

## ANTIBIOTIC RESISTANCE: A FRIGHTENING HEALTH DILEMMA

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The discovery of antibiotics, being the wonderful amiable pillars of chemotherapy, was a revolutionized turning point in human history. With the discovery of antibiotic drug Penicillin in 1928, Sir Alexander Flemming explored the role of microbial products in counteracting the pathogenic effects of microorganisms. Before 1940, antibiotics were magical drugs used as growth promoters, during the processing, storage and transportation of food products to check secondary contaminations and for the treatment of various bacterial ailments (Byarugaba, 2004). However, very frequent, inappropriate and irrational use of antibiotics against various microorganisms had a continuous survival pressure as a warning to their life and this pressure forced them to express various resistance genes in equilibrium with environment to support the rise of antibiotic resistance to counteract antimicrobial approaches and to develop antibiotic resistance, indeed (Soulsby, 2005; Zhang *et al.*, 2006).

Continued emergence of Multidrug Resistant (MRD) strains strikes a question in our mind whether future may again be hopeless with conditions of pre-antibiotic era of untreatable infections. Emerging superbugs have evolved a smarter approach of antibiotic resistance as virulence factor to shore up the activity of pathogens (Tiwari *et al.*, 2013b). "Antibiotic resistance" can be defined as "property of bacteria that blocks the inhibitory effects of antibiotics to which it was previously sensitive, leading to survival despite exposure to antimicrobials". When a bacterium harbors many resistance genes together, then it is called Multidrug Resistant (MDR), Extremely Drug-Resistant (XDR) and Totally Drug Resistant (TDR) strains. In the present scenario of globalization, resistant microorganisms fail to respond to the prescribed treatment; infectious diseases become uncontrollable; financial burden is enhanced; advanced therapeutic

approaches of organ transplantation, cancer chemotherapy and major surgery are jeopardized and ultimately resistant organisms are spreading to distant countries and continents around the globe (Witte, 2004; Hawkey and Jones, 2009).

Multiple antibiotic resistant strains of important enteric pathogens viz., *Escherichia coli*; *Salmonella* and *Shigella*; *Klebsiella*; *Vibrio cholerae* have increased the global worry (Von Baum and Marre, 2005). Some MDR organisms are Methicillin-Resistant *Staphylococcus Aureus* (MRSA), community-acquired CA-MRSA, Vancomycin-Resistant Enterococci (VRE), *Klebsiella pneumoniae* Carbapenemase (KPC) producing Gram-negatives, Extended-Spectrum  $\beta$ -Lactamase (ESBLs) producing Gram-negative bacteria, Multidrug resistant *S. enteritica* Serovar Typhimurium DT 104 (ACSSuT-phenotype), Imipenem-resistant or MDR Organisms *Acinetobacter baumannii*, *Acinetobacter baylyi*, *Pseudomonas aeruginosa*, *Bacteroides spp.*, Clindamycin-resistant *Clostridium difficile*, Streptomycin-resistant *Thermus thermophilus*, *E. coli* resistant to multiple fluoroquinolone, *Mycobacterium tuberculosis* revealing resistance to isoniazid, rifampin, Glycopeptide Intermediate *Staph. Aureus* (GISA) or Vancomycin-Intermediate *Staphylococcus Aureus* (VISA) resistant to penicillin, methicillin, tetracycline and erythromycin drugs and multiple antifungal resistant *Scedosporium prolificans* infections (Trakulsomboon *et al.*, 2001; Falagas and Karveli, 2006; Iseman, 2007).

