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NDM-2 A NOVEL CARBAPENEMASE :THE CHANGING FACE OF ANTIMICROBIAL RESISTENCE AFTER NDM-1

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New Delhi metallo-beta-lactamase-1 (NDM-1) is an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics. These include the antibiotics of the carbapenem family, which are a mainstay for the treatment of antibiotic-resistant bacterial infections.According to the laws of Darwinian evolution, antimicrobials use creates a selection pressure on micro organisms: weak ones are killed but stronger ones might adapt and survive .When pathogenic micro organisms can multiply beyond some critical mass in the face of invading antimicrobials, treatment outcome is compromised. This phenomenon is referred to as antimicrobial resistance (AMR). With the advent of antibiotics, a new era ushered in bringing within its folds, a strong defence against the invading deadly micro organisms. The war against them began in 1928 when bacteriologist "Alexander Fleming" realized that the growth of Staphylococcus Aureus was inhibited in the Petri-dish contaminated with mold.[1] With the time, new drugs were being developed, microbes also kept adapting to the hostile environment, created by these "killer molecules"- antibiotics. [2] To start with, penicillin was effective against Staphylococcus Aureus but resistance started developing and came in the form of MRSA (Methicillin Resistant Staphylococcus Aureus) treatable with Vancomycin. Resistance has developed to Vancomycin also over the past decade as VRSA (Vancomycin resistant Staphylococcus Aureus) .The last in the category is Linezolid which is effective against VRSA but scattered reports have suggested resistance to this drug as well. [3] During the past many decades, while making an attempt to control infection there has been an inadvertent and irrational use of these powerful molecules to save mankind from these microbes. They started developing resistance to our weapons to survive, which proceeded to more dangerous and multiple resistant organisms. The antibiotic resistance of bacteria only leads to a loss of functional system. "Evolution" requires a gain of functional system for bacteria to evolve into man. Therefore, antibiotic resistance of bacteria is not an example of evolution

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in action, but rather variation within the bacterial kind. It's the testimony to the wonderful design God gave the bacteria, master adaptors and survivors in the sin-cursed world [4]

Globally it's and always has been very difficult to discover novel and effective antibacterial agent with therapeutic potential for treating infections caused by gram negative pathogens. Further, this may come as a bad news for the treatment against lethal bacteria, "super bugs" like the ones recently discovered NDM-1(New Delhi Metallo-Beta Lactamases). [5]

NDM-1, which is named after the Indian city where it was first found, has the ability to jump from type of bacterium to another meaning that many more common bacteria could become resistant to all known antibiotics causing pandemics of non treatable diseases. If this ends up in a bacterium which is already resistant to many other antibiotics, then such a development would constitute a nightmare scenario.[6]

Beta lactam antibiotics which include penicillins, have a ring structure which acts to halt the replication of bacteria. The enzyme, NDM-1 breaks this ring, rendering the drug ineffective.[7] NDM-1 producing bacteria are resistant to many existing antibiotics including carbapenams – a class of drug often reserved for emergency use and last resort treatment. So far only 2 types of microbes have been found to host NDM-1; one is the gut bug E. Coli which has trebled since the turn of the century. Other one can invade the lungs called Klebsiella Pneumoniae. Both offenders can lead to urinary tract infection and blood poisoning.[8] Infectious Disease Society of America (IDSA) has labelled the resistant organisms as the "ESKAPE" pathogens, because they effectively escape the effects of antibacterial drugs which include E- Enterococcus faecium, S-Staphylococcus aureus (MRSA) , K-Klebsiella pneumonia -- Escherichia coli, A-Acenetobacter baumanni, P-Pseudomonas aerugenosa, E-Enterobacter species.[1] It all started when these organisms viz. Klebsiella Pneumoniae and Escherichia coli producing carbapenemases were originally isolated from a non resident Indian staying in Sweden.

