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Editoral

New Delhi metallo-β-lactamase (NDM-1): how real is the threat?

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During the past decade the escalation of antimicrobial resistance in *Enterobacteriaceae* has become a major concern worldwide. Antimicrobial resistance among *Enterobacteriaceae* is growing, largely due to broad spectrum beta-lactamase production. Until recently, the most common MBLs (carbapenemases) found worldwide in *Enterobacteriaceae* were VIMs and IMPs.

The most recently emerged carbapenemase is the New Delhi metallo-beta-lactamase (NDM-1). NDM-1 was named after the place (New Delhi, India) where it was assumed to have originated, similar to other nomenclature for metallo-β-lactamases, Verona imipenemase (VIM), German imipenemase (GIM), São Paulo MBL (SPM) and Seoul imipenemase (SIM). The first report of NDM-1 producing strain (*Klebsiella pneumoniae*) was from Sweden in December 2009 (the patient had received medical care in New Delhi). The strain was found to be resistant to all antibiotics except colistin[1].

Since the $bla_{\text{NDM-1}}$ gene is primarily located on a plasmid (mobile genetic element) it could transcend the genus/family barrier with ease. It has already been reported in other *Enterobacteriaceae* and non-*Enterobacteriaceae* Gram-negative organisms from around the world mainly in the United Kingdom, India, and Pakistan. Further, it is also reported from many different countries in Europe, Asia, Africa, and North America. Many of these reports indicated a link with the Indian subcontinent, corresponding to either hospital or community acquisitions. Southeast European countries have also been recently considered an additional reservoir for NDM producing microbes. There is also a report of NDM-1-Producing *K. pneumoniae* from Mauritius[2].

In the United States, *K. pneumoniae* carbapenemase (KPC) producing Gram-negative bacteria raised significant concern, because mortality rates among patients infected with these bacteria were high, especially in long-term care facilities. NDM-1 (due to its epicenter in the huge population of India) has already obscured the KPC in terms of the number of countries in which it is found. The $bla_{\text{NDM-1}}$ gene was identified initially in *K. pneumoniae* and *Escherichia coli* strains, mostly from India and Pakistan. It has been recently reported worldwide, extensively in other enterobacterial species including *A. baumannii.* The sixth enzymatic variant (NDM-6) has also been reported.

NDM, PLASMIDS & CO-RESISTANCE

Carbapenem class (imipenem, meropenem, doripenem and ertapenem) of antimicrobials are often the last resort for the safe and effective treatment of infections caused by multidrug – resistant (MDR) Gram-negative bacteria.

Resistance to carbapenems occurs through several mechanisms, including the production of carbapenemases. The $bla_{\text{NDM-1}}$on plasmid allows the gene to be readily transferred between different strains, including different genus/family of bacteria by horizontal gene transfer. Unlike other carbapenemase resistance genes, $bla_{\text{NDM-1}}$ carrying plasmids contain several antibiotic resistance genes such that the recipient bacterium is resistant to all antibiotics apart from tigecycline and colistin. Due to ever-present selective pressure, mutation is an inevitable process and this in turn will in due course lead to origin of newer strains turning resistant to all the existing antibiotics.

NDM AND HUMAN INTESTINAL FLORA

Carbapenemases in *Escherichia coli* is a major concern, since these bacteria are widespread in the environment and in water and it is an important part of human intestinal flora. *E. coli* is easily transferred by hand, water or an inanimate environment from person to person. *E. coli* is the cause of many community- acquired infections. Consequently, identification of a significant number of NDM-1 producers in *E. coli* is an

additional reason of concern as it suggests that the resistance is being disseminated in the hospital as well as in the environment.

NDM AND INFECTIONS

Regrettably more than the implications of NDM-1 producing bacteria to our health and lives, the disputes that followed it seemed to be more.
NDM-1 producing bacteria are the most common cause of urinary infections. They can also cause bloodstream infections, pneumonia, and wound infections. Most patients will have fever and fatigue. Symptoms reflect the site of the infection and it does not differ between bacteria that express NDM-1 and those that do not. However, patients who have bacteria producing NDM-1 are difficult to treat[3] and are at higher risk for complications[4].

