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THE WORLD-WIDE SPREAD OF CARBAPENEM-RESISTANT ENTEROBACTERALES

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Introduction*. Gram-negative bacilli belonging to the order Enterobacterales are normal inhabitants of the human gut, which also are the most common causative agents of both nosocomial and community acquired infections in patients of all ages. Although not even a century has passed since Fleming's discovery of penicillin, the scientists have been alarmed by the fact that the "last resort antibiotics" viz. carbapenems have been compromised.* ***Material and methods.*** *The analysis of fifty-two articles and documents regarding this topic was peformed.* ***Results.*** *The main mechanism of resistance to carbapenems in Enterobacterales is production of carbapenemases, being enzymes that destroy all or almost all β-lactam antibiotics including carbapenems. According to Ambler's classification β-lactamases can be distributed into four classes (A, B, C, and D) being based on primary amino acid sequence homology. The most important carbapenemases produced by Enterobacterales belong to class A (KPC), class B (metallo-β-lactamases NDM, VIM, IMP) and class D (OXA-48-like). Unlike other mechanisms of resistance, carbapenemase production is easily spread via plasmids making carbapenemase-producing Enterobacterales (CPE) a global challenge for healthcare providers.* ***Conclusions.*** *CPE are not readily detected in the laboratory but the ability to detect carbapenemase production in Enterobacterales has very important infection control implications and therefore is essential for local infection control programs and national and international surveillance systems. Furthermore, local epidemiology of multidrug resistant organisms has major influence on development of national clinical guidelines for antimicrobial use.*

Cuvinte cheie: *Enterobacterales carbapenem rezistente, Klebsiella pneumoniae carbapenem-rezistentă, carbapeneme, cabapenemaze.*

RĂSPÂNDIREA MONDIALĂ A ENTEROBACTERALES CARBAPENEM-REZISTENTE

Introducere. *Bacilii gramnegativi din ordinul Enterobacterales habitează la nivelul intestinului uman, dar în același timp sunt și cei mai comuni agenți cauzali ai infecțiilor nozocomiale și comunitare la pacienții de toate vârstele. Deși nu a trecut nici măcar un secol de la descoperirea penicilinei de către Fleming, suntem deja într-o situație îngrijorătoare în care „antibioticele de ultimă instanță", carbapenemele, au fost compromise.*

Material și metode. *Au fost analizate cincizeci și două de articole și documente pe tema analizată.* ***Rezultate.*** *Mecanismul principal de rezistență la carbapeneme la Enterobacterales este producerea enzimelor carbapenemaze, care distrug toate sau aproape toate antibioticele β-lactamice, inclusiv carbapenemele. Conform clasificării Ambler, β-lactamazele pot fi distribuite în patru clase (A, B, C și D) pe baza omologiei primare a secvenței aminoacizilor. Cele mai importante carbapenemaze produse de Enterobacterales aparțin clasei A (KPC), clasei B (metallo-β-lactamaze NDM, VIM, IMP) și clasei D (OXA-48-like). Spre deosebire de alte mecanisme de rezistență, producerea de carbapenemaze este ușor răspândită prin intermediul plasmidelor, făcând Enterobacterales (CPE) producătoare de carbapenemază o provocare globală pentru lucrătorii medicali.* ***Concluzii.*** *Nu este ușor de detectat CPE în laborator, dar abilitatea de a detecta producerea de carbapenemaze la Enterobacterales este foarte importantă în control infecției și, prin urmare, este esențială pentru programele locale de control al infecțiilor și sistemele de supraveghere naționale și internaționale. Mai mult, epidemiologia locală a organismelor multirezistente are o influență majoră asupra dezvoltării ghidurilor clinice naționale pentru utilizarea antimicrobienelor.*

INTRODUCTION

Enteric Gram-negative bacilli are important part of human microbiota and they used to be referred to as *Enterobacteriaceae*. However, with the new nomenclature this group of bacteria should be referred to as the order Enterobacterales which includes the family *Enterobacteriaceae* but also some other medically important families. This largest group of Gram-negative facultative anaerobes and non-spore-forming rods has a critical role in human medicine because its members are normal inhabitants of the human gut but at the same time also the most common causative agents of both nosocomial and community acquired infections in patients of all ages (1, 2). Occasionally, and mainly in people with underlying disease, these bacteria can invade the blood or tissues and cause serious infections that have been so far successfully treated with antibiotics.

