistance against commonly used antimicrobial agents. **Objective:** The purpose of the present study was to assess the prevalence and resistance pattern of ESBL, carbapenemases (MBL) and MRSA producing organisms isolated from cases of neonatal septicaemia at a tertiary care hospital Dhaka, Bangladesh. **Methodology:** This cross-sectional study was conducted in the Department of Microbiology at Dhaka Medical College, Dhaka, Bangladesh and samples were collected from the NICU of Department of Paediatrics at Dhaka Medical College Hospital, Bangladesh, from the period of July 2015 to June 2016, included neonates with suspected septicemia. Susceptibility testing was done by disc diffusion and MIC methods. All Isolates were screened for ESBL, MBL and MRSA production by phenotypic methods and genes encoding mecA, PVL among the MRSA strains, blaCTX-M-15, blaOXA-1 among phenotypically confirmed ESBLs producers and class A (KPC), class B (NDM-1, VIM, IMP), class D (OXA-48, OXA-181) carbapenemases among meropenem resistant isolates were detected by PCR. **Results:** Out of 200 neonates, 106(53%) were culture positive among them 18 (31.03%) were ESBL producers. Rate of resistance was highest for ampicillin, cephalosporins and aminoglycosides. Twelve (66.67%) ESBL producers were positive for blaCTX-M-15 and 6 (33.33%) were positive for blaOXA-1 with consensus primers. Twenty-two (56.41%) carbapenemases encoding genes were detected and all were resistant to 3rd generation cephalosporins, amoxicillin/clavulanic acid, gentamicin, cefoxitin, carbapenems and netilmycin. Fifteen (62.50%) MRSA were detected and all were mecA gene positive, 4 (26.67%) were positive for PVL gene, all MRSA were sensitive to vancomycin and linezolid. **Conclusion:** In conclusion it has found that ESBL, carbapenemase and MRSA producers in NICU are resistant to classical empirical therapy.

Keywords: antimicrobial resistance; empirical therapy; Bangladesh; neonatal sepsis

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Introduction

Neonatal sepsis is one of the major causes of morbidity and mortality among the newborns in the developing countries. It is a life-threatening clinical emergency that demands urgent diagnosis and treatment. The reported incidence of neonatal sepsis per 1000 live births varies from 7.1 to 38 in Asia, 6.5 to 23 in Africa and 3.5 to 8.9 in South America and the Caribbean[1]. Currently, neonatal mortality rate in Bangladesh is 23.30 per 1000 live births[2]. In rural Bangladesh, sepsis/meningitis constituted 12.0% of

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direct causes of neonatal deaths[3]. In Dhaka slums sepsis as a direct cause of neonatal deaths in 20.0% cases[4].

The emergence of ESBL producing strains derived from mutation in TEM and SHV enzymes, which are present in 75.0% of enterobacteriaceae isolates, is documented[5]. ESBLs are more prevalent in *Klebsiella spp* than any other enterobacterial species and outbreaks of infection caused by ESBL producing *Klebsiella spp* have been widely reported[6-9]. Carbapenemases are considered the most versatile family of β-lactamases with a very broad spectrum of activity. Many of the carbapenemases are able to hydrolyze the full spectrum of β-lactam antibiotics which include the penicillin, cephalosporins, carbapenems and monobactams and can also display inhibitor resistance to commercially available β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam[10-11]. The global emergence of MRSA is a significant challenge for public health. In 1993, MRSA isolates were reported in a small population in Australia for the first time[12]. Since then, infections with similar isolates were reported throughout the country and the isolates had multiple antibiotic resistances[13].

No systematic study has yet been done in NICU of DMCH regarding phenotypic and genotypic detection of different drug-resistant bacteria. To treat neonatal sepsis patients in NICU of DMCH, ampicillin plus aminoglycosides (amikacin/gentamicin) or 3rd generation cephalosporins plus aminoglycosides were being used as empirical therapy. *Candida* infections were not being considered. Neonatal mortality rate in NICU of DMCH among the admitted patients was around 27.0% cases. The present study was conducted to know the incidence of ESBL, carbapenemases (MBL) and MRSA productions among clinical isolates in neonatal sepsis, to assess drug resistance pattern with their association of different drug resistance genes and to see the efficacy of the currently used empirical therapy.

