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Antibiotic Resistance: An Emerging Global Headache

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1. Introduction

The discovery of antibiotics was one of the greatest achievements of the twentieth century. The subsequent introduction of sulphonamides, penicillin and streptomycin, broad spectrum bacteriostatic antibiotics, bactericidal antibiotics, synthetic chemicals and highly specific narrow spectrum antibiotics to clinical medicine transformed the treatment of bacterial diseases (Baldry, 1976). However, due to the excessive and inappropriate use of antibiotics there has been a gradual emergence of populations of antibiotic –resistant bacteria, which pose a global public health problem (Komolafe, 2003).

According to the WHO, a resistant microbe is one which is not killed by an antimicrobial agent after a standard course of treatment (WHO, 1998). Antibiotic resistance is acquired by a natural selection process. Antibiotic use to combat infection, forces bacteria to either adapt or die irrespective of the dosage or time span. The surviving bacteria carry the drug resistance gene, which can then be transferred either within the species/genus or to other unrelated species (Wise, 1998). Clinical resistance is a complex phenomenon and its manifestation is dependent on the type of bacterium, the site of infection, distribution of antibiotic in the body, concentration of the antibiotic at the site of infection and the immune status of the patient (Hawkey, 1998).

Antibiotic resistance is a global problem. While several pathogenic bacteria are resistant to first line broad spectrum antibiotics, new resistant strains have resulted from the introduction of new drugs (Kunin, 1993, Sack *et al*, 1997, Rahal *et* al, 1997, Hoge, 1998). Penicillin resistant pneumococci initially isolated in Australia and Papua New Guinea is now distributed worldwide (Hansman *et al,* 1974, Hart and Kariuki, 1998). Similarly, multi-drug resistant *Salmonella typhi* was first reported in 1987 and has now been isolated throughout the Indian sub-continent, south-east Asia and sub-Saharan Africa. (Mirza *et al,* 1996) Komolafe *et al* (2003) demonstrated a general broad-spectrum resistance to panels of antibiotics in 20% of the bacterial isolates of burns patients. Multi –drug resistant tuberculosis poses the greatest threat to public health in the new millennium (Kraig, 1998).

2. Molecular epidemiology of resistance genes

Antibiotic resistance in bacteria may be intrinsic or acquired. Intrinsic resistance mechanisms are naturally occurring traits due to the genetic constitution of the organism.

These inherited properties of a particular species are due to lack of either the antimicrobial target site or accessibility to the target site (Schwarz *et al,* 1995). For example, obligate anaerobes are resistant to aminoglycosides as they lack the electron transport system essential for their uptake (Rasmussen, 1997). Gram –negative organisms are resistant to macrolides and certain ß-lactam antibiotics as the drugs are too hydrophobic to traverse the outer bacterial membrane (Nikaido, 1989). Acquired resistance is a trait that is observed when a bacterium previously sensitive to an antibiotic, displays resistance either by mutation or acquisition of DNA or a combination of the two (Tomasz and Munaz, 1995). The methods of acquiring antibiotic resistance are as follows:

