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The role of ACT and FOX genes in *Klebsiella pneumoniae* strains isolated from hospitalized patients

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ABSTRACT

Klebsiella pneumoniae as a main opportunistic pathogen is a common cause of health-care-associated bacterial infections, which has shown high levels of drug resistance specifically in hospitalized patients. These bacteria are well-known for their ability to produce biofilm. The increase in the emergence of multidrug-resistance bacterial strains among hospital isolates of *K. pneumoniae* has reduced the efficiency of the treatment of infections resulted from these bacteria. Beta-lactamase enzymes such as AmpC enzymes are one of the strategies of antibiotic resistance in *K. pneumoniae*. In this way, this review has tried to discuss the advances and challenges of phenotypic diagnosis of AmpC enzymes and the identification of ACT and FOX genes among clinical isolates isolated from patients. Gram-negative bacteria with AmpC β-lactamases can resist to several antibiotics including cephalosporins, aminopenicillins, ureidopenicillins, carboxypenicillins, monobactams, and cephalosporins. The existence of beta-lactamase genes ACT and FOX is one of the effective reasons for drug resistance in hospital strains of *K. pneumoniae*. According to the results of this study, control infection and prevent the spread of drug-resistant bacteria, there is a need for careful management in drug administration and identification of resistant isolates.

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Introduction

Antibiotic resistance in pathogenic bacteria can be very complicated issue specifically in the case of health-care-associated bacterial infections [1]. *K. pneumoniae*, a main opportunistic pathogen with resistance to a broad range of antibiotics can lead to health-care-associated bacterial infections particularly in hospitalized patients. *K. pneumoniae* isolates are non-motile and usually encapsulated form. They ferment some sugars such as lactose and sucrose [2]. Most strains produce gas from sugars, and gas production from starch is an important diagnostic feature [3]. Almost all of them grow in citrate and Moller's KCN medium. These bacteria are found in the intestine and upper respiratory tract of humans and animals. Their G+C content is 52-58% and *K. pneumoniae* is the indicator bacterium of this group of bacteria. This bacterium is in the Enterobacteriaceae family [4]. According to the latest classification, *K. pneumoniae* subsp *rhinoscleromatis*, *K. pneumoniae* subsp *pneumoniae*, and *K. pneumoniae* subsp *ozaenae* are included in *K. pneumoniae* species [5].

Morphology and growth properties

The members of the *Klebsiella* genus are shorter and thicker than other members of the Enterobacteriaceae family and are about 0.6-6.0 µm in length and 0.3-1.0 µm in width [6]. They are seen in pairs or singles and sometimes they look like pneumococci in the form of diplobacilli. It produces many capsules in environments that contain carbohydrates and lack nitrogen. This bacterium is non-motile and possess type 1, 2, and 3 fimbriae [7]. This bacterium is destroyed within 30 min at a temperature of 55 °C, but it survives for months in a dry place as well as when stored at room

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temperature. These bacteria are facultative anaerobes and do not produce any hemolysis. The proper growth of these bacteria is at a temperature of 37 °C [8].

Biochemical activities and antigenic structures

K. pneumoniae produces gas and acid from almost all sugars. Indole and gelatin are negative and citrate, urea, mannitol lysine decarboxylate is positive. Depending on the type of polysaccharide in the capsule, there are three capsular serological types A, B, and C in *K. pneumoniae*. Moreover, other three types of D, E, F among *K. pneumoniae* subsp *ozaenae* were added to this collection and reached more than 8 types in 1949 and were renamed in the following years. In the structure of these bacteria, there is antigen O, which has several different types [9].

Pathogenic properties

K. pneumoniae is one of the important cases of community and hospital-acquired infections [10]. This bacterium is one of the most common hospital pathogens, which has a high mortality rate and causes various types of infections including pneumonia, septicemia, diarrhea, liver abscess, endophthalmitis, meningitis, urinary infections, and bacteremia, especially in four million babies die every year [11, 12]. The highest rate of death in infants is related to pneumonia, septicemia, meningitis, and diarrhea infections, infants are more vulnerable due to a lack of a complete immune system [13].

