Carbapenemase-Producing Enterobacterales

Subjects: Others

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Carbapenemase-producing Enterobacterales (CPE) are significant contributors to the global public health threat of antimicrobial resistance. OXA-48-like enzymes and their variants are unique carbapenemases with low or null hydrolytic activity toward carbapenems but no intrinsic activity against expanded-spectrum cephalosporins. CPEs have been classified by the WHO as high-priority pathogens given their association with morbidity and mortality and the scarce number of effective antibiotic treatments. In Spain, the frequency of OXA-48 CPE outbreaks is higher than in other European countries, representing the major resistance mechanism of CPEs. Horizontal transfer of plasmids and poor effective antibiotic treatment are additional threats to the correct prevention and control of these hospital outbreaks. One of the most important risk factors is antibiotic pressure, specifically carbapenem overuse.

Keywords: enterobacteria ; carbapenemase

1. Introduction

Enterobacteriaceae were identified as a public health threat since the discovery of their ability to acquire molecular resistance through extended-spectrum β-lactamases (ESBLs) [1]. In 2016, large-scale genomic sequencing data led to reclassification of various species, originally included in the family Enterobacteriaceae, in an order called Enterobacterales [2].

In order to counteract the menace of antibiotic resistant Enterobacterales, carbapenems were developed and introduced into the therapeutic arsenal during the decade of 1990 [3]. Since then, these drugs have been widely used as first-line empirical antibiotic treatment [4]. Nevertheless, this strategy resulted in an even greater problem since the lack in carbapenem stewardship has led to the development of carbapenem-resistant Enterobacterales (CRE) [5][6]. Specifically, the first carbapenemase (NmcA) producer was identified in 1993 in a clinical isolate of Enterobacter cloacae [7]. Since then, numerous CRE have been reported [8].

CRE present three main mechanisms of carbapenem resistance: enzyme production, efflux pumps and porin mutations [9]. Of these, enzyme production is the most frequent resistance mechanism and OXA-48-like enzymes represent one of the most common CRE enzymes worldwide [10]. The family takes its name from the first identified enzyme, OXA-48, and includes several sequence variants transmissible via plasmids.

Worldwide Spread

In the last years, surveillance studies have pointed that OXA-48-like cabarpenemases are the most common carbapenemases in several areas of the world [10][11][12][13]. Moreover, they are increasingly being introduced into non-endemic regions where they cause nosocomial outbreaks [14].

A search in PubMed using the terms “OXA-48” and “outbreak” reveals an increasing number of reports in the last years, from 3 in 2010 to 76 in 2020.

The first identification of this enzyme was reported in Klebsiella pneumoniae isolated from a urinary tract infection sample in 2001 in Turkey [15]. Since then, a number of nosocomial outbreaks of these bacteria have been reported in this country [16][17]. A rapid spread led to first-identification reports in colonization or infection samples in many areas of the world, especially the Mediterranean region [18].

In Europe, the first case of OXA-48 identification was reported in Belgium in 2008 [19]. In Africa, reports of carbapenem-hydrolyzing OXA-48 β-lactamase in K. pneumoniae were communicated in Tunisia in 2010 [20]. In Asia, reports of OXA-48 presence were published in 2012 in Kuwait [21]. In North America, it was first described in the United States in 2013 [22], whereas in South America, the first identification was reported in Brazil in 2014 [23]. In total, more than 50 countries have

reported outbreaks of OXA-48-producing bacteria to date [14][24]. In Spain, reports of OXA-48-producing bacteria in outbreaks were published in 2013 [25][26][27]. Since then, several outbreaks have been identified and OXA-48-producing bacteria have become one of the major causal agents of hospital outbreaks in our country [10][28][29].

2. Treatment

Optimizing therapy for CRE infections represents a fundamental and increasing research field, continuously updating and adapting to the epidemiological contexts.

The OXA-48 enzyme hydrolyzes carbapenems but shows very weak activity against extended-spectrum cephalosporins such as cefepime and ceftazidime [11], although isolates are frequently multidrug resistant as they combine multiple resistance mechanisms [30].

