Journal of Pharmaceutical Research International

33(39B): 352-357, 2021; Article no.JPRI.71761
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Review on the Carbapenem Resistance Mechanisms of *Klebsiella pneumoniae*

Wafaa Ahmed Alhazmi[1*]

[1]Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia.

Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i39B32212
Editor(s):
(1) Dr. Rafik Karaman, Al-Quds University, Palestine.
Reviewers:
(1) Anubhuti Khare, Kerala University of Health Sciences (KUHS), India.
(2) Khoirun Nisyak, STIKES Rumah Sakit Anwar Medika, Indonesia.
Complete Peer review History: https://www.sdiarticle4.com/review-history/71761

Review Article

Received 25 May 2021
Accepted 30 July 2021
Published 04 August 2021

ABSTRACT

During the past years, the emergence of multi-drug resistance Gram-negative bacilli (MDR-GNB), including the carbapenem resistant *Klebsiella pneumoniae* (CRKP) has increased leading to a significant threat to public health care. Recent advanced molecular methods have improved our knowledge on how antimicrobial resistance mechanisms develop and transferred among bacterial strains. The MDR pathogens, particularly CRKP, utilize various mechanisms of resistance such as antimicrobial agent degradation, modification of antimicrobial target and alteration of cell membrane permeability. Here, the emergence of CRKP and the major antibiotic resistance mechanisms employed by CRKP will be reviewed and described. Understanding such mechanisms can be essential to develop new antimicrobial drug and help with individual treatment decisions to use alternative options to carbapenem and β-lactam antibiotics.

Keywords: Antimicrobial resistance; gram-negative; carbapenem resistant Klebsiella pneumoniae.

1. INTRODUCTION

Klebsiella pneumoniae is an opportunistic significant Gram-negative pathogen responsible for various types of nosocomial and community-acquired infections such as pneumonia, liver abscess, sepsis and meningitis [1]. The prognosis and treatment of such infections became more challenging due to the ability of the bacteria to resist multiple antibiotics. This can be

**Corresponding author: E-mail: walhazmi@kau.edu.sa;*

achieved by several antimicrobial resistance mechanisms that are employed by an emerged multi-drug resistant bacterial pathogens. An example of these resistance mechanisms include the production of hydrolyzing or modifying enzymes, the efflux transporter systems, and the decreased permeability of the cell membrane via loss of porins [2]. The main aim of this review is to explain the significance of the emergence of multi-drug resistant *K. pneumoniae* strains and to outline their major mechanisms of antimicrobial resistance, especially carbapenem resistance.

2. EMERGENCE OF CARBAPENEM RESISTANT *K. PNEUMONIAE* (CRKP)

The occurrence of multi-drug resistance Gram-negative bacilli (MDR-GNB), especially the extended-spectrum beta-lactamases (ESBLs) producing *Enterobacteriaceae* was firstly described in the late eighties [1,3] The ESBLs producing Enterobacteriaceae have the ability to resist various β-lactam antibiotics classes, including penicillin, cephalosporins, carbapenems and monobactams [3,4]. Carbapenem resistance Enterobacteriaceae (CRE) have recently emerged as the major class of MDR-GNB that contribute to a serious threat to the public health worldwide [5]. The number of cases of carbapenem resistance *K. pneumoniae* (CRKP), have considerably increased during the last decade resulting in a serious dilemma to the healthcare system due to the high morbidity and mortality [6]. The elevated rate of antimicrobial resistance and the global emergence of CRE as MDR-GNB have been considered as significant health care issues that have increased the emphasis towards understanding the resistance mechanisms and development of novel treatments.

The resistance to carbapenem includes different mechanisms such as alteration of the bacterial cell membrane, efflux system upregulation accompanied with overproduction with hydrolyzing ESBLs enzymes or AmpC β-lactamases, especially carbapenemases [7,8]. *The K. pneumoniae producing c*arbapenemases (KPCs) has the ability to resist broad spectrum carbapenems antibiotics [3]. Carbapenemases are beta-lactamase enzymes that can be expressed by *K. pneumoniae* to hydrolyze beta-lactams including carbapenems, penicillins, cephalosporins, cephamycins, and monobactams and clavulanic acid [3,9]. The KPCs are more commonly associated with *K. pneumoniae* nosocomial infections such as urinary tract infections (UTI), pneumonia, and sepsis, rather than community-acquired infections [3].

