Review Article

NDM-1 RESISTANCE: FLEMING'S PREDICTIONS BECOME TRUE

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ABSTRACT: Bacteria, beside other microorganisms are mainly responsible for human sufferings beside their beneficial effects. After discovery of Penicillin bacterial diseases were controlled to a much extent. The name 'antibiotic' makes us feel that we, humans are superior at least from microorganisms. Serious infections caused by bacteria that have become resistant to commonly used antibiotics have become a major global healthcare problem in the 21st century. Resistance to antibiotics shows that they can fight back and challenge our knowledge and intellect. Discovery of New Delhi metallo-1 make us feel that this is the result of our own ignorance. Indiscriminate, irrational and illogical use of antibiotics is helping bacteria to fight against us. What objections are being raised at the Govt. level, and how research community defends us, keeping that apart, the question is to realize and resolve the threat rather than to overlook it. Our outlook need to be changed and health policies and guidelines need to be reevaluated and overhauled timely.
Keywords: Superbug, NDM-1, Antibiotic, Lactamases, Multidrug resistance

INTRODUCTION

Nature has been most impartial and unbiased for its creations and has given equal opportunity to everyone to get nurtured and protected. If man invented antibiotic, God has given equal opportunity to microorganisms to defend themselves by evolving resistance. After a long furious and continuous battle it seems bacteria are regaining their supreme status and they are mocking our intellect, knowledge and antibiotic weaponry.

We humans are aliens on this mother planet, Earth. This planet actually belongs to microorganisms and mainly to bacteria. There are more bacteria on earth than all other living organisms (Gaffur, 2010). It seems that we humans have invaded their habitat and they are winning against us to take it back.

Bacteria are amongst the most adaptable organisms on Earth. Long evolutionary timescales, extremely short generation times, exposure to the most diverse and often hostile environments, together with the remarkable power of natural selection have made microorganisms the most resilient of life forms on this planet (Balaram, 2010).

In very large measure, many forms of bacteria are benign and beneficial to their animal hosts; most often colonizing the guts of animals, humans amongst them, providing key enzymes for digestion and producing metabolites that are essential for normal biological function. Bacteria and fungi abound in the soil; essential contributors to maintaining an ecological balance in our environment. However, bacteria have a very poor public image; most commonly being associated with infectious diseases (Balaram, 2010). Bacteria are the cause for a wide range of difficult-to-treat human infectious diseases such as pneumonia, toxic-shock syndrome and flesh-eating diseases. Bubonic plague, tuberculosis, malaria, and the human immunodeficiency virus have affected substantial portions of the human population, causing significant morbidity and mortality (Fred, 2006).

With respect to bacterial infections, the situation dramatically improved when penicillin became available for use in the early 1940s. Alexander Fleming was awarded the Nobel Prize for the discovery of penicillin (Kekre, 2010). This discovery changed the course of modern medicine and surgery. Many infections which were untreatable became treatable. Surgical infections could be effectively treated, and surgical procedures became safer. However, the euphoria over the potential conquest of infectious diseases was short lived. Almost as soon as antibacterial drugs were deployed, bacteria responded by manifesting various forms of resistance.

Penicillin got FDA approval in 1940 and resistance was reported in 1940, Streptomycin in 1947 and resistance in same year while tetracycline got FDA approval in 1952 and resistance was reported in 1956. By 1953, during a Shigella outbreak in Japan, a strain of the dysentery bacillus (Shigella dysenteriae) was isolated which was multiple drug resistant, exhibiting resistances to chloramphenicol, tetracycline, streptomycin and the sulfonamides (Bush, 2004).

Alexander Fleming actually predicted the future and possibility of Antimicrobial resistance when he said "The time may come when penicillin can be bought by anyone in the shops. Then there is a danger that the ignorant man may easily under dose himself and by exposing his microbes to non lethal quantities of the drug make them resistant". The only difference is that in our set up the learned are more responsible for the Anti microbial resistance than the ignorant (Kekre, 2010).

Antimicrobial agents are often categorized according to their principal mechanism of action. Mechanisms include interference with cell wall synthesis (lactams and glycopeptide agents), inhibition of protein synthesis (macrolides and tetracyclines), interference with nucleic acid synthesis (fluoroquinolones and rifampin), inhibition of a metabolic pathway (trimethoprim-sulfamethoxazole), and disruption of bacterial membrane structure (polymyxins and daptomycin)(Fred,2006).

