

Prevalence and Phenotypic Detection of Carbapenem-Resistant *Enterobacter* Species from the Clinical Specimens of a Tertiary Care Hospital in Bangladesh

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ABSTRACT:

Background: Carbapenem-resistant *Enterobacter* (CRE) is an emerging threat spread rapidly around the world in the past few years, posing substantial hazards to human health. **Objective:** The study was conducted to evaluate the prevalence of carbapenem resistance and to detect carbapenemase producers phenotypically from patients of a major tertiary care hospital, in Bangladesh. **Methods:** Prospective cross-sectional study was conducted from July 2018 to June 2019, at the Dhaka Medical College hospital. Patients admitted to different wards, and intensive care units, visited the outpatient department, and samples received in the microbiology department were included in this study. A total of 350 clinical samples were collected, inoculated, and incubated in accordance to the standard protocol. Identification was done using the standard biochemical method. Antimicrobial susceptibility testing of commonly used antibiotics including imipenem was done using Kirby Bauer disk diffusion method. All the clinical isolates of *Enterobacter* were screened for carbapenem resistance as per CLSI guidelines. Such strains were then subjected to phenotypic confirmation of carbapenemase production by the Modified Hodge test. All isolates that gave a positive screening test were further evaluated for Metallo- β lactamase (MBL) production. MBL was further detected by Combined Disc Test (CD) using a combination of Imipenem and Imipenem-EDTA and double disc synergy (DDS) test. **Result:** A total of 350 clinical specimens were analyzed, of which 224 (65.14%) isolates yielded growth. Among them, 28 (12.28%) *Enterobacter* were isolated of which 12 (42.86%) were found to be Imipenem resistant (14.25%) and were labeled "Carbapenem-resistant *Enterobacter*" or CRE. Minimum inhibitory concentration (MIC) was determined among the carbapenem-resistant clinical isolates. Modified Hodge test (MHT) performed on the 12 carbapenem-resistant isolates showed 9 (75%) isolates to be carbapenemase enzyme producers. Nine out of twelve carbapenem-resistant isolates are Metallo-beta-lactamase producers detected by combined disc test (CDT) and eight (66.67%) MBL producers detected by DDS test. **Conclusion:** The finding from this study revealed a high prevalence of carbapenem resistance among isolated *Enterobacter* species in hospital settings as well as community levels. As there are limited treatment regimens, therefore, the timely and accurate detection of carbapenem-resistant *Enterobacter* species is essential for the clinical treatment and prevention of infections. Simple phenotypic methods like MHT can be used for the rapid detection of carbapenemases, and these are expected to be used routinely in clinical microbiology laboratories.

KEYWORDS: Carbapenem resistance, Carbapenemases, Prevalence, Modified Hodge test, *Enterobacter*.

INTRODUCTION

Infections caused by multidrug-resistant (MDR) Gram-negative bacteria (GNB) have become major challenges for global health institutions because of the limited antibiotic options and high mortality rates in recent years (1-4). Carbapenems are considered last-resort antibiotics for the treatment of infections caused by multidrug-resistant Gram-negative bacteria. (5). With the increasing use of carbapenems in clinical settings, the emergence of carbapenem-resistant pathogens becomes a grave threat to public health. Carbapenem-resistant *Enterobacteriaceae* (CRE) are among the top tier of the WHO list of antibiotic-resistant "priority pathogens" that pose the greatest threat to human health (6). The genus *Enterobacter* is a re-emerging pathogen associated with hospital-acquired infection that has been ranked as the third most frequent isolate following *Escherichia coli* and

Klebsiella species (7) and is increasingly associated with multidrug resistance, including the resistance to the last-resort carbapenems (8). *Enterobacter spp.* is the second most common carbapenem-resistant *Enterobacteriaceae* (CRE) in the United States (9). The emergence of carbapenem-resistant *Enterobacter* including other members of *Enterobacteriaceae* (CRE) has become a serious issue both in community-acquired infections and healthcare-associated infections (10).