3. CARBAPENEM RESISTANCE MECHANISMS

There are three major antimicrobial resistance mechanisms against carbapenem that utilized by *K. pneumoniae,* [2]. These resistance mechanisms are classified as the following:

1) *Production of carbapenem-hydrolyzing enzymes* for degrading antibiotics.
2) The efflux pumps mechanism.
3) Porin mutations to decrease permeability on the outer membrane.

Carbapenemases Production: The CRKP bacterial strains are known to produce carbapenemases as hydrolyzing enzymes that inactivate the carbapenems. All *K. pneumoniae producing c*arbapenemases (KPCs) isolates are encoded by bla_{KPCs} genes that were firstly identified in Northeastern USA in 2001 following various outbreaks in New Jersey hospitals and other countries including Brazil, Colombia, Greece, Italy, Poland and Argentina [10-12]. This international spread of KPCs isolates were associated with a single dominant strain, namely multilocus sequence type (ST258), that was reported to be responsible for nearly 70% of the USA outbreaks [13]. The dissemination of KPCs encoded genes, bla_{KPCs}, can be mediated by molecular mechanisms such as mobility of small genetic materials called transposons (e.g. Tn3 type Tn4401 transposon). Additionally, the horizontal transfer of plasmids carrying bla_{KPCs} gene is known as a major molecular resistance mechanism of KPC gene transmission via clonal spread [12,14].

The carbapenemases can be classified into four classes A, B, C and D based on their ambler class. The class A carbapenemases are identified as KPCs which have the ability to hydrolyze beta-lactams when their active sites contain serine [15]. In addition, the ambler class A (KPC) is commonly found in highly antimicrobial resistance *K. pneumoniae* strains. The class B enzymes cleave beta-lactam rings with zinc that acts as an essential cofactor. These enzymes known as metallo-beta-lactamases (MBLs) can resist beta-lactamase inhibitors [16]. The class C enzymes are known as AmpC enzymes that are chromosomally encoding cephalosporinases and these enzymes

use serine as active site similar to class A [17]. The class D carbapenemases are also serine proteases that depend on serine to hydrolyze carbapenems. O*xacillinase-48 (OXA-48)*-like enzymes belong to the ambler class D β-lactamases in *K. pneumoniae* [2].

4. THE ENERGY-DEPENDENT EFFLUX PUMPS MECHANISM

Efflux pumps play an important role as antimicrobial resistance determinants that are conserved in all microorganisms [18,19]. It was firstly described the use of efflux pumps by *Escherichia coli* as defensive mechanisms to resist tetracycline antibiotic [20,21]. There are five main types of efflux pumps transporters in prokaryotes: the adenosine triphosphate (ATP)-binding cassette ABC superfamily, the resistance-nodulation-division (RND) family [20] the small multidrug resistance (SMR) family [21], the major facilitator superfamily (MFS) [22], the multidrug and toxic compound extrusion (MATE) family [23]. The ABC, SMR, MFS and MATE families are known as major efflux transporters in both Gram-positive and Gram-negative organisms whereas the RND family are only common in Gram-negative bacteria [20,21]. The flavonide-responsive RND family of efflux transporters involves various members as shown in (Fig. 1). For instance, *E. coli* AcrAB-ToIC pump is a major member of RND family and present in other CRE strains including CRKP [24]. This pump known as a tripartite complex contributes to antibiotic resistance as it spans through the membranes of the bacteria (the periplasm, inner and outer membranes) in order to eject antibiotics out of the cell [2].

