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Superbug NDM-1: A global health problem

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ABSTRACT

The worldwide emergence of NDM-1 positive, multiresistant Enterobacteriacae have created a major global health problem. The NDM-1 can catalyze the hydrolysis of a various antibiotics including the latest generation carbapenems, which are often referred as the last line of antibiotics active against multiresistant gram-negative pathogens. Also there are few antiobiotics in pipeline active against gram-negative microbes and none that are active against NDM-1; presents a serious threat to antibiotics therapy. We are suggesting a rational use of antibiotics with an implementation of stringent policy for the prescription of antibiotics especially in the developing countries where antibiotics abuse is more common. The World Health Organization should also issue a guideline pertaining to NDM-1 positive, multiresistant Enerobacteriacae.

Keywords: New Delhi metallo-β-lactamase-1; gram-negative pathogens; resistant; carbapenems.

INTRODUCTION

New Delhi metallo-β-lactamase-1 (NDM-1) is an enzyme of β-lactamase family and recently has been in news after 'The Lancet Infectious Diseases' reported the worldwide presence of NDM-1 among several bacterial species viz. *K. pneumonia, E. coli, E. cloacae, Proteus* spp., *Citrobacter freundii, K. oxytoca, M. morganii,* and *Providencia* spp, specifically in the Indian subcontinent region, where abuse of antibiotics is more common [1]. The NDM-1 is a novel type of metallo-β-lactamase (MBL). The N and D of NDM stands for the name of the city origin, which was of much controversy, these days. The name was adopted following a common practice; as VIM-1 (Verona integron-encoded metallo-β-lactamase 1) was named after Verona, Italy [2]. The NDM-1 was first reported in 2009 in a 59 years old Swedish patient, a diabetic male of Indian origin, who had received medical treatment in New Delhi for gluteal abscess and was again operated for decubital ulcer in December 2007. In January 2008, the patient visited a Swedish hospital where a carbapenem-resistant *K. pneumoniae* carrying the novel MBL was isolated from his urine. Fecal samples of this patient also showed the presence of NDM-1 positive *E. coli* [3, 4]. To date presence of NDM-1 have been reported in many countries including Sweden, United Kingdom, India, Pakistan, Bangladesh, [1] Australia, [1,5] Netherlands, [6] USA, [3,7-8] Canada, [9] Japan, [10] China, [11] and few days back in a tourist from Taiwan, treated at hospital in New Delhi after being severely injured in a terrorist attack in India.[12] Many persons found positive for carrying NDM-1 in Europe, U.S. and Japan had travelled India or Pakistan or had received medical treatment there for various reasons including; organ transplantation, dialysis, cardiovascular and respiratory system ailments, pregnancy, road traffic accidents, and cosmetic surgery[1], indicates high prevalence of NDM-1 positive bacterial species in the Indian subcontinent.

Based upon amino acid sequences, β-lactamases are classified into four classes i.e. A, B, C and D.[13,14] Enzymes from class A, C and D contain serine-based active site while class B, the MBLs require a bivalent metal ion, usually Zn^{2+} for their activity and is perhaps the most heterogeneous class among all the classes of β-lactamases [13, 14]. It has been further divided into a number of sub-classes [14, 15]. The fluoroquinolones, aminoglycosides, and β-lactams (specially carbapenems) are the major classess of antibiotics, active against gram-negative pathogen[1]. Carbapenems (imipenem, meropenem, ertapenem, faropenem, and doripenem), [16] is a class of β-lactam antibiotics which acts by inhibiting the synthesis of bacterial cell wall [17]. The carbapenems are active against most of the β-lactamases, were developed to overcome penicillin and cephalosporin resistant bacteria [18, 19]. Though the bla_{NDM-1} gene [3] in β-lactams resistant bacteria produces NDM-1, which is also referred as carbapenemases [5] is a type of β-lactamase; an enzyme that opens up the β-lactam ring and inactivates it, [20-22] is a matter of great concern [23] as this class of antibiotics is mainstay for the treatment of gram-negative pathogens and often referred as the last line of effective antibiotics active against multiresistant Enterobacteriaceae, [24] most notably *Escherichia coli* and *Klebsiella pneumoniae*, which causes serious nosocomial and community-associated bacterial infections in people [1]. Carbapenemases producing bacteria are often referred as superbugs, because infections caused by them are difficult to treat.