Although they have been in clinical use for 75 years, beta-lactam antibiotics are the most commonly prescribed antimicrobial drugs because of their characteristics such as good safety profile (except for allergic reactions that occur rarely), high bactericidal activity, and broad spectrum (3). Carbapenems are broad spectrum β-lactam antibiotics, being highly effective against most Gram-negative infections even in cases when causative organisms are resistant to most other antibiotics. Wide use of carbapenems, even in situations when they were not needed, has led to the emergence of resistance to these valuable "last resort antibiotics". Carbapenem resistance can be mediated by different mechanisms such as the reduced cell wall permeability, hyperexpression of efflux pumps or production of enzymes that hydrolyze broad spectrum β-lactams including carbapenems viz. the carbapenemases. Carbapenemase production seems to be the most important resistance mechanism in Enterobacterales as it quite often confers high level of resistance and is easily spread *via* plasmids. Carbapenemase-producing Enterobacterales (CPE) are therefore the most important subset of carbapenem resistant Enterobacterales (CRE). Although many different bacterial species within Enterobacterales can acquire genes for carbapenemase production, of particular concern is the increasing carbapenem resistance in *Klebsiella pneumoniae* and *Escherichia coli* (4). An alarming issue is that some *K. pneumoniae* clones show particular potency for epidemic spread.

Rapid worldwide spread of CPE has become a global challenge for healthcare providers, making treatment of such patients a difficult task (5). The World Bank made an estimate that by 2050, 10 million people could die annually, because of infections caused by multidrug resistant organisms (MDROs) if no measures against antimicrobial resistance are implemented (6). Antimicrobial resistance has a direct impact on the success of infectious diseases treatment and prophylaxis and seriously jeopardizes advances in many areas of healthcare, increases mortality, prolongs stays in hospital, increases costs and is therefore recognized by World Health Organization (WHO) as a profound threat to human health (7). The indirect impact of antimicrobial resistance includes reduction in gross domestic product (GDP) caused by economic losses due to reduced productivity and higher costs of treatment which could cause global economic damage on a par with the 2008 financial crisis (8). In 2015, the study carried out by European Center for Disease Prevention and Control (ECDC), regarding the burden caused by infections with antibiotic-resistant bacteria on the European Union (EU) and the European Economic Are, estimated the highest burden of carbapenem-resistant *K. pneumoniae* (9). This study review provides an overview of the epidemiology of carbapenemase producing (CP) *K. pneumoniae*.

MATERIAL AND METHODS

Review article. A search of the literature was performed on the Internet using PubMed database, Google, Google Scholar by applying the following keywords: Enterobacterales, *Klebsiella pneumoniae*, carbapenems, beta-lactamases, carbapenemases, antimicrobial resistance surveillance. The final bibliography included 50 references.

RESULTS

Evolution of β-lactamases

Although Alexander Fleming began the antibiotic era with the discovery of penicillin in 1928, it started being widely produced and clinically used 12 years later thanks to Howard Florey and Ernest Chain (10). A broad-spectrum penicillin viz. the ampicillin, which is highly effective against some Enterobacterales was discovered 20 years later. Shortly after the introduction of ampicillin, the first enzymes that hydrolyze penicillins and early generation cephalosporins, such as