Antibiotic resistance

Treatment of infections in infants infected with organisms resistant to several drugs has become a serious problem [14-18]. The increasing trend of drug resistance among bacteria, especially hospital isolates, has limited the therapeutic options for treating infections caused by these opportunistic pathogens [19-23]. One of the resistance mechanisms in bacteria is beta-lactamases. These enzymes are considered as the main defense of Gram-negative bacteria against antibiotics [24]. Antibiotic resistance has always been a serious problem for human health and affects patients in hospitals all over the world. Therefore, the World Health Organization designated 2011 as Named the year of antibiotic resistance [25]. This organization has given many recommendations to governments to control and prevent antibiotic resistance; which includes the assessment of antibiotic resistance, the correct use of antibiotics, the sale of antibiotics only with a doctor's prescription, control and prevention of infections [26]. Figure 1a illustrate biological macromolecule targets and timeline of antibiotics discoveries [1]. Gram-negative and Gram-positive bacteria can become resistant to antibiotics for several mechanisms, as shown in Figure 1b [27, 28].
The increasing emergence of drug resistance among hospital isolates of *K. pneumoniae* has limited the therapeutic options for treating infections caused by this bacterium. Most isolates of *K. pneumoniae* are resistant to several antibiotics [29]. Among the antibiotic resistance mechanisms, beta-lactamases are considered as the main defense of Gram-negative bacteria, especially *K. pneumoniae*, against beta-lactam antibiotics [30, 31]. According to Ambler, Bush-Jacoby, beta-lactamases are divided into four groups [32]. Table 1 illustrates the classification of beta-lactamases.

Beta-lactamase

There are two main families of β-lactamases in bacteria: serine β-lactamases (function by acylation and deacylation reactions) and metallo-β-lactamases (catalyze the hydrolysis of a wide spectrum of β-lactam antibiotics such as carbapenems) [33-35]. The different mechanisms of their families are responsible for their different behavior toward metal chelating substances such as ethylenediaminetetraacetic acid (EDTA), in which serine β-lactamases are not affected by these substances, but metallo-β-lactamases are inhibited by these substances [36]. There are many differences between these two enzymes. The different mechanisms between these two enzymes cause the difference in their molecular structure and phylogeny [37]. Serine beta-lactamases belong to the acetyltransferases of the SxxK superfamily and are structurally and mechanistically related to penicillin-binding proteins [38]. Metallo-β-lactamases were discovered in 1960, and since many genes encoding metallo-β-lactamases were located on mobile genetic

elements, they quickly spread among Gram-negative bacteria [35].