Antibiotic resistance is a type of drug resistance where a microorganism is able to survive exposure to an antibiotic. Genes can be transferred between bacteria in horizontal fashion by conjugation, transduction, or transformation. Thus a gene for antibiotic resistance which had evolved via natural selection may be shared. Evolutionary stress such as exposure to antibiotics then selects for the antibiotic resistant trait. Many antibiotic resistance genes reside on plasmids, facilitating their transfer. If a bacterium carries several resistance genes, it is called multiresistant or, informally, a superbug or super bacterium. Antimicrobial resistance is now recognized as an increasingly global problem, especially Gram-negative bacteria (Slama, 2008).

Multiple drug resistant organisms are resistant to treatment with several, often unrelated, antimicrobial agents as described above in Shigella. Some of the most important types of multiple drug resistant organisms that have been encountered include:

MRSA-methicillin/oxacillin-resistant Staphylococcus aureusVRE - vancomycin-resistant enterococci ESBLs- extended-spectrum beta-lactamases (which are resistant to cephalosporins and monobactams) PRSP-penicillin-resistantStreptococcuspneumonia.

It is well known that the mechanism of antimicrobial resistance could happen by enzymatic inactivation, altered receptors or by altered antibiotic transport (Koneman, 1997). Sadly today the antibiotic resistance has become a serious threat and the golden era of last century appears to be ending and the micro organisms are steadily and surely winning the battle.

The structure determination of penicillin using X-ray diffraction by Dorothy Hodgkin, a landmark in the development of X-ray crystallography, revealed the β-lactam, a ring of four connected atoms, for the first time. Penicillin's successors, and there are many, are generically called beta-lactam antibiotics (Kumarasamy, 2010). β-Lactams have been the mainstay of treatment for serious infections, and the most active of these are the carbapenems, which are advocated for use for the treatment of infections caused by extended-spectrum b-lactamase (ESBL)-producing Enterobacteriaceae, particularly Escherichia coli and Klebsiella pneumonia (Paterson,2006). The carbapenems are a class of betalactamase antibiotics that differ from the penicillins by the substitution of a carbon atom for a sulfur atom and by the addition of a double bond to the five –membered ring of the penicillin nucleus (Spencer, 2002).

Carbapenems was first introduced in 1980 and are now frequently used as the last choice in treating serious infections.These antibiotics are stable to ß-lactamase including the extended spectrum ß -lactamase (ESBLs) and Amp C produced by gram –negative bacilli (Gladstone et al., 2005; Rodloff et al., 2006; Matsumoto et al., 1996; Zhanel et al., 2007). Carbapenems bind bacterial peptidases, the bacterial penicillin-binding proteins, which are responsible for elongation and cross –likening the peptidoglycan of the bacterial cell wall. This binding results in impairment of construction of the cell wall, inhibition of cell growth frequently, cell lysis and death. For gram-negative bacteria, it occurs in the periplasmic space between the cell wall and surrounding cell membrane (Hellinger, 1999). Carbapenems are betalactams with the broadest antibacterial spectrum currently available. They are well tolerated and drug related adverse events are few. Members of this group have a definite role in empiric and definitive therapy of serious and multi drug resistant (MDR) bacterial infections, especially where MDR Gram negative bacilli (GNB) are involved and other drugs are ineffective or inappropriate (Shah,2008;Nicolau,2008;Baldwin et al.,2008).

Unfortunately resistance to carbapenems started emerging from 1990. The resistance to carbapenems especially in P.aeruginosa results from reduced levels of drug accumulation or increased expression of pump efflux. The resistance may also be due to the production of metallo-ß-lactamase (MBL) which can be chromosomally encoded or plasmid mediated (Rahbar et al., 2008).

Most of these MBL confer resistance to not only carbapenems but also to other ß-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam (Gupta et al.,2006). Multidrug resistant including carbapenem–resistant poses a serious problem due to the lack of therapeutic options and the potential transfer of antibiotic resistance to more virulent pathogen (Rahbar et al., 2008). This is of great concern as presently to combat infections by multidrug resistant bacteria; carbapenems are considered the last resort especially in intensive care units (ICU's) and high risk wards (Gupta et al., 2006).