Methodology

Study Settings and Population: This cross-sectional study was conducted in the Department of Microbiology at Dhaka Medical College, Dhaka, Bangladesh and samples were collected from the NICU of Department of Paediatrics at Dhaka Medical College Hospital, Bangladesh, from the period of July 2015 to June 2016, included neonates with suspected septicemia after obtaining due approval from the institutional ethics committee. After proper explanation regarding the nature of the study written consent were taken from legal guardian of neonates.

Study Procedure: After taking proper history 200 blood samples were collected from suspected septicemic neonates. With all aseptic precaution, a single sample of blood was collected (1 to 2 ml) and inoculated into the BACTEC PEDS PLUS vial, incubated in system's incubator at 370 C under aerobic condition for 7 days. After 24 hours, a small volume of blood was aspirated from vial with the help of disposable syringe, blind sub-cultured on MacConkey agar, blood agar and chocolate agar Medias and incubated at 37°C for 24 hours. If no growth was obtained, the bottles were examined daily for 7 days. Any sign of growth was followed by subculture and identified by Gram staining. Gram negative rods were identified by relevant biochemical test[14]. Following CLSI guidelines, antimicrobial susceptibility test was performed by disk diffusion technique using commercially available antibiotic disks (Oxoid Ltd, Basingstoke, UK)[15]. Relevant ATCC strains were used as controls wherever necessary. Phenotypic detection of ESBL producers by Double disk synergy (DDS) test[16].

Phenotypic detection of MBL producers: MBL producers were phenotypically detected by Double-disk synergy tests (DDS)[17] and combined disk (CD) assay[18].

Detection of Methicillin resistant *Staphylococcus aureus* (MRSA): All *Staphylococcus aureus* isolates were screened for methicillin resistance by standard disc diffusion method as per CLSI standard using cefoxitin (30 µg) discs[14]. Disc method was compared with oxacillin minimum inhibitory concentration (MIC). MIC of oxacillin was ≥ 4 µg/ml was reported as MRSA.

Molecular characterization of ESBL, MBL and MRSA producers: Identification of ESBLs encoding genes (blaCTX-M-15 and blaOXA-1) among phenotypically confirmed ESBLs producers and the presence of class A (KPC), class B (NDM-1, VIM, IMP), class D (OXA-48, OXA-181) carbapenemases among imipenem resistant isolates was detected by PCR. MecA and PVL genes were also identified among the MRSA strains by PCR. Bacterial DNA was extracted by the boiling method[19].

They following pairs of previously used primers were used to yield PCR products: for CTX-M-15-CACACGTGGAATTTAGGGACT (forward), GCCGTCTAAGGCGATAAACA (reverse), for OXA-

ACCAGATTCCAACTTTCAA (forward), TCTTGGCTTTTATGCTTG (reverse), for NDM1- GGTTTGGCGATCTGGTTTTC (forward), CGGAATGGCTCATCACGATC (reverse), for KPC- CGTCTAGTTCTGCTGTCTTG (forward), CTTGTCATCCTTGTTAGGCG (reverse), for OXA-181- ATGCGTGTATTAGCCTTATCG (forward), AACTACAAGCGCATCGAGCA (reverse), for OXA-48- GCGTGGTTAAGGATGAACAC (forward), CATCAAGTTCAACCCAACCG (reverse), for IMP - GGAATAGAGTGGCTTAAYTCTC (forward), CCAAACYACTASGTTATCT (reverse), for VIM- GATGGTGTTTGGTCGCATA (forward), CGAATGCGCAGCACCAG (reverse), for mecA- AAAATCGATGGTAAAGGTTGGC (forward), AGTTCTGCAGTACCGGATTTTGC (reverse), for PVL- ATCATTAGGTAAAAATGTCTGGACATGA TCCA (forward), GCATCAASTGTATTGGATAGC AAAAGC (reverse).

The following cycling parameters were used: PCR reaction consisted of preheat at 94°C for 10 minutes followed by 36 cycles of denaturation at 940 C for 30 seconds, annealing at 52°C for 40 seconds, extension at 72°C for one minute with a final extension at 72°C for 10 minutes. Annealing temperature varies with GC contents of primers. The amplified DNA were loaded into a 1.5% agarosegel, electrophoresed at 100 volts for 35 minutes, stained with 1% ethidium bromide, and visualized under UV light. Neonatal morbidity and mortality were reviewed every month during study period and empirical therapy was changed based on study findings.

Statistical Analysis: Statistical analysis was performed by Windows based software named as Statistical Package for Social Science (SPSS), versions 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data were expressed as mean, standard deviation, minimum and maximum. Categorical data were summarized in terms of frequency counts and percentages.