TEM-1 and SHV-1 were described and named broad-spectrum-β-lactamases (11). In the 1980s, as a response to bacteria producing broad-spectrum-β-lactamases, oxyimino-cephalosporins, the third generation cephalosporins such as cefotaxime, ceftriaxone and ceftazidime were introduced into clinical use. These drugs are poor substrates for the broad spectrum β-lactamases and show high bactericidal efficacy against a wide range of Enterobacterales (11, 12). Along with the development of new generations of cephalosporins, combinations of a β-lactam and a β-lactamase inhibitor, such as amoxicillin/clavulanic acid, ampicillin/sulbactam and piperacillin/tazobactam were developed to combat resistance mediated by broad-spectrum-β-lactamases (13). The wide use of the third generation cephalosporins placed selective pressure on bacteria resulting in the evolution of variants of broad-spectrum-β-lactamases that have gained the ability to hydrolyze oxyimino-cephalosporins and these enzymes were named extended-spectrum-β-lactamases (ESBLs) (14). Another resistance mechanism against the third generation cephalosporins includes hyperproduction of AmpC β-lactamase, which was first detected in bacterial species that have chromosomally encoded inducible AmpC β-lactamase (*Enterobacter* spp., *Citrobacter freundii*, and *Serratia* spp.) (15). Later, genes encoding for AmpC β-lactamase hyperproduction were transferred by plasmids to other bacterial species such as *K. pneumoniae* and *E. coli* (15). ESBL and AmpC producing isolates spread globally during 1980s and 1990s promoting the use of carbapenems, which are often referred to as „last resort antibiotics" (2, 16). Carbapenems have a broad antibacterial activity, since they are stable to hydrolysis by ESBL and AmpC enzymes and have a safe profile in terms of side effects. Carbapenems were reliable and highly effective solution for multi-resistant Gram-negative bacteria for over 15 years, however instead of being used cautiously when only a broad coverage was required, they were often used excessively in empirical therapy without identifying the bacterial pathogen or without de-escalating antibiotic therapy in case a bacteriological finding was available. Consequently, carbapenem resistance to Gram-negative bacteria, particularly in *K. pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* has spread and represents a major on-going public health problem worldwide. Carbanem resistance in *A. baumannii* is mostly mediated by plasmid- or chromosomally-encoded OXA carbapenemases and in *P. aeruginosa* by hyperexpression of efflux pumps, cell wall impermeability, or hyperproduction of AmpC beta-lactamases (17). While carbapenem resistance is readily detected *in vitro* in *P. aeruginosa* and *A. baumannii*, detection of carbapenem resistance in Enterobacterales, e.g. *K. pnemoniae* and *E. coli*, is more challenging and required revision of minimum inhibitory concentration (MIC) breakpoints by The European Committee on Antimicrobial Susceptibility Testing (EUCAST) (18) and Clinical and Laboratory Standards Institute (CLSI) (19). Although carbapenem resistance in Enterobacterales is mostly mediated by carbapenemase production, from an infection control standpoint, it is very important to distinguish between CP and non-CP Enterobacterales as the genes encoding carbapenemases are generally located on mobile genetic elements (i.e., plasmids, transposons, and insertion sequences) and are easily transmissible to other Gram-negative organisms (20). On the contrary, carbapenem resistance in non-CP isolates commonly occurs due to the hyperproduction of ESBL or AmpC enzymes combined with a reduced cell wall permeability which is associated with a loss of organism fitness and reduced transmissibility (20). Detecting carbapenemase production and defining the carbapenemase type is crucial in monitoring the spread of successful epidemic clones, particularly of *K. pneumoniae*.

Classification of carbapenemases

Due to the large number and high diversity of β-lactamases, their classification is not an easy task (21). Classification schemes brought in a few decades ago are constantly updated and adjusted to the ever-growing number of emerging enzymes. In 1989, Karen Bush et al. presented a classification according to the functional characteristics of β-lactamases (22), while in 1980 Ambler proposed a classification by which β-lactamases can be distributed into four classes (A, B, C, and D) based on primary amino acid sequence homology (21). β-lactamases produced by Enterobacterales, which have a significant clinical role in compromising carbapenems and being epidemiologically most relevant, belong to the Ambler classes A, B and D (2, 4). *Enterobacter cloacae*, strain NOR-1, which produces carbapenemase from the Ambler class A, was the first CPE, isolated in 1993 (4).

Class A carbapenemases

Class A β-lactamases are susceptible in a varying degree to β-lactamase inhibitors such as clavulanic acid. They are often encoded on plasmids that can move by conjugation and, as a result, these enzymes are widespread sources of resistance. Broad-spectrum-β-lactamases and their variants ESBLs are examples of class A β-lactamases. The most significant representatives of the carbapenemases in the Ambler class A are *Klebsiella pneumoniae* carbapenemase (KPC), Guiana Extended-Spectrum beta-lactamase enzymes (GES), *Serratia marcescens* enzyme (SME-1), imipenem-hydrolyzing beta-lactamase enzymes (IMI), the non-metallo-carbapenemase-A enzyme (NMC-A), of which KPC is the most clinically and epidemiologically important (2, 4, 11). As new treatment options for class A carbapenemases (e.g. KPC), some combinations of β-lactam antibiotics and new β-lactamase inhibitors have recently been approved on the market. Avibactam is a first-in-class, non-β-lactam, β-lactamase inhibitor with a broad spectrum of activity, including activity against KPC enzyme (23). A combination of the third generation cephalosporin, ceftazidime and aviabactam was approved in the USA in 2015 and in Europe in 2016 (23). Meropenem/vaborbactam was approved by the US Food and Drug Administration (FDA) in 2017 as the first carbapenem β-lactamase inhibitor combination and the same combination got approval a year later in Europe (24). Imipenemcilastatin/relebactam was approved by FDA for use in the USA in 2019.