Carbapenems are β -lactam antibiotics, that bind to PBP 1 and PBP 2 of gram-negative and gram-positive bacteria, causing cell elongation and lysis (11). Bacterial resistance arises from the production of carbapenemases, which hydrolyse the carbapenem nucleus and alteration of the porin channels in the bacterial cell wall, reducing the permeability of the drugs (12). The carbapenem non-susceptible phenotypes are attributed to the production of carbapenemases or more likely, the production of extended-spectrum β -lactamase (ESBL) plus AmpC β -lactamase with dysfunctional entry routes (i.e. porin change) of carbapenems or efflux pumps etc (13). The vast majority of acquired carbapenemases belong to three of the four known classes of β -lactamases, which include class A, B, and D. Class A and D which include serine at their active site are considered serine carbapenemases, whereas class B contains metallo-carbapenemases with zinc on its active site (14-15). Therefore, it is no surprise that the carbapenem-resistant *Enterobacter* species is a part of the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), which are considered as the most concerning for the healthcare institution worldwide (16-17).

To date, the treatment options for CRE infections remain very limited. So, strict infection control measures including active surveillance for the timely detection of colonized patients are very important. Detection of carbapenems is a crucial infection control issue because they are frequently associated with extensive antibiotic resistance and treatment failures. The modified Hodge test (MHT) has been extensively used as a phenotypic method for the detection of carbapenems activity. The test is sensitive for the detection of a carbapenems-mediated mechanism of resistance to carbapenems (18).

In the current scenario, when there is an emergence of carbapenem resistance all over the world, this study was undertaken to detect carbapenem resistance phenotypically among clinical isolates of *Enterobacter* species in a major tertiary care hospital of Bangladesh as the pattern of carbapenem resistance among bacteria varies from hospital to hospital and within different geographical location. This knowledge will help to guide the selection of appropriate empirical treatments at a local level and will provide a benchmark for comparison at other sites.

METHODS:

This cross-sectional study was conducted in the Department of Microbiology of Dhaka Medical College over a period 12 months from July 2018 to June 2019. Ethical clearance was obtained from Institutional Review Committee (IRC).

A total of 350 isolates obtained from various clinical samples: wound swabs and pus, blood, urine, and endotracheal aspirates received in the microbiology laboratory from IPD and OPD were included in this study. Identification and characterization of isolates were performed on the basis of Gram staining, microscopic characteristics, colony characteristic, and biochemical tests using standard microbiological methods.

Antimicrobial sensitivity testing was performed on Muller-Hinton agar plates with commercially available disks (Oxoid) by Kirby Bauer disk diffusion method and interpreted as per CLSI guidelines. All the clinical isolates of *Enterobacter* species were screened for carbapenem resistance using imipenem as the representative member of the carbapenem group of drugs, as per initial screening test recommendations of the CLSI guidelines, 2018. To simplify the results, bacterial isolates showing intermediate-resistant were also classified as resistant strains in this study. The MIC of all carbapenem-resistant *Enterobacter* isolates was determined by the agar dilution method. Such isolates were then subjected to phenotypic confirmation of carbapenemase production by the modified Hodge test (MHT). MHT was performed on Mueller Hinton Agar plates, in accordance with CLSI guidelines. When the test isolate produces the enzyme and allows the growth of the carbapenems susceptible strain (*E.coli* ATCC 25922) towards carbapenems the disc. The result is a characteristic cloverleaf-like indentation. The results were read and interpreted as per CLSI recommendations, 2018 (18).

The modified Hodge test (MHT) was performed on the 12 carbapenem-resistant isolates in this study. In MHT, a lawn culture of 1:10 dilution of 0.5 McFarland standard *Escherichia coli* ATCC 25922 broths were done on a Mueller-Hinton agar plate. Then 0.5 McFarland standard bacterial suspensions were made by 3 imipenem-resistant *Enterobacter* species and streaked from the edge of the disc to the periphery of the plate in 3 different directions. After overnight incubation, the plate was observed for the presence of a clover leaf-shaped zone of inhibition and the plates with such zones were interpreted as MHT positive. All isolates that gave a positive screening test were further evaluated for Metallo- β -lactamase production. The technique used was the combined disk test (CD) using a combination of imipenem and imipenem-EDTA on Mueller-Hinton agar plate and a double disc synergy test. For the CD assay, two imipenem discs were placed on the inoculated Mueller-Hinton agar plate. One imipenem disc was supplemented with 5 μ l of 0.5 M EDTA solution (containing