Ethical Consideration: All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration 2013) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was granted by the local ethics committee. Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and were analyzed using the coding system.

Results

A total number of 200 clinically suspected neonatal sepsis cases were studied during the period among them 106(53.0%), shows blood culture positive. Fifty-eight neonates had Gram-negative and 30 isolates had Gram-positive septicemia. Among the Gram-negative isolates, *Klebsiella pneumoniae* (25.0%) was commonest organisms isolated followed by *Acinetobacter baumannii* (17.0%), *Escherichia coli* (8.0%) and *Pseudomonas aeruginosa* (4.0%) (Table 1).

Table 2: Gender Distribution of the Study Population (n=115)

Antimicrobial drugs	***Klebsiella pneumoniae* N=9 (%)**	***Acinetobacter baumannii* N=3 (%)**	***Esch. coli* N=3 (%)**	***Pseudomonas aeruginosa* N=3 (%)**	**Total N=18 (%)**
Ampicillin	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Amikacin	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Amoxyclav	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Ceftazidime	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Ceftriaxone	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Cefotaxime	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Ciprofloxacin	7 (77.77)	3 (100.00)	2 (66.66)	3 (100.00)	15 (83.33)
Colistin	1 (11.11)	2 (66.67)	0 (0.00)	2 (66.66)	5 (27.77)
Clindamycin	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Cefepime	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Gentamicin	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Meropenem	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Netilmycin	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)
Piperacillin with Tazobactum	9 (100.00)	3 (100.00)	3 (100.00)	3 (100.00)	18 (100.00)

N- Total number of bacteria

All the ESBL producers were resistant to penicillin's, 2nd, 3rd and 4th generation cephalosporins and aminoglycosides, 27.77% to colistin but all were sensitive to carbapenems. All the carbapenemase producers were resistant to commonly used antibiotics including carbapenems and 9.09% were resistant to colistin. Eighty-three percent gram positive isolates were resistant to ampicillin and 80% resistant to ceftriaxone, gentamicin and teicoplanin. All are sensitive to vancomycin and linezolid (Table 2).

Table 2: ESBLs encoding genes among various species of phenotypically isolated ESBL producers (N=18)

Gram negative bacteria	blaCTX-M-15 (%)	blaOXA-1(%)
Klebsiella pneumoniae (N=9)	6 (66.67)	3 (33.33)
Acinetobacter baumannii (N=3)	1 (33.33)	1 (33.33)
Esch. coli (N=3)	3 (100.00)	2 (66.67)
Pseudomonas aeruginosa (N=3)	2 (66.67)	0 (0.00)
Total	**12 (66.67)**	**6 (33.33)**

Among the isolated 58 gram negative bacteria, 18 (31.03%) were ESBL producers detected by DDS test. Twelve (66.67%) ESBL producers were positive for blaCTX-M-15 and 6 (33.33%) were positive for blaOXA-1. Among 39 meropenem resistant strains, 18 (46.15%) carbapenemase producers were detected by DDS test, 20 (51.28%) by CD assay and 22 (56.41%) by PCR. Out of 39 meropenem resistant strains 12 (30.77%) were positive for blaKPC, 9 (23.08%) were blaOXA-48/blaOXA-181, 8 (20.51%) were blaNDM-1, 7 (17.95%) were blaVIM and 6 (15.38%) were positive for blaIMP genes respectively (Table 3).

Out of 24 *Staphylococcus aureus*, 16 (66.67%) MRSA were identified by cefoxitin (30 µg) disc diffusion method and 15 (62.50%) MRSA were detected by MIC of oxacillin (MIC ≥ 256 µg/ml). All the 15 MRSA were mecA gene (62.50%) positive and 4 (26.67%) were PVL gene positive by PCR. No VRSA was detected and none were positive for vanA and vanB genes. Month to month analysis showed that mortality rate in NICU of DMCH was dropped 20% from 27% after changing empirical therapy based on the study findings.

Discussion

Neonatal sepsis is a major contributor to neonatal mortality and has to be addressed seriously. Blood culture positivity in our study was 53.0% compared to (45.9%) in Nigeria, (52.6%) in India and (54%) in Egypt[20-22]. Overcrowding in NICU of DMCH, inappropriate infection control protocol and high patient to healthcare provider ratio may be contributing factors for high isolation rate of the present study.

The present study identified 31.0% ESBL producer. Previously 8% to 27.85% ESBL producers were reported among neonatal sepsis cases from India and Bangladesh[23-24]. The reports from different studies are indicative of the fact that ESBL producers vary greatly geographically and rapidly changing over time.

