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# NDM-1- New Delhi Metallo beta Lactamase: A Review

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**Abstract**

New Delhi Metallo-ß-lactamase-1, or NDM-1 for short, is a gene carried by bacteria that makes the strain resistant to carbapenem antibiotics. This is concerning scenario because these antibiotics are some of the most powerful ones, used on hard-to-treat infections that evade other drugs. It is also found that NDM-1 can easily now jump from one strain of bacteria to another. This present major challenges for clinicians and will often demand combinations of antibiotics are used.

**Keywords:** *Klebsiella pneumoniae*, NDM-1, PCM [Plasmid-encoding Carbapenemase-resistant Metallo-B-Lactamase],superbug.

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**New Delhi metallo-beta-lactamase** (**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. The gene for NDM-1 is one member of a large gene family that encodes beta-lactamase enzymes called carbapenemases. Bacteria that produce carbapenemases are often referred to in the news media as "superbugs" because infections caused by them are difficult to treat. Such bacteria are usually susceptible only to polymyxins and tigecycline[1].

NDM-1 was first detected in a *Klebsiella pneumoniae* isolate from a Swedish patient of Indian origin in 2008. It was later detected in bacteria in India, Pakistan, the United Kingdom, the United States, Canada, Japan and Brazil. The most common bacteria that make this enzyme are Gram-negative such as *Escherichia coli* and *Klebsiella pneumoniae*, but the gene for NDM-1 can spread from one strain of bacteria to another by horizontal gene transfer[2].

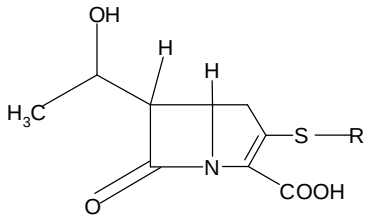
**Mechanism**

Antibiotic resistance can be a result of horizontal gene transfer, and also of unlinked point mutations in the pathogen genome at a rate of about 1 in $10^8$ per chromosomal replication. The antibiotic action against the pathogen can be seen as an environmental pressure; those bacteria which have a mutation allowing them to survive will live on to reproduce. They will then pass this trait to their offspring, which will result in a fully resistant colony [3].

**Enzyme function**

Carbapenems are a class of beta-lactam antibiotics that are capable of killing most bacteria by inhibiting the synthesis of one of their cell wall layers. The carbapenems were developed to overcome antibiotic resistance mediated by bacterial beta-lactamase enzymes. However, the $bla_{\text{NDM-1}}$ gene produces NDM-1, which is a carbapenemase beta-lactamase - an enzyme that hydrolyzes and inactivates these carbapenem antibiotics.

Carbapenemases are particularly dangerous resistance mechanisms, since they can inactivate a wide range of different antibiotics. The NDM-1 enzyme is one of the class B metallo-beta-lactamase; other types of carbapenemase are class A or class D beta-lactamases [4]. . (The class A *Klebsiella pneumoniae* carbapenemase (KPC) is currently the most common carbapenemase, which was first detected in North Carolina, USA, in 1996 and has since spread worldwide. A later publication indicated that Enterobacteriaceae that produce KPC were becoming common in the United States.) The resistance conferred by this gene ($bla_{\text{NDM-1}}$), therefore, aids the expansion of bacteria that carry it throughout a human host, since they will face less opposition/competition from populations of antibiotic-sensitive bacteria, which will be diminished by the original antibacterial treatment [5].




Structure of the carbapenem backbone.

**Origin and spread**

The NDM-1 enzyme was named after New Delhi, the capital city of India, as it was first described by Yong et al. in December 2009 in a Swedish national who fell ill with an antibiotic-resistant bacterial infection that he acquired in India. The infection was unsuccessfully treated in a New Delhi hospital, and, after the patient's repatriation to Sweden, a carbapenem-resistant *Klebsiella pneumoniae* strain bearing the novel gene was identified. The authors concluded that the new resistance mechanism "clearly arose in India, but there are few data arising from India to suggest how widespread it is." Its exact geographical origin, however, has not been conclusively verified. In March 2010, a study in a hospital in Mumbai found that most carbapenem-resistant bacteria isolated from patients carried the $bla_{\text{NDM-1}}$ gene [6].

In May 2010, a case of infection with *E. coli* expressing NDM-1 was reported in Coventry in the United Kingdom. The patient was a man of Indian origin who had visited India 18 months previously, where he had undergone dialysis. In initial assays the bacteria was fully resistant to all antibiotics tested, while later tests found that it was susceptible to tigecycline and colistin. The authors warned that international travel and patients' use of multiple countries' healthcare systems could lead to the "rapid spread of NDM-1 with potentially serious consequences" [7].

As of June 2010, there were three reported cases of Enterobacteriaceae isolates bearing this newly described resistance mechanism in the US, the Centers for Disease Control and Prevention (CDC) stated that "All three U.S. isolates were from patients having received recent medical care in India." However, US experts stated that it is unclear as to whether this strain is any more dangerous than existing antibiotic-resistant bacteria such as methicillin-resistant Staphylococcus aureus, which are already common in the USA [8].

