HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2022.56588
Haydarpasa Numune Med J 2024;64(1):111–117

REVIEW

Importance of Enterobacterales that Develop Resistance Due to Expanded-Spectrum Beta-Lactamase and Carbapenemase Production

Neval Yurttutan Uyar[1], Meltem Ayaş[2,3]

[1]Department of Clinical Microbiology, Mehmet Ali Aydinlar University, Medical Faculty, Istanbul, Turkiye
[2]Department of Medical Biotechnology, Mehmet Ali Aydinlar University, Instute of Health Science, Istanbul, Turkiye
[3]Program of Medical Laboratory Techniques, Mehmet Ali Aydinlar University, Vocational School of Health Services, Istanbul, Turkiye

Abstract

The development of antibiotic resistance is increasing worldwide. Third-generation cephalosporins-resistant Enterobacterales (ESBL-E) and carbapenems-resistant Enterobacterales (CRE) have been placed in the critical category by the World Health Organization on its list of global priority pathogens.

ESBL-E is a group of Enterobacterales bacteria that exhibit resistance to beta-lactams, broad-spectrum beta-lactams, and third-generation cephalosporins. The CTX-M-15 enzyme, responsible for resistance, is the most identified identified in the ESBL-E group bacteria.

In parallel with the increase in infectious diseases caused by the ESBL-E group bacteria, the use of carbapenems increased, resulting in an increase in carbapenem resistance. Carbapenemases are classified into three groups: A, B, and D. OXA (Oxacillin-hydrolyzing carbapenemase) enzymes that form Class D carbapenemases are endemic in Türkiye.

The first CRE strain was detected in the 1980s and soon spread worldwide. Carbapenemase groups A, B, and D are observed in various countries and are even considered endemic in some, such as Türkiye.

At EUCAST (European Committee on Antimicrobial Susceptibility Testing) and CLSI (Clinical and Laboratory Standards Institute) guidelines, the carbapenem group of antibiotics are suggested as preferred agents for the treatment of ESBL-producing Enterobacterales serious infections.

There are three approaches for treating infections caused by carbapenem-resistant Enterobacterales: 1) re-evaluation of treatment options with existing antibiotics (fosfomycin, colistin, tigecycline, such as the use of older antibiotics), 2) treatment with two carbapenems (combination of two different carbapenems), 3) treatment with new β-lactam and beta-lactamase inhibitor combinations or with new antibiotics (Ceftazidime/avibactam, Meropenem/vaborbactam, Plazomicin, Eravacyclin; the use of new antibiotics).

An increase in the prevalence of multidrug-resistant bacterial infections such as CRE and ESBL-E is causing antibiotic resistance to pose a global threat today. An international, multidisciplinary approach is needed to combat this global threat.

Keywords: Antibiotic resistance; CRE; ESBL-E.

Antibiotic resistance is a growing problem worldwide. Current resistance genes are against all antibiotics, and highly resistant pathogens are becoming prevalent. Gram-negative bacteria have developed many structural adaptations as enzymes that disrupt the structure of antibiotics, causing the widest spectrum of resistance

Correspondence: Neval Yurttutan Uyar, M.D. Department of Clinical Microbiology, Mehmet Ali Aydinlar University, Medical Faculty, Istanbul, Turkiye
Phone: +90 212 500 46 17 **E-mail:** nevaluyar@gmail.com
Submitted Date: 06.04.2022 **Revised Date:** 08.09.2022 **Accepted Date:** 16.10.2022

including expanded-spectrum beta-lactamases (ESBL), AmpC β-Lactamases, and carbapenemases[1]. Particularly, carbapenemase-producing Enterobacterales are of serious importance.

Enterobacterales are Gram-negative bacteria, a member of the intestinal flora, and also a common etiologic agent of both community and nosocomial infections. Through contaminated food, water, and hands, Enterobacterales easily spread between human beings and also develop antibiotic resistance by transferring genetic material. Most of the time, they use horizontal gene transfer mediated by plasmids and transposons[2-4].