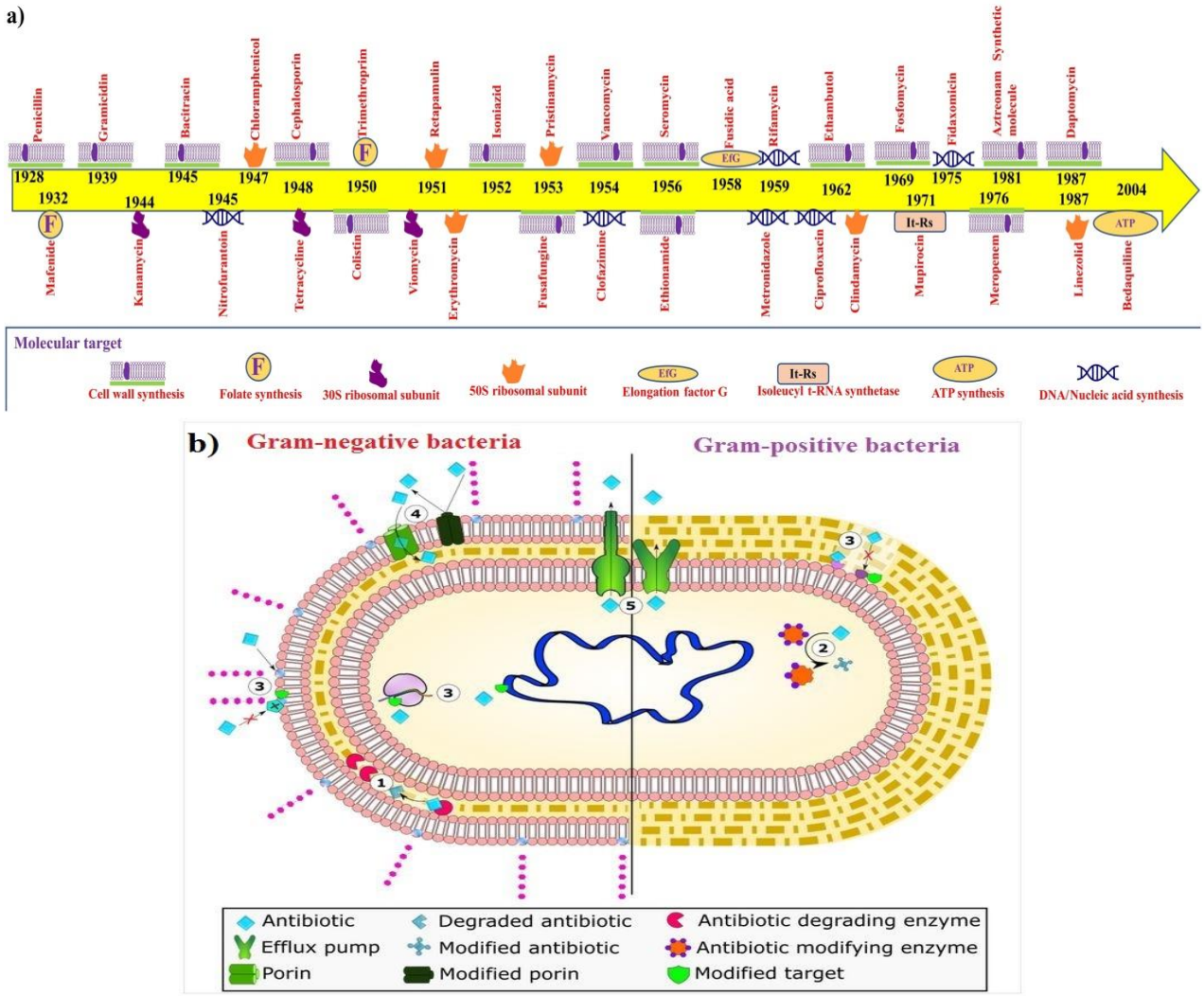

Fig. 1. a) Biological macromolecule targets and timeline of antibiotics discoveries (adapted and modified from [1]). b) Several antibacterial mechanisms for Gram-negative and Gram-positive bacteria (adapted and modified from [27]).

Beta-lactamase with a wide range

Beta-lactamases are usually classified based on two general schemes: 1-Ambler's molecular classification scheme 2-Bush-Jacoby-Medeiros functional classification system [39]. 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 classification [40]. In Ambler's classification, classes A, C, D are serine β-lactamases, while the enzymes in class B are actually metallo-β-lactamases. The basis of classification in the Bush-Jacoby-Medeiros class is the functional similarities of enzymes, such as enzyme-substrate characteristics or inhibitor characteristics [41, 42].

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) [43]. These enzymes are inhibited by clavulanic acid and have been seen in *Enterobacteriaceae*, *Pseudomonas*, and *Acinetobacter baumannii* bacteria [44]. According to the Bush-Jacoby 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 mobile genetic elements such as plasmids or chromosomes [45].

Enzyme of AmpC

The genes encoding these enzymes are located on the chromosome or plasmid. Bacteria containing this enzyme can hydrolyze the antibiotics cephalothin, cefazolin, cefoxitin, most penicillins, and beta-lactam compounds that inhibit beta-lactamase [46, 47]. In many bacteria, Amp-C enzymes are inducible and expressed at high levels due to mutation. Very high expression of these enzymes makes bacteria resistant to cephalosporins including cefotaxime, ceftazidime, and ceftriaxone antibiotics [48]. In some bacteria such as *K. pneumoniae*, *Escherichia coli*, and *Proteus*, the gene coding for these enzymes is located on a plasmid. The resistance caused by these enzymes is less than beta-lactamases with a wide spectrum. These enzymes are in group C of beta-lactamase classification [49-51]. Gram-negative bacteria having AmpC β-lactamases are resistant to various antibiotics involving cephalosporins, aminopenicillins, ureidopenicillins, carboxypenicillins, monobactams, and cephalosporins [52].

