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MINI-REVIEW

New Delhi Metallo- β -Lactamase (NDM-1): An Update

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Summary

New Delhi metallo- β -lactamase (NDM-1) is a novel broad spectrum carbapenemase with ability to inactivate all β -lactams except aztreonam. However, most of the NDM-1-producers also produce aztreonam hydrolysing- β -lactamases thereby making these pathogens absolutely resistant to all β -lactams. The *bla*_{NDM-1} gene encodes a 27.5 kDa protein of 269 amino acids. It shares very little identity with other metallo- β -lactamases. Maximum identity has been observed to VIM-1/VIM-2 (32.4%). This mini-review is an update of the scientific literature for the said enzyme. Following the recommendation of David Livermore, we further propose to combine "aztreonam" and "inhibitor of the

most frequently encountered aztreonam hydrolysing- β -lactamases in a given setting" as a possible strategy against NDM-1-producers. The inhibitor should be 'versatile' as well, i.e. it should have the ability to inhibit most of the variants of aztreonam hydrolysing- β -lactamases prevalent in the concerned setting. We strongly recommend surveillance studies using aztreonam/NXL-104-combination against NDM-1-producing pathogens in different geographical regions across the globe.

Key words: Aztreonam, carbapenemases, Gram-negative pathogens, metallo- β -lactamases, multidrug resistance, NDM-1.

INTRODUCTION

Emergence of multidrug-resistant bacteria is a cause of increasing concern in community as well as hospital settings^{1,2}. Gram-negative pathogens have been recognized as some of the most problematic bacterial challenges by The Infectious Diseases Society of America³. Out of six ESKAPE pathogens (recognized as particularly troubling), four are Gram-negative⁴. Hence the attention of the scientific community has shifted to the resistant Gram-negative bacteria⁵. Several drugs like linezolid, tigecycline⁶ and daptomycin are available for treatment of β -lactam-resistant Gram-positive infections. In contrast, carbapenems are considered as the ultimate treatment option for extended-spectrum β -lactamase (ESBL)-producing bacterial pathogens⁷. Simultaneous resistance to advanced-generation cephalosporins and carbapenems in pathogens might lead to therapeutic dead-ends⁸. Experts agree that pathogens that co-produce at least one carbapenemase together with an ESBL are particularly challenging⁵.

NEW DELHI METALLO- β -LACTAMASE (NDM-1)

Carbapenemases are either serine enzymes or metallo- β -lactamases (MBLs) that utilize at least one zinc ion for hydrolysis. New Delhi metallo- β -lactamase (NDM-1) is a novel broad spectrum β -lactamase (class B carbapenemase) with the ability to inactivate all β -lactams except aztreonam. However, most of the NDM-1 producers also produce aztreonam hydrolysing β -lactamases (e.g. CTX-M and CMY-type ESBLs) thereby making these pathogens absolutely resistant to all β -lactams⁹. NDM-1 was first characterized in 2009 from *Klebsiella pneumoniae* and *Escherichia coli* isolated from a Swedish patient who had received medical care in New Delhi, India and hence named after the Indian capital⁹. Most of the NDM-1-producing bacteria remain susceptible only to colistin and tigecycline. Renowned

experts from across the globe have considered the spread of NDM-1 as a serious threat to the treatment of Gram-negative infections by the existing antibiotic armory^{10,11}.

GLOBAL EPIDEMIOLOGY

After the first report⁹ in 2009, Indian authors reported detection of 22 NDM-1-producing strains from Mumbai, the economic capital of India¹². This was followed by detection of NDM-1-producing bacteria from the UK¹³ and the USA¹⁴. A team of scientists reported 37 NDM-1-producing isolates from the UK, 44 isolates from Chennai (South India), 26 isolates from Haryana (North India), and 73 isolates from various other sites in the Indian subcontinent¹⁵. Most of the isolates were susceptible only to colistin and tigecycline. In 2010 itself, Canada¹⁶, Japan¹⁷ and the Middle East (Sultanate of Oman)¹⁸ also confirmed their first cases of NDM-1-harboring pathogens. Subsequently, the first death due to infection by NDM-1-producing bacteria was reported in August 2010¹⁹.