The World Health Organization (WHO) recently published a Global Priority Pathogens List of the vital resistant pathogens. The third-generation cephalosporin-resistant Enterobacterales (ESBL-E) and carbapenems-resistant Enterobacterales (CRE) are in the critical category of that list[5].

Extended Spectrum Beta-Lactamase Producing Enterobacterales (ESBL-E)

Enterobacterales group bacteria that exhibit resistance to beta-lactams, broad-spectrum beta-lactams, and third-generation cephalosporins are named as ESBL-E. ESBL-E, such as TEM-1, TEM-2, SHV1, and OXA-10, has been predominantly associated with nosocomial outbreaks because the resistance is caused by point mutations and transferred by plasmid. The CTX-M-15 type ESBL-E is the most commonly identified and is common in many countries in Europe, Asia, Africa, and the United States[6-8]. It has been shown in several studies that the prevalence of health care-related infectious disease caused by ESBL-E group bacteria has increased over the years[9].

TEM- and SHV-type ESBLs are most often found in *Escherichia coli* and *Klebsiella pneumoniae*; TEM beta-lactamases have been found mainly in clinical isolates of *E. coli*[10,11]. The majority of SHV-type ESBLs are found in strains of *K. pneumoniae*. The SHV-1 beta-lactamase is most commonly found in *K. pneumoniae* and is responsible for up to 20% of the plasmid-mediated ampicillin resistance in this species[12,13].

Carbapenem Resistant Enterobacterales (CRE)

Increased ESBL-E prevalence causes excessive consumption of carbapenems, leading to the emergence and spread of carbapenem resistance, especially in Enterobacterales[14]. Attention should be taken in the diagnosis, treatment, and prevention of CRE infections. Bacteria may have multiple resistance mechanisms to carbapenems, but the most common is carbapenemase enzyme production. Carbapenem-resistant Enterobacterales produce carbapenemases by many ways to break down antibiotics[15,16].

Carbapenemases are classified into a total of three groups, A, B, and D, according to the Ambler classification.

The Class A carbapenemase, the most common group, consists of KPC (*Klebsiella pneumoniae* carbapenemase) and IMI (Imipenem-hydrolyzing beta-lactamase) type. KPC is the most common carbapenemase gene among Enterobacterales.

Class B is defined by metallo-beta-lactamase (MBL) structures. These enzymes include NDM (New Delhi metallo beta-lactamase), IMP (Imipenem-resistant Pseudomonas), and VIM (Verona integron-encoded metallo-lactamase). These carbapenemases are usually found in plasmid vectors and other transposable elements, making their transfer to other bacteria easy. High sequence diversity (15-17%) makes it difficult to detect these enzymes by molecular tests and slows down research about their prevalence. Current epidemiology studies suggest that NDM-1 is the most common cause of carbapenem resistance[17,18].

OXA (Oxacillin-hydrolyzing carbapenemase) enzymes form Class D carbapenemases. OXA-48 carbapenemases, first detected in Türkiye in 2001, also pose a public health threat. Due to variable carbapenem resistance prevalence, the spread of OXA-48 was initially underestimated. However, multiple countries have interregional distribution, and OXA-48 is endemic to Malta and Türkiye since 2015[19-23].

All around the world, researchers face and identify various carbapenemase genes due to international travel.

KPC, NDM, and OXA-48 are mostly found in *K. pneumoniae*. In a review of 4440 carbapenem-resistant Enterobacterales isolates submitted to the United States Centers for Disease Control and Prevention (CDC) in 2017, 32 percent produced a carbapenemase, and among those, 88 percent possessed the KPC beta-lactamase. OXA-48 β-lactamase was originally described in a Klebsiella pneumoniae isolate from Istanbul, Türkiye, in 2001. It is now widespread in *K. pneumoniae*, and Türkiye was reported as having the highest epidemiologic level called endemic in 2015[17,18,24,25].

