DOI: http://dx.doi.org/10.18203/issn.0019-5359.IndianJMedSci20170487

Bacterial Infections **Review Article**

New Delhi metallo-beta-lactamase-1: A weapon for the newly emerging drug-resistant bacteria

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ABSTRACT

The world has seen the emergence of many micro-organisms in the recent past which can curb the human population with their newly built genetic make-up. The latest addition to this list of panic creating organisms is, bacteria encoding the gene for New Delhi metallo-beta-lactamase (NDM)-1. NDM-1 is an enzyme that can hydrolyse and inactivate carbapenems, which are used as a last resort for the treatment of multiresistant bacterial infections. Name of these bacteria were not found in the medical literature before December 2009, because of which it can take the credit of becoming a powerful emerging bacteria which are difficult to treat. Besides *Escherichia coli* and *Klebsiella pneumoniae*, other bacterial strains have also expressed the gene for NDM-1, which are detected in many countries.

Key words: *Gene, New Delhi metallo-beta-lactamase-1, plasmid*

INTRODUCTION

The era of bacteria that had plagued mankind for millenniums, killing large numbers of people with serious infections had come to an end with the help of a miracle weapon called antibiotic. Less than a century ago human beings had started to fight the battle against microbes with the discovery of sulfamethoxazole. The emergence of penicillin had helped physicians to cure a vast range of crippling infections. These antibiotics had succeeded in destroying a large number of bacteria present inside the human body. But some bacteria, as per the Darwinian law of "survival of the fittest" survived. The gene for antibiotic resistance which evolved via natural selection may be transferred between bacteria horizontally by conjugation, transduction or transformation. Many antibiotic resistant genes reside on plasmids facilitating the ease of their transfer. A bacterium carrying several antibiotic resistant genes is called a multi-resistant bacteria or informally, a "super bacteria" or "super bug" because infections caused by them are difficult to treat. These bacteria came to limelight when an article was published in The Lancet a medical journal in August 2010, about multi-drug resistant "super bug" infection, which they named controversially as New Delhi metallo-beta-lactamase or NDM-1 based on their assumed origin.[1] Probably, a very rare "genetic fusion" had occurred between two previously known antibiotic-resistant genes that gave birth to a chimera called NDM-1 gene. The emergence of bacteria carrying such genes has threatened the mankind by challenging the medical fraternity with regard to treatment.

NDM-1 is an enzyme that makes the bacteria resistant to a broad range of antibiotics including the carbapenems, which are reserved for the treatment of resistant bacterial infections. This carbapenem beta-lactamase enzyme, produced by the $bla_{\text{NDM-1}}$ gene, can hydrolyse and inactivate the carbapenem antibiotics. The NDM-1 enzyme is one of the class B metallo-beta-lactamase; other classes of carbapenemase being class A (the most common carbapenemase) and class D beta-lactamases.[2]

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ORIGIN AND SPREAD

The NDM-1 enzyme was first described in December 2009 in a Swedish national who fell ill with an antibiotic-resistant bacterial infection which he had acquired in India.[3] The infection was unsuccessfully treated in a New Delhi hospital, and after repatriation of the patient to Sweden, a carbapenem-resistant *Klebsiella pneumoniae* strain bearing the novel gene was identified. In March 2010, a study conducted in a hospital in Mumbai found that most of the carbapenem-resistant bacteria isolated from patients carried the $bla_{\text{NDM-1}}$ gene.[4] A patient having infection with *Escherichia coli* expressing NDM-1 was reported in May 2010 in the United Kingdom, who had a history of visiting India 18 months ago for undergoing dialysis.[5] In June 2010, three isolates of Enterobacteriaceae family bearing this resistance mechanism were reported in the US, which were from patients who had recently received medical care in India.[6] In July 2010, isolation of three cases of *Acinetobacter baumanii* bearing blaNDM-1 from the intensive care unit of a hospital in Chennai, India, were reported by a team from New Delhi.[7] Though the first reported case had a history of Indian origin, its exact geographical origin, however, has not been conclusively verified. Moreover, bacteria carrying NDM-1 enzyme have been reported from patients of different countries also, suggesting its wide dissemination [Table 1].[1,3,5,8] Thus it has been proposed that the patients travelling to India for cost effective cosmetic surgery, cancer treatment and transplantation and returning to their native countries for further care, were responsible for spreading these bacteria. In addition to this, lack of antibiotic policy and registered data of hospital acquired infections in most of the hospitals in India made it easy to name the bacteria as "New Delhi Bug." But the nomenclature was strongly denied by the Indian Government saying that, it is unfortunate to attach the name of a nation to a new bug which is an environmental thing. On January 12, 2011, the editor of the Lancet apologized and acknowledged that naming a superbug after New Delhi was an error.

Most of the NDM-1 carrying bacteria reported, were from patients having a history of hospital admission. But detection of NDM-1 gene carrying bacteria in drinking water and sewage samples by a point prevalence study conducted in New Delhi between September 26 and October 10, 2010, concluded that these bacteria are also present in the environment. These genes were much more prone to swap between bacterial species at 30°C than at 25°C or

Table 1: Number of detected NDM-1 cases from different nations

Name of the nation	*Number of isolates bearing NDM-1*
United Kingdom	50
USA	3
Pakistan	25
Hong Kong	1
Australia	3
Japan	1
China	3
Singapore	6
Canada	8
Denmark	1
South Korea	2
Thirteen European countries	77
Northern India (Haryana)	26
Southern India (Chennai)	44
Other parts of India	48

NDM=New Delhi metallo-beta-lactamase

37°C (which is the body temperature) suggesting that the bacteria have found environmental mixing more important than in the gut. In addition to Enterobacteriaceae, bla_{NDM-1} gene was detected in other 11 bacterial species in which NDM-1 were not previously reported, including *Shigella boydii* and *Vibrio cholerae*. Isolates of *Aeromonas caviae* and *Vibrio cholerae* carried bla_{NDM-1} on chromosomes while others carried it on the plasmids.[9]

DETECTION

The gene for NDM-1 can be detected by polymerase chain reaction and DNA probing. In resource-poor laboratories they can be detected by phenotypic determination of the enzyme activity using modified Hodge test and re-modified Hodge test.[10]

TREATMENT

These bacteria are sensitive to older generation antibiotics like colistin and tigecycline, which can produce toxic side effects in renal disease patients. But death of a Belgian patient despite administration of colistin, in August 2010, was the first reported death due to bacteria expressing NDM-1 enzyme.[11] Discovery of the chemical compound GSK 299423 seems to bring a ray of hope, which does not allow the antibiotic-resistant to reproduce, citing a likely treatment for the NDM-1 strain.[12] To find out new drugs that can attack NDM-1, Infectious Disease Society of America has launched a "bad bugs need drugs" campaign to promote development of new antibiotics by 2020.

CONTROL AND PREVENTION

The emergence of antibiotic-resistant bacteria comes from inappropriate prescriptions or overuse, rather abuse of antibiotics in the absence of proper surveillance in the community. According to Centre for Disease Control infection control guidelines, all the carbapenem-resistant bacteria should be identified among the isolates. Surveillance should also be done to identify undetected carriers of carbapenem-resistant bacteria.

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How to cite this article: Padhi S. New Delhi metallo-beta-lactamase-1: A weapon for the newly emerging drug-resistant bacteria. Indian J Med Sci 2017;69:29-30.

Source of Support: Nil. **Conflict of Interest:** None declared.