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Research Paper

Carbapenemase-Secreting Gram-Negative Bacilli Infections: Epidemiology, Place Of New Antibiotics And Prevention Strategy.

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ABSTRACT: *β-lactamases with carbapenemase activity are the most potent mechanisms of resistance to carbapenems. These carbapenemases are increasingly identified in enterobacteria worldwide. The KPC-type carbapenemases first described in the United States in Klebsiella pneumoniae have a worldwide distribution with marked endemicity also in Israel and Greece. Metallo-enzyme carbapenemases (VIM, IMP...) have also been described worldwide with a high prevalence in Southern Europe and Asia. OXA-48 is one of the most recently described carbapenemases, structurally different from the previous ones and essentially identified in Mediterranean countries. The genes of these carbapenemases are mostly plasmid, mainly in hospital strains of K. pneumoniae, but their diffusion in the community has already been reported. Carbapenemase-producing Enterobacteriaceae infections are difficult to treat and can be the source of therapeutic impasses. The introduction of new antibiotics, described in this article, is a very incomplete response to this phenomenon. In this context, the control of the spread of emerging highly antibiotic resistant bacteria (EHARB) is based on a double strategy of reducing antibiotic prescription to limit selection pressure and preventing spread from carrier patients.*

KEYWORDS: *highly antibiotic resistant bacteria, carbapenemase-secreting Enterobacteriaceae.*

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I. INTRODUCTION

Antibiotic resistance continues to grow worldwide, especially among gram-negative bacilli, such as enterobacteria (Eschirichia coli, Klebsiella pneumoniae, Enterobacter spp...) [1]. This problem is currently dominated by resistance to carbapenems, the most recently developed β-lactams with the broadest spectrum of activity. The molecules of this family of antibiotics are Imipenem, Ertapenem, Meropenem and Doripenem. They are intended for hospital use and indicated for nosocomial infections with gram-negative bacteria resistant to other β-lactams [2]. The excellent antibiotic activity of carbapenems is linked to their rapid transmembrane penetration and their stability against most natural or acquired β-lactamases [2]. The increasing resistance to carbapenems is linked to two main mechanisms [3]. The first one is related to the production of cephalosporinases that hydrolyze carbapenems weakly and to a modification of the membrane permeability to these antibiotics. The second mechanism is linked to the expression of β-lactamases that hydrolyze carbapenems strongly: carbapenemases [3 - 4 - 5]. The control of carbapenem resistance is of particular importance, especially since these carbapenemases are plasmid-based and therefore transferable from one strain to another. These transfers would make the diffusion difficult to control, especially when they concern species responsible for community infections, such as Eschirichia coli [3].

II. EPIDEMIOLOGY OF CARBAPENEMASES

β-lactam resistance in enterobacteria is currently dominated by extended-spectrum β-lactamases (ESBLs) in both community and hospital settings. The emergence of carbapenem resistance through carbapenemase production represents a further step towards pan-antibiotic resistance in Enterobacteriaceae [3 - 6]. These carbapenemases are of different types: metallo-betalactamases (IMP, VIMP), class A carbapenemases (KPC, GES, etc.) and oxacillinases [7]. The spectrum of these enzymes is not completely superimposable, but

they at least partially hydrolyze carbapenems. Numerous outbreaks of carbapenemase-producing strains of Enterobacteriaceae have been reported worldwide and in Europe, especially in the south of the continent (Italy, Spain, Greece) [6]. Resistance to carbapenemases is variable, and is always more marked in Enterobacter sp and Klebsiella sp than in E. coli or Proteus mirabilis [8 - 9].

Originally described in the United States, KPC-type β-lactamases hydrolyze all β-lactams, their activity being partially inhibited by clavulanic acid or tazobactam. The source of these enzymes is essentially K. pneumoniae, with a distribution, it seems, mainly in hospitals. These KPC+ strains were first described on the East Coast of the United States, in South America and episodically in many European countries [6]. Currently, these K. pneumoniae strains are considered endemic in the United States, Greece and Israel where it seems that their dissemination in the health care system is hardly contained [10 -11]. They also express other β-lactamases including many types of ESBLs and possess some degree of impermeability resistance. KPC strains are therefore most often multi-resistant to β-lactams, ertapenem being the carbapenem with the highest level of resistance. These KPC genes are located on a wide variety of plasmids or associated with transposons. The mobility of these plasmids and transposons strongly contributes to the interspecies diffusion of these KPC genes. The association of KPC genes with other antibiotic resistance genes on the same genetic structures largely explains the multi-resistance of these strains.

The second type of carbapenemases is the group of metallo-β-lactamases, class B according to the Ambler classification. They correspond essentially to β-lactamases of type VIM, IMP and NDM. They hydrolyze all β-lactams except Aztreonam [2]. These metallo-enzymes use zinc as a cofactor, which explains the inhibition of their activity by EDTA (chelator of divalent cations). Their activity is not inhibited by either clavulanic acid or Tazobactam. The levels of resistance to carbapenems are quite variable. VIM and IMP enzymes have a worldwide distribution among hospital enterobacteria. On the other hand, NDM-type metallo-β-lactamases have a well identified reservoir: Indian subcontinent, Middle East and North Africa [3]. The seriousness of these NDM strains is due to several factors: near-constant multidrug resistance, the size of the reservoir, particularly the Indian subcontinent, and the community nature of the enterobacteria concerned by this resistance [3].