Change in Resistance Over the Years

Since the discovery of the CRE strain in the 1980s, it has spread exponentially around the world[26]. Surveillance studies show that some classes of carbapenemases are common in certain parts of the world. In this context, while NDM-1 type is the most common type of carbapenemase in India, Pakistan, and

Sri Lanka; KPC type in the American continent and Europe; OXA-48 is endemic in Türkiye and Malta[27].

The first case of carbapenemase-producing Enterobacterales was identified in *Serratia marcescens* in Japan during a plasmid-mediated outbreak in seven hospitals. Then, with broad spread distribution, it (bla-IMP-1) spread throughout Japan[26]. Since then, 52 IMP gene variants have been established, with endemicity restricted to Japan and Taiwan[28].

Soon, VIM was identified in *P. aeruginosa* strains[29]. In the beginning of the 2000s, VIM type carbapenemase-producing *K. pneumoniae* and *E. coli* have also been reported to be endemic in Greece[30,31].

However, the major threat to the MBL-producing Enterobacterales was revealed by the isolation of the NDM enzyme producing ST14 *K. pneumoniae* strain from a Swedish patient receiving healthcare in New Delhi, India[32].

KPC producing Enterobacterales, especially *K. pneumoniae* due to ST258 enzyme, cause aggressive pandemics. These species are endemic in Greece, Israel, and the American continent[33]. Actually, the KPC endemicity is expected; just five years after KPC was first isolated from *K. pneumoniae* at a North Carolina hospital in 1996[34], an outbreak of KPC producing bacteria occurred among hospitalized patients in the northeastern United States[35].

VIM enzymes were predominant at the beginning in Greece, one of the countries with the highest CRE ratios worldwide, but after 2007 KPC became the predominant carbapenems in the country[33]. Finally, OXA-48 outbreaks have been reported in several countries, but only in Türkiye, Japan, and Taiwan is it accepted to be endemic[36].

Treatment Options If Resistance Is Detected

According to EUCAST (European Committee on Antimicrobial Susceptibility Testing) and CLSI (Clinical and Laboratory Standards Institute) guidelines, for the treatment of Enterobacterales-caused infections, carbapenems could be used[37,38].

Carbapenems, including imipenem, meropenem, doripenem, and ertapenem, are the first-choice agents for the treatment of ESBL-producing Enterobacterales. Carbapenems are highly stable against the hydrolysis of ESBL[39].

However, with the increase of CRE, carbapenems are becoming ineffective. Considering the various mechanisms of carbapenem resistance, there are different approaches to treat CRE infections: reassessment of existing antibiotics as treatment options, combined treatment with carbapenems, and new antibiotics with new β-lactamase inhibitors[40].

1- Reconsidering Existing Antibiotics

Some "old antibiotics" could be used for the treatment of CRE.

Fosfomycin:

Fosfomycin is active against a majority of CRE, particularly *E. coli*, and has been used successfully as an oral formulation for the treatment of uncomplicated urinary tract infections for several decades. However, during monotherapy with fosfomycin, rapid resistance may develop. In vitro studies also demonstrated the appearance of resistant subpopulations within 30-40 hours of drug exposure[41].

Fosfomycin resistance can also be affected by the in vitro sensitivity method used. The approved MIC (Minimum Inhibitory Concentration) detection method is agar dilution using agar media supplemented with 25 µg/ml of glucose-6-phosphate. Resistance rates are higher in studies in which disk diffusion or microbroth dilution susceptibility testing were used than in studies with a reference agar dilution[42,43].

Fosfomycin therapy can be recommended for uncomplicated UTIs with ESBL-producing *E. coli* as a step-down outpatient therapy. However, for complicated UTIs, prostatitis, UTIs with *K. pneumoniae*, more data from well-designed studies are required[44].

Polymyxins (Colistin and Polymyxin B)

Colistin (or polymyxin E) has activity against most species in the order Enterobacterales (except for *Serratia marcescens* and *Proteus, Providencia, Morganella*, and *Hafnia* species) and is a key drug in the treatment of CRE infections. Nevertheless, CRE, especially *K. pneumoniae*, began to develop resistance to colistin, reducing the effectiveness of the drug as a monotherapy[45,46].