In a 2011 study, Walsh *et al* measured the prevalence of *bla*_{NDM-1} in drinking water and seepage samples in New Delhi while using sewage effluent samples from Cardiff Wastewater Treatment Works, Tremorfa, Wales as control. The authors detected *bla*_{NDM-1} in two of 50 drinking-water samples and 51 of 171 seepage samples from New Delhi; the gene was not found in any sample from Cardiff²⁰. In a multicenter study a total of 11,298 clinical Gram-negative bacilli, covering *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, were collected for PCR-based surveillance of *bla*_{NDM-1} from 57 hospitals representing 18 provinces in China²¹. However, only four isolates (*A. baumannii*), which were clonally unrelated were confirmed positive for *bla*_{NDM-1}²¹.

There is a significant environmental dissemination of NDM-1 across the globe²². Recently, Kus *et al* published the first re-

port of *bla*_{NDM-1}-positive bacteria which were locally acquired in Canada²³. NDM-1-producing pathogens are continually being reported from across the globe as we write this article in the year 2011²⁴⁻²⁶. May 2011 marked the first detection of NDM-1-producing pathogens in Switzerland²⁷ followed by a first report of the same from the Balkan region in June 2011²⁸. Yamamoto *et al* have reported the emergence of NDM-1-positive capsulated *E. coli* with high resistance to serum killing in Japan.

Scientists agree that *bla*_{NDM-1} is widely distributed among Enterobacteriaceae and has geographically exhibited extremely rapid and global spread²⁹. International travel does play a role in the spread of NDM-1³⁰. Several authors have found the acquisition of NDM-1-producing bacteria in their study subjects linked to previous hospitalizations in NDM-1-harboring countries like India,³¹ Pakistan, Montenegro, Kosovo etc.³². Kaase *et al* reported the first variant of NDM-1 (designated as NDM-2) in June 2011 which possessed a C to G substitution at position 82 resulting in an amino acid substitution of proline to alanine at position 28³³.

METHODS USED FOR DETECTION OF NDM-1

In a study by Nordmann *et al.*,³⁴ a combined test (imipenem/imipenem + EDTA), the Etest MBL, and automated susceptibility testing by Vitek2 (bioMérieux) identified those NDM-1 producers as verified by PCR using specific primers. The authors suggested that the screening for carriers of NDM-1 producers might be based on media such as the ChromID ESBL culture medium or the CHROMagar KPC culture medium and colonies growing on these screening media could then be verified as NDM-1 producers with molecular methods³⁴. Recently Krüttgen *et al*³⁵ described a real-time PCR assay as well as two conventional PCR assays to detect *bla*_{NDM-1}. Only minute amounts of total DNA extracted from one bacterial colony were found to be sufficient to allow detection of *bla*_{NDM-1} by real-time PCR within less than 1 h. They also introduced a chemically synthesized *bla*_{NDM-1} gene as a convenient positive control for those laboratories wishing to setup in-house assays for detection of the said gene³⁵. In a study published in June 2011, the authors reported the development of a rapid real-time-PCR assay with TaqMan probe to detect *bla*_{NDM-1} gene directly from bacterial isolates. The specificity of the assay was verified in silico as well as with a large panel of 84 clinically relevant bacteria³⁶. In another 2011 study,³⁷ the authors evaluated a DNA microarray (Check-MDR CT102) meant for the rapid detection of TEM, SHV and CTX-M type ESBLs, and also for KPC, OXA-48, VIM, IMP, and NDM-1 carbapenemases on a total of 144 Gram-negative strains. The sensitivity and specificity were 100% for most of the tested genes. The authors confirmed that the said microarray allowed accurate identification of common ESBL- and carbapenemase-producers from bacterial cultures³⁷. In the proceedings of the 21st European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) scientists recommended rapid detection of NDM-1 producers using Hodge tests, synergy tests, automated systems or agreed algorithms. The strains that test positive should be subjected to molecular tests (*bla*_{NDM} PCR)³⁸.

STRUCTURAL AND FUNCTIONAL PROPERTIES OF NDM-1

The *bla*_{NDM-1} open reading frame was found to encode a putative 27.5 kDa protein of 269 amino acids⁹ (theoretical pI=6.9). The sequence and behavior of NDM-1 during gel filtration and mass spectrometry indicated that it was actively present as a monomer. NDM-1 was found to possess a leader peptide, with probable cleavage site at position 19 between two alanines. It was found to share the additional loop of the VIM

