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The burden of severe infections due to carbapenem-resistant pathogens in intensive care unit

Pace MC *et al.* Carbapenem-resistance in ICU

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Abstract

Intensive care units (ICU) for various reasons, including the increasing age of admitted patients, comorbidities, and increasingly complex surgical procedures (*e.g.*, transplants), have become "the epicentre" of nosocomial infections, these are characterized by the presence of multidrug-resistant organisms (MDROs) as the cause of infection. Therefore, the perfect match of fragile patients and MDROs, as the cause of infection, makes ICU mortality very high. Furthermore, carbapenems were considered for years as last-resort antibiotics for the treatment of infections caused by MDROs; unfortunately, nowadays carbapenem resistance, mainly among Gram-negative pathogens, is a matter of the highest concern for worldwide public health. This comprehensive review aims to outline the problem from the intensivist's perspective, focusing on the new definition and epidemiology of the most common carbapenem-resistant MDROs (*Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacterales*) to emphasize the importance of the problem that must be permeating clinicians dealing with these diseases.

Key Words: Antimicrobial resistance; Multidrug-resistant; PDR; Carbapenem-resistance; Multidisciplinary critical care; Intensive care unit

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Core Tip: Intensive care units for various reasons have become "the epicentre" of nosocomial infections due to multidrug-resistant organisms: a perfect combination of critically ill patients and multidrug-resistant organisms, as the cause of infection, makes these patients' mortality very high. This comprehensive review aims to outline the problem from the clinician's perspective, focusing on the new definition and epidemiology of the most common multidrug-resistant organisms that are *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacterales* in order to emphasize the importance of the problem.

INTRODUCTION

Carbapenem resistance is such an important public health issue worldwide^[1,2] that the 2017 World Health Organization (WHO) global priority list of pathogens ranks carbapenem-resistant *Enterobacteriaceae* (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) in the highest priority category (*i.e.*, Critical)^[3]. Infections sustained by these bacteria lead to longer lengths of stay, increased healthcare costs, and higher mortality^[4-6] especially in patients admitted to the intensive care unit (ICU)^[7]. Many studies demonstrated the link between carbapenem use and carbapenem resistance^[8-10]. This has even greater clinical relevance when we consider that the rise in the consumption rate of carbapenems was 45% worldwide^[11]. Carbapenems are the third most widely used class of antibiotics worldwide for community-acquired infections in ICU (10.7%) and the first class for hospital-acquired infections (HAI) (21.5%)^[12]. This comprehensive review aims to analyze from the perspective of worldwide epidemiology the global burden of severe infections supported by carbapenems-resistant germs in the ICU setting.

METHODS

To review the published clinical data on the epidemiology of carbapenem resistance in the ICU setting, a systematic search of the biomedical literature was conducted. Medline (via PubMed) was searched, limited from 2012 to 2022, for articles using the following terms: [(carbapenem or imipenem or meropenem or doripenem or ertapenem) and (resistance or resistant or susceptible or susceptibility)] or (carbapenemase). The result of this search was combined with three separate searches for "*Pseudomonas aeruginosa*", "*Acinetobacter baumannii*" and "*Enterobacteriales* or *Enterobacteriaceae*". The retrieved studies were scheduled from the geographical area of origin in the five continents: "Africa", "America", "Asia", "Europe", "and Australia".

DEFINITIONS

¹⁵ Carbapenem-resistant Gram-negative bacteria (GNBs), namely, CRE (e.g., *klebsiella pneumoniae*, *Escherichia coli*), CRAB and CRPA, ¹¹ are a matter of national and international concern as they are an emerging cause of HAI that pose a significant threat to public health. The term 'CROS' is used as a generic term that refers to all of these GNBs^[13]. ¹⁶ Centers for disease control and prevention (CDC) define CRE as multidrug-resistant organisms that are resistant to at least one of the carbapenem antibiotics (ertapenem, meropenem, doripenem, or imipenem) or produce a carbapenemase. ²³ CRE is a phenotypic definition (i.e., based on the organism susceptibility pattern). A lot of different mechanisms (i.e., genotypes) can result in carbapenem resistance, for example, the production of enzymes that break down carbapenems and related antimicrobials making them ineffective: CRE that produce carbapenemases are called carbapenemase-producing CRE (CP-CRE); ¹² therefore, CP-CRE are a subset of all CRE (approximately 30% of CRE carry a carbapenemase), carbapenemase genes are often on mobile genetic elements, which can be easily shared between bacteria, leading to the rapid spread of resistance. Carbapenemases are classified by ambler into three classes - A, B and D (class C includes enzymes that hydrolyze primarily cephalosporins^[14]) based on their central