Colistin is administered as an inactive prodrug—colistin methane sulfonate—which results in a prolonged period of low plasma concentrations of the active drug and theoretically increases the risk of resistance development[46]. Consequently, colistin is used as part of dual treatment with meropenem, which reduces mortality, especially in septic shock and fatal comorbidity[47].

Polymyxin B, the other approved agent in the polymyxin class of antibiotics, is not formulated as a prodrug, which mitigates concerns related to a delayed increase in its plasma concentration. However, less is known about its pharmacokinetic, efficacy, and safety profiles. Because of

these concerns, the standard practice over the past decade has been to use colistin or polymyxin B in combination with at least one other agent of a different class when its use is warranted[48].

In addition, tigecycline is also available as an option for the treatment of CRE in some cases. The use of high doses of tigecycline has been investigated and shown to be effective in treating CRE infections[49].

2- Options of Combination Therapy

Combined Treatments with Carbapenems:

The dual use of carbapenems in the treatment of CRE infections is known as "double carbapenems." Usually, the combination consists of a long-term infusion of meropenem or doripenem over 3 or 4 hours followed by an initial dose of ertapenem, with 2 g of meropenem added every 8 hours. The greater affinity of ertapenem to KPC plays a "sacrificial role," since it is preferably hydrolyzed by carbapenemase, which allows maintaining a high concentration of the simultaneously administered second carbapenem[50,51].

Colistin–Fosfomycin Combinations:

The rationale for the combination of colistin and fosfomycin is the potentially enhanced penetration of fosfomycin resulting from the permeabilizing effect on the bacterial outer membrane caused by colistin. The real benefit of this combination is still uncertain; a small number of in vitro experiments and observational clinical studies provide some evidence. Clinical experience with fosfomycin for the treatment of MDR Gram-negative infections remains limited to small case series[52].

Tigecycline-Based Combinations:

Two in vitro studies have reported improved bactericidal activity of colistin–tigecycline compared with monotherapy. The addition of meropenem to tigecycline or to tigecycline–colistin did not show any advantage. This effect has also been observed in in vivo models. The combination of tigecycline and colistin was superior to monotherapy, even in isolates with high MICs for the two drugs[53,54].

Aminoglycoside-Based Combinations:

Aminoglycosides are an effective therapeutic option for CRE, even in the presence of colistin resistance. The rate of aminoglycoside susceptibility among CRE is variable and based on local epidemiology. An improved bactericidal effect for aminoglycosides in combination compared with monotherapy has been suggested in a few studies, even in the presence of isolates with high MIC for aminoglycosides[55,56]. Another study reported a reduced emergence of resistance at low concentrations for tigecycline–amikacin compared with other regimens (colistin–tigecycline and colistin–amikacin)[57].

3- New Antibacterial Drugs:

This group can be distinguished as newly approved antibiotics[58].

Ceftazidime/avibactam is a new β-lactam/β-lactamase inhibitor combination. The innovation is based on avibactam, a synthetic β-lactamase inhibitor active against β-lactamases from Ambler classes A, C, and D[59]. Initial trials show a decline in mortality rate from 9% to 32% when used together with colistin[60]. However, resistance to ceftazidime/avibactam has been reported during treatment[61]. This condition must be considered by clinicians when prescribing antibiotics.

Ceftazidime-avibactam and ceftolozane-tazobactam are combinations of cephalosporins (ceftazidime and ceftolozane) with inhibitors (avibactam and tazobactam) which show good activity against ESBL-producing Enterobacterales[62].

Meropenem/vaborbactamisalsoanewβ-lactam/β-lactamase inhibitor. Vaborbactam is a serine-β-lactamase inhibitor that strengthens meropenem activity[40]. This combination inhibits Ambler Class A and C serine carbapenemases. There is limited clinical data, but in vivo results have shown that 99% of KPC producing Enterobacterales are sensitive to meropenem-vaborbactam[63].