The AcrAB-ToIC multi-drug efflux pump in *K. pneumoniae* is formed by AcrA (a membrane fusion protein), AcrB (a cytoplasmic membrane protien) and ToIC (an outer membrane protein). It is encoded by *acrRAB* operon that is negatively regulated by a dimeric protien AcrR repressor . Furthermore, the acrB protein is associated with the ToIC protein that is present in other gram-negative bacteria and is mainly responsible for the removal of numerous compounds from bacterial cells [25].

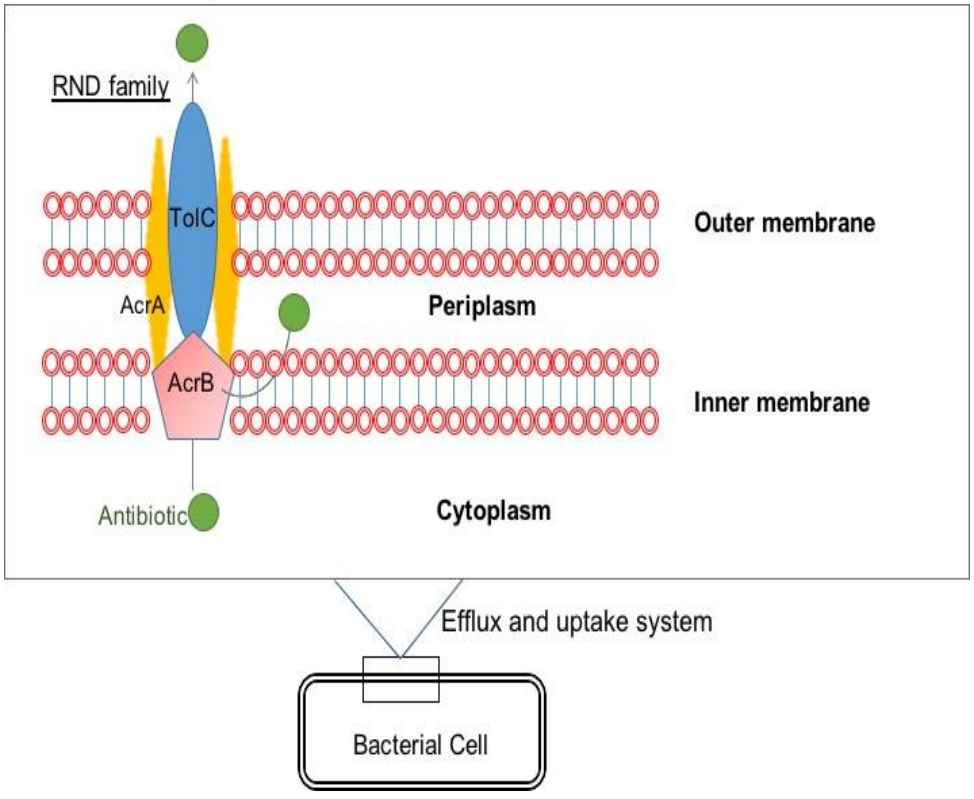

Fig. 1. Schematic diagram of the major efflux transporter system in *K. pneumoniae*. The resistance-nodulation-division (RND) family. Green circles represent antibiotic molecules

Along with carbapenem resistance, MDR-GN bacteria encoding the AcrAB-ToIC pump can lead to resistance to other antimicrobial classes such as tetracycline, fluoroquinolones, and macrolides [25].

Porin Mutations in the outer membrane: Porin mutations can decrease the permeability of the bacterial outer membrane as mechanism of antibiotic resistance. Additionally, OmpK35 and OmpK36 are major types of mutations in porin which are usually alone do not lead to carbapenem resistance in Enterobacteriaceae, however, these mutations in CTX-M and Amp-C-producing Enterobacteriaceae often lead to carbapenem resistance [2,26]. The CTX-M enzyme belong to class A β-lactamases as type of penicillinase, while Amp-C is a class C β-lactamases known as cephalosporinase. Both enzymes have a low level of carbapenem hydrolytic activity [2].