approximately 750 µg EDTA) and incubated overnight at 37°C. An increased zone of a diameter of ≥ 6 mm around the disc containing imipenem supplemented with EDTA compared to the disc containing imipenem only was interpreted as MBL production (19). For the DDS test, an imipenem disc(10µg) and a blank disc containing 20µl of Tris EDTA (0.1 M Tris HCL, 0.1M EDTA, pH approximately 8.0) and 20µl of 1:320 diluted 2-mercaptoprppionic acid (MPA) were placed 20 mm apart (center to center) in an inoculated Mueller-Hinton agar plate and incubated at 37°C for 24 hours. A clear extension of the edge of the inhibition zone of the imipenem disc towards the Tris-EDTA-MPA disc was interpreted as MBL production. (20).

RESULTS:

A total of 350 specimens were collected from different wards, ICU, and samples were received in the microbiology laboratory of Dhaka medical college for aerobic bacterial culture and antimicrobial susceptibility during the study period. These comprised 124 consecutive clinical samples of urine, 113 consecutive clinical samples of wound swabs and pus, 58 samples of endotracheal aspirates, and 55 samples of blood. Of the total 350 specimens, 122 (34.86%) did not yield any growth on aerobic bacterial culture. Of the remaining 228 (65.14%) samples that did show growth of which 28 (12.28%) were *Enterobacter species*.

In the present study, by disk diffusion method, from 28 isolated *Enterobacter* strains, 12 (42.86%) were found resistant to imipenem. Isolates susceptible to imipenem were excluded. Thus, all carbapenem-resistant *Enterobacter* isolates were tentatively considered carbapenemase producers as well. In the current study, resistance to imipenem was found in all age groups and in both sexes. But resistance to imipenem is seen less in pediatric and geriatric populations compared to others (Figure I).

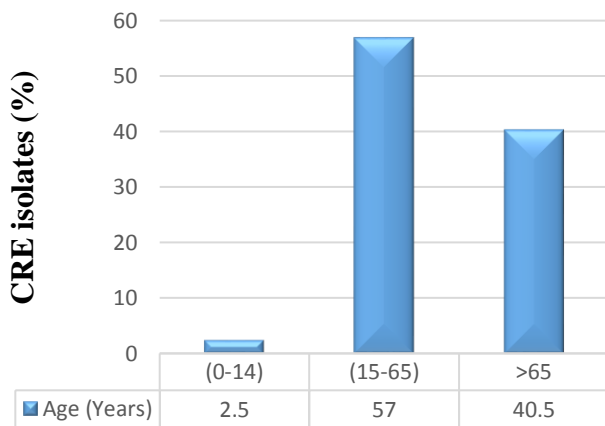


Figure I: Age-wise distribution of carbapenem-resistant *Enterobacter* isolates.

Carbapenem-resistant *Enterobacter species* was isolated from both nosocomial and community-acquired infection; although the nosocomial mode of dissemination seems to be high (75% from IPD and 25 % from OPD) in the present study. (Figure II)

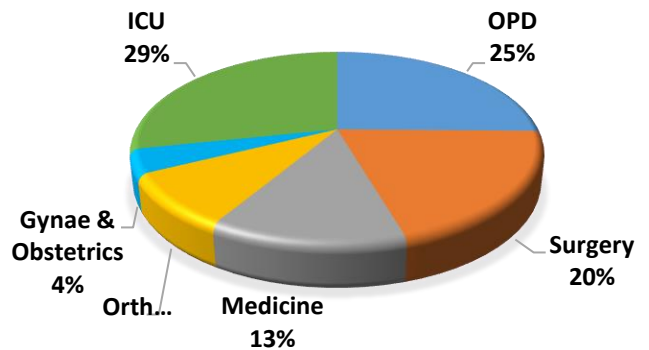


Figure II: Ward-wise distribution of samples.