Plasomycin is a new generation semi-synthetic aminoglycoside[64] with activity against bacteria that produce aminoglycoside-modifying enzymes. Studies report that plasomycin has a higher potential against KPC-producing Enterobacterales compared to other aminoglycosides. Plasomycin showed wide spectrum activity against Gram-positive cocci and Gram-negative bacilli, but MBL producers, especially NDM-producers with methyl transferase, are resistant to this antibiotic[65]. In addition, clinical studies in which plasomycin is used to treat various ESBL-producing bacteria-caused infections show similar results to standard treatment regimens[62].

Eravacycline is a synthetic fluoroquinolone[66] with broad-spectrum antimicrobial activity against Gram-positive, Gram-negative, and anaerobic bacteria, regardless of their resistance to other classes of antibiotics.

In addition to the drugs currently approved, imipenem/silastatin and relebactam (Merck), cefiderocol (Shionogi),

SPR741 (SperoTherapeutics), zidebactam (Wockhardt), nacubactam (Roche), and VNRX 5133 (VenatoRx Pharmaceuticals)[58] are new molecules in their beginning development periods.

As a result, CRE creates a rapidly increasing global threat as reported by WHO. These bacteria have various and multiple drug resistance mechanisms that make them difficult to control and to diagnose early. The rapid evolution of CRE and ESBL-E in terms of developing resistance to antibiotics is one of the biggest threats to infection treatment. An international, multidisciplinary approach is urgently needed to overcome this global threat. This context is an urgent call for developing new therapeutic guidelines for treating CRE infections, including the reuse of existing antibiotics and the development of new drugs.

Peer-review: Externally peer-reviewed.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hayden Z, Brian K. Carbapenem Resistant Enterobacteriaceae (CRE). Treasure Island (FL): StatPearls Publishing; 2020. p.1–22.
2. Partridge SR. Analysis of antibiotic resistance regions in Gram-negative bacteria. FEMS Microbiol Rev 2011;35:820–55. [CrossRef]
3. Stokes HW, Gillings MR. Gene flow, mobile genetic elements and the recruitment of antibiotic resistance genes into Gram-negative pathogens. FEMS Microbiol Rev 2011;35:790–819.
4. Toleman MA, Walsh TR. Combinatorial events of insertion sequences and ICE in Gram-negative bacteria. FEMS Microbiol Rev 2011;35:912–35. [CrossRef]
5. World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva: World Health Organization; 2017. Available at: https://remed.org/wp-content/uploads/2017/03/lobal-priority-list-of-antibiotic-resistant-bacteria-2017.pdf. Accessed Dec 4, 2023.
6. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: A clinical update. Clin Microbiol Rev 2005;18:657–86. [CrossRef]
7. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Available at: https://www.ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2015. Accessed Dec 4, 2023.
8. Lee MY, Ko KS, Kang CI, Chung DR, Peck KR, Song JH. High prevalence of CTX-M-15-producing Klebsiella pneumoniae isolates in Asian countries: Diverse clones and clonal dissemination. Int J Antimicrob Agents 2011;38:160–3. [CrossRef]
9. Yurttutan N, Aksaray S. Hastane kaynaklı Klebsiella suşlarında genişlemiş spektrumlu β-laktamaz araştırılması. Uzmanlık Tezi. Ankara: T.C. Sağlık Bakanlığı Ankara Numune Eğitim ve Araştırma Hastanesi, Mikrobiyoloji ve Klinik Mikrobiyoloji Bölümü; 2000.
10. Bret L, Chanal C, Sirot D, Labia R, Sirot J. Characterization of an inhibitor-resistant enzyme IRT-2 derived from TEM-2 beta-lactamase produced by Proteus mirabilis strains. J Antimicrob Chemother 1996;38:183–91.[CrossRef]
11. Lemozy J, Sirot D, Chanal C, Huc C, Labia R, Dabernat H, et al. First characterization of inhibitor-resistant TEM (IRT) beta-lactamases in Klebsiella pneumoniae strains. Antimicrob Agents Chemother 1995;39:2580–2. [CrossRef]
12. Tzouvelekis LS, Bonomo RA. SHV-type beta-lactamases. Curr Pharm Des 1999;5:847–64. [CrossRef]
13. Bradford PA. Extended-spectrum beta-lactamases in the 21st century: Characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 2001;14:933–51. [CrossRef]
14. McLaughlin M, Advincula MR, Malczynski M, Qi C, Bolon M, Scheetz MH. Correlations of antibiotic use and carbapenem resistance in enterobacteriaceae. Antimicrob Agents Chemother 2013;57:5131–3. [CrossRef]
15. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: An evolving crisis of global dimensions. Clin Microbiol Rev 2012;25:682–707. [CrossRef]
16. 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. Lancet Infect Dis 2013;13:785–96. [CrossRef]
17. Marsik FJ, Nambiar S. Review of carbapenemases and AmpC-beta lactamases. Pediatr Infect Dis J 2011;30:109–-5. [CrossRef]
18. Poirel L, Benouda A, Hays C, Nordmann P. Emergence of NDM-1-producing Klebsiella pneumoniae in Morocco. J Antimicrob Chemother 2011;66:2781–3. [CrossRef]
19. Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL; European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) working group. Carbapenemase-producing Enterobacteriaceae in Europe: Assessment by national experts from 38 countries, May 2015. Euro Surveill 2015;20. [CrossRef]
20. Carrër A, Poirel L, Eraksoy H, Cagatay AA, Badur S, Nordmann P. Spread of OXA-48-positive carbapenem-resistant Klebsiella pneumoniae isolates in Istanbul, Turkey. Antimicrob Agents Chemother 2008;52:2950–4. [CrossRef]
21. Potron A, Poirel L, Rondinaud E, Nordmann P. Intercontinental spread of OXA-48 beta-lactamase-producing Enterobacteriaceae over a 11-year period, 2001 to 2011. Euro Surveill 2013;18:20549. [CrossRef]
22. Potron A, Kalpoe J, Poirel L, Nordmann P. European dissemination of a single OXA-48-producing Klebsiella pneumoniae clone. Clin Microbiol Infect 2011;17:E24–6.