The low porin expression when is combined with the overexpression of hydrolytic β-lactamases can lead to “antibiotic trapping phenomenon” in which the carbapenem can be irreversibly bound by the degrading enzymes (trapped) rather than degraded [26]. The *omp*K35/36 porin variants isolated from KPC-producing *K. pneumoniae* in Italy which were associated with carbapenem resistance causing a significant potential threat to nosocomial settings [27]. Moreover, it was reported that *omp*K36 porin variant present in KPC-producing *K. pneumoniae* was linked with high level of carbapenem resistance and reduced response against carbapemenm-colistin treatment [28,29]. A previous multicenter study in the USA showed that both two porin mutations *omp*K35 and *omp*K36 were found in 84% and 34% of CRKP strains, respectively [30].

5. CONCLUSION

To summarize, CRKP strains utilize various mechanisms to resist broad spectrum antimicrobial agents including carbapenems. In this review, three major antimicrobial resistance mechanisms employed by MDR *K. pneumoniae* were described including hydrolytic extended spectrum β-lactamases, the efflux pump systems, and the loss of porins causing decreased permeability of the cell membrane. Understanding these mechanisms along with the significance of the emergence of carbapenem resistance strains can be essential to develop novel antimicrobial agents that can improve the prognosis of CRKP pathogens and help clinicians in treatment decisions in selected cases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Van Duin D, Perez F, Rudin SD, Cober E, Hanrahan J, Ziegler J, et al. Surveillance of carbapenem-resistant Klebsiella pneumoniae: tracking molecular epidemiology and outcomes through a regional network. Antimicrob Agents Chemother. 2014;58(7):4035-41.
2. Eichenberger EM, Thaden JT. Epidemiology and mechanisms of resistance of extensively drug resistant Gram-negative bacteria. Antibiotics. 2019;8(2):37.
3. Chen L, Mathema B, Chavda KD, DeLeo FR, Bonomo RA, Kreiswirth BN. Carbapenemase-producing Klebsiella pneumoniae: molecular and genetic decoding. Trends in microbiology. 2014;22 (12):686-96.
4. Iredell J, Brown J, Tagg K. Antibiotic resistance in Enterobacteriaceae: mechanisms and clinical implications. Bmj. 2016;352.
5. Mckenna M. Antibiotic resistance: the last resort. Nature News. 2013;499(7459):394.
6. Nordmann P. Carbapenemase-producing Enterobacteriaceae: overview of a major public health challenge. Med Mal Infect. 2014;44(2):51-6.
7. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobac-teriaceae: an evolving crisis of global dimensions. Clin Microbiol Rev. 2012;25(4):682-707.
8. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global