ACT-1 gene was first detected in 1997 in America and in *K. pneumoniae* bacteria. ACT-1 gene is connected to ampR genes and can be induced. In addition, the expression level of this gene increases with the loss of ampD function [53]. *E. coli* strains containing ACT-1 that are defective in ampD are sensitive to imipenem, but *K. pneumoniae* isolates that have plasmid ACT-1 gene and lack outer membrane proteins are resistant to imipenem. Bacteria with this gene are resistant to cephalosporins and inhibition by clavulanic acid [54, 55]. So far, 37 variants (Table 1) of ACT have been identified in the world [56].

The FOX gene was first reported in 1994 from Argentina in *K. pneumoniae*. FOX-type beta-lactamase is 72% similar to CMY-type enzyme in these bacteria. FOX-1 was first detected in *K. pneumoniae* and FOX-2 in Escherichia coli bacteria. Two new members of the FOX family have been reported in Italy and Spain. In the United States, strains of Escherichia coli and *K. pneumoniae* producing FOX-type beta-lactamase have been reported. Bacteria containing this gene are resistant to cephalosporins and inhibition by clavonic acid. So far, 12 types of FOX (Table 2) have been identified in the world [57].

Table 1. ACT type beta-lactamases.

Enzyme	Nucleotide
ACT-1	U58495
ACT-2	AM076977
ACT-3	EF125013
ACT-4	EU427302
ACT-5	FJ237369
ACT-6	FJ237366
ACT-7	FJ237368
ACT-8	Assigned
ACT-9	HQ693810
ACT-10	JN848330
ACT-11	Assigned
ACT-12	JX440355
ACT-13	HE819402
ACT-14	JX440354
ACT-15	JX440356
ACT-16	AB737978
ACT-17	KF992026
ACT-18	KF992028
ACT-19	KF992029
ACT-20	KF526117
ACT-21	KF526118
ACT-22	KF992027
ACT-23	KF515536
ACT-24	KJ207207
ACT-25	KJ207208
ACT-26	Withdrawn
ACT-27	KJ207209
ACT-28	KJ207206
ACT-29	KM087832
ACT-30	KM087833
ACT-31	KM087843
ACT-32	KM087835
ACT-33	KM987834
ACT-34	Assigned
ACT-35	LC004922
ACT-36	Assigned
ACT-37	Assigned

Table 2. FOX type beta-lactamases.

Enzyme	Nucleotide
FOX-1	X77455
FOX-2	Y10282
FOX-3	Y11068
FOX-4	AJ277535
FOX-5	AY007369
FOX-6	AY034848
FOX-7	AJ703795
FOX-8	HM565917
FOX-9	JF896803
FOX-10	JX049131
FOX-11	Assigned
FOX-12	Assigned

Conclusions

Antibiotic resistance in the various strains of *K. pneumoniae* can be complicated issue specifically in the case of health-care-associated bacterial infections. Opportunistic pathogenic bacteria of *K. pneumoniae* can resist a wide range of antibiotics causing health-care-associated bacterial infections, particularly in hospitalized patients. The transfer of productive genes from the effective use of microbiology laboratories for correct diagnosis and preventing the spread of resistant pathogens reduces the need to use unnecessary drugs. The existence of beta-lactamase genes ACT and FOX is one of the effective reasons for drug resistance. If effective measures are not taken to prevent the development of antibiotic resistance, perhaps bacterial resistance to cephalosporins such as carbonicillin and piperacillin will reach 100%. Beta-lactamase-producing bacteria with a wide spectrum are resistant to the antibiotic aztreonam.

Study Highlights

- Antibiotic resistance in the various strains of *K. pneumoniae* can be complicated issue in health-care-associated bacterial infections.
- Beta-lactamase-producing bacteria with a wide spectrum are resistant to the antibiotic aztreonam.
- Bacteria of *K. pneumoniae* can resist a wide range of antibiotics causing health-care-associated bacterial infections, particularly in hospitalized patients.
- The existence of beta-lactamase genes ACT and FOX is one of the effective reasons for drug resistance.

