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Prevalence of Class I Integron Gene in Carbapenem-Resistant Enterobacteriaceae Strains Isolated from Hospitalized Patients

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ABSTRACT

Background: The prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) is a growing global public health concern due to the significant morbidity and mortality associated with infections caused by these bacteria. The main objective of this study was to determine the prevalence of class I integron in CRE isolates collected from patients in teaching hospitals affiliated to Mazandaran University of Medical Sciences (MAZUMS).

Materials & Methods: A total of 100 *Enterobacteriaceae* isolates were collected during March 2022 to March 2023 from MAZUMS teaching hospitals using a consecutive sampling technique. The isolates were distinguished using standard microbiological methods. The antibiotic resistance of the isolated strains to carbapenem was subsequently detected using antibiotic discs including imipenem and meropenem. Using the disc diffusion method, 73 carbapenem-resistant isolates were identified and subsequently investigated by genetic analysis using polymerase chain reaction (PCR).

Findings: Among the 73 carbapenem-resistant isolates, the most commonly found bacterial isolates were *Klebsiella pneumoniae* (39.72%), *Escherichia coli* (30.13%), and *Serratia rubidaea* (12.32%), respectively. Also, 100% of the isolates were resistant to meropenem, while these isolates showed lower resistance to imipenem (70%). Also, out of the 73 isolates, 64.38% were positive for the *intI1* gene. *K. pneumoniae* isolates had the highest prevalence of the *intI1* gene (89.65%).

Conclusion: The prevalence of class I integron among patients in MAZUMS educational hospitals is relatively high, exceeding 50%. Therefore, it is crucial to implement effective infection prevention measures and identify this gene in hospitals to hinder the rapid dissemination of these hazardous organisms.

Keywords: Polymerase chain reaction, Carbapenem-resistant *Enterobacteriaceae*, Integron

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Introduction

The *Enterobacteriaceae* family consists of a vast group of gamma proteobacteria. While this family encompasses over 70 different types of bacteria, the significance lies in species such as *Klebsiella*, *Escherichia coli*, *Enterobacter*, and *Salmonella* [1]. Organisms belonging to these species are often responsible for infections that are transmitted both in the community and in healthcare facilities. In recent decades, antibiotic resistance within the *Enterobacteriaceae* family has prompted physicians to prescribe carbapenems as a last resort [2]. However, resistance to carbapenem drugs has also been observed in several members of the *Enterobacteriaceae* family, mediated through various mechanisms [3]. Beta-lactam medications, including broad-spectrum penicillins, cephalosporins, monobactams, carbapenems, fluoroquinolones, and aminoglycosides (such as gentamicin), are extensively utilized in the management of infections caused by *Enterobacteriaceae* [4]. Carbapenems serve as the ultimate recourse within the realm of antibiotic treatment when dealing with Gram-negative bacterial infections in the medical field [5].

Beta-lactam resistance mechanisms in *Enterobacteriaceae* could be divided into two different categories: enzymatic and non-enzymatic mechanisms. One of the enzymatic mechanisms responsible for beta-lactam resistance is the presence of carbapenemases. Carbapenemases are a specific type of beta-lactamases that have the ability to hydrolyze carbapenems [4]. The emergence and dissemination of plasmid-mediated carbapenem-hydrolyzing β-lactamases are currently on the rise [6,7]. Carbapenem resistance begins with hydrolysis of the β-lactam ring, which may be initiated by carbapenemase or alterations in membrane permeability due to mutations of efflux pumps or porins [8,9].