DISCUSSION

The β-lactams [penicillins (Fig. 1), cephalosporins (Fig. 2), carbapenems (Fig. 3), monobactams (Fig. 4), clavulanic acid (Fig. 5), sulbactam (Fig. 6) and tazobactam], aminoglycosides and fluoroquinolones are present day antimicrobials used in the treatment of Enterobacteriaceae [1]. Bacteria in self-defence produce β-lactamases, [25] which opens up the β-lactam ring of antibiotics to form an ester, and which in turn further hydrolysed into acid confer the resistant against β-lactams [16,19-20]. To overcome this problem, a novel class of β-lactam antibiotics, carbapenems and monobactams were developed. The carbapenems are referred as last line of treatment active against multiresistant Enterobacteriaceae [24]. Though β-lactam ring of this class is also hydrolysed by new type of β-lactamase i.e. NDM-1. In august 2010, Kumarasamy et al. in The Lancet Infectious Diseases highlighted the presence of NDM-1 in multiresistant Enterobacteriaceae.[1] The NDM-1 carrying bacteria are resistant to fluoroquinolones, aminoglycosides and all β-lactams except aztreonam (monobactam, monocyclic β-lactams)[1] and few other antibiotics polymyxin B and colistin (polypeptide antibiotics) and novel tigecycline (Fig. 7) [26, 27].