There are many types of beta-lactamases. Most are only active against older beta-lactam antibiotics but are not active against newer agents like the carbapenems. However, bacteria that produce NDM-1 are resistant to all commonly used beta-lactam antibiotics, including carbapenems. Some antibiotics like aminoglycosides and fluoroquinolones do not contain betalactam rings. Unfortunately, the bacteria that have acquired NDM-1 have also acquired other resistance factors and most are already resistant to aminoglycosides and fluoroquinolones. The addition of NDM-1 production has the ability to turn these bacteria into true superbugs (bacteria resistant to usually two or more antibiotics) which are resistant to virtually all commonly used antibiotics.

The enzyme is encoded by a gene carried on a plasmid, and thus can spread from one organism to another. This is the first time a metallo betalactamase, the most potent of drug resistant enzyme in its class, has been found on a plasmid in clinically relevant cases. The New Delhi metallo-beta-lactamase (NDM-1) is a novel type of MBL named after the city of origin - which has been recently criticized - following a common practice with transferable

MBLs since VIM-1 was named after Verona, Italy (Lauretti et al., 1999).

The NDM-1 encoding gene is located on different large plasmids (a 180-kb plasmid for K. pneumoniae and a 140-kb plasmid for E. coli) that are easily transferable to susceptible E. coli J53 at a high frequency (Yong et al., 2009). These plasmids also harbour genes conferring resistance to almost all antibiotics, thus making their rapid dissemination in clinically relevant bacteria a serious threat for therapy. Most plasmids detected in these bacteria were easily transferable and capable of wide rearrangement suggesting a widespread transmission and plasticity among bacterial population (JeanMarc et al., 2010).

The first β -lactamase was identified in Escherichia coli prior to the release of penicillin for use in medical practice (Abraham andChain, 1940). In Gram negative pathogens, β-lactamase production remains the most important contributing factor to β-lactam resistance (Medeiros, 1997).

In Gram negative bacteria these enzymes remain in the periplasmic space, where they attack the antibiotic before it can reach its receptor site (Stratton, 2007). Based on molecular studies, carbapenem hydrolyzing enzymes are classified into four groups A, B, C and D. Metallo b-lactamase (MBL) enzymes belong to Ambler molecular class B and are characterized by the ability to hydrolyze carbapenems and by their resistance to the commercially available β-lactamase inhibitors but susceptibility to inhibition by metal ion chelators (Queenan and Bush, 2007).

Class B β-lactamases called as metallo beta lactamases (MBLs), act on penicillins, cephalosporins and carbapenems but not on monobactams. MBLs differ from other b-lactamases in using metal ion zinc, linked to a histidine or cysteine residue to react with the carbonyl group of the amide bond of most penicillins, cephalosporins and carbapenems (Walsh et al.;2005). The increase in resistance of Gram-negative bacteria is mainly due to mobile genes on plasmids that can readily spread through bacterial populations.

NDM-1 shares very little identity with other MBLs, with the most similar MBLs being VIM-1/VIM-2, with which it has only 32.4% identity (Kumarasamy, 2010).

The first metallo β-lactamases for which an amino acid sequence was determined was the BCII metallo b-lactamase from Bacillus cereus, the prototypical metallo b-lactamase (Hussain et al., 1985). There has been a dramatic increase in the spread of these metalloenzymes. The most common metallo b-lactamase families include the VIM, IMP, GIM, and SIM enzymes, which are located within a variety of integron structures (Queenan and Bush, 2007).

New Delhi metallo-β-lactamase (NDM-1) was first detected in a Klebsiella pneumoniae isolate in 2008, reported in 2009 in a Swedish patient of Indian origin, who travelled to New Delhi and acquired a urinary tract infection due to a carbapenem-resistant K. pneumoniae strain resistant to all antibiotics tested except colistin and it has since been reported in increasing numbers of infections in patients from India, Pakistan, and the United Kingdom (Kumarasamy et al.,2010; Yong et al.,2009;Muir et al.,2010).