Abbreviations

EDTA: Ethylenediaminetetraacetic acid

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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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References

1. Imchen M, Moopantakath J, Kumavath R, Barh D, Tiwari S, Ghosh P, et al. Current trends in experimental and computational approaches to combat antimicrobial resistance. Frontiers in Genetics. 2020;11:563975. doi:https://doi.org/10.3389/fgene.2020.563975
2. Darniati D, Setiyaningsih S, Agungpriyono DR, Handharyani E. First evidence of Klebsiella pneumoniae infection in Aceh cattle: Pathomorphology and antigenic distribution in the lungs. Vet World. 2021;14(4):1007-13. doi:https://doi.org/10.14202/vetworld.2021.1007-1013
3. Tolonen AC, Beauchemin N, Bayne C, Li L, Tan J, Lee J, et al. Synthetic glycans control gut microbiome structure and mitigate colitis in mice. Nature Communications. 2022;13(1):1244. doi:https://doi.org/10.1038/s41467-022-28856-x
4. Wyres KL, Lam MMC, Holt KE. Population genomics of Klebsiella pneumoniae. Nature Reviews Microbiology. 2020;18(6):344-59. doi:https://doi.org/10.1038/s41579-019-0315-1
5. Gao M, Wang C, Qiang X, Liu H, Li P, Pei G, et al. Isolation and Characterization of a Novel Bacteriophage Infecting Carbapenem-Resistant

Klebsiella pneumoniae. Current microbiology. 2020;77(5):722-9. doi:https://doi.org/10.1007/s00284-019-01849-8
6. Grimont PAD, Grimont F. Klebsiella. Bergey's Manual of Systematics of Archaea and Bacteria. p. 1-26. doi:https://doi.org/10.1002/9781118960608.gbm01150
7. Sharma D, Garg A, Kumar M, Rashid F, Khan AU. Down-Regulation of Flagellar, Fimbriae, and Pili Proteins in Carbapenem-Resistant Klebsiella pneumoniae (NDM-4) Clinical Isolates: A Novel Linkage to Drug Resistance. Frontiers in microbiology. 2019;10. doi:https://doi.org/10.3389/fmicb.2019.02865
8. Mariz BALA, Sánchez-Romero C, Romañach MJ, de Almeida OP, Carlos R. Respiratory scleroma: A clinicopathologic study of 51 cases from Guatemala. Oral Diseases. 2020;26(3):670-6. doi:https://doi.org/10.1111/odi.13264
9. Shi Y, Yang H, Chu M, Niu X, Huo X, Gao Y, et al. Chapter 13 - Klebsiella. In: Amaresan N, Senthil Kumar M, Annapurna K, Kumar K, Sankaranarayanan A, editors. Beneficial Microbes in Agro-Ecology: Academic Press; 2020. p. 233-57. doi:https://doi.org/10.1016/B978-0-12-823414-3.00013-7
10. Lam MMC, Wick RR, Watts SC, Cerdeira LT, Wyres KL, Holt KE. A genomic surveillance framework and genotyping tool for Klebsiella pneumoniae and its related species complex. Nature Communications. 2021;12(1):4188. doi:https://doi.org/10.1038/s41467-021-24448-3
11. Russo TA, Marr CM. Hypervirulent Klebsiella pneumoniae. Clin Microbiol Rev. 2019;32(3). doi:https://doi.org/10.1128/cmr.00001-19
12. Martin RM, Bachman MA. Colonization, Infection, and the Accessory Genome of Klebsiella pneumoniae. Frontiers in cellular and infection microbiology. 2018;8. doi:https://doi.org/10.3389/fcimb.2018.00004