CRE have historically been susceptible to polymyxins, tigecycline or aminoglycosides (especially gentamicin). Accordingly, these treatments have been widely used as antibiotics of choice for CRE infections. However, varying rates of resistance to all of them have been reported, thus different antibiotics are continuously being tested. Treatment of OXA-48 CRE with ceftazidime-avibactam could be effective according to a study conducted in Italy [31], which is consistent with the resistance profile of an OXA-48 CRE outbreak in Russia [32]. A study performed in Australia also reported effectiveness of other avibactam combinations (imipenem-avibactam or aztreonam-avibactam), suggesting that avibactam may be the most potent β-lactamase inhibitor [33]. Although the authors stated that combined therapy is more effective, successful outcomes were observed in 70% of the patients treated with ceftazidime-avibactam in monotherapy. Carbapenem in combination with amikacin or colistin may be useful in certain cases, but recent reports of resistance are concerning [32].

In Spain, treatment for CRE with ceftazidime-avibactam has proven to be promising, and other novel combinations including meropenem-vaborbactam, imipenem-relebactam, plazomicin, cefiderocol, eravacycline and aztreonam-avibactam [34]. However, meropenem-vaborbactam [35] and imipenem-relebactam [36] are not effective against OXA-48 producers, and limited data are available on eravacycline against CRE [37]. Therefore, the β-lactamase inhibitor with more contrasted efficacy on OXA-48 producers is avibactam. Regarding cephalosporins, despite the paucity of clinical data and the fact that OXA-48 CRE are associated with ESLBs (which implies resistance to cephalosporins), a recent Spanish systematic review suggested that ceftazidime without avibactam could be a therapeutic option [38]. Plazomicin is another therapeutic alternative, which has been reported to be effective in some CREs [39], although it is not commercialized in Spain. Cefiderocol showed encouraging results in terms of efficacy and safety in a clinical trial [40], covering a very wide spectrum of bacteria. Given its siderophore mechanism of action, based on the use of ferric iron transporter systems [41], cefiderocol has been referred to as a “Trojan horse” antibiotic. This drug is available in Spain and has been advocated as a promising future therapeutic option. Finally, ertapenem and meropenem have shown in vitro synergistic activity against CRE [42], although they are not currently recommended for the treatment of OXA-48 producers. Other new drugs with activity against some CPE isolates are at different stages of development [38] and will probably be incorporated into the commercialized therapeutic arsenal in Spain in the next years.

It is important to note that several OXA-48-like variants, such as OXA-163, completely lose their ability to hydrolyze carbapenems and display an ESBL phenotype. Accordingly, they hydrolyze ceftazidime and confer high levels of resistance to this drug when expressed in Enterobacterales.

Overall, the therapeutic approach to OXA-48 CRE infections must be individualized according to susceptibility, type and severity of infection, and to the characteristics of the patient. Limited data are currently available on the best strategy for OXA-48 CRE, thus future studies might be crucial for optimizing the therapeutic approaches.

3. Conclusions

The frequency of CRE colonization or infection is increasing in hospital outbreaks around the world. In Spain, this frequency is higher than the European average. OXA-48 is the most common enzymatic resistance mechanism of CRE in Spain [43]. Colonization in the ICU and infections of the surgical site are especially complicated and, therefore, specific preventive measures should be implemented in these settings. Plasmid transfer between different species has been described, and the presence of possible host bacteria in patients should be considered in order to implement appropriate isolation and preventive measures when an OXA-48 outbreak is identified. One of the most preventable risk factors for hospital outbreaks caused by OXA-48 bacteria is a lack of adequate antibiotic stewardship. In Spain, an overall high frequency of carbapenem overuse (especially ertapenem) has been described in 2019, although regional differences in the percentage of antibiotic use in hospitalization were also reported. Accordingly, specific programs focused on

optimizing antibiotic stewardship are required. Finally, preventive control measures need to be reinforced and continuously updated and adapted to identify and control OXA-48 CRE in Spanish hospitals with the aim to stop this growing global health threat.