NDM-1 positive bacteria are around 89-100 per cent susceptible to colistin and 56-67 per cent susceptible to another antibiotic called tigecycline. In other words, these two antibiotics work on or kill NDM-1 positive bacteria. Colistin, which gave the best results, was tested on NDM-1 positive bacteria at Pandit B D Sharma PG Institute of Medical Sciences at Rohtak in Haryana and at the University of Madras in Chennai (India). At Rohtak, the bacteria were found to be 100 per cent susceptible to colistin. In Chennai, it was found 94 per cent susceptible. However, the problem with colistin is that it is not considered safe and used as a last resort (Thacker and Khyati, 2010). Colistin (Polymixins) acts by disrupting bacterial cell membrane but are highly neurotoxic and nephrotoxic (Rang and Dale,2007).

10 years ago, concern centred on Gram-positive bacteria, particularly meticillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus spp. Now, however, clinical microbiologists increasingly agree that multi drug resistant Gram-negative bacteria pose the greatest risk to public health. Not only is the increase in resistance of Gram-negative bacteria faster than in Gram-positive bacteria (Paterson, 2006; Livermore and Woodford, 2006) but also there are fewer new and developmental antibiotics active against Gram-negative bacteria (Cornaglia et al.,2007) and drug development programmes seem insufficient to provide therapeutic cover in 10–20 years(Cohen et al.,2010; Lunt and Carrera,2010).

Due to increasing diversity, the rapid spread of these enzymes, and the fact that they are often encoded on mobile genetic elements (integrons, transposons, plasmids) together with other resistance genes, treating infections caused by such strains is a therapeutic challenge because of the limitations posed by high-level resistance to various groups of antibiotics (Cornaglia et al.,2007).

As antimicrobial usage increased, so did the level and complexity of the resistance mechanisms exhibited by bacterial pathogens. The struggle to gain the upper hand against infections continues to this day, although the number of scientists who are developing new antibacterial agents is beginning to dwindle, even as bacteria evolve ever more clever mechanisms of resistance (Krause, 1992).

EPIDEMIOLOGY

In the August issue of the journal The Lancet Infectious Diseases, a multinational team reported the emergence and spread of 180 cases of patients infected by bacteria carrying the NDM-1, including 37 cases in the United Kingdom and 143 cases in various sites in Pakistan and India, thus suggesting a widespread dissemination (Kumarasamy et al.,2010). Among the 25 patients detected in the UK, 17 patients had travelled to India or Pakistan within 1 year and 14 had been hospitalized in these countries showing a worldwide dissemination of a new 'superbug' from a local source in Asia. Since August 2010, spreading and dissemination has occurred with several cases being reported by national and international medias from other countries in all continents including United States and Canada, Europe (Sweden, United Kingdom, Austria, Belgium, France, Netherlands, Germany), Japan, Africa, Oman, and Australia(JeanMarc et al.,2010).

Moreover, the NDM-1 spread poses once again at least four major problems frequently highlighted when dealing with MBLs (1), namely: i) the lack of routine standardized phenotypic test for MBL detection; ii) the consequent probable high prevalence of unrecognized asymptomatic carriers, allowing an international dissemination of such bacteria; iii) the scarcity of available effective antibiotics so far, and iv) the possibility to disseminate in many different Gram-negative bacteria.

On 13th August 2010; first death due to NDM 1 was reported when an unidentified Belgium man, who had become infected while his treatment in hospital in Pakistan, died in Belgium. He died despite of being administered colistin, a powerful antibiotic (Allovoices, 2010 APF news, 2010).

MEDICAL TOURISM AND NDM-1

Medical tourism refers to patients who travel to a country to get medical care that is not available or is more expensive in their own country. The three first cases of NDM-1 infection in the United States were identified in June 2010 in Americans who had recently sought medical care in India.

Medical tourism in India is a concept which has recently developed whereby patients & their attendants visit India. This fulfils their medical needs & gives them a chance to visit innumerable destinations of tourism interest for pleasure and relaxation. India is well known throughout the world about its potential regarding tourism, however it is only since last decade or so that some medical institutions centres have come up to international standards providing highest degree of technical expertise in patient care. The results provided by these medical institutes are definitely at par with the best in the world and few are even better. The number of patients visiting India has been continuously increasing for the last 3-4 years. In this context in 2010- 11, India expects more than 3.5 lakh patients visit India for medical tourism. This includes patients not only from underdeveloped countries or developing world, but also from developed regions too (Kaul and Chhinna, 2010). A heart surgery which costs USD 30,000 in USA, costs as low as USD 7,000 in India. Same is true in the other fields, diagnostics and aftercare.