- **Spontaneous mutations** – Spontaneous mutations or growth dependent mutations, that occur due to replication errors or incorrect repair of damaged DNA in actively dividing cells may be responsible for generating antibiotic resistance (Krasovec and Jerman, 2003). Point mutations that not only produce antibiotic resistance, but also permit growth are attributed to antibiotic resistance (Woodford and Ellington, 2007). For example, the quinolone resistance phenotype in *Escherichia coli* is due to mutations in seven positions in the *gyrA* gene and three positions in the *parC* gene (Hooper, 1999).
  As a bacterial cell has several targets, access and protection pathways for antibiotics, mutations in a variety of genes can result in antibiotic resistance. Studies showed that mutations in the genes encoding the targets of rifamicins and fluoroquinolones, i.e. RpoB and DNA-topoisomerases respectively, results in resistance to the compounds (Martinez and Baquero, 2000; Ruiz, 2003). Adewoye *et al* (2002) reported that mutation in *mexR,* in *P. aeruginosa* resulted in upregulation of the *mexA-mexB-oprM* operon, which was associated with resistance to ß-lactams, fluoroquinolones, tetracyclines, chloramphenicol and macrolides. Expression of antibiotic uptake and efflux systems may be modified by mutations in the regulatory gene sequence or their promoter region (Depardieu *et al*., 2007; Piddock, 2006). Mutations in the *E. coli* mar gene results in up regulation of AcrAB, involved in the efflux of ß-lactams, fluoroquinolones, tetracyclines, chloramphenicol from the cell (Barbosa and Levy, 2000).
- **Hypermutation** – In the last few years, studies have focussed on the association between hypermutation and antibiotic resistance. In the presence of prolonged, non-lethal antibiotic selective pressure, a small population of bacteria enters a brief state of high mutation rate. When a cell in this 'hyper mutable' state acquires a mutation that relieves the selective pressure, it grows, reproduces and exits the state of high mutation rate. While the trigger to enter the hyper mutable state is unclear, it ahs been suggested that it is dependent on a special SOS –inducible mutator DNA polymerase (pol) IV (Krosovec and Jerman, 2003). Hypermutators have been found in populations of *E. coli, Salmonella enterica, Neisseria meningitidis, Haemophilus influenzae, Staphylococcus aureus, Helicobacter pylori, Streptococcus pneumoniae, P. aeruginosa* with frequencies ranging from 0.1 to above 60% (Denamur *et al*., 2002; LeClerc *et al*., 1996). It has been observed that the hypermutators isolated from the laboratory as well as from nature have a defective mismatch repair system (MMR) due to inactivation of the *mutS* or *mutL* genes (Oliver *et al*, 2002). The MMR system eliminates biosynthetic errors in DNA replication, maintains structural integrity of the chromosome and prevents recombination between non-identical DNA sequences (Rayssiguier *et al*., 1989) Studies have shown that the hypermutators play a significant role in the evolution of antibiotic resistance and may also be responsible for the multiresistant phenotype (Martinez and Baquero, 2000; Giraud *et al*., 2002; Chopra *et al*., 2003; Blazquez, 2003, Macia *et al*., 2005).

- **Adaptive mutagenesis** – Recent studies have demonstrated that in addition to spontaneous mutations, mutations occur in non-dividing or slowly dividing cells in the presence of non-lethal selective pressure. These mutations, known as adaptive mutations, have been associated with the evolution of antibiotic resistant mutants under natural conditions (Krasovec and Jerman, 2003; Taddei *et al.*, 1997; Bjedov *et al.*, 2003). Adaptive mutagenesis is regulated by the stress responsive error prone DNA polymerases V (*umuCD)* and IV (*dinB)* (Rosche and Foster, 2000; Sutton *et al*., 2000). Piddock and Wise (1997) demonstrated that some antibiotics like quinolones induce a SOS mutagenic response and increase the rate of emergence of resistance in *E.coli.*
- **Horizontal gene transfer** – Transfer of genetic material between bacteria, known as horizontal gene transfer is responsible fro the spread of antibiotic resistance. Resistance genes, consisting of a single or multiple mutations, may be transferred between bacteria by conjugation, transformation or transduction, and are incorporated into the recipient chromosome by recombination. These genes may also be associated with plasmids and/or transposons. Simjee and Gill (1997) demonstrated high level resistance to gentamycin and other aminoglycosides (except streptomycin) in enteroccoci. The resistance gene was found to be associated with narrow and broad host range plasmids. Due to the conjugative nature of the plasmids, spread of the resistance gene to other pathogenic bacteria is likely.
- Horizontal transfer of resistance genes is responsible for the dissemination of multiple drug resistance. Gene cassettes are the smallest mobile genetic entities that carry distinct resistance determinants for various classes of antibiotics. Integrons are DNA elements, located on the bacterial chromosome or on broad host range plasmids, with the ability to capture one or more gene cassettes within the same attachment site. Movement of the integron facilitates transfer of the cassette-associated resistance genes from one DNA replicon to another. When an integron is incorporated into a broad host range plasmid, horizontal transfer of the resistance gene may take place. A plasmid with a pre-existing resistance gene cassette can acquire additional resistance gene cassettes from donor plasmids, thereby resulting in multiresistance integrons (Rowe-Magnus and Mazel, 1999; Ploy *et al*., 2000). Over 40 gene cassettes and three distinct classes of integrons have been identified (Boucher *et al*., 2007). Dzidic and Bedekovic (2003) investigated the role of horizontal gene transfer in the emergence of multidrug resistance in hospital bacteria and demonstrated the transfer of antibiotic resistance genes between Gram-positive and Gram negative bacilli from the intestine. The fact that bacteria that have been separately evolving for upto 150 million years can exchange DNA, has strong implications with regard to the evolution of antibiotic resistance in bacterial pathogens (Dzidic *et al*., 2003; Vulic *et al*., 1997; Normark and Normark, 2002).

