JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Detection and characterization of carbapenemase-producing *Enterobacteriaceae* in cancer patients: first Sri Lankan report of blaVIM in *Enterobacteriaceae*

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Abstract

Background: Carbapenem-resistant *Enterobacteriaceae* (CRE) are an important cause of infections in cancer patients. The proportion of carbapenem resistance and the types of carbapenemase-encoding genes in *Enterobacteriaceae* isolated from cancer patients were determined in this study.

Methodology: Bacteria isolated from adult, in-ward cancer patients with lower respiratory tract infections (LRTI), skin and soft tissue infections (SSTI), or urinary tract infections (UTI) were included in the study. *Enterobacteriaceae* were identified up to the species level by API® 20E test kits. Carbapenem resistance was defined as non-susceptibility to either imipenem or meropenem in the disc diffusion test. Major carbapenemase-encoding genes (*bla*KPC, *bla*NDM, *bla*OXA-48, *bla*IMP, and *bla*VIM) were detected by the GeneXpert® Carba-R real-time PCR instrument.

Results: *Enterobacteriaceae* comprised 57% (94/165) of the bacterial isolates. Carbapenem resistance among *Enterobacteriaceae* was 46.8% (44/94). *Klebsiella pneumoniae* (65.9%, 29/44) was the predominant CRE isolate followed by *Escherichia coli* (25%, 11/44). The majority of CRE isolates (72.7%, 32/44) had a meropenem MIC of ≥ 32 µg/mL. Carbapenemase-encoding genes were identified in 43 of the 44 CRE isolates. *bla*NDM was the most prevalent carbapenemase-encoding gene and was detected in 67.4% (29/43) of *Enterobacteriaceae* isolates. No isolate was positive for *bla*IMP. Sixteen (37.2%) isolates co-harbored more than one carbapenemase-encoding gene. Two *Enterobacteriaceae* isolates were found to harbor *bla*VIM.

Conclusions: Nearly all CRE isolated in this study were carbapenemase producers. This study documented the emergence of *bla*VIM harboring *Enterobacteriaceae* for the first time in Sri Lanka.

Key words: Carbapenem-resistant Enterobacteriaceae (CRE); cancer patient; carbapenemase-encoding gene.

J Infect Dev Ctries 2024; 18(11):1715-1720. doi:10.3855/jidc.19499

(Received 02 November 2023 – Accepted 19 March 2024)

Introduction

Cancer patients are more vulnerable to severe infections due to the suppression of their immune defenses from various treatment approaches, notably cytotoxic chemotherapy, and hematopoietic stem-cell transplantation. Antibiotic therapy plays a vital role in ensuring the survival of these patients. Antibiotic resistance has emerged as a major concern among cancer patients. As a result of drug-resistant infections occurring in immunosuppressed cancer patients, nearly 50% of oncologists surveyed in the UK predicted that chemotherapy as a cancer treatment would soon be unavailable [1]. Extended-spectrum β-lactamase (ESBL) producing and carbapenem-resistant *Enterobacteriaceae* (CRE) have emerged as the most important Gram-negative bacteria responsible for antibiotic-resistant infections in cancer patients [2]. Several studies revealed poor outcomes/survival rates for patients with malignancies who were colonized with CRE [3]. The prevalence of carbapenem-resistant Gram-negative bacilli among cancer patients has increased by nearly six-fold in the last decade [4].

In *Enterobacteriaceae*, carbapenem resistance is primarily mediated through two main mechanisms. The first mechanism involves acquiring carbapenemase genes, which encode enzymes capable of breaking down carbapenems. The second mechanism entails compromised outer membrane permeability due to porin loss, combined with the increased expression of cephalosporinases like AmpC [5]. Carbapenemase-

encoding genes are commonly located on transferrable plasmids, enabling high mobility of the resistance genotype leading to rapid spread among different bacterial species. In contrast, carbapenem resistance mediated by porin loss spreads by clonal expansion as it is encoded in the bacterial chromosomes [6]. Carbapenemase-nonproducing carbapenem-resistant bacterial isolates are regarded as considerably less significant from a public health standpoint compared to carbapenemase producers. At present, the biggest challenge related to antibiotic resistance in *Enterobacteriaceae* is the rapid dissemination of carbapenemase-producing strains [7].