Integrons belong to the category of mobile genetic elements that have the ability to transport genes associated with resistance to antibacterial agents among various bacterial species, including *E. coli* and other strains of *Enterobacteriaceae* [10]. Integrons could be considered as agents of concern as they could play an important role in the spread of antimicrobial resistance genes [11]. By studying the nucleotide sequence of the integrase gene, researchers have categorized integrons into five classes [12,13]. Among *K. pneumoniae* clinical isolates, class I integrons have the highest prevalence, while class II integrons are only occasionally present, and class III integrons are rarely reported in these bacterial strains [14]. The gene cassettes contain not only the genes responsible for resistance but also a recombination site called *attC* [15]. The recombination process between *attI* and *attC* leads to the integration of the gene cassette into the downstream region of the promoter, mediated by *IntI* [16]. Given the increasing prevalence of antibiotic resistance [17], several recent studies have investigated the prevalence of class I integrons in clinical isolates of various bacteria and their central role in conferring antibiotic resistance. For example, Wang et al. (2023) described that class I integrons could be found in CRE isolates, so that CRE isolates containing class I integrons were more resistant to ceftazidime, amikacin, trimethoprim/sulfamethoxazole, and gentamicin than those without class 1 integrons ($p< .05$) [18]. In another study by Shahkolahi et al. (2022), class I integron was indicated as the most common integron among the isolates studied [19]. Taati Moghadam et al. (2016) also reported that 63.7% (n=37) of *K. pneumoniae* isolates included *intI1,* while only three (5.1%) isolates had *intI2* gene [20].

Objectives: The objective of the current study was to examine the prevalence of class

I integrons in CRE strains.

Materials and methods

Bacterial isolates: Various clinical specimens (sputum, broncho alveolar-lavage (BAL), urine, blood, and wound) were collected as part of routine diagnostic procedures from patients already admitted to two teaching hospitals affiliated to MAZUMS. These patients received standard clinical care, which might have included the administration of antibiotics. Seventy-three clinical strains suspected of CRE were obtained from hospitalized patients during March 2022 to March 2023. These isolates were characterized and validated using established biochemical assays such as Gram staining, oxidase, catalase, citrate utilization, motility, TSI (triple sugar-iron), SIM (sulfide, indole, motility), H_2S production, glucose, and lactose fermentation tests. The confirmed strains were stored at −80 °C in Trypticase Soy Broth (TSB) with 20% (w/w) glycerol for further studies. All of microbial culture media were purchased from Merck (Darmstadt, Germany).

Antimicrobial susceptibility test: The antibiogram test was performed using the conventional disc diffusion technique on Mueller-Hinton agar (MHA) (Merck, Germany) in accordance with the guidelines of the Clinical and Laboratory Standards Institute (CLSI, 2022). The antibiotic resistance of the isolated strains to carbapenem was subsequently detected using antibiotic discs including imipenem (10 µg) and meropenem (10 µg) from MastGroup Ltd., Merseyside, United Kingdom. The standard disc diffusion method on MHA was used for antibiotic susceptibility testing. Quality control strains used for antimicrobial susceptibility testing included *E. coli* ATCC 25922 (American Type Culture Collection), *Enterococcus faecalis* ATCC 29212, and *Pseudomonas aeruginosa* ATCC 27853.

Molecular detection of class I integrons: In the present study, DNA extraction was carried out using the boiling method. First, the bacterial colonies were placed in a test tube containing one mL of distilled water and then placed in a bain-marie at 100 °C for 10 min. They were then centrifuged at a rotation speed of 1000 rpm for 5 min to obtain the supernatant containing DNA.

The presence of the *intI1* gene was then examined using specific primers as described in a previous study [21]. The primers used in the current study were: F1: 5′-CCTCCCGCACGATGATC-3′ and R1: 5′-TCCACGCATCGTCAGGC-3′.

The procedural steps were performed with a final volume of 15 µL containing 7.5 µL of PCR master mix (Ampliqon Taq DNA Polymerase), 0.3 µL of forward and reverse primers (10 pmol), 6.4 µL of distilled water, and 0.5 µL of DNA (300 ng). It is essential to note that in each PCR test series, control DNA (*P. aeruginosa* ATCC 27853) and negative control (distilled water together with all components including master mix and primers) were processed simultaneously with clinical samples.

The reaction conditions for amplification of DNA to detect *intI1* were as follows: an initial denaturation step at 94 °C for 5 min, followed by 30 cycles of denaturation at 94 °C for 45 s, annealing at 58 °C for 60 s, and extension at 72 °C for 30 s, and a final extension step at 72 °C for 10 min. The PCR amplification was performed using a T100 Thermal Cycler (BioRad, USA)

Statistical analysis: Correlations between antibiotic resistance and the presence of the *intI1* gene were evaluated using the Pearson test (all variables met the normality assumption). Differences were considered significant at $p < .05$. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) software Version 17.0 (SPSS; Chicago, IL, USA).

