CHAPTER – 1

INTRODUCTION

Antibiotic resistance is a major concern of contemporary medicine. The continuing emergence of resistant organisms that cause nosocomial infections contribute substantially to the morbidity and mortality of hospitalized patients. Extensive data indicate that the intensive care units (ICU) are the epicenter for the spawning multidrug resistance within hospitals, since patients in ICU undergo invasive procedures, treatment with antibiotic combinations and greater chance of exposure to resistant pathogens [Paramythiotou et al. 2004]. Increase in antibiotic resistance, among Gram negative bacteria is a notable example of how bacteria can procure, maintain and express new genetic information that can confer resistance to one or several antibiotics. This increase has prompted calls for infection control measures to curb their dissemination. [Walsh et al. 2005]

The advent of carbapenems in the 1980s heralded a new treatment option for serious bacterial infections. The most commonly use carbapenems include imipenem, meropenem, ertapenem and doripenem. Of the many hundreds of different β-lactams, carbapenems possess the broadest spectrum of activity and greatest potency against Gram-negative bacteria. As a result, they are often used as “last-line agents” or “antibiotics of last resort”. They are reliably active against multidrug-resistant Gram-negative bacteria and form the mainstay in the treatment of serious infections in most hospitals across the world today. These antibiotics are stable to β -lactamases including the extended spectrum β -lactamases (ESBLs) and Amp C produced by gram negative bacilli (GNB). [Wallace et al. 2011]
Resistance to the carbapenems started emerging from 1990 and has been reported worldwide over the years with varying frequencies. *Pseudomonas aeruginosa* and *Acinetobacter* spp. in particular are most often associated with carbapenem resistance. Later when such resistance emerged among the Enterobacteriaceae, this resistance representing a major public health threat worldwide. [Prakash S, 2006].

Resistance to carbapenem may be due to the following mechanisms

1. Production of β-lactamases (carbapenemases) that hydrolyse the carbapenems
2. Changes in outer-membrane porins that block the entry of these antibiotics
3. Active pumping of the antibiotic out of the cell using complex “efflux pumps.”

Carbapenemases are beta-lactamases with versatile hydrolytic capacities. They have the ability to hydrolyze penicillins, cephalosporins, monobactams, and carbapenems thus limiting the treatment options. Carbapenemases may be members of the molecular class A, B, and D beta-lactamases. Class A and D enzymes have a serine-based hydrolytic mechanism, while class B enzymes are metallo-beta-lactamases (MBL) that contain zinc in the active site. The class A carbapenemase group includes members of the SME, IMI, NMC, GES, and KPC families. The class B MBLs belong to the IMP, VIM, SPM, GIM and SIM families and have been detected primarily in *Pseudomonas aeruginosa*; however, there are increasing numbers of reports worldwide of this group of beta-lactamases in the Enterobacteriaceae. The class D carbapenemases consist of OXA-type beta-lactamases frequently detected in *Acinetobacter baumannii*. [Kattan et al.2008, Queenan et al.2007]
In addition, chromosomally encoded cephalosporinases (class C/Amp C) produced by Enterobacteriaceae may possess slightly extended activity towards carbapenems, but their clinical significance remains debatable. [Cantón et al. 2012].

The genes encoding carbapenemases are associated with mobile genetic elements that allow their rapid dissemination in the clinical setting. The transmissible enzymes can be acquired unpredictably by important pathogens such as *P. aeruginosa, A. baumannii*, and members of the family *Enterobacteriaceae*. The chromosomal enzymes occur predictably in less common pathogens namely *S. maltophilia, Aeromonas* species, and *Chryseobacterium* species.