The last type of carbapenemases identified in enterobacteria is the oxa-48 type enzymes. These β-lactamases have a narrower spectrum of hydrolysis since they hydrolyze mainly penicillins and carbapenems [9]. Their activity is not inhibited by clavulanic acid or tazobactam. Their presence is often coupled with other ESBLs, leading to multidrug resistance of the secreting strains. In the absence of co-production of extended-spectrum β-lactamases, oxa-48 strains remain susceptible to third-generation cephalosporins (cefotaxime, ceftazidime) [9]. OXA-48 have largely emerged in the Mediterranean region. They are particularly widespread in Greece, Morocco, India, and to a lesser extent in Italy and other countries around the Mediterranean.

III. PLACE OF NEW ANTIBIOTICS IN THE MANAGEMENT OF CARBAPENEMASE-PRODUCING ENTEROBACTERIA:

In view of the increasing use of carbapenems in hospitals and the growing emergence of carbapenemase-producing strains, new molecules have been marketed in order to limit the use of carbapenems and preserve their effectiveness.

A. Ceftazidime/Avibactam: Zavicefta®

Zaficefta® combines an old β-lactam, Ceftazidime, with a new β-lactamase inhibitor, Avibactam [10]. This combination is active on the majority of enterobacteria and is not inhibited by class A, class C and class D β-lactamases [10]. Nevertheless, it remains inactive against most gram-positive and anaerobic bacteria [10]. The spectrum of activity of Zaficefta®, and in particular its activity on extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, may allow carbapenem sparing [10].

B. Ceftozolane/Tazobactam: Zerbaxa®

Zerbaxa®, a combination of a new 5th generation cephalosporin, Ceftozolane, and an old β-lactamase inhibitor, Tazobactam, would be particularly active on P. aeruginosa strains presenting multiple resistances (Piperacillin, Ceftazidime, Imipenem, fluoroquinolones, aminoglycosides) [11]. Its combination with Tazobactam would also allow it to be active on ESBL-producing Enterobacteriaceae, and thus limit the use of carbapenems [11].

C. Aztreonam/Avibactam

Aztreonam/Avibactam combines a monobactam not hydrolyzed by metallo-β-lactamases (Aztreonam) with a class A, C and D β-lactamase inhibitor (Avibactam) [8]. This combination would ensure efficacy on all

enterobacteria. It is currently in the development phase with phase II clinical trials underway [8]. Due to the in vitro activity of Aztreonam/Avibactam on MBL-enterobacteria, a prospective, observational, multicenter study was conducted in 3 hospitals in Italy and Greece to evaluate the efficacy of the combination of Ceftazidime/Avibactam + Aztreonam in MBL-producing enterobacteria bacteremia [10]. The latter involved 82 MDN infections and 20 IMV infections. Mortality at D30 was 19.2% in the CAZ-AVI + ATM group (vs. 44% with other active treatments), confirming the clinical value of this combination [10].

D. Imipenem/Relebactam

Relebactam is a class A and C β-lactamase inhibitor that restores the in vitro efficacy of Imipenem against carbapenemase-producing enterobacteria. The combination is not currently available for marketing pending the results of phase III clinical studies [8].

E. Cefiderocol

Cefiderocol is a siderophore-type cephalosporin that is effective on all carbapenemase-secreting bacteria. The mechanism of action is based on the destruction of the bacterial wall thanks to the complex formed with the ferric ion. In vitro, it is active on all GNB including multi-resistant Acinetobacter baumanii and Pseudomonas aeruginosa. Clinical trials are still in phase II, but at this stage of development it is considered one of the greatest innovations in the fight against GNB [12].

IV. USE OF NEWER B-LACTAMS AND REDUCED USE OF CARBAPENEMS

French studies on the use of Zaficefta® and Zerbaxa® do not all agree with the relevance of the use of these new antibiotics as a carbapenem-sparing strategy. Indeed, L. Blanchard-jacquet et al published a retrospective study conducted at the Saint-Louis Hospital in Paris, France in 2019, and concluded that these two antibiotics do not currently fit into a carbapenem sparing strategy [13]. Similarly, L. escaut et al publish the results of a prospective study carried out at Le kremlin bicêtre University Hospital in 2019, and conclude that these new combinations are not an alternative to carbapenems. However, they are effective in serious infections with gram-negative bacilli that are totally resistant [14]. On the other hand, a randomized clinical trial published in "Le Lancet" by Bassetti et al in 2021 (the CREDIBLE-CR trial), disseminates encouraging results and considers Cefiderocol as a therapeutic option for carbapenem-resistant BGN infections, regardless of the mechanism of resistance involved, including NDM [15]. Thus, despite the marketing of these new molecules that are effective against carbapenemase-secreting gram-negative bacilli, their use in clinical practice remains to be clarified. Most of the new molecules marketed or under evaluation do not present any therapeutic innovation and have not demonstrated superiority in terms of efficacy.