Findings

Investigation of CRE isolates by type of microorganism: A total of 73 *Enterobacteriaceae* isolates that demonstrated resistance to carbapenem were successfully identified. The most prevalent organism was *K. pneumoniae* with 29 samples, comprising 39.72% of all CRE samples. *E. coli* with 22 (30.13%) samples and *S. rubidaea* with nine (12.32%) samples were placed in the next categories. *Enterobacter gergoviae*, *Citrobacter diversus*, and *Proteus vulgaris* organisms had the lowest prevalence with one sample each (Figure 1).

In this study, meropenem and imipenem were used, and meropenem resistance was considered as a decisive factor for carbapenem resistance of *Enterobacteriaceae*. Out of a total of 73 samples, all showed resistance to meropenem, and 51 (70%) samples showed resistance to imipenem. Totally, among *K. pneumoniae* isolates, accounting for the largest number of samples, 21 (72.4%) out of 29 samples showed resistance to imipenem. Also, 13 (59%) out of 22 *E. coli* isolates showed resistance to this antibacterial agent. Similarly, all nine *S. rubidaea* isolates showed resistance to imipenem, which corresponds to 100%.

Investigation of class I integron gene in carbapenem-resistant isolates: In this study, a total of 47 (64.38%) out of 73 isolates harbored the *intI1* gene. Among all *K. pneumoniae* isolates, 26 (of 29, 89.65%) isolates harbored the *intI1* gene. Additionally, 15 (of 22, 68.18%) *E. coli*, three (of 9, 33.3%) *S. rubidaea*, two (of 3, 66.6%) *E. aerogenes,* and one (of 3, 33.3%) *P. mirabilis* isolates harbored the *intI1* gene, respectively.

It is worth noting that the *intI1* gene was not detected in any other microorganisms identified in this study (Figure 2), and it should also be mentioned that all susceptible isolates lacked the *intI* gene. In total, among 73 CRE, 51 strains were resistant to imipenem, and 47 isolates (which were resistant to IPM) carried the *intI1* gene. Statistical analysis revealed a significant association between imipenem resistance and the presence of the *intI1* gene (p-value < 0.05). Figure 3 shows the PCR amplification of the *intI1* gene (280 bp).

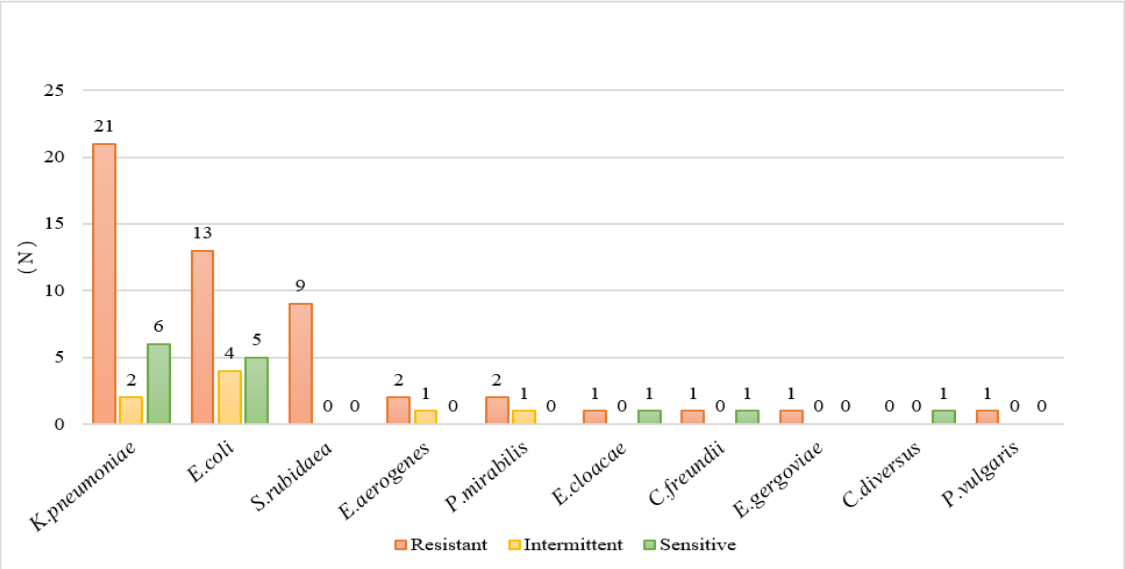

Figure 1) Antibiotic resistance or susceptibility profile was developed by testing CRE isolates against imipenem. Orange bar represents number of resistant isolates, yellow bar shows the isolates which had itermediate resistance, while green bars shows the number of susceptible isolates to imipenem. N: number of isolates