expansion of Klebsiella pneumoniae carbapenemases. The Lancet Infectious Diseases. 2013;13(9):785-96.
9. Papp-Wallace KM, Bethel CR, Distler AM, Kasuboski C, Taracila M, Bonomo RA. Inhibitor resistance in the KPC-2 beta-lactamase, a preeminent property of this class A beta-lactamase. Antimicrob Agents Chemother. 2010;54(2):890-7.
10. Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among Enterobacteriaceae worldwide. Clin Microbiol Infect. 2014;20 (9):821-30.
11. Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL, European Survey of Carbapenemase-Producing Enterobacteriaceae working g. Carbapenemase-producing Enterobact-eriaceae in Europe: assessment by national experts from 38 countries, May 2015. Euro Surveill. 2015;20(45).
12. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence. 2017;8(4):460-9.
13. Arnold RS, Thom KA, Sharma S, Phillips M, Kristie Johnson J, Morgan DJ. Emergence of Klebsiella pneumoniae carbapenemase-producing bacteria. South Med J. 2011;104(1):40-5.
14. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. J Infect Dis. 2017;215(suppl_1):S28-S36.
15. Pitout JD, Nordmann P, Poirel L. Carbapenemase-producing Klebsiella pneumoniae, a key pathogen set for global nosocomial dominance. Antimicrobial agents and chemotherapy. 2015;59(10): 5873-84.
16. Iredell J, Brown J, Tagg K. Antibiotic resistance in Enterobacteriaceae: mechanisms and clinical implications. BMJ. 2016;352:h6420.
17. Meletis G, Chatzidimitriou D, Malisiovas N. Double- and multi-carbapenemase-producers: the excessively armored bacilli of the current decade. Eur J Clin Microbiol Infect Dis. 2015;34(8):1487-93.
18. Martinez JL, Sanchez MB, Martinez-Solano L, Hernandez A, Garmendia L, Fajardo A, et al. Functional role of bacterial multidrug efflux pumps in microbial natural ecosystems. FEMS Microbiol Rev. 2009;33 (2):430-49.
19. Martinez JL, Fajardo A, Garmendia L, Hernandez A, Linares JF, Martinez-Solano L, et al. A global view of antibiotic resistance. FEMS Microbiol Rev. 2009;33 (1):44-65.
20. Nikaido H. Structure and mechanism of RND-type multidrug efflux pumps. Advances in enzymology and related areas of molecular biology. 2011;77:1.
21. Blanco P, Hernando-Amado S, Reales-Calderon JA, Corona F, Lira F, Alcalde-Rico M, et al. Bacterial Multidrug Efflux Pumps: Much More Than Antibiotic Resistance Determinants. Microorganisms. 2016;4(1).
22. Law CJ, Maloney PC, Wang DN. Ins and outs of major facilitator superfamily antiporters. Annu Rev Microbiol. 2008;62: 289-305.
23. Kuroda T, Tsuchiya T. Multidrug efflux transporters in the MATE family. Biochim Biophys Acta. 2009;1794(5):763-8.
24. Bialek-Davenet S, Lavigne J-P, Guyot K, Mayer N, Tournebize R, Brisse S, et al. Differential contribution of AcrAB and OqxAB efflux pumps to multidrug resistance and virulence in Klebsiella pneumoniae. Journal of Antimicrobial Chemotherapy. 2015;70(1):81-8.
25. Padilla E, Llobet E, Domenech-Sanchez A, Martinez-Martinez L, Bengoechea JA, Alberti S. Klebsiella pneumoniae AcrAB efflux pump contributes to antimicrobial resistance and virulence. Antimicrob Agents Chemother. 2010;54(1):177-83.
26. Goessens WH, van der Bij AK, van Boxtel R, Pitout JD, van Ulsen P, Melles DC, et al. Antibiotic trapping by plasmid-encoded CMY-2 beta-lactamase combined with reduced outer membrane permeability as a mechanism of carbapenem resistance in Escherichia coli. Antimicrob Agents Chemother. 2013;57(8):3941-9.
27. Garcia-Fernandez A, Villa L, Carta C, Venditti C, Giordano A, Venditti M, et al. Klebsiella pneumoniae ST258 producing KPC-3 identified in italy carries novel plasmids and OmpK36/OmpK35 porin variants. Antimicrob Agents Chemother. 2012;56(4):2143-5.
28. Shields RK, Nguyen MH, Potoski BA, Press EG, Chen L, Kreiswirth BN, et al. Doripenem MICs and ompK36 porin genotypes of sequence type 258, KPC-producing Klebsiella pneumoniae may

predict responses to carbapenem-colistin combination therapy among patients with bacteremia. Antimicrob Agents Chemother. 2015;59(3):1797-801.

29. Clancy CJ, Hao B, Shields RK, Chen L, Perlin DS, Kreiswirth BN, et al. Doripenem, gentamicin, and colistin, alone and in combinations, against gentamicin-susceptible, KPC-producing Klebsiella pneumoniae strains with various ompK36 genotypes. Antimicrob Agents Chemother. 2014;58(6):3521-5.
30. Satlin MJ, Chen L, Patel G, Gomez-Simmonds A, Weston G, Kim AC, et al. Multicenter Clinical and Molecular Epidemiological Analysis of Bacteremia Due to Carbapenem-Resistant Enterobacteriaceae (CRE) in the CRE Epicenter of the United States. Antimicrob Agents Chemother. 2017;61(4).

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/71761