References

1. Pana, Z.D.; Zaoutis, T. Treatment of extended-spectrum ß-lactamase-producing Enterobacteriaceae (ESBLs) infections: What have we learned until now? F1000Res 2018, 7, 1347.
2. Adeolu, M.; Alnajar, S.; Naushad, S.S.; Gupta, R. Genome-based phylogeny and taxonomy of the 'Enterobacteriales': Proposal for Enterobacterales ord. nov. divided into the families Enterobacteriaceae, Erwiniaceae fam. nov., Pectobacteriaceae fam. nov., Yersiniaceae fam. nov., Hafniaceae fam. nov., Morganellaceae fam. nov., and Budviciaceae fam. nov. Int. J. Syst. Evol. Microbiol. 2016, 66, 5575–5599.
3. Hawkey, P.M. The growing burden of antimicrobial resistance. J. Antimicrob. Chemother. 2008, 62, i1–i9.
4. D'Angelo, R.G.; Johnson, J.K.; Bork, J.T.; Heil, E.L. Treatment options for extended-spectrum beta-lactamase (ESBL) and AmpC-producing bacteria. Expert Opin. Pharmacother. 2016, 17, 953–967.
5. Sheu, C.C.; Lin, S.Y.; Chang, Y.T.; Lee, C.Y.; Chen, Y.H.; Hsueh, P.R. Management of infections caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae: Current evidence and future prospects. Expert Rev. Anti. Infect. Ther. 2018, 16, 205–218.
6. Centers for Disease Control and Prevention. Facility Guidance for Control of Carbapenem-Resistant Enterobacteriaceae (CRE)—November 2015 Update CRE Toolkit. Available online: https://www.cdc.gov/hai/organisms/cre/Cre-toolkit/index.html (accessed on 1 December 2020).
7. Nordmann, P.; Mariotte, S.; Naas, T.; Labia, R.; Nicolas, M.H. Biochemical properties of a carbapenem-hydrolyzing betalactamase from Enterobacter cloacae and cloning of the gene into Escherichia coli. Antimicrob. Agents Chemother. 1993, 37, 939–946.
8. Naas, T.; Nordmann, P. Analysis of a carbapenem hydrolyzing class A beta-lactamase from Enterobacter cloacae and of its LysR-type regulatory protein. Proc. Natl. Acad. Sci. USA 1994, 91, 7693–7697.
9. Haidar, G.; Clancy, C.J.; Chen, L.; Samanta, P.; Shields, R.K.; Kreiswirth, B.N.; Nguyen, M.H. Identifying spectra of activity and therapeutic niches for ceftazidime-avibactam and imipenem-relebactam against carbapenem-resistant Enterobacteriaceae. Antimicrob. Agents Chemother. 2017, 61, e00642-17.
10. Suay-García, B.; Pérez-Gracia, M.T. Present and Future of Carbapenem-resistant Enterobacteriaceae (CRE) Infections. Antibiotics 2019, 8, 122.
11. Mairi, A.; Pantel, A.; Sotto, A.; Lavigne, J.P.; Touati, A. OXA-48-like carbapenemases producing Enterobacteriaceae in different niches. Eur. J. Clin. Microbiol. Infect. Dis. 2018, 37, 587–604.
12. Evans, B.A.; Amyes, S.G.B. OXA β-lactamases. Clin. Microbiol. Rev. 2014, 27, 241–263.
13. Poirel, L.; Potron, A.; Nordmann, P. OXA-48-like carbapenemases: The phantom menace. J. Antimicrob. Chemother. 2012, 67, 1597–1606.
14. Pitout, J.; Peirano, G.; Kock, M.M.; Strydom, K.A.; Matsumura, Y. The Global Ascendency of OXA-48-Type Carbapenemases. Clin. Microbiol. Rev. 2019, 33, e00102-19.
15. Poirel, L.; Héritier, C.; Tolün, V.; Nordmann, P. Emergence of oxacillinase-mediated resistance to imipenem in Klebsiella pneumoniae. Antimicrob. Agents Chemother. 2004, 48, 15–22.
16. Carrër, A.; Poirel, L.; Eraksoy, H.; Cagatay, A.A.; Badur, S.; Nordmann, P. Spread of OXA-48-positive carbapenem-resistant Klebsiella pneumoniae isolates in Istanbul, Turkey. Antimicrob. Agents Chemother. 2008, 52, 2950–2954.
17. Azap, O.; Otlu, B.; Yeşilkaya, A.; Yakupoğulları, Y. Detection of OXA-48-like Carbapenemase-Producing Klebsiella pneumoniae in a Tertiary Care Center in Turkey: Molecular Characterization and Epidemiology. Balk. Med. J. 2013, 30, 259–260.
18. Djahmi, N.; Dunyach-Remy, C.; Pantel, A.; Dekhil, M.; Sotto, A.; Lavigne, J.-P. Epidemiology of carbapenemase-producing Enterobacteriaceae and Acinetobacter baumannii in Mediterranean Countries. Biomed. Res. 2014, 2014, 305784.
19. Cuzon, G.; Naas, T.; Bogaerts, P.; Glupczynski, Y.; Huang, T.D.; Nordmann, P. Plasmid-encoded carbapenem-hydrolyzing beta-lactamase OXA-48 in an imipenem-susceptible Klebsiella pneumoniae strain from Belgium. Antimicrob. Agents Chemother. 2008, 52, 3463–3464.