In an article in Lancet "Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study" researchers have indicated that this bug with a new type of carbapenem resistance gene blaNDM-1 has originated either from India or Pakistan. Speculations, that this gene is prevalent in Indian hospitals may adversely affect medical tourism to India (Kaul and Chhinna, 2010). It may be seen as a conspiracy of developed nations against flourishing medical tourism sector in India but taking a positive stand, we must look into the circumstances and practices that have helped to originate and spread this superbug.

The government strongly objected to the naming of this enzyme as New Delhi metallo β lactamase -1 (NDM-1) and refuted the conclusion that hospitals in India were not safe for treatment.

The conclusions of the study are “loaded with inference" that the antibiotic-resistant organism possibly originated in India, an official statement by the Ministry of Health and Family Welfare said in New Delhi on 12.08.2010. “While such organisms may be circulating more commonly in the world due to international travel, to link it with the safety of surgery hospitals in India and citing isolated examples to show that India is not a safe place to visit due to the presence of such organism in Indian environment are wrong,” V.M. Katoch, Director-General, Indian Council of Medical Research, said. Many researchers and scientists in India too have objected to the terminology used for labelling this gene as New Delhi Metallo Beta lactamase 1 gene because no conclusive scientific evidence is available to link this gene to New Delhi (Kaul and Chhinna, 2010).

REASONS TO WORRY

The widespread use of antibiotics both inside and outside of medicine is playing a significant role in the emergence of resistant bacteria (Goossens et al., 2005). In some countries antibiotics are sold over the counter without a prescription which also leads to the creation of resistant strains. In supposedly well-regulated human medicine the major problem of the emergence of resistant bacteria is due to misuse and overuse of antibiotics by doctors as well as patients (WHO, 2002). Other practices contributing towards resistance include the addition of antibiotics to the feed of livestock (Mathew et al., 2007; Ferber, 2002). Household use of antibacterials in soaps and other products, although not clearly contributing to resistance, is also discouraged (as not being effective at infection control). The volume of antibiotic prescribed is the major factor in increasing rates of bacterial resistance rather than compliance with antibiotics (Pechere, 2001). A single dose of antibiotics leads to a greater risk of resistant organisms to that antibiotic in the person for up to a year (Costelloe et al.,2006). Sub optimum antibiotic concentrations in critically ill people increase the frequency of antibiotic resistance organisms (Thomas et al., 2008). Among Gram-negative bacteria, the emergence of resistance to expanded-spectrum cephalosporins has been a major concern.

Chinese scientists have completed research and development for a new antibiotic which they hope will tackle this superbug. The developer has applied for a license from the State Food and Drug Administration for the drug, named "Kelimeisu," which was created using genetic engineering technology. Scientists hope drug-resistant superbug NDM-1, an enzyme called New Delhi metallo-beta-lactamase, will not be resistant to the new antibiotic and the new antibiotic is expected to be available on the market next year (http://www.ndm1bacteria.com/new-drug-to-tackle-ndm-1-superbug).

CONCLUSION

Unfortunately lacklustre guidelines and inadequate policies have led to indiscriminate and unjustified usage of higher end antibiotics in India when actually they are not needed. Any doctor can prescribe and pharmacists can dispense any antibiotic without knowing its specificity and toxicity precisely. Clinicians and research community, microbiologists in particular have a very crucial role to play in the prevention of spread of these multiresistant pathogens. They should actively participate in the clinical decision making with regard to the treatment of infections.

There is an urgent need for the government to mandate ongoing monitoring and reporting of antibiotic sensitivity and resistance patterns from large hospitals as well as small health care units. The availability of information that is compiled periodically from such reports will support rational prescribing of antibiotics and early identification of emerging resistance patterns. Regulations are also needed to restrict the ubiquitous availability of reserve antibiotics.

Taking an optimistic stand, development of resistance is not a new phenomenon and for decades it has been there. We need to be optimistic as if bacteria are able to evolve newest mechanisms to resist antibiotics we have to keep on discovering new methods to destroy them as ‘survival of fittest’ is the law of nature.

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