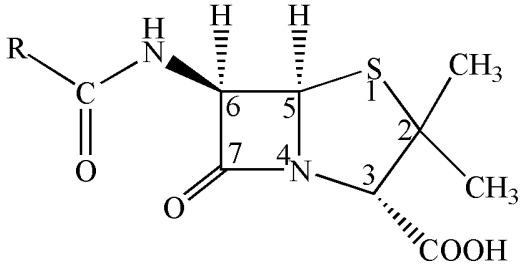

Fig. 1. Penicillins

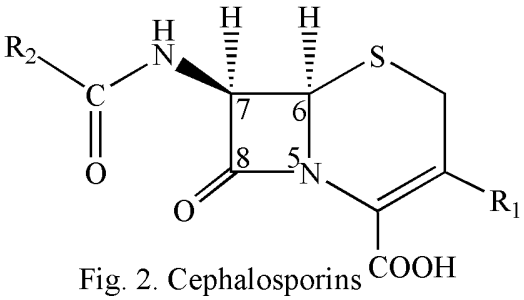

Fig. 2. Cephalosporins

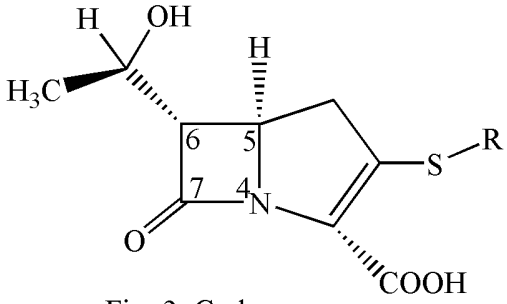

Fig. 3. Carbapenems

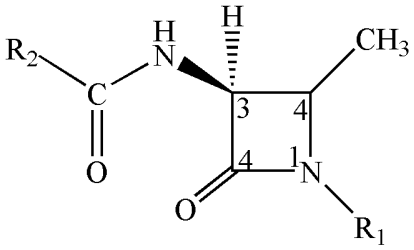

Fig. 4. Monobactams

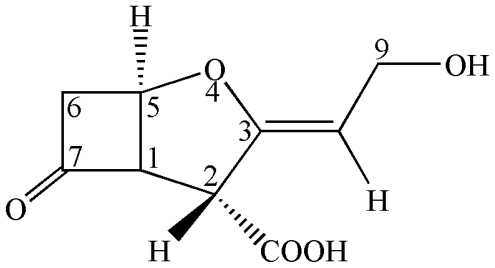

Fig. 5. Clavulanic acid

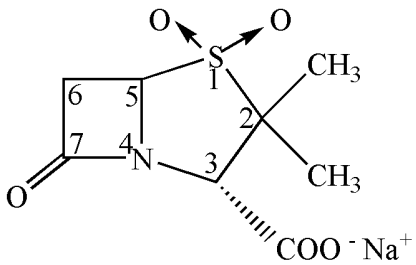

Fig. 6. Sulbactam

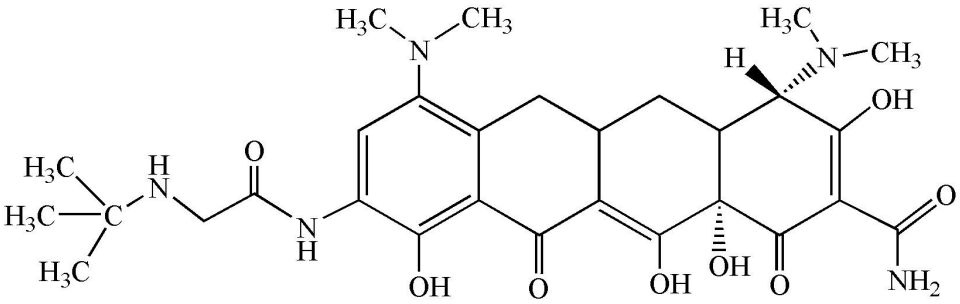

Fig. 7. Tigecycline

Based on substrate specificities, four major groups of β-lactamases are known: penicillinases, AmpC-type cephalosporinases, extended-spectrum β-lactamases (ESBLs), and carbapenemases [28]. The carbapenemases are again divided into two major groups; one MBLs contains at least one zinc atom at their active site, can be inactivated by β-lactamase inhibitors and can be inhibited by EDTA as well while second group serine-β-lactamases utilize serine at their active sites, inactivated by β-lactamase inhibitors, and cannot be inhibited by EDTA. To date several types of MBLs have been reported viz. IMP, VIM, SPM-1, GIM-1, SIM-1 and recently a new type NDM-1 have been reported. The NDM-1 is a carbapenemase, a class B β-lactamase [29], which can be further subdivided into, B-1, B-2, and B-3 [30]. Class B contains specific signature or motifs[28] in the sequence of H-90, D-92, L-117, H-168, G-204 and H-236 as conserved residues located at the bottom of the active site. Few of these motifs accommodate Zn^{2+}, which is the required for the activity of this class [31, 32]. Production of MBLs can be screened by modified Hodge test (clover leaf test) involving distorted carbapenem inhibition zones, imipenem-EDTA synergy tests by disc, MBL E test (AB bioMerieux, Solna, Sweden), spectrophotometric assays (spectrophotometric measurement of carbapenem hydrolysis), and molecular methods (PCRs, real-time PCRs, DNA hybridization and sequencing) [24,33]. The NDM-1 has a molecular mass of 27.5 kDa and contains 269 amino acids. It is present as a monomer and cleavage site is located at position 19 between two alanines. NDM-1 share very little identity with other MBLs and is the most closely related to VIM-1/VIM-2, with which it has only 32.4% identity [28]. The NDM-1 encoding gene "*bla*$_{NDM-1}$", is located on plasmids (a 180-kb plasmid for *K. pneumoniae* and a 140-kb plasmid for *E. coli*) [3] which can be easily transferred to other bacterial strains by horizontal gene transfer [5]. These plasmids also harbor some other genes conferring resistance to almost all antibiotics, thus making their rapid dissemination in clinically relevant bacteria a serious threat for therapy [2]. These gene mediated changes results in decreased antibiotic concentrations such as decreased porin function or increased efflux may diminish the amount of potentially lethal antibiotic, but also may result in reduced amounts of essential nutrients. In many Gram-negative pathogens, combinations of β-lactamase production and porin deletions contribute to the overall resistance profile, with recruitment of an army of β-lactamases remaining a major β-lactam resistance mechanism [34].

Kumarasamy et al. reported the emergence and spread of NDM-1 carrying multiresistant Enterobacteriaceae from India, Pakistan, and United Kingdom [1]. The presence of NDM-1 have also been reported in Bangladesh, [1] Australia, [1, 5] Netherlands, [6] USA, [3, 7, 8] Canada, [9] Japan, [10] and China [11] indicating that "*bla*$_{NDM-1}$", is widely spread all over the world. It is a matter of great concern as the the multiresistant bacteria carrying NDM-1 reported from India were primarily related with community acquired urinary tract infections, pneumonia, and blood-stream infections [1].