catalytic domain and substrate preference^[15]. Class A[e.g., *klebsiella pneumoniae* carbapenemase (CRKP), imipenem-hydrolyzing β -lactamase and *Serratia marcescens* enzyme] and d[oxacillin carbapenemase/oxacillinase (OXA)] carbapenemases have serine residues in their active sites and hence are called serine-proteases, while Class B[New Delhi metallo- β -lactamase (NDM), Verona integron-encoded metallo- β -lactamase (VIM) and imipenemase metallo- β -lactamase (IMP)] enzymes are metallo- β -lactamases with zinc in the active site^[16]. The five carbapenemases most frequently identified in CRE are CRKPKPC, which was the first carbapenemase identified in the United States in 2001, the NDM, VIM, oxacillinase-48 (OXA-48-type), and IMP^[17]. the European committee on antimicrobial susceptibility testing defined the meropenem breakpoints for *Escherichia coli* and *Klebsiella pneumoniae* as $S \leq 2$ mg/L and $R > 8$ mg/L; the corresponding breakpoints for ertapenem are $S \leq 0.5$ mg/L and $R > 0.5$ mg/L. Isolates with meropenem minimum inhibitory concentration (MIC) > 2 mg/L and/or ertapenem MIC > 0.5 mg/L are considered resistant and should be investigated for carbapenem resistance mechanisms. This approach will not identify all *Escherichia coli* and *klebsiella pneumoniae* isolates but will detect most isolates with clinically significant carbapenem non-susceptibility. As the CDC also the European CDC encourages proceeding with the detection of carbapenemase production in carbapenem non-susceptible isolates with MIC values above the susceptible breakpoint^[18].

EPIDEMIOLOGY

To monitor antibiotic resistance and plan contrast strategies, the different continents established epidemiological surveillance networks: European antimicrobial resistance surveillance network and central Asian and eastern European surveillance of antimicrobial resistance in Europe and Asia while the national healthcare safety network at the CDC in the United States. They documented that multidrug-resistant organisms (MDROs) have become much more prevalent during the last decade^[19-21]. CDC estimates that each year in the United States, at least 2.8 million people get an antibiotic-resistant infection, and more than 35000 people die. The estimated national cost to treat infections

caused by six MDROs identified in the last CDC report and frequently found in healthcare can be substantial—more than \$4.6 billion annually^[22]. In a report conducted for “the review on antimicrobial resistance (AMR)”⁴, commissioned in July 2014 by the United Kingdom prime minister, it is predicted that the toll of global antimicrobial resistance will be 10 million deaths per year and up to \$100 trillion lost to the global economy by 2050^[23]. In a survey promoted by the European society of intensive care medicine, 12.4% of ICU physicians reported that they had, during the preceding six months, at least one patient with an infection caused by a bacterium resistant to all or almost all antibiotics available in their ICU^[24].⁸ An international multicenter study concluded that 19% of patients admitted to the ICU for more than 24 h acquired an infection, with rates ranging between 2.3% and 49.2% depending on the hospital unit^[25].⁸ The most common ICU-acquired infections are pneumonia, surgical site infection, gastrointestinal infection, urinary tract infection (UTI) and bloodstream infection (BSI)^[26]. In a large surveillance report from 183 us hospitals, 84% of BSI were related to the use of a central line catheter, 39% of pneumonia cases were ventilator-associated pneumonia and 68% of UTIs were related to urinary catheters^[27].²⁰ According to the results of gram staining, bacteria can be classified into 2 categories: GNBs and Gram-positive bacteria (GPBs). Infections caused by multidrug-resistant GNBs are more frequent than multidrug-resistant GPBs, compared to the past. in a large prevalence study on infected ICU patients with isolates from 75 countries, 62% were GNBs, 47% were GPBs and 19% were fungal^[28]. many acronyms help clinicians remember the most prevalent germs: ESKAPE organisms identify a group of highly resistant germs that 'escape' to β-lactam antibiotics and consist of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter* spp, *Pseudomonas aeruginosa*, and *Enterobacter* spp^[29,30].⁹ ESKAPE organisms represent the 6 most common MDROs of HAI^[31]. However, since it was pointed out that this acronym excluded other enteric GNBs including *Escherichia coli*, it was modified into ESKAPE+C⁴ where “c” refers to *Clostridium difficile*, an important nosocomial pathogen that may easily acquire an MDROs phenotype and “e” refers *Enterobacteriaceae* covering all enteric GNBs including *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus* spp and

