Emerging Carbapenem Resistance in the Context of a New Metallo-β-lactamase (NDM-1)

Multidrug-resistant bacteria are an emerging problem that infection control practitioners, researchers, hospital epidemiologists and clinicians are struggling to overcome. In the battle between bacteria and mankind, bacteria are constantly evolving newer mechanisms of resistance, which makes the latest group of antibiotics ineffective. The strategy to win this battle would be to use a holistic approach of awareness, surveillance, research, implementation of appropriate policies and the realization that antibiotics may not be the only answer to bacterial resistance.

Carbapenems, till recently, were the last resort for the treatment of severe infections. However, the emergence of carbapenem resistance in *Enterobacteriaceae* worldwide has further limited the treatment options available.[1,2] Carbapenem resistance in *Enterobacteriaceae* can occur due to modifications of outer membrane permeability of these bacteria, along with production of extended spectrum beta-lactamases (ESBLs) or over-expression of AmpC type β-lactamases. This mechanism of permeability change and expression of ESBL/AmpC is generally weakly active against carbapenems. The other, more important, mechanism of resistance is production of carbapenemases. Carbapenemases are a family of β-lactamases with a spectrum of activity unrivalled by other β-lactam-hydrolysing enzymes.[2] Acquired carbapenemases can either be metallo-β-lactamases (MBLs) such as VIM and IMP, or non-metallo-β-lactamases such as IMI/NMC, SME, KPC or OXA. Both groups of enzymes hydrolyse carbapenems well. The major concern is the carbapenemases as they are present in mobile genetic elements and can be easily disseminated.

Recently, a new MBL, designated New Delhi metallo-β-lactamase-1 (NDM-1) has been detected in *Escherichia coli* and *Klebsiella pneumoniae* from various parts of the world, both developing and developed nations—UK, India, Pakistan and Bangladesh.[3,4] This new member to the already proliferating group of carbapenemases has caused added concern as infections due to such organisms are reported to be virtually impossible to treat. The concern is reasonable but the expression of that concern is not.

The article by Kumarasamy *et al*. has triggered a reaction all over India.[4] There are two aspects of this: first, the presence of this gene in *Enterobacteriaceae* in India, and secondly the naming of this enzyme as New Delhi metallo-β-lactamase (NDM-1) and connecting it to medical tourism. These two aspects need to be examined separately.

The study by Kumarasamy *et al.* shows isolation of NDM-1 harbouring isolates from 9 locations in India, 8 cities in Pakistan and Dhaka, Bangladesh.[4] This indicates that the plasmid is widely distributed in the subcontinent. Our experience in a remote neonatal set up in India also demonstrates the presence of this gene. In November 2009, 4 neonates developed sepsis with carbapenem-resistant *E. coli* carrying $bla_{\text{NDM-1}}$ (the gene that codes for the enzyme NDM-1). While the emergence of this new mechanism is bad news, the good news is that simple measures such as handwashing and hand hygiene with antiseptic agents could prevent the spread of $bla_{\text{NDM-1}}$ even in susceptible neonates. Enforcement of cleaning hands with chemical disinfectants apart from routine handwashing with soap and water controlled the spread of the infection. In the following 10 months, we closely monitored the situation and no more neonates with septicaemia due to $bla_{\text{NDM-1}}$ have been detected.

The other aspect is about the nomenclature of the enzyme. The naming of the enzyme has become a bigger controversy, particularly because the earlier authors[4] in their conclusion linked this to avoiding medical treatment in India. This implication of NDM-1 and avoiding medical tourism is not appropriate. Just because this enzyme was found in a patient who had travelled to India does not necessarily mean that the NDM-1 gene originated in India. Extensive epidemiological investigations are needed to establish that it originated in India. Nevertheless, the naming of this enzyme would not have been objectionable if it had not been linked aggressively with medical tourism. It should be noted that carbapenem resistance due to other enzymes, also on mobile genetic elements, such as the KPC (*Klebsiella pneumoniae* carbapenemase)

has been reported from many parts of the world.[1] The National (UK) Resistance Alert of the Health Protection Report specifically mentioning $bla_{\text{NDM-1,}}$ issued on 3 July 2009, mentions the importation of carbapenemase (other than NDM-1) carrying organisms into UK from a number of sites in the Eastern Mediterranean.[5]

One has to accept that prescription policies, over-the-counter availability of drugs, use of antibiotics in animal fodder and infection control policies in India have compounded the problem of antibiotic resistance. However, antibiotic resistance is a global problem and numerous articles in reputed journals have documented this fact.[6–8] The essentials of better control of antibiotic resistance are known—enhanced surveillance, reduction in the consumption of antibiotics and improved hygiene. It is thus important to know the breadth of this problem in India so that corrective measures can be taken. Surveillance data even at the local level would help doctors choose appropriate antibiotics. To reduce antibiotic consumption what is needed is education of doctors to change their prescription policies and measures to improve public awareness on the risks and benefits of antibiotic use.[7,9] Improving hygiene can also have a remarkable impact on decreasing resistance in bacteria. Adherence to protocols in hospitals and continuous staff training can bring down resistance rates.

While the reaction in India to NDM-1 is understandable, this should not deter microbiologists, infection control practitioners and clinicians from conducting research and publishing their work, as only research can show the path ahead. Our experience has shown that a simple meticulous handwash could go a long way in treating this problem even in susceptible neonates. The reduction in the chasm between what we know and what we do about it will go a long way towards solving this problem.

REFERENCES

1 Woodford N, Tierno PM Jr, Young K, Tysall L, Palepou MF, Ward E, *et al.* Outbreak of *Klebsiella pneumoniae* producing a new carbapenem-hydrolyzing class A β-lactamase, KPC-3, in a New York Medical Center. *Antimicrob Agents Chemother* 2004;**48:**4793–9.

2 Queenan AM, Bush K. Carbapenemases: The versatile beta-lactamases. *Clin Microbiol Rev* 2007;**20:**440–58.

3 Yong D, Toleman MA, Giske CG, Cho HS, Sundman K, Lee K, *et al.* Characterization of a new metallo-beta-lactamase gene, bla (NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother* 2009;**53:**5046–54.

4 Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, *et al.* Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. *Lancet Infect Dis* 2010;**10:**597–602.

5 HPA. *Health protection report*. London:Health Protection Agency; 2009. Available at *http://www.hpa.org.uk/hpr/archives/2009/Volume 3 Number 26* (accessed on 15 September 2010).

6 Pfeifer Y, Cullik A, Witte W. Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. *Int J Med Microbiol* 2010;**300:**371–9.

7 Högberg LD, Heddini A, Cars O. The global need for effective antibiotics: Challenges and recent advances. *Trends Pharmacol Sci* 2010; doi:10.1016/j.tips.2010.08.002

8 Kollef MH. Bench-to-bedside review: Antimicrobial utilization strategies aimed at preventing the emergence of bacterial resistance in the intensive care unit. *Critical Care* 2005;**9:**459–64.

9 Huovinen P, Cars O. Control of antimicrobial resistance: Time for action. *BMJ* 1998;**317:**613–14.

SULAGNA BASU
Division of Bacteriology
National Institute of Cholera and Enteric Diseases
supabasu@yahoo.co.in

ARUN K. SINGH
Department of Neonatology
Institute of Postgraduate Medical Education and Research and S.S.K.M. Hospital

G. BALAKRISH NAIR
Division of Bacteriology
National Institute of Cholera and Enteric Diseases
P33, CIT Road, Scheme XM
Beliaghata
Kolkata
West Bengal