To date, more than 50 variants of KPCs are known (25), KPC-2 and KPC-3 being the most common (26). The KPCs show hydrolytic activity to all penicillins, cephalosporins, aztreonam and carbapenems (27). Genes bla_{KPC} are often not the only ones located on plasmid, but are frequently associated with genes responsible for resistance to other classes of antimicrobial agents such as quinolones, aminoglycosides, tetracyclines, trimethoprim and sulphonamides what makes KPC isolates multidrug- or even worse pandrug-resistant (26). Although *K. pneumoniae* is generally the most common bacterial species that produces this enzyme, KPC can also be found in some other species such as *E. coli, C. freundii, S. marcescens*, *Enterobacter* spp., and *Pseudomonas* spp. (26). The first isolate of *K. pneumoniae* producing KPC (KPC-1) was detected in the USA in a North Carolina hospital in 1996 and it was uncommon until 2001 when it spread to other states on the east coast of the USA (New York and New Jersey) and after that throughout the country (2, 27, 28). This carbapenemase spread not only across the USA but also worldwide because of its epidemic potential and clonality of *K. pneumoniae,* predominantly the sequence type (ST) 258 (12, 29). It is interesting how a small isolated USA territory, the island Porto Rico became a place of origin for some KPC variants that soon became endemic (27). The first *K. pneumoniae* KPC (KPC-2) was identified in 2005, in Paris, from urine and blood culture of a patient who had previously been treated in a New York City hospital, thus resulting from an intercontinental transfer (27, 30). The other reported cases across the USA were from Colombia in 2006 and from China and Israel a year later (31). Just as in France, the first KPC case in Israel was imported from the USA, leading to an increasing incidence of KPC producers during 2006, which quickly resulted in the emergence of a nationwide outbreak and an endemic site for KPCs (27, 32). However, the compliance with the infection control measures and guidelines has successfully stabilized the spread of these resistant strains (27, 32). *K. pneumoniae* clone ST258 predominates in many parts of the world but there are other successful clones like the clone ST11 which is responsible for the spread of KPC in China (27). The first Italian report on *K. pneumoniae* KPC dated from 2008, which soon evolved into an endemic situation (27). One of the first European countries to become endemic for *K. pneumoniae* KPC was Greece and the recent surveillance report from ECDC shows that Greece struggles with more than 60% of carbapenem-resistant isolates among invasive *K. pneumoniae*, which shows the highest prevalence in Europe (33, 34). A nationwide multicentric study demonstrated that KPC is the most common carbapenemase (66,5%) in Greece (35).

To sum it up, the worldwide spread of KPC producing *K. pneumoniae* is linked to the dissemination of a few very successful clones and has led to the endemicity areas in the USA, South America, Greece, Italy, China and Israel (29, 33).

Class B carbapenemases

The Ambler class B β-lactamases are zinc metalloenzymes commonly referred to as metallo-β-lactamases (MBLs). These enzymes degrade all

β-lactams except aztreonam (4, 36). Since zinc ion(s) is (are) required for the activity of these enzymes, it follows that ethylene-diaminetetraacetic acid (EDTA) and other metal cation chelators are inhibitors of these carbapenemases (37). Other β-lactamase inhibitors, including a novel non-β-lactam, β-lactamase inhibitor avibactam are not effective against MBLs (23). The Verona integron–encoded metallo-β-lactamase (VIM), imi-penemase (IMP) and the New Delhi metallo-β-lactamase-1 (NDM-1) are the most frequent β-lactamases that belong to this class of carbapenemases. MBLs are classified in three subclasses B1, B2 and B3 with clinically most relevant class B carbapenemases VIM, IMP and NDM belonging to the subclass B1 (37).