15
Enterobacter spp^[32]. In Europe and other areas, of particular concern is the rapid spread of resistance mediated by extended-spectrum β -lactamases (ESBLs), especially in *Klebsiella pneumoniae*. 10
ESBLs organisms are usually resistant to multiple antimicrobials, including third-generation and fourth-generation cephalosporins and aztreonam^[33]. Sader and colleagues in their large cross-national research study reported that among *Escherichia coli* isolates from the ICUs, 13.7% were ESBLs producers while ESBLs-*klebsiella spp* were 17.2%^[34]. Another antibiotic class that over time increased the resistance of *Escherichia coli* is that of fluoroquinolones, usually considered active in this species^[35,36]. 10
Resistance of *Pseudomonas aeruginosa* to fluoroquinolones and imipenem has increased rapidly; above 10% of *Pseudomonas aeruginosa* are now resistant to multiple antibiotics classes such as cephalosporins, carbapenems, aminoglycosides and fluoroquinolones^[33]. The increased use of carbapenems, which are among the most effective classes of antibiotics active against MDROs contributed to the emergence of CRE or CRAB^[37,38]: up to 25% of *Acinetobacter baumannii* isolates are CRAB^[33]. The CRAB prevalence in Europe seems to be higher in south-eastern Europe, with the highest prevalence in Romania (86.5% meropenem 94.6% imipenem resistance)^[39]. In the American continent, there seems to be a north-south gradient with all isolated *Acinetobacter baumannii* resistant to carbapenems in Uruguay^[40], and practically absent in Canada^[41]. More contained data come from Asia with China which seems to have the greatest number of CRAB. As for the African continent, there are few studies on the prevalence of carbapenem resistance^[42,43]; in a study conducted in Uganda, the prevalence of CRAB is 81.25%^[44]. Table 1 and Figure 1 report the worldwide prevalence of meropenem-resistant *Acinetobacter baumannii*; we decided to use meropenem as a benchmark to determine the occurrence of carbapenem resistance, to make tables and figures easier to read because *in vitro* studies involving isolates from ICU patients indicate that meropenem is more active against most GNBs than other comparators (including imipenem)^[45]. More contained data concern the CRPA: In Europe, the data are more varied with very variable resistance, also between homogeneous nations in terms of geography, economy, and social progress; for example, in the Netherlands, the prevalence is 8.3%-17%^[46] while in Germany it is 66.7%^[47]. In

North America the prevalence does not seem to exceed the two-fifths of the isolates, on the contrary, in a study conducted in Costa Rica, these exceeded four-fifths^[48]. In Asia, the highest prevalence is in Korea with 92.9% of the BSI isolated from a burn ICU^[49]. In Africa, the prevalence varies from about half of the isolates to almost all, as in Uganda with 88.8% of the CRPA^[44] (Table 2). In Figure 2 is showed the worldwide prevalence of meropenem-resistant *Pseudomonas aeruginosa*.