In July 2010, a team in New Delhi reported a cluster of three cases of *Acinetobacter baumannii* bearing $bla_{\text{NDM-1}}$ that were found in the intensive care unit of a hospital in Chennai, India in April 2010. As previously, the bacteria were fully resistant to all the aminoglycoside β-lactam and quinolone antibiotics, but were susceptible to tigecycline and colistin. This particularly broad spectrum of antibiotic resistance was heightened by the strain's expressing several different resistance genes in addition to $bla_{\text{NDM-1}}$ [9].

A study by a multi-national team was published in the August 2010 issue of the journal *The Lancet Infectious Diseases*. This examined the emergence and spread of bacteria carrying the $bla_{\text{NDM-1}}$ gene. This reported on 37 cases in the United Kingdom, 44 isolates with NDM-1 in Chennai, 26 in Haryana, and 73 in various other sites in Pakistan and India. The authors' analysis of the strains showed that many carried $bla_{\text{NDM-1}}$ on plasmids, which will allow the gene to be readily transferred between different strains of bacteria by horizontal gene transfer. All the isolates were resistant to multiple different classes of antibiotics, including beta-lactam antibiotics, fluoroquinolones, and aminoglycosides, but most were still susceptible to the polymyxin antibiotic colistin [10].

On August 21, 2010, Ontario, Canada had its first confirmed case of the "superbug" in Brampton. There were other confirmed cases in British Columbia and Alberta [11].

In August 2010, a chemical compound GSK 299423, was found to significantly fight against antibiotic-resistant bacteria by making such bacteria unable to reproduce,

citing a likely treatment to the NDM-1 strain [12].

On September 6, 2010, Japan detected its first ever case of the NDM-1 enzyme. In May 2009, a Japanese man in his 50s who had recently returned from vacation in India was struck with a fever and hospitalized, later making a full recovery. Hospital officials confirmed that tests carried out after the patient's recovery were positive for the NDM-1 enzyme. An environmental point prevalence study conducted between September 26 to October 10, 2010 found bacteria with the NDM-1 gene in drinking water and seepage samples in New Delhi. 50 tap water samples and 171 seepage samples were collected from sites within 12 km of central New Delhi. Of these samples, 20 strains of bacteria were found to contain NDM-1 gene in 51 out of 171 seepage samples and 2 out of 50 tap water samples. Research team from University of Cardiff in UK had taken sample of water and other sample from New Delhi in April 2011 and fund the deadly viruses NDM1 and the facts was published in British Medical Journal "Lancet"[13].

On January 12th 2011, the editor of The Lancet, Richard Horton (editor) apologized and acknowledged that naming a superbug after New Delhi was an “error” [14-16]. Following this, Ajai R. Singh, editor of Mens Sana Monographs, demanded that such 'geographic names giving' be abandoned and replaced by 'scientific names giving'. He proposed changing NDM-1 to PCM [Plasmid-encoding Carbapenemase-resistant Metallo-B-Lactamase] [17].

**How NDM-1 Effects human body**

* Multi drug-resistant bacteria are already a growing problem in hospitals across the world, marked by the rise of “superbug” infections like methicillin-resistant Staphyloccus aureus (MRSA).
* NDM-1 makes bacteria highly resistant to almost all antibiotics, including the most powerful class called carbapenems.
* Most worryingly, NDM-1-producing bacteria are resistant to many antibiotics including carbapenems.
* The scientists said, a class of the drugs generally reserved for emergency use and to treat caused by other multi-resistant bacteria such as MRSA and C-Difficile [18].

**Symptoms of super bug NDM-1 bacterial, *Klebsiella pneumoniae* and *Escherichia Coli* Symptoms**

* Klebsiella bacteria contains the superbug NDM-1.
* Klebsiella pneumoniae symptoms include sudden Onset, of High Fever and Hemoptysis .
* Klebsiella pneumoniae is a common gram-negative bacteria seen worldwide.
* It is also causing Urinary Tract Infections, Nosocomial Pneumonia, and Intra abdominal infections.
* NDM-1 which is found in the E. Coli bacteria may be the cause of Urinary Tract Infections.
* E. Coli is the leading cause of urinary tract infections outside of hospitals.
* E. Coli is Antibiotic-resistant.
* E. Coli is also responsible for cases of Fatal Pneumonia and other infections [19].

**Prevention of superbug NDM-1**

To prevent spread of Superbug NDM-1 Bacteria, Doctors advise to provide adequate cleaning and sanitizing of all areas is the best means of preventing further spread of the superbug bacteria. Hospitals and doctors are under advise to stay on top of the cleanliness issue.

- Provision of good hygienic conditions, with adequate cleanliness and sanitization is the best bet against further spreading of this

superbug.

- Reporting any incidence of Superbug NDM-1 and isolating that patient at the earliest, is essential and helps prevent the further spread of such organisms.
- Isolation of patients and preventing them from contracting such diseases that are likely to be affected by super bug NDM-1 gene gives better results than treating the patient once exposed.
- Never share your antibiotics with friends or family, even if you are 100% sure that they have the same infection. Let your doctor do the exam and write a new prescription.

Controlling the spread of Superbug NDM-1 is largely related to stopping further mutation of the gene that causes it. Since it is largely confined to the hospitals, its further spread can be prevented by ensuring that those dealing with such patients wear long sleeved disposable gowns and use disposable gloves. Also, frequent fumigation and other such measures go a long way in preventing it [20].

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