A maximum number of imipenem-resistant isolates were obtained from urine sample 5 (41.67%) followed by wound swabs and pus 4 (33.33%) (Figure III).

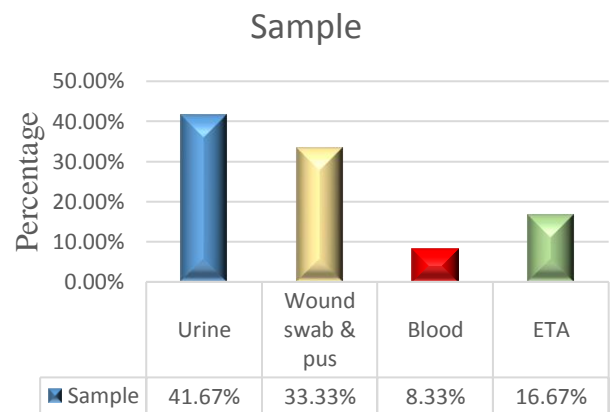


Figure III: Sample-wise distribution of carbapenem-resistant *Enterobacter* isolates *ETA-Endotracheal aspirates

Among 12 isolates tested, 9 (75%) isolates showed MIC values ranging from 32 µg/ml to 64 µg/ml for imipenem as per CLSI guidelines. Three, out of 12 isolates tested, showed MIC values below 8 µg/ml. In addition, the rate of resistance to cephalosporin was relatively high. Specifically, 100%, 97.8%, and 85.9% of isolates were resistant to ceftriaxone, ceftazidime, and cefoxitin respectively.

Modified Hodge test (MHT) was performed on the 12 imipenem-resistant isolates. After 24 hours of incubation, the plate was examined for a clover leaf-type indentation at the intersection of the test organism and the *E. coli* ATCC 25922, within the zone of inhibition of the carbapenem disc. The presence of indentation or 'cloverleaf pattern' in the growth of *E. coli* ATCC 25922 around the test strain within the disc diffusion zone was regarded as a carbapenemase producer. 9

(75%) isolates came out to be carbapenemase enzyme producers while 3 (25%) gave a negative result. Combined disc test (CDT) was conducted on the 12 isolates of CRE. The technique used was the combined disk test using a combination of imipenem and imipenem-EDTA on Mueller-Hinton agar plates. CDT and DDS tests detected Metallo- β lactamase (MBL) enzyme production in 9 (75%) isolates and 8 (66.67%) isolates respectively. (Table I).

Table I: Phenotypic detection of carbapenemase producers among carbapenem-resistant *Enterobacter* isolates (N=12).

Total no. of isolates (N)	MHT		CDT		DDS	
	Positive	Negative	Positive	Negative	Positive	Negative
12	9 (75%)	3 (25%)	9 (75%)	3 (25%)	8 (66.67%)	4 (33.33%)

*MHT-Modified hodge test; CDT- Combined disc test; DDS- Double disc synergy

DISCUSSION:

Currently, the major threat of antibiotic-resistant bacteria is from MDR Gram-negative organisms, particularly those which have developed resistance to carbapenem. The global spread of carbapenem-producing organisms is a major concern in antimicrobial resistance (AMR) issues. Bangladesh is a developing south Asian country which is known to have a high prevalence of carbapenem-resistant organisms (21). *Enterobacter* species, a member of Enterobacteriaceae has been identified as an important pathogen causing many types of hospital-acquired infections (HAIs) (22). Carbapenem-resistant *Enterobacter* can cause severe health complications, especially in some risk groups such as the elderly, immunocompromised patients, diabetic patients, burned or multiply traumatized patients, and patients who are undergoing immunosuppressive therapy (23) In this study, we provided data on the prevalence of carbapenem resistance and their phenotypic detection among clinical isolates of *Enterobacter species* collected from a major tertiary care hospital, in Bangladesh.

