

CARBAPENEMASES AND GRAM-NEGATIVE BACTERIA: A REVIEW

AISHWARYA J RAMALINGAM*

Department of Microbiology, Sree Balaji Medical College & Hospital, Bharath University, Chrompet, Chennai, Tami Nadu, India.

Email: jhaish@rediffmail.com

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ABSTRACT

The emergence of resistance in Gram-negative pathogens has alarmed many clinicians and health-care workers both in community and hospital settings. Antibiotics, such as carbapenems, are used as a last resort in the treatment of multi-drug resistant (MDR) Gram-negative pathogens. Carbapenemases are the enzymes that hydrolyze carbapenems. The global spread of these MDR organisms has posed a public health problem due to its difficulty in empirical treatment of hospital and community acquired infections.

Keywords: Carbapenems, Carbapenemase, Gram-negative bacteria, Multi-drug resistant organisms.

Gram-negative bacilli can cause a variety of infections in humans which may be either community-acquired or hospital-acquired. They include urinary tract infections (UTI), respiratory tract infections, bacteremia, septicemia, surgical site infections (SSI), and meningitis. Gram-negative bacilli have the inherent competence to produce various mechanisms which augment drug resistance and the ability to transfer the resistance determinants to other bacteria. Thus, they also acquire resistance with the help of certain genetic materials thereby facilitating its spread [1]. The emergence of resistance in Gram-negative pathogens has alarmed many clinicians and health-care workers both in community and hospital settings. Multi-drug resistant (MDR) bacteria have caused an increase in the incidence of nosocomial infections. They are often associated with prolonged and expensive treatment, which is a major drawback in developing countries [2].

The common Gram-negative bacilli causing nosocomial infections include *Escherichia coli*, *Klebsiella* species, *Pseudomonas* spp., *Citrobacter* spp., *Enterobacter* spp., and *Acinetobacter* spp. *E. coli* is the most common pathogen associated with UTI followed by *Klebsiella* spp., the latter being highly prevalent in respiratory tract infections such as pneumonia. UTI, respiratory tract infections and SSI due to *Pseudomonas aeruginosa* are the most life-threatening, particularly in the Intensive Care Unit [3]. The mortality rate is found to be high in patients with endocarditis, septicemia particularly in patients with malignancy, burns or drug addiction [4]. Ventilator-associated pneumonia is one of the most common nosocomial infection related to high morbidity and mortality, particularly when caused by MDR organisms and due to delayed or inappropriate antibiotic usage. Among the MDR Gram-negative pathogens, the major problem is of carbapenem resistance, where the carbapenemase production is the major defense mechanism [5].

The discovery of penicillin in 1928, by Alexander Fleming marked a milestone in modern medicine. Thus, the "antibiotic revolution" saved millions of lives during Second World War. Subsequently, this paved a way for the advent of new antibiotics against dreadful infections. The evolution of antibiotic resistance in bacteria is primarily due to the drug selection pressure, which involves the use of drugs both in humans and animals. It is of epidemiological concern as the resistance may spread locally, regionally, or globally. [2] Emergence of "Superbugs" (bacteria highly resistant to antimicrobial agents) has severely threatened therapeutic options in the last few decades. The battle against these pathogens is an ultimate challenge. The Infectious Diseases Society of America brought global attention against the acronym ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella*

pneumoniae, *Acinetobacter baumannii*, *P. aeruginosa*, and *Enterobacter* species [spp.]) and to the need for novel antimicrobials [6].

Although there is an increase in the frequency of antimicrobial resistance in both Gram-positive and Gram-negative pathogens, there is a rapid escalation in resistance due to Gram-negative bacilli. New drugs, such as linezolid and daptomycin, are employed against infections caused by resistant Gram-positive pathogens, but the treatment of infections caused by Gram-negative resistant pathogens is challenging as new drugs against them are still in the developmental stage. Further, prompt implementation of infection control is necessary to avoid dissemination of the microbes [7].

