The carbapenems issue

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Abstract

The development of antibiotics remains one of the great advances in medicine. Antibiotics have saved countless lives. Unfortunately, the widespread use of antimicrobials has led to the development of antimicrobial resistance. Antibiotic resistance is an important concern for public health; it is associated with poor outcomes. Carbapenems, members of the β-lactam class of antibiotics, have the broadest spectrum of antimicrobial activity. Carbapenem resistance is one of the toughest challenges in infectious diseases; it is associated with high mortality and is seen more often now due to the proliferation of multi-drug resistant bacteria. Multiple genes that cause carbapenem resistance have been identified. Resistance transmission is usually nosocomial, but community-acquired infections with resistance have been reported. Early recognition of high risk patients for multi-drug resistant infections is fundamental for adequate management. The rational use of antibiotics is required to prevent the spread of antimicrobial resistance; this requires multidisciplinary efforts among clinicians, Infection Control departments, and Antimicrobial Stewardship programs.

Keywords: Resistance, Antibiotics, Carbapenem, Carbapenemase, β-lactamase

Antibiotic resistance is a matter of the highest concern for worldwide public health. The correct use of antibiotics has saved millions of lives since Fleming's penicillin discovery in the 1920s.[1] It is no news that the widespread use and abuse of antibiotics have caused a new problem, namely resistance. Antibiotic resistance has been associated with at least 25,000 deaths/year in the United States and costs more than $20 billion in additional medical expenses every year.[1,2] This problem has driven scientists and physicians to develop and use more antibiotics with different antimicrobial activity, but resistance is just a matter of time. Medical centers deal daily with some of the toughest challenges in infectious diseases, i.e., carbapenem resistance. Carbapenems are the broadest spectrum antibiotics, previously considered the last line resource in antibiotic therapy, but some clinicians now use them routinely as first or second line antibiotic choices. This scenario can only result in more resistance.

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Carbapenems, members of the β-lactam class of antibiotics that kill bacteria by binding to penicillin-binding proteins and inhibiting cell wall synthesis, were first used in the United States in the 1980s to treat resistant bacteria, mainly extended spectrum β-lactamases (ESBL) producing bacteria. They are used in a wide variety of infections that include bacteremia, intra-abdominal and pelvic infections, meningitis, pneumonia, urinary tract infections, soft tissue infections, osteomyelitis, etc.[3] Carbapenems are used to treat most infections caused by Gram-negative and anaerobic bacteria, and they also have excellent Gram-positive coverage, including oxacillin-susceptible *Staphylococcus aureus*, but they lack activity against *Stenotrophomonas maltophilia* and

Enterococcus faecium.[3] Ertapenem lacks coverage against *Pseudomonas aeruginosa* and *Acinetobacter baumanii*.[3] Meropenem and imipenem have excellent central nervous system (CNS) penetration, although imipenem has the highest risk for seizures.[4] There is a lack of data about CNS penetration for doripenem and ertapenem.[4] Dose adjustment may be required for renal impairment but not for liver impairment.

Due to widespread use of carbapenem, especially since the 2000s, there has been an alarming surge of carbapenem resistance worldwide. In a recent European study, carbapenem resistance was reported in up to 7% of all the *Klebsiella pneumoniae* bloodstream isolates.[1,5] This alarming increase in antimicrobial resistance mandates the development of a rational approach to antibiotic use. At the University Medical Center, Lubbock, Texas, there has been an increase in the incidence of carbapenem resistance. Recently, 16 cases of *Pseudomonas aeruginosa* with Verona integron-encoded metallo-β-lactamase (VIM), a type of carbapenemase not usually found in the United States, were identified. Previous outbreaks have occurred in the United States. The first outbreak was reported in 2005.[6]

Carbapenem resistant infections have been reported to have an associated mortality rate between 40–80%.[1,5] Carbapenem resistance transmission is usually plasmid-related, although chromosomal transmission has also been well documented. Different genes have been identified, including *Klebsiella pneumoniae* carbapenemase or bla_{KPC} (worldwide spread), New Delhi metallo-β-lactamase or bla_{NDM-1} (now endemic in southeast Asia), and others like OXA-48, VIM (usually found in Europe, Asia and South America), Imipenemase-1, etc.[1,5,7]

Carbapenem resistance transmission is usually nosocomial, but it has also been reported in the community, which represents a serious public health matter.[7] The critical question is how to prevent further spread of carbapenem resistance. The first step is to identify the risk factors for carbapenem resistance and other multi-drug resistant (MDR) organisms, which include a recent admission to an acute care facility, prior admission to a long-term care facility, history of dialysis or chemotherapy in the last 12 months, previously known infection or carriage,[8] immune suppression, recent antimicrobial exposure, admission to an intensive care unit, and previous solid-organ or bone marrow transplant.[9] These patients should be handled with strict infectious control measures to avoid further MDR spread. Hospital antimicrobial stewardship programs may also have an important role in the judicious use of antimicrobials.

The second crucial question is how to treat these infections. Currently, there are no guidelines regarding appropriate antimicrobial management of these patients, and as previously mentioned the mortality is high. Tigecycline, polymyxins, and aminoglycosides have been used,[1] as well as anecdotal reports of double carbapenem coverage.[10] In the last few years, the development of newer antibiotic combinations like ceftazidime-avibactam and ceftolazone-tazobactam have been successfully used for these infections.[1] More recently, newer drugs have been approved by the Food and Drug Administration or have been submitted for approval to manage these multidrug resistant infections (e.g., meropenem-vaborbactam, aztreonam-avibactam, plazomicin, cilastin-imipenem, eravacycline).

We recommend reserving carbapenems use to situations in which cultures shows bacteria resistant to all other antibiotics, in critically-ill patients known to be colonized with MDR bacteria, or in patients with high-risk factors for MDR infections. It is also important to differentiate between simple colonization and true infection such as in elderly patients with chronic Foley catheters. These patients have been exposed to multiple antibiotics and often grow ESBL organisms in urine that may not require treatment. Treatment should be reserved for symptomatic patients, i.e., presence of fever, abdominal pain, and/or altered mental status. Simple cystitis may be adequately treated by changing the Foley catheter and using nitrofurantoin or other antibiotics with a narrow spectrum.

Due to the associated mortality, prevention and management of carbapenem-resistant *Enterobacteriaceae* infections should be a high priority in hospitals and long-term health facilities. Antimicrobial stewardship may be a key element in the prevention of development of local resistance both in inpatient and outpatient settings. Infection control is crucial in containing imported

cases from other facilities. Judicious use of carbapenems is also fundamental to prevent development of local resistance; these agents should be reserved to high-risk patients for MDR infections. Once a carbapenem-resistant *Enterobacteriaceae* infection is documented, infectious diseases consultation to assist in infection management is recommended.

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