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Relationship between MOX genes and antibiotic resistance in *Klebsiella pneumoniae* strains in nosocomial infections

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ABSTRACT

Drug resistance in microorganisms, specifically bacteria pathogens, is a serious threat to patients worldwide. Multidrug-resistance of bacteria to a broad spectrum of conventional antibiotics is the main hindrance to treating patients admitted to hospital. In this case, the increased emergence of multidrug-resistance mechanisms among *Klebsiella pneumoniae* nosocomial infections has limited the therapeutic options for treating bacterial infections such as intra-abdominal, urinary tract, and pneumonia infections. The beta-lactamase enzymes in these bacteria, as extended-spectrum beta-lactamases (ESBL), are the primary defence of gram-negative bacteria against a wide range of beta-lactam antibiotics. This review aimed to evaluate the role of MOX genes in the antibiotic resistance of *K. pneumoniae* strains isolated from hospitalized patients.

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Introduction

Antibiotic resistance in bacterial pathogens is considered a serious threat to patients worldwide [1-10]. Therefore, the World Health Organization (WHO) named 2011 as the year of antibiotic resistance [11]. *K. pneumoniae* is an opportunistic pathogen from the Enterobacteriaceae family that causes septicemia, bacteremia, meningitis, enteritis, urinary tract and soft tissue infections [12]. Especially in people with immune system deficiency, diabetes mellitus, and chronic bacterial or viral lung disorders suffer severe illnesses from these bacteria [13-17]. The significant mechanisms, including active drug efflux, inactivating an antibiotic, modifying an antibiotic target, and limiting the antibiotic uptake, have been identified for antibiotic resistance [18]. The increasing emergence of antibiotic resistance among hospital isolates of *K. pneumoniae* has limited the therapeutic options for treating infections caused by this bacterium [19]. Most isolates of *K. pneumoniae* are resistant to a wide range of antibiotics [20]. Among the antibiotic resistance mechanisms, beta-lactamases are considered the primary defense of Gram-negative bacteria, especially *K. pneumoniae*, against beta-lactam antibiotics [21].

Beta-lactamases are usually classified according to two general schemes: 1: Ambler's molecular classification scheme and 2: Bush-Jacoby-Medeiros functional classification system [22, 23]. In Ambler's classification scheme, beta-lactamases are classified into 4 main classes: A, B, C, and D. The basis of this classification is protein homology or amino acid similarity of these proteins, and phenotypic characteristics are not considered in this type of

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classification. In Ambler's classification, A, C, and D classes are serine β-lactamases, while the enzymes in class B are metallo-β-lactamases (Figure 1) [23, 24]. The basis of classification in the Bush-Jacoby-Medeiros class is the functional similarities of enzymes, such as enzyme-substrate or inhibitor characteristics [22]. Bacteria with a wide spectrum of beta-lactamase are resistant to many antibiotics, including penicillin, first, second, and third generation cephalosporins, and aztreonam (except cephamycins and carbapenems) [24]. These enzymes are inhibited by clavulanic acid (Figure 2a) and have been seen in Enterobacteriaceae, Pseudomonadaceae, and Moraxellaceae (*Acinetobacter baumannii*) families [25]. According to the Bush-Jacoby-Medeiros classification, these enzymes are in group 2be (class A enzymes), and some others are in class 2d (class D enzymes). The genes encoding these enzymes are located on chromosomes and mobile genetic elements such as plasmids [26].