Carbapenemases are beta lactamases which hydrolyse carbapenems. They belong to the molecular classes A, B, and D. Class A comprises of carbapenemases sensitive to inhibition by Clavulanic acid mostly chromosomally encoded. Class B carbapenemases are metallo beta-lactamases .The resistance continues to increase because of the ability of the plasmids to acquire additional resistance determinants, turning many pathogens producing beta- lactamases into multi drug resistant ones. The class D carbapenemases most frequently confer resistance only in the presence of porin alternations.

The frequent use of beta lactamase inhibitors in hospitals and general practice poses a selection pressure which favours spread of such strains in hospital and community. With the changing outlook, even the pharmaceutical companies are shifting from the development of newer antibiotics because of them becoming auto-obsolete. The drug development

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pipeline in this category is not very encouraging. One of the reasons for this may be most multinational companies are channelizing money into research and development to develop drugs for chronic diseases like diabetes and cardiovascular ailments which are more lucrative because of the sheer size of patients inflicted with those ailments. Also the drug discovery process is itself risky and fraught with many failures, with some molecules faltering on safety and efficacy account even at the final stages. The industry has a thin and a drying pipeline of high-end antibiotics to fight against these infections, which may sometimes be fatal. In India too, "there are hardly any drugs to fight against these superbugs", doctors and industry experts say. Physicians and surgeons are treating NDM-1 with an antibiotic cocktail in a hope of controlling the spread of contagion with the medicines like broad spectrum antibiotics, and carbapenems (the recent additions) including imipenem/cilastatin, and others like tigecycline.[5] According to the *Lancet* report, bacteria with the NDM-1 gene have proven resistant to all antibiotics except **tigecycline** and **colistin.**

Detection of NDM-1 gene depends upon the phenotypic determination of the enzyme activity. These enzymes are zinc dependent and therefore termed as metallo beta lactamase. Indian studies have been done which demonstrate their dependency on zinc and the ability of zinc chelating agents like EDTA to decrease their activity. The Modified Hodge Test and a newly developed Re-Modified Hodge Test were developed for detection on a routine basis in resource limited laboratories[9] ,

The superbug is making international headlines requiring very close monitoring of the researchers. One must empirically treat serious infections with a regimen. Resistance has reached unacceptable levels in the pathogens most common in developing countries and trends show further increase. It appears to spread rapidly with more important consequences for the individual patient and public health. Till promising drugs come-in to combat this "threat" the guidelines given by Centre of Disease Control (CDC) must be followed viz, proper infection control measures which may include contact isolation for persons infected with NDM 1, good hand washing lasting for 15 to 20 seconds with antibacterial soap before and after touching the patient, administering food or medications, whenever changes of dressing are done both before and after and whenever gloves are visibly soiled one should be cautious. Using gloves for all procedures with proper disposal of contaminated dressings are the other measures which may bring about tremendous change. Instructions to the patient and the family concerning infection control measures are other few precautions for controlling its spread For global containment of antimicrobial resistance before irreparable damage is done to mankind, meticulous infection control practice and judicious antibiotic use should be done apart from creating awareness among the general public because its all of us who are at risk. [10]

Now question arises will all these efforts will really stop the menace ?. It seems to

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be doubtful because the mechanisms responsible for carbapenem resistance in one Acinetobacter baumannii isolate recovered from a patient transferred to Germany from an Egyptian hospital.Sequencing of the PCR product obtained using primers for bla(NDM-1) revealed a variant of NDM-1 that had a C to G substitution at position 82 resulting in an amino acid substitution of proline to alanine at position 28. This variant was designated NDM-2. Genes encoding extended-spectrum β-lactamases or 16S RNA methylase were not detected. The strain lacked detectable plasmids and bla(NDM-2) was not transferred by conjugation. MLST showed that the isolate belonged to a new ST, ST103.(ST-sequence types) [11]

This work further underlines the spread of NDM carbapenemases in A. baumannii, and the spread of the corresponding gene in the Middle East. It also describes the first variant of NDM-1. So we have to develop further strategy for prevention and cure from this changing bug and before it creeps globally and poses a threat to mankind.

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