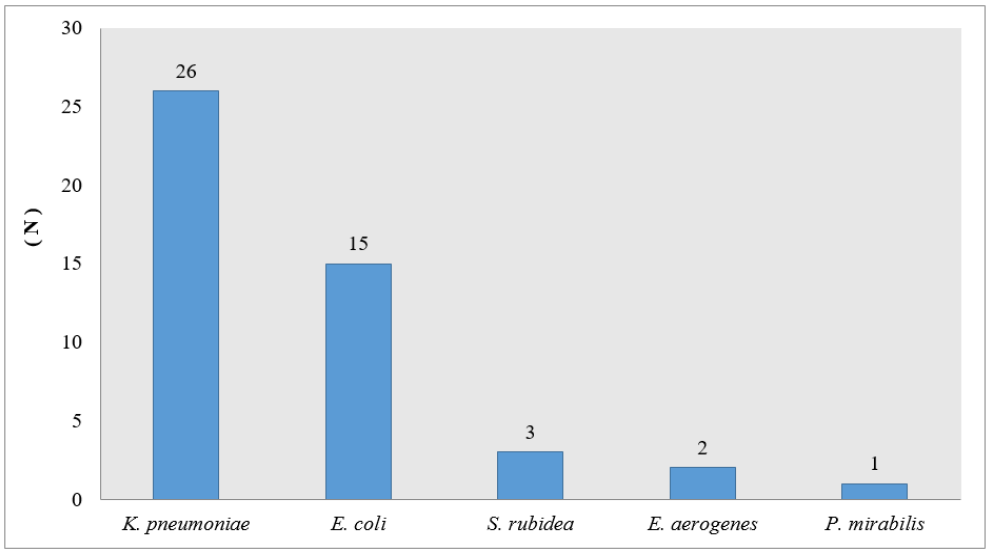

Figure 2) The number of CRE isolates harboring the *intI1* gene. N: number of isolates

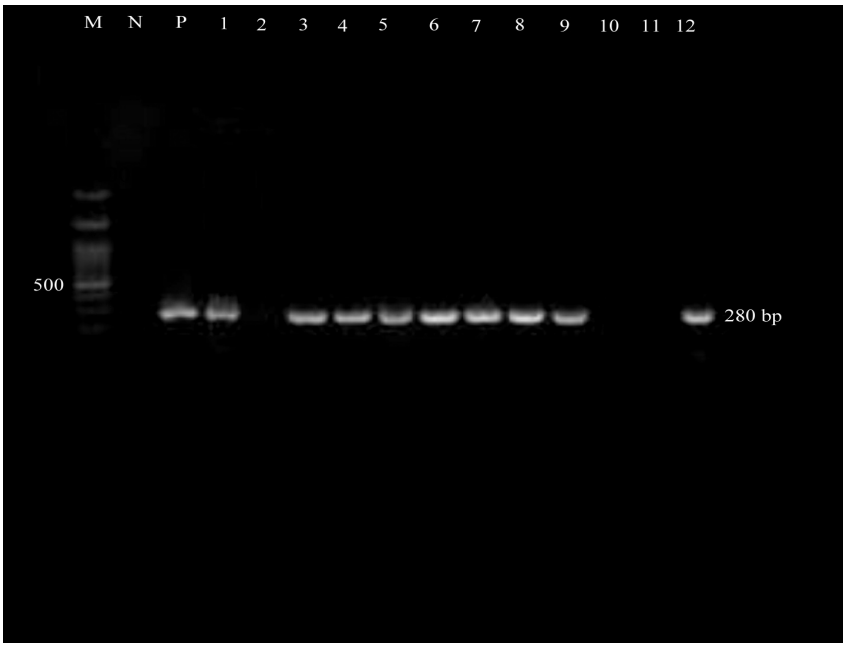

Figure 3) PCR gel showing of studied *intI1* genes in tested strains, Lane M: DNA ladder 100-3kb bp, Lane N: Negative control, Lane P: Positive control, Lanes 1-12: CRE strains.