Carbapenemase-producing *Enterobacteriaceae* (CP-CRE) is highly transmissible and more likely to trigger outbreaks compared to non-CP-CRE [8]. Therefore, an intensive infection control approach is necessary to contain the dissemination of CP-CRE. Further, CP-CRE were found to be more virulent than non-CP-CRE and were associated with poorer clinical outcomes [9]. Prompt identification of the carbapenemase type can help to guide antibiotic therapy as the susceptibility of some antibiotics may slightly vary against different carbapenemase types. *Enterobacteriaceae* harboring class B and D carbapenemases are susceptible to aztreonam, while strains producing class A carbapenemases are resistant [10]. Newer antibiotic agents such as ceftazidime-avibactam and meropenem-varbobactam have activity against the majority of KPC and OXA-48-like carbapenemase producers, but not against metallo-β-lactamases such as NDM [11,12]. In this regard, the differentiation of CP-CRE and non-CP-CRE as well as the identification of carbapenemase types are of utmost importance.

The molecular epidemiology of CRE infections in Sri Lanka is largely unexplored, particularly in vulnerable patient populations such as cancer patients. This study aimed to ascertain the proportion of carbapenem resistance and identify the types of carbapenemase-encoding genes present in *Enterobacteriaceae* isolates obtained from cancer patients at the largest cancer treatment facility in Sri Lanka.

Methodology

A laboratory-based, cross-sectional study was performed, focusing on adult (> 18 years), in-ward cancer patients with diagnosed lower respiratory tract infection (LRTI), skin and soft tissue infection (SSTI), or urinary tract infection (UTI). These patients had clinically significant positive bacteriological cultures, as determined by the consultant microbiologist. The ethical clearance for the study was obtained from the Ethics Review Committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka (Ref. No. 63/17). This study was carried out from August 2018 to April 2019 at Apeksha Hospital which is the main public hospital in Sri Lanka dedicated to cancer care. Bacterial isolates obtained from patients who had been receiving antibiotic treatment for over 48 hours prior to specimen collection for culture were not included in the study. This exclusion was made due to the potential impact of prolonged antibiotic exposure on the spectrum of isolated bacteria. Information on antibiotic prescriptions was extracted from in-patient medical records/ bed head tickets (BHT). Repetitive cultures of a patient for a single infection episode with similar results were also excluded.

Isolation and identification of bacteria

Bacterial isolates were obtained from the bacteriological cultures performed as a part of the routine diagnosis process of patients suspected to have the three selected infections. The bacterial isolates identified as pathogens by the consultant microbiologist were sub-cultured specifically for research purposes. These cultures underwent separate processing with specific tests relevant to the study. Bacteria were identified by colony morphology, Gram staining, and standard biochemical methods [13]. All culture media (Blood agar base, MacConkey agar, and Mueller-Hinton agar) were purchased from Oxoid Limited, UK. Bacteria initially identified as *Enterobacteriaceae* based on colony morphology and biochemical methods were further classified to the species level using the API® 20E identification system (BioMérieux, USA).

Antibiotic susceptibility tests (ABST)

Antibiotic susceptibility tests for pathogenic bacterial isolates were conducted distinctively from routine laboratory ABSTs for research purposes. Antibiotic susceptibility of bacterial pathogens was determined by performing disk-diffusion sensitivity tests according to the Clinical and Laboratory Standards Institute (CLSI) 2018 guidelines [14]. Antibiotic discs were purchased from Mast Group Ltd., UK (MASTDISCS® AST). The evaluation of extended-spectrum β-lactamase (ESBL) production was conducted using the disc diffusion technique, following the guidelines outlined by CLSI. Subsequent ESBL confirmation was accomplished through the combination disc method. *Enterobacteriaceae* isolates exhibiting resistance or intermediate susceptibility to

imipenem or meropenem as per CLSI criteria, were classified as carbapenem non-susceptible. The determination of bacterial multi-drug resistance was based on the criteria outlined by Magiorakos *et al* [15].

Determination of meropenem minimum inhibitory concentration (MIC) in carbapenem non-susceptible Enterobacteriaceae

The meropenem minimum inhibitory concentrations (MICs) of carbapenem non-susceptible *Enterobacteriaceae* isolates were assessed using Epsilometer strips (E-strips) (Himedia®, India). Bacteria were streaked on Mueller-Hinton agar for the standard disk diffusion sensitivity method. An E-strip with a meropenem concentration ranging from 0.002–0.32 µg/mL was placed on the center of the agar plate using the applicator stick provided. The plates were incubated at 35 ± 2 °C for 16–20 hours. The ellipses of inhibition created around the E-strips after incubation were read at the point where the ellipse crossed the edge of the strip. The results were interpreted according to the CLSI break-point criteria [14].