3. Mechanisms of resistance

The mechanisms that bacteria exhibit to protect themselves form antibiotic action can be classified into the following types. Table 1 gives an overview of representative antibiotics and their mechanisms of resistance.

- **Antibiotic inactivation** - Inactivation of antibiotic could be a result of either inhibition of activation *in vivo* or due to modification of the parent antibiotic compound, resulting in loss of activity. Loss of enzymes involved in drug activation is a relatively new

mechanism of drug resistance. Studies have demonstrated that mutations in the *nfsA* and *nfsB* genes, which encode cellular reductases that reduce members of the nitrofuran family (nitrofurantion, nitrofurazone, nitrofurazolidone, etc.), are associated with nitrofuran resistance (Kumar and Jayaraman, 1991; Zenno *et al.,* 1996; Whiteway *et al.,* 1998).

β-lactamase enzymes cleave the four membered β-lactam ring of antibiotic like penicillin and cephalosporin, thereby rendering the antibiotic inactive. The large number of β-lactamases identified have been classified based on their structure and function. (Bush *et al.,* 1995). The enzymes discovered early (the TEM-1, TEM-2 and SHV-1 β-lactamases) were capable of inactivating penicillin but not cephalosporin. However, subsequent variants with a variety of amino acid substitutions in and around their active sites were identified in many resistant organisms. These have been collectively called 'extended spectrum β-lactamases (ESBLs)' and act on later generation β-lactam antibiotics (Bradford, 2001).

While most of the ESBLs are derivatives of the early enzymes, newer families of ESBLs, like cefotaximases (CTM-X enzymes) and carbapenemases have been discovered recently (Bonnet, 2004; Walther-Ramussen, 2004; Canton and Coque, 2006, Livermore and Woodford, 2000; Nordman and Poirel, 2002; Queenan and Bush, 2007). The CTM-X genes are believed to have descended from progenitor genes present in *Klyuvera* spp. (Decousser *et al*., 2001; Poirel *et al*., 2002; Humeniuk *et al*., 2002). These ESBLs pose a significant threat as they provide resistance against a broad antibacterial spectrum (Bradford, 2001).

Enzymatic acetylation of chloramphenicol is the most common mechanism by which pathogens acquire resistance to the antibiotic (Schwarz *et al.,* 2004). Mosher *et al.* (1995) established that O-phosphorylation of chloramphenicol affords resistance in *Streptomyces venezuelae* ISP 5230.