CRE account for approximately 20%-70% of *Enterobacterales* isolated in Europe^[50,51], in North America, they remain almost non-existent in Canada^[41], with a prevalence similar to the European one in the United States^[52-55]. in Asia data are very varied with a prevalence in China of 56.6%-76.7% of CRKP^[56,57]. From studies conducted in the African continent, Tunisia seems to be the country with the highest prevalence with a percentage of 85.2% of CRKP^[58]. In Table 3 we reported the worldwide prevalence of meropenem-resistant *Enterobacterales*, and Figure 3 is shown the worldwide prevalence of CRKP which is the most common CRE.

RISK FACTORS

Many risk factors can contribute to the genesis of antimicrobial resistance. They can be categorized as host, environmental, human, and protective barrier integrity factors^[109]. Host risk factors include advanced age, organ and bone marrow transplant, end-stage renal disease in dialysis, intra-abdominal surgical procedures, cancer chemotherapy, immunosuppressive disease or therapy^[26,110-112]. Prior use of antibiotics (90 days), prolonged antimicrobial usage and hospitalization (more than 5 days), use of indwelling catheters, long mechanical ventilation and residence in nursing homes and long-term care facilities are other important risk factors^[110,112,113]. Numerous drugs used in ICU can be a risk factor predisposing patients to infections such as pneumonia (e.g., sedatives and muscle relaxants because they can reduce the cough and swallow reflexes) or gastrointestinal infections (e.g., proton pump inhibitors for stress ulcer prophylaxis because they disrupt the normal non-pathogenic bacterial flora)^[110]. In this category, an important independent risk factor is previous MDROs infection or MDROs colonization.

If the latter case occurs the probability of developing an infection is high^[113]. Considering that some microorganisms can survive on surfaces, environmental, is a category of risk factors, very dangerous for the genesis of antimicrobial resistance: It includes poor cleaning and disinfection of environmental surfaces as well as medical devices used for patient care (e.g., stethoscopes, thermometers, suction apparatus) that so became a source or reservoir to disseminate germs to other patients^[114]. Among environmental risk factors, colonization pressure is of great importance. First described by Bonten for vancomycin-resistant *Enterococci*^[115], and later for other bacteria as well^[116-118], it is a critical parameter in the epidemiology of MDROs defined as ²¹ the proportion of patients colonized with a microorganism in a given geographic area for a specified period^[119]. It can be used to estimate the probability of cross-contamination^[118], which is in turn an important indicator of poor hygiene especially when there is a clonal relationship of isolates^[120]. In their study, Arvaniti *et al*^[121] found that out of the total number of patients admitted to their ICU, 5.7% were already colonized at the hospitalization and of these 15.7% acquired *Acinetobacter spp.* during their ICU stay.

The main physical barriers of our body are the skin and mucosa membranes. They represent the first defensive bulwark against infections in general and therefore also for those supported by MDROs. Damage or interruption of their integrity using invasive devices in the ICU increases ⁵ the risk of infections. In a recent meta-analysis by Hui Ang and Xuan it was found that ⁵ male gender (OR 1.40, 95%CI: 1.09, 1.80), having an operative procedure (OR 1.31, 95%CI: 1.10, 1.56), a central venous catheter (OR 1.22, 95%CI: 1.01, 1.48), mechanical ventilation (OR 1.25, 95%CI: 1.07, 1.46), previous antibiotic therapy (OR 1.66, 95%CI: 1.41, 1.96), length of ICU stay (weighted mean difference 8.18, 95%CI: 0.27, 16.10) were the identified risk factors associated with MDROs infections in ICU^[122].

CURRENT AND FUTURE STRATEGIES AGAINST ANTIMICROBIAL RESISTANCE IN ICU

Infection prevention strategies can be divided into vertical or horizontal approaches^[123,125]. Both go to integrate themselves into complex and various strategies to