20. Cuzon, G.; Naas, T.; Lesenne, A.; Benhamou, M.; Nordmann, P. Plasmid-mediated carbapenem-hydrolysing OXA-48 betalactamase in Klebsiella pneumoniae from Tunisia. Int. J. Antimicrob. Agents 2010, 36, 91–93.

21. Poirel, L.; Carbonnelle, E.; Bernabeu, S.; Gutmann, L.; Rotimi, V.; Nordmann, P. Importation of OXA-48-producing Klebsiella pneumoniae from Kuwait. J. Antimicrob. Chemother. 2012, 67, 2051–2052.

22. Lascols, C.; Peirano, G.; Hackel, M.; Laupland, K.B.; Pitout, J.D. Surveillance and molecular epidemiology of Klebsiella pneumoniae isolates that produce carbapenemases: First report of OXA-48-like enzymes in North America. Antimicrob. Agents Chemother. 2013, 57, 130–136.

23. Sampaio, J.L.M.; Ribeiro, V.B.; Campos, J.C.; Rozales, F.P.; Magagnin, C.M.; Falci, D.R.; da Silva, R.C.F.; Falarosa, M.G.; Luz, D.I.; Vieira, F.J.; et al. Detection of OXA-370, an OXA-48- related class D β-lactamase, in Enterobacter hormaechei from Brazil. Antimicrob. Agents Chemother. 2014, 58, 3566–3567.

24. Taggar, G.; Attiq Rheman, M.; Boerlin, P.; Diarra, M.S. Molecular Epidemiology of Carbapenemases in Enterobacteriales from Humans, Animals, Food and the Environment. Antibiotics 2020, 9, 693.

25. Oteo, J.; Hernández, J.M.; Espasa, M.; Fleites, A.; Sáez, D.; Bautista, V.; Pérez-Vázquez, M.; Fernández-García, M.D.; Delgado-Iribarren, A.; García-Picazo, L.; et al. Emergence of OXA-48-producing Klebsiella pneumoniae and the novel carbapenemases OXA-244 and OXA-245 in Spain. J. Antimicrob. Chemother. 2013, 68, 317–321.

26. Gomez, S.; Pasteran, F.; Faccone, D.; Bettiol, M.; Veliz, O.; De Belder, D.; Rapaport, M.; Gatti, B.; Petroni, A.; Corso, A. Intrapatient emergence of OXA-247: A novel carbapenemase found in a patient previously infected with OXA-163-producing Klebsiella pneumoniae. Clin. Microbiol. Infect. 2013, 19, E233–E235.

27. Oteo, J.; Saez, D.; Bautista, V.; Fernández-Romero, S.; Molina, J.M.H.; Pérez-Vázquez, M.; Aracil, B.; Campos, J.; Spanish Collaborating Group for the Antibiotic Resistance Surveillance Program. Carbapenemase producing Enterobacteriaceae in Spain in 2012. Antimicrob. Agents Chemother. 2013, 57, 6344–6347.

28. Argente, M.; Miró, E.; Martí, C.; Vilamala, A.; Alonso-Tarrés, C.; Ballester, F.; Calderón, A.; Gallés, C.; Gasós, A.; Mirelis, B.; et al. Molecular characterization of OXA-48 carbapenemase-producing Klebsiella pneumoniae strains after a carbapenem resistance increase in Catalonia. Enferm. Infecc. Microbiol. Clin. 2019, 37, 82–88.