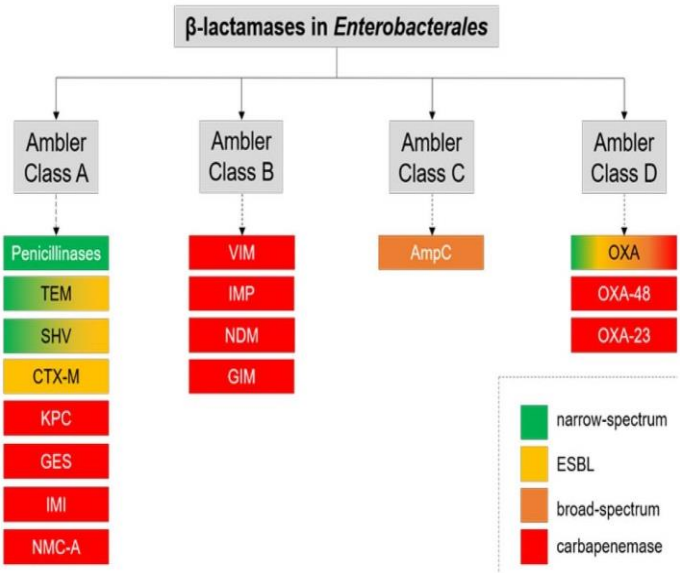

Fig. 1. Ambler's classification of the main β-lactamases in Enterobacterales [23].

AmpC-type beta-lactamases (Figure 2b) were identified in the late 1970s. Most of these enzymes are cephalosporinases. However, to some extent, they can hydrolyze other beta-lactams [27]. These enzymes hydrolyze broad-spectrum cephalosporins such as ceftazidime, ceftriaxone, cefepime, and monobactams such as aztreonam and vancomycin. Still, they are not blocked via β-lactamase inhibitors such as clavulanic acid [27, 28].

AmpC enzymes are often inducible by beta-lactams, encoded by chromosomal genes, and present in many Gram-negative bacteria [29]. In addition, more than 20 types of AmpC beta-lactams have been identified through plasmids [30]. AmpC beta-lactamases include MIR, CMY, ACT, FOX, MOX, and FOX gene causes resistance to cefoxitin, MOX, resistance to moxalactam (latamoxef), and ACT causes resistance to cephalosporins [31]. The MOX gene was first reported in 1993 from Japan in *K. pneumoniae*. This gene is located on a plasmid, easily transferred to other bacteria, and is in class C of Ambler's classification. Bacteria containing this gene are resistant to cephalosporins, moxalactam, and inhibition by clavonic acid [32].

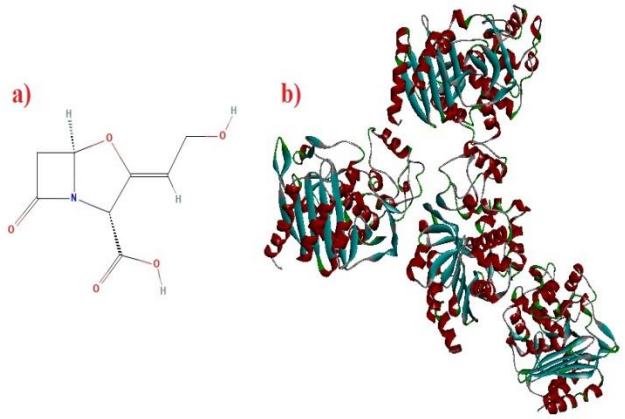

Fig. 2. a) Chemical structure of a β-lactamase inhibitor of clavulanic acid (PubChem) and b) the structure of ACT-1, the first plasmid-mediated AmpC-type beta-lactamase (PDB: 2ZC7).

In a study conducted by Woodford et al. (2006) in England, 173 isolates of *Escherichia coli* and *K. pneumoniae* were investigated. The combination disk method was used to identify AmpC enzymes and PCR method was used to detect genes. Among the isolates, 64 *E. coli* strains (49%) and 21 *K. pneumoniae* strains (55%) contained Amp-C enzyme, among which 11 *K. pneumoniae* isolates, 3 *E. coli* isolates had the FOX gene, and all of them lacked the gene were MOX [33]. In a similar study, 2129 Enterobacteriaceae isolates were investigated to identify AmpC enzymes. Hybrid disc method was used according to CLSI guidelines. 33 (3.2%) of *E. coli* strains and (0.6%) 2 *K. pneumoniae* strains contained AmpC enzyme [34].