prevent MDROs infections. Vertical approaches involve the reduction of the risk of colonization, infection and transmission from high-risk pathogens or a specific group of them (e.g., *Clostridium difficile*, multidrug-resistant GNBs, and others)^[124]. For this reason, they are valuable tools in controlling and managing an outbreak^[123,124]. Vertical approaches are centred on the use of active surveillance testing to detect patients who are MDROs carriers (i.e., asymptomatic colonizers) and separate them from patients who are not colonized with that specific pathogen. This is because asymptomatic colonizers can spread the microorganism contaminating the environment and devices and favouring transmission through direct and indirect contact^[124]. Examples of active surveillance testing are a rectal culture for CRE. Vertical strategies include also contact precaution and targeted decolonization (TD) for specific pathogens. TD has some limitations: the different decolonization strategies reduce the diffusion of a single specific target organism and not all-important organisms, such as multidrug-resistant GNBs and VRE, have options for decolonization^[126]. Horizontal infection prevention strategies aim to reduce the risk of infections sustained by a broad spectrum of pathogens^[124]. They include standard precautions (such as hand hygiene and use of personal protective equipment) and antimicrobial stewardship (AS). It should be noted that some interventions falling within the vertical approach, such as the use of gloves with or without gowns or the decolonization of the skin, can be applied to all patients (i.e., in a horizontal approach), not just those with a specific pathogen. According to the CDC and the WHO, hand hygiene remains the simplest and most important practice in infection control. In May 2009 the WHO drew up a simple and precise infographic (called "The 5 moments of hand hygiene") for hand hygiene or the transition from one patient to the next, to prevent cross-transmission^[127]. Despite the evidence showing the effectiveness of hand hygiene in preventing infections and efforts to increase compliance rate, it remains low at between 40% and 60%^[128,129]. AS is a set of strategies used to improve the use of antibiotics and limit the onset of resistance. It is centred on a systematic approach in multidisciplinary teams^[130,131].

An AS programme should provide for: (1) The systematic search for causal agents

by carrying out targeted crop surveys. The use of molecular biology tests can also enable important data to be obtained quickly; (2) Limiting the use of broad-spectrum drugs and reducing the duration of empirical therapy through de-escalation strategies^[132], with timely replacement of these drugs with other narrow-spectrum drugs; (3) Base therapies on pharmacokinetic and pharmacodynamic criteria adapted to the conditions of critical patients and any changes in the volume of distribution, metabolism, and elimination of drugs; and (4) Optimization of therapy (*i.e.*, adequate dosage, optimal mode of administration for the shortest possible time).

About AS it is important to note that data suggest that 30% to 60% of antibiotics prescribed in ICU are unnecessary, inappropriate, or suboptimal^[133]. One of the possible reasons for this is the widespread belief that once the diagnosis of infection is made it is necessary to immediately start the antibiotic therapy with broad-spectrum drugs as each delay is associated with a worsening of the patient's outcome. This is true in infections with a rapid evolution (*e.g.*, Meningitis) or for patients hemodynamically unstable. However, data suggest that in patients with infection but stable, a limited delay in the start of antibiotic therapy allowing the execution of targeted cultures would allow a more appropriate treatment and an improvement of the outcome^[134]. It seems to be essential to identify protocols for the quickest identification of the germ causing the infection^[135], in order not to use combination therapies whose efficacy on MDROs is not always the most effective^[136, 137]. A paradigmatic case seems to be the use of colistin in combination, which is the most common use in clinical practice^[138], but randomized studies have not shown any benefits even in strains resistant to retrospectively identified as colistin-resistant^[139]. Environmental cleaning and disinfection are other essential horizontal strategies for the control of infections and especially the prevention of cross-contamination^[109]. It is important that in every hospital there is a systematic protocol for environmental cleaning and disinfection. It should address regular daily high-touch areas frequently exposed to human contact and emphasize adequate disinfection of the discharged patient's room as a terminal cleaning practice^[140].

Currently, antibiotics are still the first therapeutic weapon for patients with MDROs