V. FOCUS ON SEVERE ACINETOBACTER SPP AND PSEUDOMONAS AERUGINOSA INFECTIONS.

In the CREDIBLE-CR trial, mortality of patients infected with carbapenem-resistant Acinetobacter spp in the cefiderocol group was higher than in the other treatment group (50% mortality vs. 18%), but it should be noted that patients in the cefiderocol group were more severe at inclusion [15]. In the same trial, clinical cure was achieved in 46% of patients infected with carbapenem-resistant P. aeruginosa treated with cefiderocol. Cured patients had MIV, IMP, PDC, OXA-23-like, OXA-24/72-like, confirming clinical efficacy in PA with different resistance mechanisms.

A descriptive study by Falcone et Al treats 10 critical care patients with imipenem-resistant Acinetobacter baumanii (ABRI) bacteremia or VAP. Cure at day 30 was 70%. There were two microbiological failures [16].

VI. CONTROLLING THE SPREAD OF CPE:

In this context, where the short-term perspective of new antibiotics is particularly limited, the control of the spread of emerging highly antibiotic-resistant bacteria (EHARB), such as carbapenemase-producing Enterobacteriaceae (CPE), must be based on a dual strategy of reducing antibiotic prescribing in order to limit selection pressure and preventing spread from carrier patients. As CPEs belong to the intestinal microbiota, they are likely to be carried for a long time in the digestive tract of patients and to spread widely in the hospital but also in the community. Patients "suspected" of being carriers of an CPE are those who have been hospitalized for more than 24 hours in the last 12 months, regardless of the sector, or who have been managed in a specific care sector (e.g. dialysis), patients who have been in contact with a patient carrying a EHARB, and finally patients who were previously known to be carriers of EHARB. Other opportunistic pathogens, in particular saprophytes such as Pseudomonas aeruginosa or Acinetobacter baumanii, although potentially carrying transferable mechanisms of resistance to carbapenems of the carbapenemase type, do not justify the same

preventive measures because of a risk of dissemination limited to health care institutions or even limited to a few hospital sectors with a high transmission potential (intensive care unit, etc.).

Digestive carriage is demonstrated by the search for CPE in the stool or, failing that, by rectal swabs. Stool or rectal swabs are plated on selective agar plates appropriate for the search for CPE, and incubated for 24 to 48 hours. To date, no selective medium allows the detection of all CPE. However, some rapid tests have been developed such as the CARBA-NP test, performed directly from colonies grown on selective media. The principle of this test is based on the detection of an acidification of the medium during the hydrolysis of Imipenem by a carbapenemase [17 - 18]. The pH indicator changes color (from red to yellow) when the medium becomes acidic, indicating the presence of a carbapenemase. The result, obtained in less than 2 hours, has excellent specificity and sensitivity. Molecular methods of gene detection have also been recently developed. These techniques are based on the use of PCR, supplemented or not by a sequencing technique of the amplified DNA (useful only for epidemiological purposes). The current epidemiological data of CPE in Morocco imply the need to use molecular techniques capable of detecting at least the genes encoding carbapenemases of type OXA-48, NDM and KPC, thus covering most of the CPE detected in our kingdom. The detection of patients with CPE only allows us to institute precautionary measures to minimize the risk of diffusion of microorganisms, because we have no recognized means of decontaminating the digestive tract of patients. Thus, one of the two pillars of the "search and destroy" strategy, which has been successfully implemented in European countries for nasal carriers of methicillin-resistant Staphylococcus aureus (MRSA), cannot currently be applied in the context of digestive tract carriage.

The precautions to be applied to minimize the risk of diffusion of microorganisms must be pragmatic and adapted to the epidemiological situation. In addition to the standard precautions (wearing gloves, gowns, masks, hand hygiene, treatment of waste and linen), and additional precautions (single room, signalling of infectious status, dedicated equipment, use of an over-gown), specific precautions related to EHARB must be observed if at least one carrier patient has been identified. These measures may vary according to the type of situation (sporadic or epidemic case), with: geographic grouping of EHARB carriers, stopping inter-departmental transfers of cases and contacts, limitation of admissions, active surveillance of other carrier cases, dedicated care team, reinforcement of environmental control.

VII. CONCLUSION

Faced with the development of resistance phenomena throughout the world, research and development of new antibiotics is insufficient. Most of the new molecules marketed or under evaluation do not present any therapeutic innovation and have not demonstrated any superiority in terms of efficacy. There is no universal antibiotic and the new molecules only provide a response to one of the existing resistance mechanisms. In this context, where the short-term perspective of new antibiotics is particularly limited, the control of the spread of emerging highly antibiotic-resistant bacteria (EHARB), such as carbapenemase-producing Enterobacteriaceae (CPE), must be based on a dual strategy of reducing antibiotic prescribing in order to limit the selection pressure and preventing the spread from carrier patients. The prevention strategy is based on the systematic application of standard precautions for all patients, and specific additional precautions for patients carrying EHARB.

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