The worldwide spread of multi-resistant NDM producing Enterobacteriaceae will have serious implications for the empirical treatment of hospital associated and community associated infections. To make matters worse, there are very few antibiotics in development with activity against Gram-negative bacteria and none that are active against NDM-1[32]. Of particular concern is that, NDM enzymes are present in *E coli*; the most common cause of community associated urinary tract infections [5]. Infection caused by MBLs producing strains are associated with mortality rate ranging from 25-75%. Data from Brazil and Canada shows that there was an increase in mortality among patients with MBLs producing *P. aeruginosa* infection compared with patients with non MBLs producing *P. aeruginosa* (17.3% vs 11.8% in Brazil, 25% vs 13% in Canada) [29]. The NDM-1 carrying multiresistant Enterobacteriaceae are emerging public health threat[5] and if we will not pay duly attention and take preliminary measures to stop antibiotics abusing, sooner or later medical community will have to deal with β-lactams-resistant Enterobacteriaceae which causes common infections of daily life, will result into treatment failures and increase in healthcare cost [5].

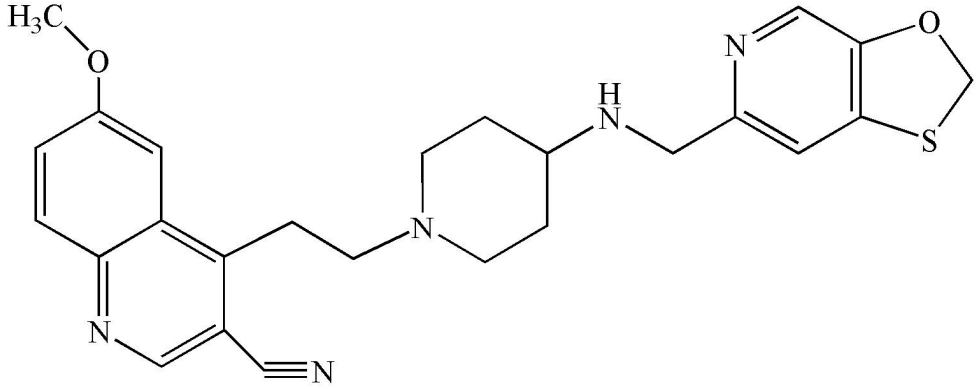

Fig. 8. GSK 299423

CONCLUSION

Let us consider Lancet report as a wakeup call, as we are left with very few options available to treat NDM-1 positive bacteria and worldwide presence of NDM-1 have heralded the end of β-lactams era. It is highly essential to explore rapidly the alternative classes of antimicrobials active against NDM-1. Medical community cannot entirely rely on β-lactams, because antibiotics with β-lactam ring are always prone to hydrolysis by β-lactamase and subsequently resistant to these antibiotics arises. There should be rational use of antibiotics and stringent policy should be implemented for the prescription of antibiotics, particularly in developing countries where antibiotics are easily available for layman as over the counter without producing the prescription of physicians. NDM-1 positive cases can be treated with aztreonam, polymyxin, colistin and tigecycline and in early August 2010, a chemical compound GSK 299423 (Fig. 8), was found to fight significantly against NDM-1 resistant bacteria by making such bacteria unable to reproduce, citing a likely treatment to the NDM-1 strain [36].

Many people from Europe, U.S. and Africa, prefer India for medical treatment majorly due to economic reasons and in some cases long waiting time in their home countries [37]. This so-called medical tourism to India might grow by 30% each year over the next 5 years [38]. We strongly disagree with the outlook that India should be excluded from medical tourism; instead, corrective measures should be taken up to minimize the spread of NDM-1as well as to eradicate the existing threat. The Indian health ministry has disputed the conclusion of the August 2010 *Lancet* study report that the NDM-1 gene originated in India or Pakistan, recounting this conclusion as unfair and states that Indian hospitals are perfectly safe for treatment. Moreover 'The Lancet' team having carried out the study only in India, Pakistan, and United Kingdom but not in other parts of the world, it is inappropriate to blame India or Pakistan for the origin of NDM-1.

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