New defense strategy of tiny superbugs involve molecular basis of antibiotic resistance which may be intrinsic or acquired. The antibiotic resistance disseminate in the nature either by clonal spread of resistant lineages or by horizontal gene transfer by conjugation, transduction and transformation. Mutation in the target, post-transcriptional/post-translational

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modification of the drug target, Reduced uptake and active efflux of the drug, chromosomally derived multidrug resistance, R-factor, expression or suppression of genes *in vivo* that may be different from the condition *in vitro*, gene deletion such as deletion of Penicillin Binding Protein gene encoding (PBP 3) in case of *Burkholderia pseudomallei* develop resistance against ceftazidime, the stress to which bacteria are exposed both within the host and also in the environment, results in development of adoptive mechanism like development of antibiotic resistance and formation of biofilms for their survival (Cirz *et al.*, 2005). Antibiotic producing microorganisms harbor r-genes and R-factors in plasmids to confer their own protection from inhibitory or lethal actions of secondary metabolites produced from them naturally. Mobile genetic elements such as transposons, prophages, integrons, resistance islands (R factor), self replicating plasmids all carry resistance genes. Plasmid-mediated quinolone resistance is emerging globally as a multifaceted threat. Integrons are genetic elements associated with the resistance (r) genes related with transferable plasmid-mediated resistance. OXA beta-lactamase genes responsible for resistance against Beta lactam antibiotics are present on plasmids. R-plasmid pTP10 of the *Corynebacterium xerosis* carries resistance genes for tetracycline, erythromycin, kanamycin and chloramphenicol (Hall, 1997). Conjugative plasmids are part of enterobacteria such as Plasmid F of *Escherichia coli* K-12, R-factor NR1 in *Proteus mirabilis* and other in *Salmonella*, *Shigella*, *Klebsiella*, *Proteus* and *Escherichia*.

As per World Health Organization (WHO), excessive and unnecessary use of antibiotics lead to a serious public health implications with negative impacts due to presence of harmful residues in meat, milk, eggs and raw animal food (Mathew *et al.*, 2007; WHO, 2013). Teeth staining due to excessive tetracycline residues and high concentrations of sulfonamide and penicillin residues in food items causing severe anaphylactic and hypersensitivity reaction in consumers are good examples. Antibiotic susceptibility tests help in determining the inhibitory activity of antibacterial agent and there are methods to detect antibiotic residues viz; Gas Chromatography (GC), High-Performance Liquid Chromatography (HPLC) with UV, Mass Spectrometry (MS) and nano quantity analyte detectors, microfluidic and electrochemical methods, European Union four-plate test (EU4pt), Frontier Post Test (FPT), microbiological methods as *Sarcina lutea* kidney test followed by *Bacillus subtilis* BGA test, Enzyme Linked Immunesorbent Assay (ELISA) and Fluorescence

Immunoassays (FIA), molecular beacon based Polymerase Chain Reaction (PCR) and DNA chips for detection of Methicillin Resistant *Staph. Aureus* (MRSA) and liquid culture systems and molecular line probe assays for detection of drug-resistant tuberculosis. The maximum residual limit of antibiotic varies from country to country and with the antibiotics used (Fluit *et al.*, 2001; Stead *et al.*, 2004; Pikkemaat, 2009).

Being an alarming public health threat worldwide antibiotic resistance demands holistic approach and sound strategies by implementation of affordable and cost-effective sustainable control programs to check this precarious problem. WHO has recommended six-point policy package for governments and regulatory bodies to halt the problem of antibiotic resistance including development of a national plan for strengthening the surveillance and laboratory capacity to promote rational use of medicines and encourage innovation of new therapeutic tools. Surveillance systems viz. National Healthcare Safety Network (NHSN) with National Antimicrobial Resistance Monitoring System (NARMS), National Tuberculosis Surveillance System (NTSS) and United States Department of Agriculture (USDA) are playing an active role in restricting antibiotic resistance and analysis of Multidrug-Resistant Organisms (MDROs). To overcome with the hurdles of microbial resistance various alternative emerging novel therapies (Dhama *et al.*, 2013) include use of lytic bacteriophages (Ghannad and Mohammadi, 2012), cytokine therapy, therapeutic intervention of virophages and mycophages, chicken egg Yolk antibodies (IgY), probiotics, ethno-veterinary and herbal medicines (Mahima *et al.*, 2012; Tiwari *et al.*, 2013a) and panchgavya therapy are opening new avenues to fight against these superbugs.

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