While the resistance to aminoglycosides due to inhibition of drug uptake in Gram negative organisms is well documented, aminoglycoside inactivating enzymes have been detected in many bacteria and plasmids. The presence of multiple NH_2 and OH groups enables inactivation of aminglycosides. Inactivation occurs through acylation of NH_2 groups and either phosphorylation or adenylation of the OH groups. (Azucena and Mobashery, 2001) Doi and Arakawa (2007) reported a plasmid-mediated mechanism of aminoglycoside resistance involving methylation of 16S ribosomal RNA.

Fluroquinolones (ciprofloxacin, norfloxacin, ofloxacin) inhibit DNA replication by targeting the enzymes, DNA gyrase and topoisomerase IV. Fluoroquinolone resistance occurs either through mutations in the genes coding for the subunits of DNA gyrase (*gyrA* and *gyrB*) and topoisomeraseIV (*parC* and *parE*), drug efflux, or a combination of both mechanisms. (Levy, 1992; Nikaido, 1996; Li and Nikaido, 2004; Ruiz, 2003; Oyamada *et al.,* 2006). However, Robiscek *et al* (2006) and Park *et al* (2006) demonstrated that a gene encoding an aminoglycoside-specific acetylase could mutate further to give an enzyme which could inactivate fluoroquinolones. This is an example to show that genes encoding minor and perhaps unrecognized activities, besides the major activity, could mutate further to gain extended activity and could be selected by appropriate selection pressures.

Type A and type B streptogramins bind to the 50S ribosomal subunit and inhibit translation (Wright, 2007). Resistance to type A streptogramin has been found to be

mediated by an enzyme called VatD (virginiamycin acetyl transferase) acetylates the antibiotic (Seoane and Garcia-Lobo, 2000; Suganito and Roderick, 2002). Resistance to type B streptogramin is brought about by the product of the *vgb* gene, a C–O lyase (Mukhtar *et al*., 2001). Homologues and orthologues of the genes encoding both the enzymes have been detected in a variety of nonpathogenic bacteria, environmental bacteria and plasmids (Wright, 2007).

- **Exclusion from the internal environment** - Alterations in permeability of the outer membrane of bacteria confers antibiotic resistance. This is commonly observed in Gram negative bacteria, such as *Pseudomonas aeruginosa* and *Bacteroides fragilis*. Reports have suggested that the loss or modification of, which are non-specific protein channels spanning the outer membrane, have resulted in antibiotic resistance. (Nikaido, 1989)

  Activation of efflux pump, which pump out the antibiotics that enter the cells thereby preventing intracellular accumulation, is also responsible for antibiotic resistance. (Nikaido, 1996; Li and Nikaido, 2004). The AcrAB/TolC system in *E. coli* is the best studied efflux system. The inner membrane protein, Acr B, and outer membrane protein, Tol C are linked by the periplasmic protein, Acr A. When activated, the linker protein is folds upon itself thereby, bringing the Acr B and Tol C proteins in close contact. This results in a channel from inside to the outside of the cell, through which antibiotics are pumped out. In antibiotic-sensitive cells, by the product of *acrR* gene, represses the AcrAB/TolC system. A mutation in *acrR*, causing an arg45cys change, activates expression of the system and consequent drug efflux. (Webber *et al*, 2005). Figure 1 shows the AcrAB/TolC efflux system in *E.coli.*

