

## Review Article

### ANTIBIOTIC RESISTANCE; CONTRIBUTING FACTORS

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The spectre of widespread antimicrobial resistance in a world without effective antibiotics against common and banal or rare and exotic infections is looming large on the horizon, raising the possibility of patients dying from otherwise easily treatable infections. The World Health Organization is devoting the next World Health Day on 7 April 2011 to raise awareness around the issue.<sup>(1)</sup>

Microbial antibiotic resistance is a common and menacing problem of today's medical practice. There are many aspects of this problem. Because of the irrational and indiscriminate use of antibiotics in our hospitals and in our general practices, strains of bacteria are emerging which are resistant to one or more antibiotics. The number of unqualified medical practitioners (so called quacks) in any society is a big contributor of antibiotic misuse. This species is to be very commonly found in our subcontinent. Add to this scenario, over the counter sale of antibiotics to patients without a prescription. We have often heard stories of patients taking antibiotics {like septran (Sulphamethoxazole, Trimethoprim)} for headaches or body aches or for other minor complaints which have not even the remotest connection to its prescribed indications.

There is very little information available on the contamination of our water supply systems and river waters with the antibiotics, which are being inappropriately used in the poultry industry and in the cattle and dairy animals. "A full forty percent, almost half of the antibiotics used in the United States do not go to treat human disease but are frivolously given to cattle for the purpose of

fattening them rapidly and in the process fattening the profits of industrialized agribusiness".<sup>(2)</sup>

Indiscriminate use of antibiotics in food animals, in the USA is a known source of development of resistant strains in the environment, that ultimately infect the humans. In 2000, the US Food and Drug Administration (FDA) recommended to stop fluoroquinolone use in poultry production, because enough evidence was shown about emergence of fluoroquinolone resistant campylobacter strains in humans. It took five years for the the executive to effect this decision.

In 2001, the Union of Concerned Scientists estimated that greater than 70% of the antibiotics used in the US are given to food animals (e.g. chickens, pigs and cattle) in the absence of disease.<sup>(3)</sup>

The practice of antibiotic misuse is going on over the years; in fact this is so since the antibiotic era began. There is some justification in the routine use of antibiotics in some situations e.g. the use of oral penicillin or other narrow spectrum antibiotics against gram positive streptococcal infection of the upper respiratory tract in the vulnerable age group to prevent rheumatic fever. By this strategy we have been able to curtail the burden of rheumatic heart disease in our society. But the routine use of multiple antibiotics in fever or non fever conditions, or their use in almost all the operated patients in our country is a dangerous trend. This is likely to result in a dreadful scenario of infective organisms not responding to available antimicrobials.

This, in fact has already happened in our country. For example we see a lot of patients suffering from enteric fever, resistant to treatment with one or more anti typhoid drugs or in rare instances to all of them.<sup>(4)</sup>

The emergence of multidrug resistance in mycobacterium tuberculosis, a major health

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hazard plaguing many societies including our own, is another aspect of the same problem, where admittedly some of the fault lies with the non compliant patient, looking for a quick cure, while many of us, the physicians, should share the blame for incomplete treatment of many patients and not following the guidelines.

We are all aware of the menace of hospital acquired infections with Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp.<sup>(5)</sup>

Now multidrug-resistant strains of gram-negative bacteria are posing a great risk to public health. The pace of development of resistance is so fast that the numbers of effective antibiotics to treat such bacteria are getting less and less as the time passes. In fact the discovery of new antimicrobial compounds cannot match with this rising trend of antibiotic resistance.<sup>(6,7,8,9,10,11)</sup>

The bacteria develop resistance through genetic change. As described by Li, X, Nikadio H the mechanisms of resistance to antimicrobials exhibited by microorganisms can be listed under four main headings.<sup>(12)</sup>

Antibiotic gets deactivated by enzymatic action of bacteria, for example  $\beta$ -lactamases destroy penicillins

1. Alteration of target site: e.g. MRSA and other penicillin-resistant bacteria. alter their Penicillin Binding Protein site.
2. Alteration of metabolic pathway.
3. Reduction of the drug accumulation; by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface.

The resistant genes in bacteria develop as a result of natural selection resulting from the evolutionary stress of exposure to antibiotics. Transfer of genes between bacteria occurs in a horizontal fashion by conjugation, transduction, or transformation. In many bacteria antibiotic resistance genes reside on plasmids which facilitates their transfer.

Mobile genes on plasmids, spreading through bacterial populations, are the main source of increase in antibiotic resistance of Gram-negative bacteria. Improvement in methods of plasmid typing are increasing our insight into the mechanisms of transfer of these genes and guiding us on their worldwide spread.<sup>(13,14)</sup>

The increase of air travel and the rising trend of population migration are causing transport of resistance genes in bacterial plasmids and clones across the countries and continents. The spread of microbial resistance into the normal commensals in the intestines can turn them into a source of endogenous infections. Moreover they could transfer the resistance to other strains by plasmid transfer. All this has a very sinister significance when we consider that the resistance patterns could lead to the development of strains which are resistant to all the available antibiotics.

This in fact has been shown to have occurred in the subcontinent of India and Pakistan as reported recently in the September 2010 issue of *Lancet Infect Dis.*, by Kumarasamy KK et al.<sup>(15)</sup>

The gene, CTX-M-15 extended-spectrum  $\beta$ -lactamase (ESBL) encoded by *bla*CTX-M-15 was first reported in India in the mid-1990s<sup>(16,17)</sup> This ESBLs in Enterobacteriaceae is a common and serious problem in India, according to surveys. This kind of resistance pattern requires use of reserved antibiotics such as carbapenems.<sup>(18,19)</sup>

As a result selection pressure for carbapenem resistance in Enterobacteriaceae, is emerging as a public health concern.<sup>(20)</sup>

A totally new type of carbapenem resistance gene, designated *bla*NDM-1<sup>22</sup> in a patient, colonised by *K pneumoniae* and *Escherichia coli* with *bla*NDM-1 on plasmids of varying size is described by them. They looked for molecular, biological, and epidemiological data on New Delhi metallo- $\beta$ -lactamase 1 (NDM-1) positive Enterobacteriaceae in India and Pakistan and investigated importation of the resistance gene into the UK by patients returning from the Indian subcontinent.

They say that this is a potentially a major global health problem and investigated the prevalence of NDM-1, in multidrug-resistant Enterobacteriaceae in India, Pakistan, and the UK. And warn about the possibility of spread of this gene resistant almost to all the available antibiotics in routine practice.<sup>(15)</sup>

The dooms day scenario which has been predicted by epidemiologists is already here. There is a great need for renewed thinking on the use of antibiotics in our society and formulation of guidelines with all the stake holders involved. Meanwhile, it is recommended that individual guidelines should be adopted urgently by all hospitals<sup>(21,22,23)</sup>

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