enzymes at positions 34 and 47. Moreover, NDM-1 was found to possess a unique additional sequence at positions 162 to 166. It shared very little identity with other MBLs. Maximum identity was observed to VIM-1/VIM-2 (32.4%). NDM-1 was also found to possess a tyrosine at position 222 instead of the universally conserved tryptophan⁹. NDM-1 showed tight binding (low *K_m* values) to most cephalosporins and, in particular, to cefuroxime, cefotaxime, and cephalothin. Contrary to most MBLs, NDM-1 was observed to have a relatively tight binding to the penicillins. It was found to bind less tightly to the carbapenems as compared to IMP-1 or VIM-2⁹. In an important study by Wang and Chou, the authors reported docking of NDM-1 with imipenem and meropenem³⁹. The authors observed that imipenem and meropenem were hydrolyzed while sitting in a binding pocket of NDM-1 formed by 9 and 12 amino acid residues, respectively³⁹. Based on their findings, they proposed a model for a catalytic mechanism of NDM-1. As per their model, the metal binding Asp60 acted as the general base that activated the water nucleophile, while the protonation of Asp60 resulted in the cleavage of its bond to the metal ion³⁹.

As a recent development, Zhang and Hao reported the crystal structure of NDM-1 in complex with a hydrolyzed ampicillin at its active site at 1.3-Å resolution⁴⁰. The authors found that ampicillin binds to the more hydrophobic L3 loop of NDM-1 through hydrophobic interactions. The study disclosed a longer distance between the 2 zinc ions at the active site, thereby giving insight into the lower activity of the enzyme for the studied ligand. Interestingly, structural comparisons with other MBLs revealed a new hydrolysis mechanism applicable to all three subclasses of MBLs in which a proton comes from the newly formed carboxyl group in the β-lactam ring. The authors expected that the results of their study might be helpful in the design of common inhibitors to all MBLs⁴⁰.

THERAPY AGAINST NDM-1-PRODUCING PATHOGENS

As stated elsewhere in this article, NDM-1 does not attack aztreonam, a monobactam antibiotic. However, aztreonam resistance in NDM-1-producers occurs due to simultaneous presence of other β-lactamases capable of hydrolyzing aztreonam (like CTX-M or CMY-type enzymes) in the same pathogen. Moreover, directly targeting NDM-1 enzyme by β-lactamase inhibitors available to date is not possible because it has a metal ion (Zinc) in its active site instead of serine. We agree with the suggestion of the honorable expert, David Livermore, who pleaded with industry to combine NXL-104 with aztreonam. NXL-104 is a novel β-lactamase inhibitor (trans-7-oxo-6-(sulfoxy)-1,6-diazabicyclo[3.2.1]octan-2-carboxamide, a representative of a novel class of bridged bicyclo[3.2.1]diazabicyclo-octanones) that inactivates active serine-β-lactamases by forming a stable covalent complex. It shows excellent inhibition properties against bacterial enzymes belonging to Ambler classes A and C, including: TEM, SHV, CTX-M-type ESBLs (and also other minor variants); Class A carbapenemases (most notably KPC-2); Resident AmpC-type β-lactamases (*E. coli*, *P. aeruginosa*); and plasmid-mediated class C β-lactamases (e.g. CMY-type enzymes)⁴¹. David Livermore has recently shown the potential of aztreonam-NXL-104 combination against NDM-1-producing bacteria⁴². The authors found that aztreonam-NXL104 was active against all carbapenemase producers at 4 and 4 μg/ml, including those with metallo-β-lactamases⁴².

SUGGESTION

Following this, we further propose to combine aztreonam and "inhibitor of the most frequently encountered aztreonam hydrolyzing-β-lactamases in a given setting" as a possible strategy against NDM-1 producers. The status of "most efficient

aztreonam hydrolyzing- β -lactamases-inhibitor” and subsequently the empirical treatment against NDM-1 producing pathogens would vary from region to region. For instance, in a previous study, we tested the efficiency of traditional β -lactamase-inhibitors against CTX-M variants⁴³. CTX-Ms are the most prevalent ESBL type in India⁴⁴ and hence “the most frequently encountered aztreonam hydrolyzing- β -lactamases” in the said region. We found sulbactam as the most efficient CTX-M-inhibitor. NXL-104 however, was not included in the study⁴³. Similarly, there is a predominance of CTX-M genotype among the ESBL-producing bacteria in Saudi Arabia⁴⁵. Hence combining aztreonam and “the most efficient CTX-M-inhibitor” might be the therapy of choice for NDM-1-producing pathogens in this setting as well. The inhibitor should be versatile as well, i.e. it should have the ability to inhibit most of the CTX-M variants prevalent in the concerned setting, if not all. In view of emerging evidence,⁴² we strongly recommend surveillance studies to investigate the potential of the aztreonam/NXL-104 combination against NDM-1-producing pathogens in different geographical regions across the globe.

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