In the study of Clayton da Silva Dias and colleagues in 2007 in Brazil, 123 isolates of Enterobacteriaceae

were investigated. Hodge test method was used to identify Amp-C enzymes and the Multiplex PCR method was used to identify Amp-C plasmid genes. Out of 123 isolates, 65 (53%) were multidrug-resistant (MDR) isolates, and none of the Amp-c plasmid genes were found among the samples [35]. In the research conducted by Shafiq et al. in 2013 in Pakistan, 511 isolates of Enterobacteriaceae, including 414 isolates of *E. coli* and 97 isolates of *K. pneumoniae* were investigated. A hybrid disc method was used according to CLSI guidelines to identify Amp-C enzymes. 33 (40.74%) *E. coli* strains and (54.55%) 12 *K. pneumoniae* strains contained Amp-C enzyme [36].

In a study by Wassef *et al*. [37] in 2014 in Egypt, 1073 Gram-negative bacteria were examined. The combination disc containing boronic acid was used to identify the Amp-C enzyme, and the Multiplex PCR method was used to identify the MOX, FOX, EBC, ACC, and DHA genes. In addiiotn, 57.7% of the isolates produced Amp-c enzyme, and 22 isolates contained genes producing Amp-C enzyme, of which 9 genes were related to MOX, FOX family, and three samples simultaneously contained FOX, MOX, and CIT genes.

In addition, out of 168 *K. pneumoniae* clinical isolates, 119 isolates (%70.8) were positive in terms of ESBLs production in the initial screening, of which (%83.2) 99 isolates were positive in the confirmatory phenotypic test and (%8.4) 10 isolates had AmpC genes, which Among them, 9 strains contained FOX gene and MOX gene was not found among the isolates [38].

For another investigation, in Arak city of Iran, 100 isolates of *K. pneumoniae* were investigated by PCR method to identify Amp-C genes. Out of 100 *K. pneumoniae* isolates, 19 isolates (19%) had Amp-C beta-lactamase genes. 7 isolates (7%) had MOX family genes, 8 isolates (8%) had CIT family genes, 3 isolates (3%) had DHA family genes, and 1 isolate (1%) had EBC family genes. In contrast, ACC family genes and FOX was not found in any of the isolates [39]. 11 types of MOX gene (Table 1) have been identified in the world [40]. In Iran, various beta-lactamases have been identified, as demonstrated in Figure 3 [41].

Table 1. MOX type beta-lactamases.

Enzyme	Nucleotide
MOX-1	D13304
MOX-2	AJ276453
MOX-3	EU515248
MOX-4	FJ262599
MOX-5	GQ152600
MOX-6	GQ152601
MOX-7	GQ152602
MOX-8	JX173956
MOX-9	Assigned
MOX-10	Assigned
MOX-11	Assigned

Fig. 3. Distribution of β-lactamase genes in Iran [41].

Conclusions

The mechanism or function of antibiotic resistance in pathogenic bacteria should be determined to choose the best option for treating hospitalized patients. There are the primary mechanisms for antibiotic resistance, including active drug efflux, inactivating an antibiotic, modifying an antibiotic target, and limiting the uptake of an antibiotic. Hospital personnel and doctors should acquire the necessary information about the resistance of bacteria and the ways of transmission of these bacteria so that they can take the necessary measures if they are observed. In this regard, the resistance of *K. pneumoniae* strains to beta-lactams due to the presence of the AmpC beta-lactamase enzyme is one of the most critical challenges in the clinical sector. According to this review, all microorganisms with ESBL enzymes should be reported as resistant to all broad-spectrum cephalosporins unless their sensitivity to the antibiotic is proven.

Study Highlights

- The mechanism of antibiotic resistance in bacteria should be indicated to choose the best option for treating hospitalized patients.
- Active drug efflux, inactivating an antibiotic, modifying an antibiotic target, and limiting the uptake of an antibiotic are the primary mechanisms for antibiotic resistance.
- The resistance of *K. pneumoniae* strains to beta-lactams due to the presence of the AmpC beta-lactamase enzyme is one of the most critical challenges in the clinical sector.

Abbreviations

ESBL: Extended-spectrum beta-lactamases
MDR: Multidrug-resistant

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Conflict of interest

The authors declare that they have no conflict of interest for this study.

Ethical approval

This article does not contain any studies with animals or human participants.

Authors' contribution

SA: conceptualization, preparing the first draft, and revising; GE, AT and AH: revising of the manuscript.

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