23. Kilic A, Aktas Z, Bedir O, Gumral R, Bulut Y, Stratton C, et al. Identification and characterization of OXA-48 producing, carbapenem-resistant Enterobacteriaceae isolates in Turkey. Ann Clin Lab Sci 2011;41:161–6.
24. Woodworth KR, Walters MS, Weiner LM, Edwards J, Brown AC, Huang JY, et al. Vital signs: Containment of novel multidrug-resistant organisms and resistance mechanisms-United States, 2006-2017. MMWR Morb Mortal Wkly Rep 2018;67:396–401.
25. Bedenić B, Sardelić S. Carbapenemases. In: Bedenić B, Sardelić S, editors. Growing and handling of bacterial cultures. United Kingdom: IntechOpen; 2018 [CrossRef].
26. Ito H, Arakawa Y, Ohsuka S, Wacharotayankun R, Kato N, Ohta M. Plasmid-mediated dissemination of the metallo-beta-lactamase gene blaIMP among clinically isolated strains of Serratia marcescens. Antimicrob Agents Chemother 1995;39:824–9. [CrossRef]
27. Nordmann P, Poirel L. The difficult-to-control spread of carbapenemase producers among Enterobacteriaceae worldwide. Clin Microbiol Infect 2014;20:821–30. [CrossRef]
28. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing enterobacteriaceae. Emerg Infect Dis 2011;17:1791–8. [CrossRef]
29. Lauretti L, Riccio ML, Mazzariol A, Cornaglia G, Amicosante G, Fontana R, et al. Cloning and characterization of blaVIM, a new integron-borne metallo-beta-lactamase gene from a Pseudomonas aeruginosa clinical isolate. Antimicrob Agents Chemother 1999;43:1584–90. [CrossRef]
30. Queenan AM, Bush K. Carbapenemases: The versatile beta-lactamases. Clin Microbiol Rev 2007;20:440–58.
31. Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo-beta-lactamases: The quiet before the storm? Clin Microbiol Rev 2005;18:306–25. [CrossRef]
32. Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. Antimicrob Agents Chemother 2009;53:5046–54. [CrossRef]
33. 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):S28–36. [CrossRef]
34. Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. Antimicrob Agents Chemother 2001;45:1151–61. [CrossRef]
35. Bradford PA, Bratu S, Urban C, Visalli M, Mariano N, Landman D, et al. Emergence of carbapenem-resistant Klebsiella species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 beta-lactamases in New York City. Clin Infect Dis 2004;39:55–60. [CrossRef]
36. Poirel L, Bonnin RA, Nordmann P. Genetic features of the widespread plasmid coding for the carbapenemase OXA-48. Antimicrob Agents Chemother 2012;56:559–62. [CrossRef]
37. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of mics and zone diameters, version 9.0; 2019. Available at: http//www.eucast.org. Accessed Jul 25, 2019.
38. CLSI. M100 Performance standards for antimicrobial susceptibility testing. 29th ed. CLSI supplement; Clinical and Laboratory Standards Institute: Wayne, PA, USA, 2019. Available: https://clsi.org/media/2663/m100ed29_sample.pdf. Accessed Dec 5, 2023.
39. Pitout JD. Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: Changing epidemiology and drug treatment choices. Drugs 2010;70:313–33. [CrossRef]
40. Karaiskos I, Lagou S, Pontikis K, Rapti V, Poulakou G. The "Old" and the "New" antibiotics for MDR gram-negative pathogens: For whom, when, and how. Front Public Health 2019;7:151.
41. Dijkmans AC, Zacarías NVO, Burggraaf J, Mouton JW, Wilms EB, van Nieuwkoop C, et al. Fosfomycin: Pharmacological, clinical and future perspectives. Antibiotics (Basel) 2017;6:24.
42. Falagas ME, Kastoris AC, Kapaskelis AM, Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: A systematic review. Lancet Infect Dis 2010;10:43–50. [CrossRef]
43. Aris P, Boroumand MA, Rahbar M, Douraghi M. The activity of fosfomycin against extended-spectrum beta-lactamase-producing isolates of enterobacteriaceae recovered from urinary tract infections: A single-center study over a period of 12 years. Microb Drug Resist 2018;24:607–12.
44. Rosso-Fernández C, Sojo-Dorado J, Barriga A, Lavín-Alconero L, Palacios Z, López-Hernández I, et al. Fosfomycin versus meropenem in bacteraemic urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli (FOREST): Study protocol for an investigator-driven randomised controlled trial. BMJ Open 2015;5:e007363. [CrossRef]
45. Sader HS, Castanheira M, Duncan LR, Flamm RK. Antimicrobial susceptibility of enterobacteriaceae and pseudomonas aeruginosa isolates from united states medical centers stratified by infection type: Results from the international network for optimal resistance monitoring (INFORM) surveillance program, 2015-2016. Diagn Microbiol Infect Dis 2018;92:69–74. [CrossRef]
46. Tran TB, Velkov T, Nation RL, Forrest A, Tsuji BT, Bergen PJ, et al. Pharmacokinetics/pharmacodynamics of colistin and polymyxin B: Are we there yet? Int J Antimicrob Agents 2016;48:592–7. [CrossRef]
47. Daikos GL, Tsaousi S, Tzouvelekis LS, Anyfantis I, Psichogiou M, Argyropoulou A, et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: Lowering mortality by antibiotic combination schemes and the role of carbapenems. Antimicrob Agents Chemother 2014;58:2322–8. [CrossRef]
48. Doi Y. Treatment options for carbapenem-resistant gram-negative bacterial infections. Clin Infect Dis 2019;69(Suppl 7):S565–75. [CrossRef]