The VIM-producing Enterobacterales are mostly found in Europe, predominantly southern Europe and in the Mediterranean area (38). The first VIM-type enzyme was described in Italy in 1997, detected in an isolate of *P. aeruginosa* (37, 39). Currently, there are known more than 60 variants of VIM enzyme (25). The VIM producers have expanded around the world mostly because of *P. aeruginosa* isolates (38). This enzyme is not only detected in *P. aeruginosa*, but also increasingly in Enterobacterales, especially in *E. coli, Enterobacter* spp. and *K. pneumonia*, the latter being the most predominant one (36). The first VIM-producing *K. pneumoniae* in Greece was detected in 2002 in Athens and it disseminated rapidly over the country resulting in an endemic for MBL (33, 40). Apart from being endemic in Greece, VIM enzyme is also widely disseminated in Spain, Italy and Hungary where inter-regional spread was observed in 2014-2015 (33, 36).

A novel MBL gene, designated $bla_{\text{NDM-1}}$, encoding for New Delhi Metallo-β-Lactamase was reported for the first time in 2008 in *K. pneumoniae* and *E. coli* isolated from a Swedish patient of Indian origin after being hospitalized in New Delhi (38, 41). Among β–lactamases in class B, NDM is one of the most clinically significant. More than 20 variants of NDM have been assigned so far (25). According to amino acid identity, NDM-1 is not similar to other MBLs (38). Most NDM positive strains were reported from Asia, particularly in China and India (42). The Indian subcontinent (Pakistan, India, Sri Lanka, Bangladesh) is considered as an endemic and crucial reservoir of NDM producers (12, 38). In India, NDM-1 is the most observed carbapenemase (43). Other likely-reservoirs accountable for the spread of NDM producers are considered to be the Balkans, the Arabian Peninsula and North African countries (38). Due to its close relationship with India and Pakistan, the UK consequently has a significant incidence of *K. pneumoniae* NDM isolates (38, 43). In Europe, an inter-regional spread of NDM producers was noted in three European countries: Poland, Romania and Denmark in 2014-2015 (33).

The first report of IMP-1 detected in *P. aeruginosa* was published in 1991 in Japan (44). These carbapenemases are not common in Enterobacteriales and such isolates are mostly detected in the South Pacific and Asia (e.g. Japan, Taiwan, eastern China) (38, 45), and are rare in Europe (33). So far, more than 80 variants of IMP have been assigned (25).

Class D carbapenemases

The Ambler Class D β-lactamases mainly consist of oxacillinases (OXAs) and so far there are more than 800 variants with different hydrolytic spectrum (25). Some of them have a narrow-spectrum β-lactamase activity, the others are ESBLs, and some of them act as carbapenemases (26). The latter can be found in specialized literature also as the carbapenem-hydrolyzing class D β-lactamases (CHDLs) (46). The CHDLs weakly hydrolyze carbapenems, and if not associated with other resistance mechanisms (such as altered permeability), do not pose a threat for developing high resistance to carbapenems (38). Furthermore, extended-spectrum cephalosporins are mostly not their substrate, but they hydrolyze temocillin (26, 38). The clavulanic acid, tazobactam and sulbactam, as classical β-lactamase inhibitors, are not successful against enzymes in this class (46). However, a novel β-lactamase inhibitor avibactam, which has already been mentioned above, exhibits both an activity against enzymes in the Ambler class A and class C but also inhibits certain enzymes in class D (eg. OXA-10, OXA-48) (23).

The OXA carbapenemases can be subcategorised in two groups, one is associated with A. baumannii, and the other one, the OXA-48-like carbapenem-hydrolysing oxacillinases are products of *Enterobacterales* and include several variants of which the most important are the following: OXA-48, OXA-162, OXA-181, OXA-204, OXA-232, OXA 244, OXA 245, OXA-247, OXA-436, OXA-484, and OXA-519 (47). The enzyme OXA-48