13. Vading M, Nauclér P, Kalin M, Giske CG. Invasive infection caused by Klebsiella pneumoniae is a disease affecting patients with high comorbidity and associated with high long-term mortality. PloS one. 2018;13(4):e0195258. doi:https://doi.org/10.1371/journal.pone.0195258
14. Abbas-Al-Khafaji ZK, Aubais-aljelehawy Qh. Evaluation of antibiotic resistance and prevalence of multi-antibiotic resistant genes among Acinetobacter baumannii strains isolated from patients admitted to al-yarmouk hospital. Cellular, Molecular and Biomedical Reports. 2021;1(2):60-8. doi:https://doi.org/10.55705/cmbr.2021.142761.1015
15. Ahmadi S. Antibacterial and antifungal activities of medicinal plant species and endophytes. Cellular, Molecular and Biomedical Reports. 2022;2(2):109-15. doi:https://doi.org/10.55705/cmbr.2022.340532.1042
16. Ahmadi S, Ahmadi G, Ahmadi H. A review on antifungal and antibacterial activities of some medicinal plants. Micro Nano Bio Aspects. 2022;1(1):10-7
17. Alavi M, Hamblin MR, Mozafari MR, Rose Alencar de Menezes I, Douglas Melo Coutinho H. Surface modification of SiO2 nanoparticles for bacterial decontaminations of blood products. Cellular, Molecular and Biomedical Reports. 2022;2(2):87-97. doi:https://doi.org/10.55705/cmbr.2022.338888.1039
18. Alavi M, Kowalski R, Capasso R, Douglas Melo Coutinho H, Rose Alencar de Menezes I. Various novel strategies for functionalization of gold and silver nanoparticles to hinder drug-resistant bacteria and cancer cells. Micro Nano Bio Aspects. 2022;1(1):38-48
19. Alavi M, Martinez F, Delgado DR, Tinjacá DA. Anticancer and antibacterial activities of embelin: Micro and nano aspects. Micro Nano Bio Aspects. 2022;1(1):30-7
20. Alavi M, Rai M. Antisense RNA, the modified CRISPR-Cas9, and metal/metal oxide nanoparticles to inactivate pathogenic bacteria. Cellular, Molecular and Biomedical Reports. 2021;1(2):52-9. doi:https://doi.org/10.55705/cmbr.2021.142436.1014
21. Alavi M, Rai M, Martinez F, Kahrizi D, Khan H, Rose Alencar de Menezes I, et al. The efficiency of metal, metal oxide, and metalloid nanoparticles against cancer cells and bacterial pathogens: different mechanisms of action. Cellular, Molecular and Biomedical Reports. 2022;2(1):10-21. doi:https://doi.org/10.55705/cmbr.2022.147090.1023
22. Alavi M, Thomas S, Sreedharan M. Modification of silica nanoparticles for antibacterial activities: mechanism of action. Micro Nano Bio Aspects. 2022;1(1):49-58
23. Aubais aljelehawy Qh, Hadi Alshaibah LH, Abbas Al- Khafaji ZK. Evaluation of virulence factors among Staphylococcus aureus strains isolated from patients with urinary tract infection in Al-Najaf Al-Ashraf teaching hospital. Cellular, Molecular and Biomedical Reports. 2021;1(2):78-87. doi:https://doi.org/10.55705/cmbr.2021.144995.1017
24. Hansen GT. Continuous Evolution: Perspective on the Epidemiology of Carbapenemase Resistance Among Enterobacterales and Other Gram-Negative Bacteria. Infectious Diseases and Therapy. 2021;10(1):75-92. doi:https://doi.org/10.1007/s40121-020-00395-2
25. Nadeem SF, Gohar UF, Tahir SF, Mukhtar H, Pornpukdeewattana S, Nukthamna P, et al. Antimicrobial resistance: more than 70 years of war

