Journal of
Anaesthesiology
Clinical Pharmacology

Vol. 26 **No. 4** **October, 2010**

EDITORIAL

Medical Tourism and New Delhi Metallo β - Lactamase 1 A Concern and Threat

Medical tourism in India is a concept which has recently developed whereby patients & their attendants visit India. This fulfills their medical needs & gives them a chance to visit innumerable destinations of tourism interest for pleasure and relaxation. India is well known throughout the world about its potential regarding tourism, however it is only since last decade or so that some medical institutions / centres have come upto international standards providing highest degree of technical expertise in patient care. The results provided by these medical institutes/ centres are definitely at par with the best in the world and few are even better. The number of patients visiting India has been continuously increasing for the last 3-4 years. In this context in 2010-11, India expects more than 3.5 lakh patients visit India for medical tourism. This includes patients not only from under-developed countries or developing world, but also from developed regions too. India now has become a "global Health Destination". There needs to be a medical renaissance in the country to provide best possible patient care to achieve the highest international standards leading to great boom for Indian economy. The departments which are most often visited are Dental, Eye, ENT, Cardiac Surgery, Orthopaedics, Plastic & Cosmetic surgery, Urology and even for IVF treatments. All these facilities are provided at a cost much less as compared to the medically developed world. A heart surgery which costs USD 30,000 in USA, costs as low as USD 7,000 in India. Same is true in the other fields, diagnostics and aftercare.

Has this lead to healthy or unhealthy competition? Is the recognition & identification of New Delhi Metallo β-lactamase-1(NDM-1), given wide publicity & prefixed with word New Delhi any indication in this context ?

A new superbug spreading from Southeast Asia has been detected in a Swedish patient who underwent medical treatment in this region. The so-called NDM-1 gene was identified in Cardiff University last year in *Klebsiella pneumoniae* and *Escherichia coli* isolates. In an article in Lancet "Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study" researchers have indicated that this bug with a new type of carbapenem resistance gene bla_{NDM-1} has originated either from India or Pakistan. NDM-1 shares very little identity with other MBLs, with the most similar MBLs being VIM-1/VIM-2, with which it has only 32.4% identity.[1] This bug has also been identified by researchers from USA, UK, Australia & Canada. Yong et al reported on the genetic and biochemical characterization of a new subgroup of MBL, designated NDM-1.[2] Many researchers and scientists in India have objected to the terminology used for labeling this gene as New Delhi Metallo Beta lactamase 1 gene because no conclusive scientific evidence is available to link this gene to New Delhi. Speculations, that this gene is prevalent in Indian hospitals may adversely affect medical tourism to India. There is no doubt that this organism whatever be its name should be contained and eliminated. Simple hospital control policies like handwashing and standard precautions by healthcare workers are the best way to prevent spread of this bug. Whether the name New Delhi Metallo Beta lactamase-1 is justified is open to speculations.

The growing increase in the rates of antibiotic resistance is a major cause for concern in both nonfermenting bacilli and isolates of the *Enterobacteriaceae* family. β-Lactams have been the mainstay of treatment for serious infections, and the most active of these are the carbapenems, which are advocated for use for the treatment of infections caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae,* particularly *Escherichia coli* and *Klebsiella pneumoniae*.[3] Based on molecular studies, carbapenem hydrolyzing enzymes are classified into four groups A, B, C and D. Metallo β-lactamase (MBL) enzymes belong to Ambler molecular class B and are characterized by the ability to hydrolyze carbapenems and by their resistance to the commercially available β-lactamase inhibitors but susceptibility to inhibition by metal ion chelators.[4] The first metallo β-lactamases for which an amino acid sequence was determined was the BCII metallo β-lactamase from *Bacillus cereus*, the prototypical metallo β-lactamase for many years.[5] There has been a dramatic increase in the spread of these metalloenzymes. The most common metallo β-lactamase families include the VIM, IMP, GIM, and SIM enzymes, which are located within a variety of integron structures.[4]

Carbapenems are the agents of last resort against many multi drug resistant Gram negative bacteria. Carbapenem resistance and carbapenemase production conferred by bla_{NDM-1} is detected reliably with phenotypic testing methods currently recommended by the Clinical and Laboratory Standards Institute, including disk diffusion test and the modified Hodge test.

Further characterization and identification of the enzyme can be done only by molecular methods.[6]

In a recent study, Carbapenemase production amongst the 24 carbapenem resistant *Enterobacteriaceae* isolates was confirmed by Modified Hodge test and presence of NDM-1 gene was detected using a single target PCR in which 475bp product was amplified by the NDM primers and visualized on 3% agarose gel. NDM PCR was positive for 22 of 24 isolates.[7]

During January–June 2010, three *Enterobacteriaceae* isolates carrying NDM-1 were identified from three U.S. states at the CDC antimicrobial susceptibility laboratory. This is the first report of NDM-1 in the United States, and the first report of metallo-beta-lactamase carriage among *Enterobacteriaceae* in the United States. These isolates, which include an *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* carry bla_{NDM-1}, which confers resistance to all beta-lactam agents except aztreonam (a monobactam antimicrobial).[8]

The mobile genes on plasmids which readily spread through bacterial populations are mainly responsible increasing resistance of Gram negative bacteria. *Enterobacteriaceae* isolates were studied from two major centres in India—Chennai (south India), Haryana (north India)—and those referred to the UK's national reference laboratory. Antibiotic susceptibilities were assessed, and the presence of the carbapenem resistance gene bla_{NDM-1} was established by PCR. Isolates were typed by pulsed-field gel electrophoresis of XbaI-restricted genomic DNA. NDM-1 was mostly found among *Escherichia coli* and *Klebsiella pneumoniae*, which were highly resistant to all antibiotics except tigecycline and colistin.[1]

Carbapenems are the only antibiotics reliably active against many otherwise multi-resistant Gram-negative bacteria, particularly those with extended-spectrum beta-lactamases (ESBLs). The growing emergence and diversity of carbapenemase producing strains is therefore a major concern. Most isolates with NDM-1 enzyme are resistant to all standard intravenous antibiotics for treatment of severe infections. Polymyxin is usually active in vitro (though not vs. *M. morganii,* an intrinsically resistant species) but of uncertain clinical efficacy, especially in pneumonia, owing to poor lung penetration. Tigecycline is often active in vitro, but has low serum levels, and is of unproven efficacy in severe infections.

Carbapenems are widely used in India owing to prevalent cephalosporin resistance, and have exerted selection pressure. The non existence of antibiotic policies and guidelines is a major cause of emergence and spread of multidrug resistance.

Current CDC infection control guidance for carbapenem-resistant *Enterobacteriaceae* also is appropriate for NDM-1 producing isolates. This includes recognizing carbapenem-resistant *Enterobacteriaceae* when cultured from clinical specimens, placing patients colonized or infected with these isolates in contact precautions.[9]

Anaesthesiologists & Microbiologists have a very important role in the prevention of spread of these multiresistant pathogens. They should actively participate in the clinical decision making with regard to the treatment of infections. The hospitals should make strict antibiotic policies and take all preventive measures to stop the spread of infections whether they are by New Delhi Metallo Beta lactamase-1 or any other bacteria.

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