Discussion

This study aimed to identify class I integrons in CRE isolates from patients hospitalized in teaching hospitals affiliated to MAZUMS from March 2022 to March 2023. The study followed a descriptive cross-sectional study design. The most prevalent organisms identified in this study were *K. pneumoniae* and *E. coli*, respectively. Two antibiotics from the carbapenem family, meropenem and imipenem, were used to determine resistance to carbapenems. It was observed that resistance to meropenem was higher than that to imipenem. This difference in resistance levels could possibly be due to the difference in the pattern of antibiotic use in the studied hospitals. Also, 64% of CRE isolates had the *intI1* gene, and a clear

association was found between the presence of this gene and resistance to antibiotics ($p<$ .05). The highest prevalence of this gene was among *K. pneumoniae* and *E. coli* isolates, respectively.

As mentioned above, 73 clinical strains suspected of CRE were obtained from hospitalized patients admitted to two teaching hospitals affiliated to MAZUMS during March 2022 to March 2023. Kim et al. (2020) conducted a study in Korea on carbapenemase-producing *Enterobacteriaceae* (CPE) and identified *K. pneumoniae* as the predominant organism in 69% of 45 patients with CPE [22]. In a study conducted by Yan et al. (2017) in China on a total of 78 *K. pneumoniae* isolates showing resistance to at least one carbapenem, the prevalence of the *intI1* gene was documented as 66.7%. Moreover, the *intI1* gene was identified as one of the influential factors contributing to the development of antibiotic resistance [23]. In another study by Liu et al. (2022) in China, the *intI1* gene was detected in 92 out of 117 *E. coli* samples that displayed resistance to carbapenem, which corresponds to around 83.7%. It was also found that resistance to various types of antibiotics, including meropenem, was notably higher in bacteria containing the class I integron gene than in bacteria lacking this particular gene [24]. In a study conducted by Kargar et al. (2015) in Iran, among 164 *E. coli* isolates, known to cause diarrhea in children under 5 years, the frequency of the *intI1* gene was documented to be 73.73%. Moreover, a remarkable association was found between the presence of the *intI1* gene and the development of antibiotic resistance [25]. In another investigation by Wang et al. (2023) in China, among 161 CRE samples, a total of 78 (48.4%) samples had the *intI1* gene [26]. Jabalameli et al. (2022) from Iran examined *K. pneumoniae* isolates obtained from urine samples. Among 80 *K. pneumoniae* isolates, 29 (36.2%) isolates were found to be positive for the *intI1* gene [27]. In the two aforementioned studies, the prevalence of the *intI1* gene was less than 50%. The differences observed in the findings of different studies could be attributed to the differences in antibiotic consumption patterns, geographical regions, resistance patterns in different regions, methods used to evaluate the factors causing resistance (i.e. the presence of resistance genes, including bla_{VIM}, bla_{IMP}, bla_{KPC}, $bla_{\text{OXA-48}}$, efflux-pumps, and genetic mutations, each of which could influence the resistance rate), and bacterial strains studied. These factors are suggested to be investigated in future research. In addition, the notably high level of resistance of strains to certain antibiotics is an indication of the overuse of these antibiotics in our country. The current study also had some limitations. In this study, we employed disk diffusion to identify carbapenem-resistant isolates; however, future research should include minimum inhibitory concentration (MIC) testing to validate the carbapenem-resistant isolates. Also, according to the results, the quantity of some studied organisms such as *E. gergoviae*, *C. diversus,* and *P. vulgaris* was insufficient, which made the examination of these organisms unreliable. Another limitation of the present study was our lack of access to comprehensive demographic data regarding the patients. It should be also mentioned that certainly in the next steps, with additional budget, we will use the different typing techniques to determine the clonal relationship.

Conclusion

The present study results indicate that the prevalence of carbapenem-resistant isolates, especially *E. coli* and *K. pneumoniae*, and class I integrons in patients hospitalized in MAZUMS-affiliated educational-therapeutic centers is comparatively high. Therefore, it is of utmost importance to take effective

measures to prevent infections and detect this genetic element in medical facilities to prevent the rapid spread of these harmful microorganisms.

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