infection in ICU^[141]. Despite government efforts and incentives for pharmacological research of new molecules, few antimicrobial agents remain effective against MDROs that are available in clinical practice. New antimicrobial agents recently approved or in advanced phases of clinical development including the new beta-lactam and beta-lactamase inhibitor combinations (ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/cilastatin/relebactam, aztreonam/avibactam), siderophore cephalosporins (cefiderocol), aminoglycosides (plazomicin) and tetracyclines (eravacycline)^[142]. Numerous incentives have been provided to encourage researchers to work on alternative strategies to reverse the resistance trend. There are numerous alternative therapeutic weapons to antimicrobials in the study that could be used in the future^[141]. Our microbiota remains an important ally in the battle against MDROs infections. Therefore, it must remain unaltered. Two therapeutic options are currently being investigated to remove the antibiotic residues active in the colonic space where the highest concentrations of intestinal bacteria are found. The first is the use of an engineered, broad-spectrum beta-lactamase that aims at decaying any beta-lactamase in the gut. The first is colon-delivered active charcoal, which aims to adsorb free colonic compounds^[141]. Phage therapy is another therapeutic alternative with an interest in the future. A serious advantage of phages over antibiotics is that are highly specific. For this, they can be a perfect weapon to decontaminate MDROs from the gastrointestinal tract, as only MDROs strains would be targeted while commensal strains would be spared^[141]. Like phage another specific future possibility against MDROs infection is antibodies. To overcome the issue of immune reaction against monoclonal antibodies, they are now humanized. Examples of antibodies that are being developed in this context target virulence factors: Alpha-toxin of *Staphylococcus Aureus*, the type III secretion system of *Pseudomonas Aeruginosa*, and the toxin B of *Clostridium difficile*^[141]. In addition, a vaccine against multidrug-resistant *Acinetobacter baumannii* is also under investigation at the preclinical stage^[141].

A Specific carbapenem-resistant and carbapenemase-producing Organism Prevention Program for Public Health and Healthcare is recently uploaded by the

California Department of Public Health; it is clearly articulated ten different points: (1) Laboratory Identification (implement the updated laboratory breakpoints for carbapenems and *Enterobacterales*); (2) Surveillance (ensure that the laboratory rapidly notifies infection prevention and clinical staff when a patient with carbapenem resistance is identified); (3) Colonization Testing (perform CRE colonization testing upon ICU admission of high-risk patients); (4) Infection Control Measures (place patients infected or colonized with CRE in a single room whenever possible, and implement Standard and Contact precautions); (5) Adherence Monitoring (use infection control assessment and adherence monitoring tools); (6) Environmental Cleaning (Ensure thorough daily and terminal environmental cleaning. Focus on high-touch surfaces or any shared reusable medical equipment); (7) Interfacility Communication (Communicate CRE status to the receiving facility ahead of time to ensure appropriate care is maintained when transferring a patient); (8) AS (Implement strategies to limit the use of broad-spectrum antimicrobial agents and an antimicrobial stewardship program); (9) Regional Prevention (Participate in regional efforts to prevent the spread of drug-resistant infections); and (10) Reporting (Report CPO cases through CalREDIE electronic laboratory reporting^[143]).

CONCLUSION

Antimicrobial resistance remains a huge public health problem on a global scale whose weight has a huge cost in terms of health expenditure and human lives. At present, antimicrobial agents remain the only causal therapeutic strategy available. Thanks to the efforts of research, in the future, we could use new therapeutic weapons as alternatives or even superior to antimicrobial agents^[141]. At present, it is important to preserve the effectiveness of the last molecules put on the market, through a systematic implementation of strategies to minimize or prevent risk factors (first the pressure selection) and the spread of MDROs. For this purpose, *in primis*, the knowledge of local epidemiology and the creation of antimicrobial programs and diagnostic stewardship are mandatory to ensure the appropriateness of antimicrobial therapies. The WHO Global Action Plan on antimicrobial resistance gives strategic objectives, one of which is to

strengthen knowledge through surveillance. To cover the gaps in knowledge on the incidence, prevalence, and range of antimicrobial resistance across different geographical regions^[144]. In our review, it is evident that there are huge differences in the epidemiology of different nations and that in most of the geographical regions, there are no data. Finally, a multidisciplinary approach including intensivists, microbiologists, pharmacists, and infectious disease specialists should play a key role to optimize antimicrobial treatment and minimizing inappropriate use of antibiotics in an era of limited pharmacological options^[142]. ⁶ To our knowledge, this is the first comprehensive review of the global of severe infections due to carbapenem-resistant pathogens focusing on ICU, as well as an evaluation of the limited availability of data. Previous reports focused on the overall antimicrobial resistance aggregating data from different inpatient wards and not exclusively from ICU^[145].

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