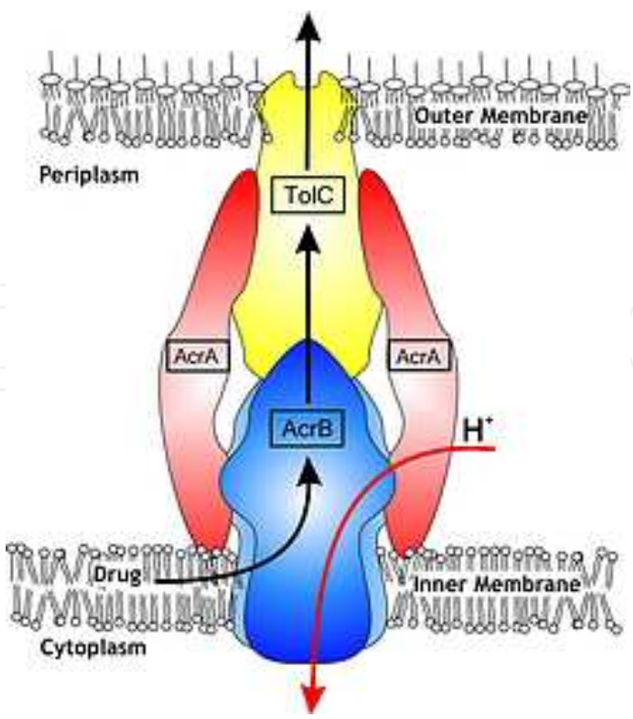

Fig. 1. Efflux system in E. coli (AcrAB/TolC) system (Pos, 2009)

Nine proton-dependent efflux pumps have been identified in *E. coli* so far. These cause the efflux of multiple antibiotics leading to multidrug resistance (Viveiros *et al.,* 2007). Ruiz (2003) demonstrated that although fluoroquinolone resistance occurred commonly due to target mutations, efflux mechanisms were also responsible for the phenomenon.

- **Target alteration** – Structural changes in the target site of the antibiotic prevent interaction of the antibiotic and its target, thus inhibiting the biological activity of the antibiotic. This is exemplified by penicillin resistance due to penicillin binding proteins (PBPs). PBPs are trans-peptidases which catalyse the crosslinking reaction between two peptides each linked to *N*-acetyl-muramic acid residues of the peptidoglycan backbone of the cell wall. Penicillin and other antibiotics which are structurally similar to the cross-linked dipeptide forma stable covalent complex with PBPs, inhibit the crosslinking reaction, resulting in weakening and lysis of the cell. Mutational changes in PBPs, which result in reduction in the affinity of PBPs to penicillin, over expression of endogenous, low-affinity PBPs encoding genes result in penicillin resistance (Zapun *et al.,* 2008).

  Vancomycin binds non-covalently to the cell-wall precursors of Gram-positive bacteria. The binding, which occurs through a set of five hydrogen bonds between the antibiotic and the *N*-acyl-D-ala–D-ala dipeptide portion of the stem pentapeptides linked to the *N*-acetyl muramic acid backbone, blocks the crosslinking transpeptidase reaction catalysed by the PBPs. As a result the cell walls are less rigid and more susceptible to lysis. In vancomycin-resistant organisms, the stem peptides terminate in D-lactate as against D-alanine in the sensitive strains. This eliminates the formation of the crucial hydrogen bond and results in a 1000-fold decrease in the affinity for vancomycin and consequent resistance to the same. This process is regulated by a two-component regulatory system involving a set of five genes (*vanR*, *vanS*, *vanH*, *vanA* and *vanX*). *Enterococci* as well as *Staphylococcus aureus* have been shown to acquire resistance to vancomycin by this mechanism, known as vancomycin evasion. (Walsh *et al*., 1996; Arthur *et al*., 1996; Courvalin, 2006)

  Ruiz (2003) reported that the eight amino acid substitutions in *gyrA* , which have been attributed to fluroquinolone resistance, are predominantly located in the quinolone resistance determining region (QRDR). Rifampicin resistance due to mutation in *rpoB*, the gene encoding the (R)-subunit of RNA polymerase has been observed in rifampicin resistant strains of Mycobacterium *tuberculosis,* laboratory strains of *E. coli,* other pathogens and non pathogens (Jin and Gross, 1988; Anbry-Damon *et al*., 1998; Padayachee and Klugman, 1999; Somoskovi *et al*., 2001).