According to the CLSI document, carbapenemase-producing isolates usually test intermediate or resistant to one or more carbapenems on susceptibility is the most sensitive indicator of carbapenems production. The present study revealed that 42.68% (12/28) of *Enterobacter species* were carbapenem-resistant. Patidar et al observed, 47% of *Enterobacter* were carbapenem-resistant in a study in India which is in accordance with our findings (24). Although our finding is lower than a study by Mashaly who reported carbapenem-resistance among Egyptian patients was 53% (25). This prevalence is also consistent with recent reports of surveillance studies of

carbapenem resistance among patients with HAI caused by Gram-negative bacteria in Egypt (54.1%) (26) and in India (53.84%) (27). Imipenem resistance among the species varies widely in different parts of the world. A study in India suggested CRE is mainly observed among *Enterobacter species*, *E. coli*, and *Klebsiella species* (24).

The current study observed most carbapenem-resistant isolates were obtained from admitted patients of different wards and ICU rather than outdoor patients which are in accordance with other studies. A study by Nair and Vaz reported most of the CRE isolates were detected from admitted patients (42%) and the ICU (26%) followed by OPD (32%) (28). A similar finding was also observed by Chauhan et al (29).

On sample-wise distribution, a maximum number of carbapenem-resistant *Enterobacter* was isolated from urine sample 5 (41.67%) followed by wound swab and pus 4 (33.33%) which is slightly higher than a study conducted in India which showed the highest number of CRE was urine sample 29 (26.36%) followed by pus 27 (24.54%), blood 22 (20%) (30). In a comparable study in north India, most of the carbapenem-resistant organism was isolated from urine 47.1% (n=20) followed by pus 27.1% (n=13) (31). In another study Mohamudha RP et al, also found that the distributions of the sources of the isolates were: urine 37% (n=39), blood 22.3% (n=23), wound discharge 11.7% (n=12) (32)

In the current study among 12 carbapenem-resistant isolates tested, 9 (75%) MIC values ranged from 32 μ g/ml to 64 μ g/ml. Three, out of 12 isolates tested, showed MIC values below 8 μ g/ml which is in accordance with a study in India which showed 68.57% carbapenem-resistant *Enterobacter* isolates had MIC values of 32 μ g/ml to 64 μ g/ml (27).

In our study, 75% of carbapenem-resistant strains tested positive with the Modified Hodge test (Cloverleaf indentation) using 10 μ g Ertapenem discs as per CLSI guidelines. Our finding is in line with the studies reported from India in which 81.81% of carbapenem-resistant strains tested positive for MHT (30). Similar findings were observed in other studies, where 71.93% of carbapenem-resistant strains tested positive for MHT (29). Although Khajuria showed 54.29% carbapenems were detected by MHT among resistant *Enterobacter species* (27). The MHT is probably the most well-known approach for carbapenemase detection proposed by the clinical and laboratory standards institute (CLSI) for phenotypic screening of carbapenemases producers but diverse specificity values have been reported by authors, so should be aware of false-positive results (18).

In our study, we used the Combined Disc Test (CDT) and DDS test to detect Metallo- β -lactamase (MBL) enzyme production among 12 carbapenem-resistant isolates. We found 9 (75%) isolates to be MBL producers which are in accordance with the study by Chauhan at a tertiary care hospital in India, 68.42% of CRE were MBL producers (29). Another study by Khajuria showed 55.71% of carbapenem-resistant *Enterobacter* were MBL producers. In the present study, the DDS test detects 66.67% of MBL producers which is similar to a study in India where they found 60% of MBL producers were detected by the DDS test (27).

CONCLUSION:

Carbapenem-resistant *Enterobacteriaceae* (CRE) has dramatically increased and become a serious public threat due to the wide use of carbapenem in clinical practice in the last decades. Carbapenem-resistant *Enterobacter* species appeared as a worrying resistant ICU bug in recent years. Therefore, constant monitoring is important to check the prevalence of resistance to carbapenem in Gram-negative organisms. Although molecular techniques are regarded as the most appropriate method for the detection of carbapenem resistance, it seems quite impractical in a routine diagnostic laboratory setup due to the availability of a molecular setup. The MHT is one of the simplest techniques can be used to detect carbapenems activity. Intensive surveillance and effective control measures should be taken to reduce the spread of carbapenem resistance among *Enterobacter* in hospital settings as well as community levels.

CONFLICT OF INTEREST:

The authors declares that there is no conflict of interest regarding the publication of this article.

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