NDM AND MEDICAL TOURISM

The rapid dissemination of NDM-1 in clinically relevant bacteria has become a global concern. There is a growing trend of people visiting Asia for medical care (surgeries) as it is often more cost-effective than in the West. There is implication that this practice of going overseas for medical care ("medical tourism") could provide a route for the worldwide spread of NDM-1.

NDM AND LAST RESORT OF ANTIMICROBIALS

Treatment of infections caused by NDM-1 producing pathogens presents a major challenge for clinicians, due to its limited therapeutic options. These organisms mostly are resistant to all antibiotics except colistin (polymyxin E) and, less consistently, tigecycline. Hence colistin and tigecycline, the final resort antimicrobials have been tried with limited success. There are already studies reporting resistance to colistin and tigecycline. Further, colistin could be nephrotoxic and tigecycline is not licensed for treatment of urinary tract infections. In few cases combination of antibiotics have been tried with little success, the idea being that it is unlikely a bacterium could be resistant to all of them. The activity of doubtful agents (fosfomycin, arbekacin and isepamicin) and novel compounds is under investigation, but none is readily accessible for therapy. The lack of proven effective therapies emphasizes the need for new agents for the treatment of infections caused by NDM-1–producing bacteria and other carbapenem-resistant organisms.

NDM AND LABORATORY DIAGNOSIS

From a laboratory diagnostic perspective, NDM-1 is not easily identified in clinical bacteria. Some methods of detection lack the sensitivity necessary for the rapid and assured detection of NDM-1 that facilitates antibiotic stewardship and the introduction of measures to control the spread of infection. Detection of NDM-1 gene phenotypically is usually done by Modified Hodge test. However, MBL E-test, or imipenem-EDTA double synergy test, and determination of minimum inhibitory concentrations (MICs) also have been employed. To avoid false negatives in phenotypic testing, Polymerase Chain Reaction (PCR) could be used for the detection of this specific carbapenemase encoding gene.

NDM AND REALITY OF THE THREAT

Infections caused by NDM-1 positive bacterial pathogens are difficult to treat, however it doesn't by itself make pathogens more virulent or transmissible. These infections have ranged from mild to severe, though some have been fatal. The patient's immunocompromised status could be a risk factor for these infections. NDM-1 positive pathogens cannot lead to pandemics like bird or swine flu, but diseases caused by NDM-1 positive pathogens could result in clinical complications[4].

CONCLUSION/ NDM AND MEASURES TO BE TAKEN

The $bla_{\text{NDM-1}}$ gene has"an alarming potential" to spread and diversify among bacterial populations. Hence early identification of cases of NDM-related infections and prevention of their spread by implementing screening, hygiene measures and the isolation of carriers is needed. The indiscriminate use of Carbapenem in major ICU and critical care unit cases, burns and other severe infection leads to carbapenem resistance. Carbapenem antibiotics should be treated as the last resort and reserved for severe infections.The key to stopping the spread will be identifying new cases early and insisting on good hygiene in hospitals, such as disinfecting medical instruments and ensuring increasing hand washing compliance of health care workers including physicians, nurses, radiologic technicians and physical therapists.
There is a plan for a systematic monitoring of both infected patients and possible asymptomatic carriers returning to the West from Asia. Resistance to antibiotics is becoming a serious threat for several countries because of the popular habit of popping pills at will. Drug control officials of India have decided to notify a new drug schedule, H1, only to be sold against a prescription that the chemist will have to retain and further, to conduct surprise checks on compliance of retailers once H1 is notified.
Among the various proposals from the World Health Organisation (WHO) to curb ever-growing

antibiotic resistance, here are certain key points: banning the use of non-prescribed antibiotics and self-medication; implementing stringent infection control policies; initiating prudent antibiotic formularies in hospitals; establishing national surveillance programs and increasing collaboration with international groups to further our understanding of antibiotic resistance.

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