29. Hernandez-Garcia, M.; Leon-Sampedro, R.; Perez-Viso, B.; Morosini, M.I.; Lopez-Fresnena, N.; Diaz-Agero, C.; Coque, T.M.; Ruiz-Garbajosa, P.; Canton, R. First report of an OXA-48- and CTX-M-213-producing Kluyvera species clone recovered from patients admitted in a university hospital in Madrid, Spain. Antimicrob. Agents Chemother. 2018, 62, e01238-18.

30. Evren, E.; Azap, O.K.; Colakoglu, S.; Arslan, H. In vitro activity of fosfomycin in combination with imipenem, meropenem, colistin and tigecycline against OXA 48-positive Klebsiella pneumoniae strains. Diagn. Microbiol. Infect. Dis. 2013, 76, 335–338.

31. Tumbarello, M.; Losito, A.R.; Giamarellou, H. Optimizing therapy in carbapenem-resistant Enterobacteriaceae infections. Curr. Opin. Infect. Dis. 2018, 31, 566–577.

32. Shaidullina, E.; Shelenkov, A.; Yanushevich, Y.; Mikhaylova, Y.; Shagin, D.; Alexandrova, I.; Ershova, O.; Akimkin, V.; Kozlov, R.; Edelstein, M. Antimicrobial Resistance and Genomic Characterization of OXA-48- and CTX-M-15-Co-Producing Hypervirulent Klebsiella pneumoniae ST23 Recovered from Nosocomial Outbreak. Antibiotics 2020, 9, 862.

33. Stewart, A.; Harris, P.; Henderson, A.; Paterson, D. Treatment of Infections by OXA-48-Producing Enterobacteriaceae. Antimicrob. Agents Chemother. 2018, 62, e01195-18.

34. Martínez-Martínez, L.; González-López, J.J. Carbapenemases in Enterobacteriaceae: Types and molecular epidemiology. Enferm. Infecc. Microbiol. Clin. 2014, 32, 4–9.

35. Gill, C.M.; Asempa, T.E.; Nicolau, D.P. Efficacy of human-simulated exposures of meropenem/vaborbactam and meropenem against OXA-48 β-lactamase-producing Enterobacterales in the neutropenic murine thigh infection model. J. Antimicrob. Chemother. 2021, 76, 184–188.

36. Karlowsky, J.A.; Lob, S.H.; Kazmierczak, K.M.; Hawser, S.P.; Magnet, S.; Young, K.; Motyl, M.R.; Sahm, D.F. In vitro activity of imipenem/relebactam against Gram-negative ESKAPE pathogens isolated in 17 European countries: 2015 SMART surveillance programme. J. Antimicrob. Chemother. 2018, 73, 1872–1879.

37. Clark, J.A.; Kulengowski, B.; Burgess, D.S. In vitro activity of eravacycline compared with tigecycline against carbapenem-resistant Enterobacteriaceae. Int. J. Antimicrob. Agents. 2020, 56, 106178.

38. 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.

39. Livermore, D.M.; Warner, M.; Mushtaq, S. Activity of MK-7655 combined with imipenem against Enterobacteriaceae and Pseudomonas aeruginosa. J. Antimicrob. Chemother. 2013, 68, 2286–2290.

40. Bassetti, M.; Echols, R.; Matsunaga, Y.; Ariyasu, M.; Doi, Y.; Ferrer, R.; Lodise, T.P.; Naas, T.; Niki, Y.; Paterson, D.L.; et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): A randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect. Dis 2020. online ahead of print.
41. Ito, A.; Nishikawa, T.; Matsumoto, S.; Yoshizawa, H.; Sato, T.; Nakamura, R.; Tsuji, M.; Yamano, Y. Siderophore Cephalosporin Cefiderocol Utilizes Ferric Iron Transporter Systems for Antibacterial Activity against Pseudomonas aeruginosa. Antimicrob. Agents Chemother. 2016, 60, 7396–7401.
42. Fredborg, M.; Sondergaard, T.E.; Wang, M. Synergistic activities of meropenem double and triple combinations against carbapenemase-producing Enterobacteriaceae. Diagn. Microbiol. Infect. Dis. 2017, 88, 355–360.
43. Sánchez-López, J.; Cantón, R. Current status of ESKAPE microorganisms in Spain: Epidemiology and resistance phenotypes. Rev. Esp. Quimioter. 2019, 32, 27–31.