Detection of carbapenemase-encoding genes in Enterobacteriaceae

All *Enterobacteriaceae* isolates that demonstrated carbapenem non-susceptibility were tested for carbapenemase-encoding genes. Xpert® Carba-R (Cepheid, USA) multiplex real-time PCR assay was used to detect the main five carbapenemase-encoding genes, namely *bla*KPC, *bla*NDM, *bla*VIM, *bla*IMP, and *bla*OXA-48. This instrument was housed in the microbiology laboratory at the Sri Jayewardenepura General Hospital. Xpert Carba-R assay was performed on the GeneXpert® platform according to the manufacturer's instructions. The instrument functioned through the GeneXpert Dx software (version 4.8). External positive and negative controls were KPC-harboring *K. pneumoniae* ATCC-BAA 1705™ and carbapenem-sensitive *E. coli* ATCC 25922™, respectively.

Results

The study included 165 consecutive bacterial isolates obtained from 157 cancer patients. Among these isolates, 57% (94/165) were identified as belonging to the family *Enterobacteriaceae*. *K. pneumoniae* was the most prevalent species (27.3%, 45/165) among isolated bacteria followed by *E. coli* (18.8%, 31/165).

The majority of isolated *Enterobacteriaceae* (71.3%, 67/94) were multidrug-resistant (MDR). *Enterobacteriaceae* exhibited the highest susceptibility to amikacin (83%, 78/94), with the lowest susceptibility observed for amoxicillin-clavulanic acid (20.2%, 19/94). ESBL production was detected in 19.1% (18/94) of the *Enterobacteriaceae* isolates and the carbapenem non-susceptibility was found to be 46.8% (44/94). The observed proportion of CRE among *Enterobacteriaceae* isolates varied across infection categories, with the highest proportion found in LRTI (53.1%, 17/32) followed by SSTI (46.1%, 12/26) and UTI (41.7%, 15/36).

Meropenem MICs of CRE

Meropenem MICs were determined in all carbapenem non-susceptible *Enterobacteriaceae* isolates (resistant isolates 43; intermediately susceptible isolates 01). Table 1 shows the MICs of CRE isolates.

The majority of the CRE were *K. pneumoniae* (65.9%, 29/44). Among the CRE isolates, the majority (72.7%, 32/44) exhibited a meropenem MIC of ≥ 32 µg/mL. All CRE isolates were multi-drug resistant (MDR). These CRE showed the highest susceptibility to amikacin (63.6%, 28/44) followed by gentamicin (40.9%, 18/44).

The frequency of common carbapenemase-encoding genes in CRE isolates

Among the 44 CRE isolates examined, 43 tested positive for carbapenemase-encoding genes. The most frequently encountered carbapenemase-encoding gene was *bla*NDM 34.8% (15/43). *bla*IMP gene was not detected in any of the isolates. A total of 16 isolates (37.2%) simultaneously carried multiple

Table 1. Meropenem MICs of the CRE isolates obtained from cancer patients.

Species	No. of isolates with MIC (µg/mL)						Total
	≥ 32	24	16	8	6	4	
K. pneumoniae	25	2	–	2	–	–	29
E. coli	3	2	–	2	1	3	11
E. aerogenes	2	–	–	–	–	–	2
K. oxytoca	2	–	–	–	–	–	2
Total	32	4	0	4	1	3	

MIC: Minimum Inhibitory Concentration; CRE: Carbapenem-Resistant *Enterobacteriaceae.*

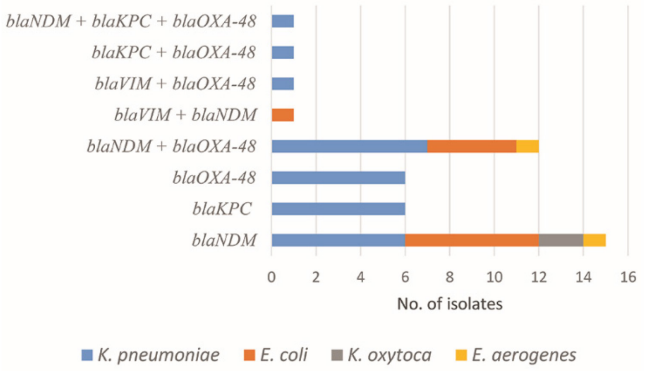
carbapenemase-encoding genes. The co-existence of *bla*NDM and *bla*OXA-48 genes was the most frequent (n = 12). *bla*NDM was detected in all *E. coli* isolates. Two bacterial isolates, one *K. pneumoniae,* and one *E. coli*, obtained from patients with LRTI, were identified as carriers of the *bla*VIM gene. These isolates demonstrated the co-existence of *bla*VIM gene with another carbapenemase-encoding gene. Figure 1 shows the distribution of carbapenemase genes among CRE species.