Detection and surveillance of carbapenemase-producing organisms is important for the selection of appropriate therapeutic schemes and the implementation of infection prevention measures. In the clinical microbiology laboratory, GNB with carbapenem-intermediate or -resistant result should be tested for possible carbapenemase production. However in members of the family *Enterobacteriaceae* and *Acinetobacter* spp., reduced carbapenem susceptibility though within the susceptible range should raise the suspicion of carbapenemase production. [Thomson, 2010]

As carbapenemase production cannot be simply inferred from the resistance profile, criteria must be established for which isolates should be subjected to and screening tests for carbapenemase production, and for which confirmatory tests (phenotypic and/or genotypic) should be employed for confirmation of the resistance mechanism. In addition, strategies should be devised for surveillance of carbapenemase producers in order to enable the implementation of effective surveillance programs. [Miriagou et al. 2010]
By tradition the nomenclature of these beta lactamases is based on their substrates, biochemical properties, location of their discovery, location of the gene on the chromosome, strains of bacteria, after the cities associated with them, patients providing the sample or even after the investigator who described them. [Rodrigues C, 2011].

Carbapenemases potentially herald the end of treatment of Gram-negative infections because of all the major mechanisms conferring resistance the most menacing are these hydrolyzing enzymes. Additionally, there is the inevitable co-resistance to the other main classes of commonly used antibiotics, namely the fluoroquinolones and the aminoglycosides. A combination of multiple mechanisms described confers high levels of resistance to carbapenems in certain bacterial species, such as *Klebsiella pneumoniae*, *P. aeruginosa*, and *A. baumannii*. There is paucity of data on the prevalence of carbapenem resistance in the Indian literature, which is required for devising management strategies of serious nosocomial infections and to initiate measures for curbing their dissemination. [Rodrigues C, 2011].

The emergence and spread of carbapenemase producers will possibly mirror what has been extensively described for ESBL producers causing nosocomial infections since the 1980s. There are many reasons to believe that carbapenemase-expressing *K. pneumoniae* and *Enterobacter* spp. will act as the main source of nosocomial infections, as was described in the case of ESBL producers. Screening of carriers is of fundamental importance, and should first be proposed for the most vulnerable patients such as immunocompromised patients and those hospitalized in units at high risk of colonization by multidrug-resistant bacteria (such as intensive-care units). In addition, it should be considered that carbapenemase-producing *E. coli*
(mostly harbouring enzymes of the NDM and OXA-48 types) may spread at a lower rate but become rapidly uncontrollable in community settings, as observed for CTX-M producers among *E. coli*. [Nordmann *et al*, 2012 a].

The acquisition of these resistant bacteria within the hospital may be a consequence of selection pressure exerted by the use of antibiotics and / or horizontal dissemination. The distinction between these two mechanisms and the epidemiological interrelationship can be confirmed only by molecular typing. Identifying an outbreak using molecular methods enables us to establish clonality between clinical isolates and to propose a mechanism whereby patient contamination may have occurred [Kotsanas *et al*. 2013]. The inevitable use of carbapenems is consequently bound to exert greater selective pressure. Extensive antibiotic usage is the main driver of resistance, and resistance is clearly a function of the volume consumed. It has been shown that inappropriate duration of antibiotic therapy also triggers development of resistance. Sub-therapeutic concentrations of the drug are another important cause of development of resistance. [Prakash S,2006]

From the perspective of medical health, there is an urgent call to take stock of the situation and salvage what we can. National antibiotic policies should form the framework and these guidelines will help in maximizing the outcome for an individual patient while minimizing the collateral damage to our microbial ecology. Additionally, development and evaluation of advanced, improved and rapid diagnostic methods is a vital need. [Lakshmi 2008, Raghunath 2010]

Good infection prevention policies in hospitals that prevent cross-transmission of resistant bacteria from patient to patient are certainly warranted. Measures to reduce antibiotic resistance include evidence-based selection of antibiotics, shorter
courses of appropriately selected antibiotics with adequate dosages, surveillance for resistance, prevention of spread of resistant organisms, cyclical use if new antibiotics become available, education of consumers and prescribers about use and misuse of antibiotics, development of new drugs to circumvent or block-resistance mechanisms and revival of susceptible bacteria through more appropriate antibiotic use or potential use of probiotics. Unless these steps are taken, this menace would erode the strength of life-saving antibiotics. [Prakash S, 2006]