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RESEARCH ARTICLE

THE LAST RESORT ANTIBIOTICS: CARBAPENEMS.

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Abstract

Carbapenem play a critically important role in our antibiotic armamentarium. The carbapenem are used as the drug of choice for the treatment of severe infections caused by Extended Spectrum Beta Lactamases producing *Enterobacteriaceae*. Carbapenem resistance mainly among Gram negative pathogens is an ongoing public – health problem of global dimensions. The emergence of carbapenem resistant organisms is worrisome since antimicrobial treatment options are very restricted. In this article, important key points related to carbapenem resistance are reviewed.

Introduction:-

Beta-lactams are widely used antibiotics worldwide and includes the penicillin, Cephalosporins, monobactams and carbapenems[1]. Carbapenems among the beta lactams is an antibiotic class including Ertapenem, Imipenem, Meropenem and Doripenem. Carbapenems are the new class of antibiotics having versatile usage, and particularly used as last potent defender against multi drug resistant bacterial sepsis. There has been six fold increases in uses and misuses of antibiotics, including carbapenem sale which is a powerful life saving beta lactam antibiotic used to treat dangerous infections occurred by MDR (multi drug resistant) and gram negative and positive pathogens. Centre for disease dynamics, economics and policy in Washington D.C. conducted a research which states that carbapenem sale has been increased from 0.21-1.23 unit per million in years 2005- 2010 resulting in raising antibiotic resistance[2.] In 1990's resistance to carbapenem emerged in *Enterobacteriaceae* and other organisms. The genes that encode for carbapenamase are found on the same plasmids as genes that encode resistance to aminoglycosides and sulfonamides, and many *Enterobacteriaceae* species posses changes that confer high level resistance to quinolones. This means that carbapenamase producing *Enterobacteriaceae* in hospitals and ICU are commonly multi drug resistant, which posses the challenge for the treatment of nosocomial infections in critically ill patients in this article the attempt has been made to look for various factors responsible for carbapenem resistance.

Following classification scheme was proposed by Shah and Isaacs[3]:-

1. Group 1 includes broad-spectrum carbapenems, with limited activity against non-fermentative Gram-negative bacilli that are particularly suitable for community acquired infections (e.g. Ertapenem).
2. Group 2 includes broad-spectrum carbapenems, with activity against non-fermentative Gram-negative bacilli that are particularly suitable for nosocomial infections (e.g. imipenem and meropenem).

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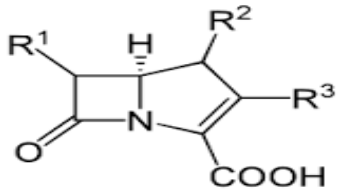
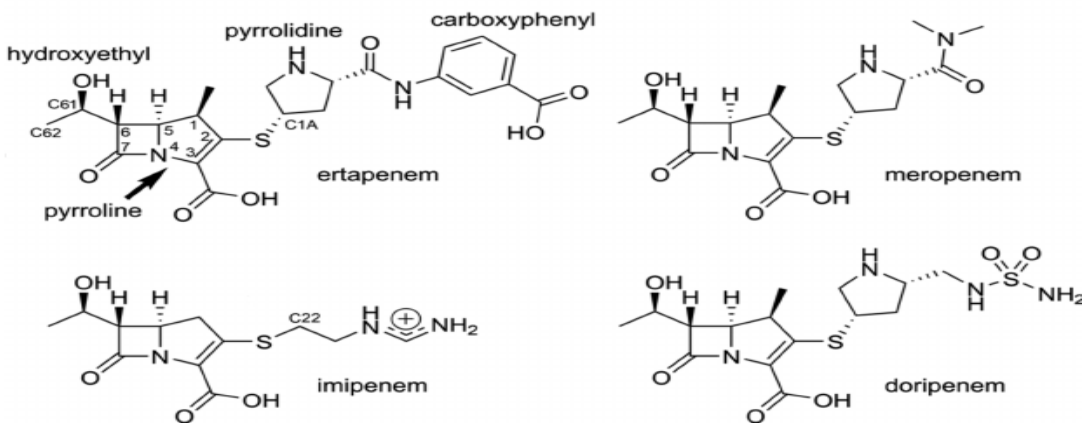
3. Group 3 includes carbapenem with clinical activity against methicillin-resistant Staphylococcus aureus.

Chemistry of carbapenem:-

Their unique molecular structure is due to the presence of a carbapenem together with the beta-lactam ring. This combination confers exceptional stability against most beta-lactamases (enzymes that inactivate betalactams) including ampicillin and carbenicillin (AmpC) and the extended spectrum beta-lactamases (ESBLs).