between humans and bacteria. Critical Reviews in Microbiology. 2020;46(5):578-99. doi:https://doi.org/10.1080/1040841X.2020.1813687
26. Gu Y, Fujitomo Y, Ohmagari N. Outcomes and Future Prospect of Japan's National Action Plan on Antimicrobial Resistance (2016–2020). Antibiotics. 2021;10(11):1293. doi:https://doi.org/10.3390/antibiotics10111293
27. Varela MF, Stephen J, Lekshmi M, Ojha M, Wenzel N, Sanford LM, et al. Bacterial Resistance to Antimicrobial Agents. Antibiotics. 2021;10(5):593. doi:https://doi.org/10.3390/antibiotics10050593
28. kheyrodin H, Jami R, Rehman FU. Cellular structure and molecular functions of plants, animals, bacteria, and viruses. Cellular, Molecular and Biomedical Reports. 2022;2(1):33-41. doi:https://doi.org/10.55705/cmbr.2022.330941.1021
29. Caneiras C, Lito L, Melo-Cristino J, Duarte A. Community- and Hospital-Acquired Klebsiella pneumoniae Urinary Tract Infections in Portugal: Virulence and Antibiotic Resistance. Microorganisms. 2019;7(5):138. doi:https://doi.org/10.3390/microorganisms7050138
30. Aurilio C, Sansone P, Barbarisi M, Pota V, Giaccari LG, Coppolino F, et al. Mechanisms of Action of Carbapenem Resistance. Antibiotics. 2022;11(3):421. doi:https://doi.org/10.3390/antibiotics11030421
31. Wang G, Zhao G, Chao X, Xie L, Wang H. The Characteristic of Virulence, Biofilm and Antibiotic Resistance of Klebsiella pneumoniae. International Journal of Environmental Research and Public Health. 2020;17(17):6278. doi:https://doi.org/10.3390/ijerph17176278
32. Sawa T, Kooguchi K, Moriyama K. Molecular diversity of extended-spectrum β-lactamases and carbapenemases, and antimicrobial resistance. Journal of Intensive Care. 2020;8(1):13. doi:https://doi.org/10.1186/s40560-020-0429-6
33. Bush K, Bradford PA. Interplay between β-lactamases and new β-lactamase inhibitors. Nature Reviews Microbiology. 2019;17(5):295-306. doi:https://doi.org/10.1038/s41579-019-0159-8
34. Salahuddin P, Kumar A, Khan AU. Structure, Function of Serine and Metallo-β-lactamases and their Inhibitors. Curr Protein Pept Sci. 2018;19(2):130-44. doi:https://doi.org/10.2174/092986652466617072416 0623
35. Bahr G, González LJ, Vila AJ. Metallo-β-lactamases in the Age of Multidrug Resistance: From Structure and Mechanism to Evolution, Dissemination, and Inhibitor Design. Chemical Reviews. 2021;121(13):7957-8094. doi:https://doi.org/10.1021/acs.chemrev.1c00138
36. Maraki S, Mavromanolaki VE, Moraitis P, Stafylaki D, Kasimati A, Magkafouraki E, et al. Ceftazidime-avibactam, meropenen-vaborbactam, and imipenem-relebactam in combination with aztreonam against multidrug-resistant, metallo-β-lactamase-producing Klebsiella pneumoniae. European Journal of Clinical Microbiology & Infectious Diseases. 2021;40(8):1755-9. doi:https://doi.org/10.1007/s10096-021-04197-3
37. Philippon A, Arlet G, Labia R, Iorga BI. Class C β-Lactamases: Molecular Characteristics. Clinical microbiology reviews.0(0):e00150-21. doi:https://doi.org/10.1128/cmr.00150-21
38. Peitsaro N, Polianskyte Z, Tuimala J, Pörn-Ares I, Liobikas J, Speer O, et al. Evolution of a family of metazoan active-site-serine enzymes from penicillin-binding proteins: a novel facet of the bacterial legacy. BMC Evol Biol. 2008;8:26. doi:https://doi.org/10.1186/1471-2148-8-26
39. Noster J, Thelen P, Hamprecht A. Detection of Multidrug-Resistant Enterobacterales—From ESBLs to Carbapenemases. Antibiotics. 2021;10(9):1140. doi:https://doi.org/10.3390/antibiotics10091140
40. Zhang S-Y, Suttner B, Rodriguez-R LM, Orellana LH, Conrad RE, Liu F, et al. ROCker Models for Reliable Detection and Typing of Short-Read Sequences Carrying β-Lactamase Genes. mSystems. 2022;7(3):e01281-21. doi:https://doi.org/10.1128/msystems.01281-21
41. Tooke CL, Hinchliffe P, Bragginton EC, Colenso CK, Hirvonen VHA, Takebayashi Y, et al. β-Lactamases and β-Lactamase Inhibitors in the 21st Century. Journal of Molecular Biology. 2019;431(18):3472-500. doi:https://doi.org/10.1016/j.jmb.2019.04.002
42. Avci FG, Tastekil I, Jaisi A, Ozbek Sarica P, Sariyar Akbulut B. A review on the mechanistic details of OXA enzymes of ESKAPE pathogens. Pathogens and Global Health. 2022:1-16. doi:https://doi.org/10.1080/20477724.2022.2088496
43. Carcione D, Siracusa C, Sulejmani A, Leoni V, Intra J. Old and New Beta-Lactamase Inhibitors: Molecular Structure, Mechanism of Action, and Clinical Use. Antibiotics. 2021;10(8):995. doi:https://doi.org/10.3390/antibiotics10080995
44. Bush K. Past and Present Perspectives on β-Lactamases. Antimicrobial agents and chemotherapy. 2018;62(10). doi:https://doi.org/10.1128/aac.01076-18
45. Viana Marques DDA, Machado SEF, Ebinuma VCS, Duarte CDAL, Converti A, Porto ALF. Production of β-Lactamase Inhibitors by Streptomyces Species. Antibiotics. 2018;7(3):61. doi:https://doi.org/10.3390/antibiotics7030061
46. Russ D, Glaser F, Shaer Tamar E, Yelin I, Baym M, Kelsic ED, et al. Escape mutations circumvent a tradeoff between resistance to a beta-lactam and