In *E. coli* and *Klebsiella* spp., β -lactamases play a major role in resistance to β -lactams. These enzymes prevent the binding of β -lactams to penicillin binding proteins (PBPs) on the cell wall. TEM- and SHV-type β -lactamases (derived from *Temoniera* and sulfhydryl variable, respectively) which were discovered from *E. coli* in 1960s and 1970s were dynamic against penicillin and first generation cephalosporins. Later other bacteria were also discovered to produce these enzymes. They were called broad-spectrum β -lactamases. Further, in late 1970s second and third generation cephalosporins with oxyimino β -lactam ring were introduced which could resist action of β -lactamases [8]. But in 1982, β -lactamases active against oxyimino-cephalosporins were reported [9]. They were called extended-spectrum β -lactamases (ESBLs) because of the ability to cleave the oxyimino β -lactam ring and susceptible to inhibition by clavulanic acid. But however, some ESBLs are not inhibited by a clavulanic acid such as plasmid-mediated AmpC β -lactamases. They were classified into Ambler molecular class A, and Bush and Jacoby functional class 2 β -lactamases [8].

Earlier, resistant Gram-negative bacterial infections were successfully treated with penicillin group of antibiotics such as carbenicillin, ticarcillin, and piperacillin. Out of all β -lactams, carbapenems have maximum antimicrobial spectrum. This is due to their high affinity for PBP 2, good stability against most serine based β -lactamases and excellent outer membrane permeability. Carbapenems are the antibiotics used as a last resort for treatment of MDR Gram-negative pathogens. However, resistance to this group of drugs has developed due to its increased usage [10].

Carbapenems currently having Food and Drug Administration approvals for clinical use are imipenem, meropenem, ertapenem, and doripenem. Nevertheless, bacteria can acquire carbapenem-hydrolyzing β -lactamases called carbapenemases. These enzymes have emerged in

various parts of the world, namely Europe, the Indian subcontinent and the United States. Many of the carbapenemases recognize almost all hydrolysable β -lactams; including oxyimino β -lactams and most are stable against inhibition by all β -lactamase inhibitors. However, some carbapenemases are less active, and they require additional mechanisms for exhibiting resistance. The commonly encountered organisms include *K. pneumoniae*, *E. coli*, *Pseudomonas* spp., *Acinetobacter* spp., *Citrobacter* spp., and *Enterobacter* spp. [11].

Carbapenemases are classified broadly into two major groups, namely, metallo- β -lactamases (MBLs) and serine β -lactamases. MBLs contain one zinc atom at their active site. They can be inhibited by β -lactamase inhibitors and ethylene diamine tetra-acetic acid (EDTA). Serine β -lactamases contain a serine at their active sites which are inhibited by β -lactamase inhibitors but not by EDTA. There are several types of MBLs which are reported worldwide. They include imipenemase, Verona integron-encoded MBL, São Paulo MBL-1, German imipenemase-1, Seoul imipenemase-1. Of particular concern is New Delhi MBL [12].

The emergence and spread of NDM-1 were reported from India, Pakistan, and the UK. Later it was reported from Bangladesh, Australia [13,14], Netherlands, Canada, USA [15], China [16], and Japan [17]. This indicates that there is worldwide spread of "*bla*_{NDM-1}" gene. It was found that NDM-1 producing MDR bacteria in India were associated with UTI, bloodstream infections and pneumonia [13]. NDM enzymes producing *E. coli* are the most common organisms isolated from community associated UTI [14]. The mortality rate ranges from 25% to 75%. Studies from Canada and Brazil show that MBL producing *P. aeruginosa* (25% and 17.3%, respectively) was a major cause of mortality when compared with non-MBL producing *P. aeruginosa* (13% and 11.8%, respectively) [18]. The global spread of these organisms has posed a public health problem due to its difficulty in empirical treatment of hospital and community acquired infections because the antimicrobials active against NDM-1 are still in the development stage. If the present scenario continues, there would be an increase in common infections which causes treatment failures and prolonged hospital stay [14].

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