49. Giamarellou H, Poulakou G. Pharmacokinetic and pharmacodynamic evaluation of tigecycline. Expert Opin Drug Metab Toxicol 2011;7:1459–70. [CrossRef]
50. Bulik CC, Nicolau DP. Double-carbapenem therapy for carbapenemase-producing Klebsiella pneumoniae. Antimicrob Agents Chemother 2011;55:3002–4. [CrossRef]
51. Anderson KF, Lonsway DR, Rasheed JK, Biddle J, Jensen B, McDougal LK, et al. Evaluation of methods to identify the Klebsiella pneumoniae carbapenemase in Enterobacteriaceae. J Clin Microbiol 2007;45:2723–5. [CrossRef]
52. Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M, et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. Int J Antimicrob Agents 2014;43:52–9. [CrossRef]
53. Betts JW, Phee LM, Hornsey M, Woodford N, Wareham DW. In vitro and in vivo activities of tigecycline-colistin combination therapies against carbapenem-resistant Enterobacteriaceae. Antimicrob Agents Chemother 2014;58:3541–6. [CrossRef]
54. Toledo PV, Aranha Junior AA, Arend LN, Ribeiro V, Zavascki AP, Tuon FF. Activity of antimicrobial combinations against KPC-2-producing Klebsiella pneumoniae in a rat model and time-kill assay. Antimicrob Agents Chemother 2015;59:4301–4. [CrossRef]
55. Hirsch EB, Guo B, Chang KT, Cao H, Ledesma KR, Singh M, et al. Assessment of antimicrobial combinations for Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. J Infect Dis 2013;207:786–93. [CrossRef]
56. Le J, McKee B, Srisupha-Olarn W, Burgess DS. In vitro activity of carbapenems alone and in combination with amikacin against KPC-producing Klebsiella pneumoniae. J Clin Med Res 2011;3:106–10. [CrossRef]
57. Ni W, Wei C, Zhou C, Zhao J, Liang B, Cui J, et al. Tigecycline-Amikacin combination effectively suppresses the selection of resistance in clinical isolates of KPC-Producing klebsiella pneumoniae. Front Microbiol 2016;7:1304. [CrossRef]
58. Suay-García B, Pérez-Gracia MT. Present and future of carbapenem-resistant enterobacteriaceae (CRE) infections. Antibiotics (Basel) 2019;8:122. [CrossRef]
59. de Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. In vitro susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible enterobacteriaceae isolates collected during the INFORM global surveillance study (2012 to 2014). Antimicrob Agents Chemother 2016;60:3163–9. [CrossRef]
60. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant enterobacteriaceae. Clin Infect Dis 2018;66:163–71. [CrossRef]
61. Nelson K, Hemarajata P, Sun D, Rubio-Aparicio D, Tsivkovski R, Yang S, et al. Resistance to ceftazidime-avibactam is due to transposition of KPC in a porin-deficient strain of klebsiella pneumoniae with increased efflux activity. Antimicrob Agents Chemother 2017;61:e00989–17. [CrossRef]
62. Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, Pascual A. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing enterobacteriaceae. Clin Microbiol Rev 2018;31:e00079–17.
63. Lomovskaya O, Sun D, Rubio-Aparicio D, Nelson K, Tsivkovski R, Griffith DC, et al. Vaborbactam: Spectrum of beta-lactamase inhibition and impact of resistance mechanisms on activity in enterobacteriaceae. Antimicrob Agents Chemother 2017;61:e01443–17. [CrossRef]
64. Landman D, Babu E, Shah N, Kelly P, Bäcker M, Bratu S, et al. Activity of a novel aminoglycoside, ACHN-490, against clinical isolates of Escherichia coli and Klebsiella pneumoniae from New York City. J Antimicrob Chemother 2010;65:2123–7. [CrossRef]
65. Walkty A, Adam H, Baxter M, Denisuik A, Lagacé-Wiens P, Karlowsky JA, et al. In vitro activity of plazomicin against 5,015 gram-negative and gram-positive clinical isolates obtained from patients in canadian hospitals as part of the CANWARD study, 2011-2012. Antimicrob Agents Chemother 2014;58:2554–63. [CrossRef]
66. Zhanel GG, Cheung D, Adam H, Zelenitsky S, Golden A, Schweizer F, et al. Review of eravacycline, a novel fluorocycline antibacterial agent. Drugs 2016;76:567–88. [CrossRef]