resistance to a beta-lactamase inhibitor. Nature Communications. 2020;11(1):2029. doi:https://doi.org/10.1038/s41467-020-15666-2
47. Lai CKC, Ng RWY, Leung SSY, Hui M, Ip M. Overcoming the rising incidence and evolving mechanisms of antibiotic resistance by novel drug delivery approaches – An overview. Advanced Drug Delivery Reviews. 2022;181:114078. doi:https://doi.org/10.1016/j.addr.2021.114078
48. Zhou D, Sun Z, Lu J, Liu H, Lu W, Lin H, et al. Characterization of a Novel Chromosomal Class C β-Lactamase, YOC-1, and Comparative Genomics Analysis of a Multidrug Resistance Plasmid in Yokenella regensburgei W13. Frontiers in microbiology. 2020;11. doi:https://doi.org/10.3389/fmicb.2020.02021
49. Elshamy AA, Saleh SE, Alshahrani MY, Aboshanab KM, Aboulwafa MM, Hassouna NA. OXA-48 Carbapenemase-Encoding Transferable Plasmids of Klebsiella pneumoniae Recovered from Egyptian Patients Suffering from Complicated Urinary Tract Infections. Biology. 2021;10(9):889. doi:https://doi.org/10.3390/biology10090889
50. Santiago GS, Gonçalves D, da Silva Coelho I, de Mattos de Oliveira Coelho S, Neto Ferreira H. Conjugative plasmidic AmpC detected in Escherichia coli, Proteus mirabilis and Klebsiella pneumoniae human clinical isolates from Portugal. Brazilian Journal of Microbiology. 2020;51(4):1807-12. doi:https://doi.org/10.1007/s42770-020-00355-5
51. Rodríguez-Guerrero E, Callejas-Rodelas JC, Navarro-Marí JM, Gutiérrez-Fernández J. Systematic Review of Plasmid AmpC Type Resistances in Escherichia coli and Klebsiella pneumoniae and Preliminary Proposal of a Simplified Screening Method for ampC. Microorganisms. 2022;10(3):611. doi:https://doi.org/10.3390/microorganisms10030611
52. Jameel NU, Ejaz H, Zafar A, Amin H. Multidrug resistant AmpC β-lactamase producing Escherichia coli isolated from a paediatric hospital. Pak J Med Sci. 2014;30(1):181-4. doi:10.12669/pjms.301.4045
53. Philippon A, Arlet G, Labia R, Iorga BI. Class C β-Lactamases: Molecular Characteristics. Clinical microbiology reviews.0(0):e00150-21. doi:https://doi.org/10.1128/cmr.00150-21
54. Hussain HI, Aqib AI, Seleem MN, Shabbir MA, Hao H, Iqbal Z, et al. Genetic basis of molecular mechanisms in β-lactam resistant gram-negative bacteria. Microbial Pathogenesis. 2021;158:105040. doi:https://doi.org/10.1016/j.micpath.2021.105040
55. Bush K, Bradford PA. Epidemiology of β-Lactamase-Producing Pathogens. Clinical microbiology reviews. 2020;33(2):e00047-19. doi:https://doi.org/10.1128/CMR.00047-19
56. Jacoby GA. AmpC β-Lactamases. Clinical microbiology reviews. 2009;22(1):161-82. doi:https://doi.org/10.1128/CMR.00036-08
57. Queenan AM, Jenkins S, Bush K. Cloning and Biochemical Characterization of FOX-5, an AmpC-Type Plasmid-Encoded β-Lactamase from a New York CityKlebsiella pneumoniae Clinical Isolate. Antimicrobial agents and chemotherapy. 2001;45(11):3189-94. doi:https://doi.org/10.1128/AAC.45.11.3189-3194.2001

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