Table 3: Antimicrobial drug resistance pattern among different species of carbapenemase producers (N=22).

Antimicrobial drugs	*Klebsiella pneumoniae* (N=12) n (%)	*Acinetobacter baumannii* (N=9) n (%)	*Esch. coli* (N=1) n (%)	Total (N=22)n (%)
Ampicillin	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Amikacin	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Amoxyclav	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Ceftazidime	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Ceftriaxone	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Cefotaxime	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Ciprofloxacin	10 (83.33)	9 (100.00)	1 (100.00)	20 (90.90)
Colistin	1 (8.33)	1 (11.11)	0 (0.00)	2 (9.09)
Clindamycin	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Cefoxitin	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Cefepime	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Gentamicin	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Meropenem	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Netilmycin	12 (100.00)	9 (100.00)	1 (100.00)	22 (100.00)
Piperacillin with Tazobactum	9 (75.00)	8 (88.89)	1 (100.00)	18 (81.82)

Widespread use of 3rd generation cephalosporins as a first- line antibiotics may be major cause of the mutations in TEM and SHV enzymes that led to the emergence of the ESBLs[25].

Present study found 12 (66.67%) blaCTX-M-15 and 6 (33.33%) blaOXA-1 producers among 18 ESBL producers which were not previously reported from neonatal sepsis cases in DMCH. The high prevalence (100.0%) of CTX-M-15 type ESBL among Escherichia coli identified in the present study reflect the global trend toward a pandemic spread of blaCTX-M-15 type ESBL in *Escherichia coli*.

Carbapenems are used to treat ESBL producing bacteria, and colistin is used to treat carbapenems resistant bacteria in our NICU. But in this study, 27.8% of the ESBLs and 9.1% of the carbapenemase producers were resistant to colistin respectively which is alarming as we have no other reserve drugs at this moment to control these infections.

In this study we found 56.4% carbapenemase producers among meropenem resistant bacteria. Carbapenemase encoding genes are commonly found in Pseudomonas spp. and Acinetobacter spp., the presence of carbapenemase encoding genes in the species of *K. pneumoniae* and *E. coli* in our study suggests that plasmid-mediated horizontal transfer of the carbapenemase genes continuously occurs among gram-negative bacilli, as reported previously[26]. Like ESBL genes, so far there are no reports of carbapenemase genes positive isolates among neonatal sepsis cases in DMCH. The findings of the present study indicated dissemination of carbapenemase carrying organisms in Bangladesh.

In the NICU, proportion of MRSA among the isolated *Staph. aureus* has been increased to 62.50% in 2015, from 34.09% in 2013, isolated from postoperative wound infected patients[27]. The reasons behind the high isolation rate of MRSA might be due to the fact that MRSA infection control policy is not adequate in NICU. Also healthcare associated transmission and colonization in NICU may lead to high isolation rate of MRSA in our study.

The high incidence of ESBLs, MBLs and MRSA in our study among the isolated organisms highlights the emerging therapeutic challenge in NICU of Bangladesh. Based on present study, to treat seriously ill neonatal sepsis patients, vancomycin or linezolid for gram positive cocci and colistin for gram negative bacilli may be included in empirical therapy in NICU of DMCH. The outcome of this study will definitely help to obtain SDG for Bangladesh.

Conclusions

The purpose of the present studsy was to assess the prevalence and resistance pattern of ESBL, carbapenamases (MBL) and MRSA producing organisms isolated from cases of neonatal septicaemia at a tertiary care hospital Dhaka, Bangladesh. Regular surveillance of ESBL, carbapenemase producers, MRSA and VRSA should be undertaken periodically to recognize the accurate prevalence of these organisms and to treat them accordingly. Policy makers should focus on emergence of antimicrobial resistant strain of bacteria and formulate a strict antibiotic prescription policy, which would aware the practitioners and care givers to make a prudent use of antibiotics.

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Conflict of Interest

There are no any potential conflicts of interest; this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Authors' contributions

Rahman MA, Uddin BMM conceived and designed the study, analyzed the data, interpreted the results, and wrote up the draft manuscript. Uddin BMM, Ratan ZA contributed to the analysis of the data, interpretation of the results and critically reviewing the manuscript. Ratan ZA, Salman MN, Yeasmin MM, Mahjabin M involved in the manuscript review and editing. Rahman MA as collector of Data and Data Analyst. All authors read and approved the final manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

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