Discussion

According to our findings, nearly 47% of the *Enterobacteriaceae* isolates were carbapenem-resistant. We conducted a separate study within the same timeframe among non-cancer patients who had infections similar to the cancer patients in this study. Notably, the rate of CRE in those non-cancer patients was found to be 8.5% [16]. The majority of CRE isolates in the current study demonstrated meropenem MICs of ≥ 32 µg/mL. Extended antibiotic exposure in cancer patients may contribute to the observed high meropenem minimum inhibitory concentrations (MICs) among *Enterobacteriaceae.* Cancer patients often require prolonged and intensive antibiotic therapy due to various factors, including prophylactic measures, prolonged infections, or complications associated with their disease or treatment. This extensive exposure to antibiotics can exert selective pressure on the microbial population, favoring the emergence and persistence of drug-resistant strains. The high meropenem MIC is a concern because it has been shown that patients infected with bacteria that had a carbapenem MIC of ≥ 4 mg/L had worse outcomes than patients whose isolates had a lower MIC [17].

This study detected *bla*NDM as the most frequent carbapenemase-encoding gene among CRE isolates. The *bla*NDM gene was initially identified in India in 2009 [18] and it has since become the most common carbapenemase-encoding gene among CRE in India [19]. India has the highest global burden of NDM producers and the proximity of Sri Lanka to the Indian subcontinent with frequent travelling between these destinations, especially medical tourism can be a factor leading to the high prevalence of *bla*NDM in Sri Lanka. In this current study, *bla*NDM was detected in all *E. coli* isolates, either as a single carbapenemase-encoding gene or in combination with another gene.

Figure 1. The distribution of carbapenemase-encoding genes among CRE species.



The findings in this report are consistent with two previous studies done in Sri Lanka where *bla*NDM was the most prevalent carbapenemase gene detected among *Enterobacteriaceae* [20,21]. One of these studies was conducted among patients with hematological malignancies [20]. The observed order of frequency of carbapenemase genes in that study was the same as in the present study. However, the previous study tested only three carbapenemase-encoding genes (*bla*NDM, *bla*OXA-48, and *bla*KPC) [20]. The second study identified *bla*NDM and *bla*OXA-48-like genes in CRE isolated from urine specimens, while the remaining three common carbapenemase genes were not detected [21]. The presence of *bla*OXA-48-like carbapenemase-encoding genes was also reported among *K. pneumoniae* isolated from respiratory specimens and blood [22,23]. A study conducted at the Colombo North Teaching Hospital (CNTH) found that the *bla*OXA-48-like gene was the most frequently detected carbapenemase gene among *Enterobacteriaceae*, with a prevalence of 88.9% [24]. The rate observed in the present study was much lower than that (13.9%). None of the studies conducted in Sri Lanka, including the current research, have detected *bla*IMP in *Enterobacteriaceae* [21-24].

The present study detected *bla*VIM in *Enterobacteriaceae* for the first time in Sri Lanka. More than 40 allelic variants of VIM carbapenemases, primarily classified into three phylogenetic clusters (VIM-1-like, VIM-2-like, and VIM-7-like), have been identified globally [25]. VIM-1-like enzymes have been reported in *Enterobacteriaceae*. Several outbreaks caused by blaVIM harboring *Enterobacteriaceae* have been reported worldwide [26-28]. Recent Indian studies have also reported the presence of the blaVIM gene in *Enterobacteriaceae* [29-31].

In a previous study conducted at the same institution, patients with haematological malignancies had a CRE gut colonization rate of 35.2%, with *K. pneumoniae* being the most prevalent carbapenem-resistant colonizer [20]. Our study also identified *K. pneumoniae* as the main carbapenem-resistant

pathogenic isolate. The high colonization burden in this population likely is what led to the emergence of CRE infections. The increased occurrence of CRE infections among patients with malignancy is concerning, especially when considering the vulnerability of this population to infection. Our findings highlight the magnitude of CRE burden in Sri Lankan cancer patients and further investigations are required to identify the causes and effective preventive strategies.

Conclusions

The prevalence of carbapenem-resistant *Enterobacteriaceae* is high among cancer patients. These bacteria are multidrug-resistant, and the best sensitivity is observed for amikacin. Nearly all CRE isolated in this study were carbapenemase producers and the most prevalent carbapenemase encoding gene is *bla*NDM. This indicates a potential threat of dissemination of carbapenemase genes into other carbapenem-sensitive bacterial strains. Therefore, continuous surveillance and strict adherence to infection prevention and control strategies are essential in this high-risk patient population.

Acknowledgements

This study was funded by the University of Sri Jayewardenepura, Sri Lanka [Research grant no. RE/MED/2017/36].

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Conflict of interests: No conflict of interests is declared.