Structure of carbapenem



Group of carbapenem antibiotic

Carbapenem Uses:-

Carbapenems are most appropriately used for the treatment of severe community acquired infections. They are indicated for treatment of pneumonia, skin and soft tissue infection, severe sepsis, acute diverticulitis with perforation and abscess, acute cholecystitis, acute gastric and duodenal perforation, severe urinary tract infections, intra abdominal abscess including liver and spleen.

Mechanism of Action:-

As a class of β-lactams, carbapenem are not easily diffusible through the bacterial cell wall[4].Generally speaking; carbapenem enter Gram-negative bacteria through outer membrane proteins (OMPs), also known as poring. After transferring the periplasmic space, carbapenem "Permanently" aculeate the PBPs[5, 6]. PBPs are enzymes (i.e., transglycolases, transpeptidases,and carboxypeptidases) that catalyze the formation of peptidoglycan in the cell wall of bacteria. Current insights into this process suggest that the glycan backbone forms a right-handed helix with a periodicity of three per turn of the helix[7]. Carbapenems act as mechanism-based inhibitors of the peptidase domain of PBPs and can inhibit peptide cross linking as well as other peptidase reactions. A key factor of the efficacy of carbapenems is their ability to bind to multiple different PBPs[5]. Since cell wall formation is a dynamic "Three-dimensional process" with formation and autolysis occurring at the same time, when PBPs are inhibited, autolysis continues [7]. Eventually the peptidoglycan weakens and the cell bursts due to osmotic pressure.

Mechanism of resistance of carbapenem:-

It is noteworthy that resistance to carbapenems in some species is intrinsic. Intrinsic resistance to carbapenems, however, is not common among clinically important bacteria and for most of them carbapenem resistance is acquired by mutational events or gene acquisition via horizontal gene transfer.

Gram-positive bacteria become resistant to carbapenems and other beta-lactams through mutation-derived changes of their PBPs, while Gram-negatives commonly recruit other mechanisms to overcome the effect of carbapenem antibiotics. Certain species are able to prevent carbapenems reaching their PBPs by diminishing the permeability of their outer membrane for eg. OprD.[8]

Hydrolysation of carbapenem are readily done by class B β-lactamases, these are zinc dependent Metalloenzymes. The most effective Carbapenemases, in terms of carbapenem hydrolysis and geographical spread, are KPC, VIM, IMP, NDM and OXA-48 types[9]. KPCs inactivate all betalactams antibiotics and are only partially inhibited by beta-lactamase inhibitors like clavulanic acid, tazobactam and moronic acid. MBLs are able to hydrolyze all beta-lactams except aztreonam and are not inhibited by the aforementioned inhibitors. They bear zinc in their active centre; therefore their inhibition is achieved in vitro using metal cheaters, such as ethylenediaminetetraacetic acid.

Enzyme-mediated resistance to carbapenems is due to the production of beta-lactamases that are able to inactivate carbapenem together with other beta-lactam antibiotics and therefore called carbapenemases[10, 11]. This type of resistance is the most important clinically because these enzymes hydrolyze all or almost all beta-lactams, confer high levels of carbapenem minimum inhibitory concentrations (MICs), are encoded by genes that are horizontally transferable by plasmids or transposes and are commonly associated with genes encoding for other resistance determinants.

A different mechanism that may contribute to carbapenem resistance is the active expulsion of carbapenems out of the periplasmic space after their entrance. This is mediated by tripartite efflux pump systems composed of a protein transporter of the cytoplasm membrane, a periplasmic connective protein and an outer membrane porin[12].

Causes:-

Overuse:

The overuse of antibiotics clearly drives the evolution of resistance[13, 14]. Epidemiological studies have demonstrated a direct relationship between antibiotic consumption , the emergence and dissemination of resistant bacteria strains[15]. In many other countries, antibiotics are unregulated and available over the counter without a prescription[15, 16]. This lack of regulation results in antibiotics that are easily accessible, plentiful, and cheap, which promotes overuse[16]. The ability to purchase such products online has also made them accessible in countries where antibiotics are regulated[16].

Inappropriate Prescribing:

Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria[13]. Incorrectly prescribed antibiotics have questionable therapeutic benefit and expose patients to potential complications of antibiotic therapy[17.] Sub inhibitory and sub therapeutic antibiotic concentrations can promote the development of antibiotic resistance by supporting genetic alterations, such as changes in gene expression, HGT, and mutagenesis[18].

Availability of few new antibiotics

The availability, ease of use, and generally low cost of antibiotics has also led to the development of carbapenem resistance.

Conclusion:-

Mortality of carbapenem is decreasing very slowly; causes are due to many factors like their overuse, their inappropriate prescribing, availability of few new antibiotics etc.

Until a reliable alternative to carbapenem is found or the presence of carbapenamase effectively overcome, the application of strict infection control measures whenever carbapenem resistance is detected and the active surveillance for the presence of carbapenamase encoding genes are of the outmost importance.

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