- **Production of alternative target** – Bacteria may protect themselves from antibiotics, by production of an alternative target resistant to inhibition along with the original sensitive target. The alternative target circumvents the effect of the antibiotic and enables survival of the bacteria. In methicillin resistant *Staphylococcus aureus* (MRSA) alternative penicillin binding protein (PBP2a) is produced in addition to penicillin binding protein (PBP). As PBP2a is not inhibited by antibiotics the cell continues to synthesise peptidoglycan and has a structurally sound cell wall. It has been suggested that the evolution of vancomycin resistant enterococci may lead to transfer of genes to *S. aureus* resulting in vancomycin resistant MRSA (Michel and Gutmann, 1997).

Antibiotic Category	Examples	Mode of action	Major mechanisms of resistance
ß-lactams	Penicillin, Cephalosporin, Cetoximes, Carbapenems	Inhibition of cell wall synthesis	Cleavage by ß-lactamases, ESBLs, CTX-mases, Carbapenemases, altered PBPs
Aminoglycosides	Streptomycin, Gentamycin, Tobramycin, Amikacin	Inhibition of protein synthesis	Enzymatic modification, efflux, ribosomal mutations, 16S rRNA methylation
Quinolones	Ciprofloxacin, Ofloxacin, Norfloxacin	Inhibition of DNA	Efflux, modification, target mutations
Glycopeptides	Vancomycin	Inhibition of cell wall synthesis	Altered cell walls, efflux
Tetracyclines	Tetracycline	Inhibition of translation	Efflux
Rifamycins	Rifampicin	Inhibition of transcription	Altered ß-subunit of RNA polymerase
Streptogramins	Virginamycins, Quinupristin, Dalfoprisitin	Inhibition of cell wall synthesis	Enzymatic cleavage, modification, efflux
Oxazolidinones	Linezolid	Inhibition of formation of 70S ribosomal complex	Mutations in 23 S rRNA genes follwed by gene conversion.

Table 1. Representative antibiotics and their mechanisms of resistance. Adapted from Jayaraman, 2009

4. Conclusion

Emergence of antibiotic resistance is driven by repeated exposure of bacteria to antibiotics and access of bacteria to a large antimicrobial resistance pool. Pathogenic and non-pathogenic bacteria are becoming increasingly resistant to conventional antibiotics. While initial studies on antibiotic resistance investigated methicillin resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus spp.,* the focus has now shifted to multi drug resistant Gram –negative bacteria. The emergence of Gram negative *Enterobacteriaceae* resistant to carbapenem due to New Delhi metallo – ß –lactamase 1 (NDM-1) has been identified as a major global health problem. (Kumarasamy *et al,* 2010). However, it must be noted that resistance selected in non pathogenic or commensal bacteria could act as a reservoir of resistance genes, resulting in emergence of resistance in pathogens. There is a need to review the use and check the misuse of antibiotics and to adopt good infection control practices in order to control antibacterial resistance, since increasing antibiotic resistance has the potential to transport clinical medicine to the pre-antibiotic era.

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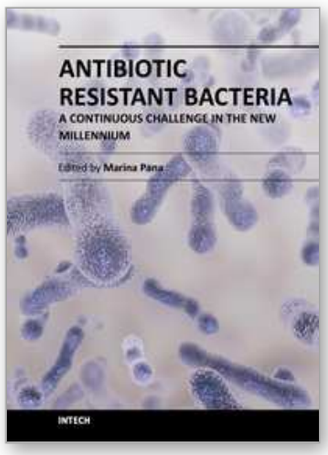

Antibiotic Resistant Bacteria - A Continuous Challenge in the New Millennium

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Antibiotic-resistant bacterial strains remain a major global threat, despite the prevention, diagnosis and antibiotherapy, which have improved considerably. In this thematic issue, the scientists present their results of accomplished studies, in order to provide an updated overview of scientific information and also, to exchange views on new strategies for interventions in antibiotic-resistant bacterial strains cases and outbreaks. As a consequence, the recently developed techniques in this field will contribute to a considerable progress in medical research.

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