emerged in Turkey in 2001 where this carbapenemase was described in an isolate of *K. pneumoniae* (2, 48). After a rapid expansion throughout Turkey and causing nosocomial outbreaks, OXA-48 enzyme spread to the Middle East, North Africa and Europe (49). The gene $bla_{\text{OXA-48}}$ is located on the plasmid that does not possess any other genes for resistance, however due to its high conjugation rate, it easily and rapidly spreads among other species of order Enterobacterales (38). Besides the Mediterranean area, OXA-48 producers have been reported in some other European countries (26). In contrast to Europe, the OXA-181 enzyme variant identified in India is the dominant carbapenemase from the OXA-48-like subfamily, being spread from there to other countries (38). Although OXA enzymes can be found worldwide, there are areas such as countries of North and South America, Australia, Russia and China that have recorded low prevalence of OXA-48 produ-cers (38, 43). An inter-regional spreading is characteristic for Europe, Belgium, Spain, Romania and France, whereas Malta and Turkey are endemic areas for OXA-48 carbapenemase as assessed in 2014-2015 (33). Along with these two countries in Europe, some countries of North Africa (e.g. Morocco, Libya, Egypt) as well as India are also considered endemic areas for *K. pneumoniae* OXA-48 (43). Unlike KPC and VIM producers, OXA-48 producing Enterobacterales are still rare in Greece (33).

Epidemiology of cre in Europe

High rates of carbapenem resistance in invasive *K. pneumoniae* are seen in some countries that regularly report to EARS-Net and CAESAR surveillance networks (34, 50). Greece and Belarus reported proportions more than 50%, and Georgia, Italy, Romania, the Russian Federation, Serbia, Turkey and Ukraine reported proportions between 25% and 50%. However, resistance rates do not necessarily reflect the true epidemiological burden of resistant strains. Therefore, in 2012, the ECDC initiated the „European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE)“ project to collect data about occurrence of CPE across Europe and improve laboratory capacity for diagnosis and surveillance of CPE in European countries (33). The participating countries were the 28 EU Member States, Iceland, Norway, the seven EU enlargement countries (Albania, Bosnia and Herzegovina, Kosovo, Montenegro, the former Yugoslav Republic of Macedonia, Serbia and Turkey) and Israel, in total 38 countries (33). In 2013, a national expert of each of the EuSCAPE participating countries got a questionnaire on CPE issue and health system responses, and the second one followed in 2015, after finishing the project. A novel epidemiological staging system was applied to describe the magnitude of CPE and while comparing the two questionnaire reports, it was proven that the epidemiological situation obviously worsened during a 2-year period (2013-2015). A rapid spread of OXA-48- and NDM-producing Enterobacterales was reported. In 2017, the European Antimicrobial Resistance Gene Surveillance Network (EURGen-Net) was set up to carry out the surveys of carbapenem and/or colistin-resistant Enterobacterales in Europe as a continuation of the EuSCAPE project (5). This time all 37 participating countries had confirmed CPE isolates (Israel did not participate). In most countries the epidemiological situation didn’t change, however it worsened in 11 countries, which however showed a favorable outcome after the implementation of control measures in Slovenia (5). The overall highest incidence of CP *K. pneumoniae* is found in southern and southeastern Europe with Greece, Italy, Malta and Turkey mostly affected with endemic situation for CPEs (5).

CONCLUSIONS

CPEs present a serious threat to public health and limit treatment options for critically ill patients. It is of utmost importance, therefore, to develop laboratory capacity and ability to detect carbapenemase production in Enterobacterales as this has important infection control implications and is essential in organizing a reliable surveillance network. Based on local, national and international surveillance data a set of measures tackling prudent antimicrobial prescribing and infection prevention and control precautions should be implemented. Local and national clinical guidelines for antimicrobial use should be developed based on local epidemiology of MDROs. When developing guidelines, special care should be taken to preserve the efficacy of broad-spectrum antibiotics such as carbapenems through promoting bacteriological testing and targeted narrow spectrum antibiotic therapy. Whenever possible de-escalation policy should be implemented. To increase bacteriological testing and enable targeted antibiotic

therapy, clinical involvement of microbiologists and laboratory availability seven days a week should be encouraged. Communication of microbiologists, infectious disease specialists, infection control practitioners among each other and with other health care workers on daily basis is crucial in tailoring antimicrobial therapy and restricting the spread of resistant clones. Among MDRO, CP *K. pneumoniae* presents a special challenge for the laboratory, clinicians and epidemiologists as carbapenem resistance in Enterobacterales is not as readily detected as in other bacterial species, there are very few options for treatment left and it seems that the burden of carbapenem-resistant *K. pneumoniae* is increasing at the accelerating speed in Europe.

CONFLICT OF INTERESTS

The authors declare no conflict of financial or non-financial interests.

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