

## Antibiotic resistance: A growing concern

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Received: 24 August 2015 ; Accepted: 14 September 2015

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### INTRODUCTION

The patterns of epidemics appear to have shifted from infectious diseases to lifestyle diseases. In the 20<sup>th</sup> century, antibiotics provided healthcare professionals a confidence that no infectious diseases can be a serious threat to individuals or the population. Eventually, the resistant infectious diseases replaced the conventional bacteria.<sup>[1]</sup> The advent of Methicillin resistant *Staphylococcus aureus*, NDM-1E.coli, VRE, Klebsiella pneumonia, etc. better known as “Superbugs” showed extended resistance to conventional antibiotics.<sup>[2,3]</sup> In India, many people develop resistance to antibiotics. Excessive use of antibiotics leads to mutations in bacteria, which are essentially adaptations to overcome the assault of the chemotherapeutic agents. The irrational use of antibiotics is difficult to control. For example, the antibiotics used in the hospitals for treating patients are likely to enter the sewage system of hospitals which may serve as a source of resistant organisms. The indiscriminate use of antibiotics for self-medication by procuring them over the counter is another reason for antibiotic resistance leading to irrational use of antibiotics although a potential threat difficult to ban and prevent. Similarly, many antibiotics are used in sub-therapeutic doses leading to bacterial resistance.

The productivity of the R&D in the pharmaceutical field worldwide has been affected as far as anti-infective agents are

concerned. There have been no significant breakthroughs in developing new antibiotics, resulting in failure to develop a new molecular entity that is effective against major resistant bacterial strains. Advances in molecular biology and microbiology can be used to decipher the mechanism of antibiotic resistance. A majority of nosocomial infections are caused by gram-negative bacteria.<sup>[8]</sup> The most recently discovered class of antibiotics effective against the gram-negative bacteria were discovered 27 years ago in 1987.<sup>[7]</sup> Nosocomial infections caused by gram-negative bacteria like *Acinetobacter baumannii* and *Klebsiella sp.* are still being treated with old antibiotics such as Colistin.<sup>[9]</sup>

### Nature of resistance

#### A: Intrinsic and acquired resistance

Resistance in bacteria emanates via different mechanisms. Intrinsic bacterial resistance is due to the genetic makeup of the bacteria and is inherited from the parent to progeny whereas acquired resistance can be either due to acquisition of a resistant gene by horizontal transfer from resistant bacteria or via mutation. Acquired resistance can be inherited as intrinsic resistance. Both these types of resistances are stable and permanent. Adaptive resistance on the other hand is activated by environmental factors such as presence of antibiotics and is transitory in nature. It can be backslid after the environmental trigger is removed.<sup>[10]</sup>

Bacteria can employ one or more mechanisms to acquire



**Table 1: List of bacteria identified in hospitals and community with antibiotic resistance**

| Name of organism   | Resistant to (antibiotics)  | Reference |
|--|---|-----------|
| <i>Pseudomonas aeruginosa</i>  | Meropenem<br>Imipenem<br>Ceftazidime<br>Cefepime<br>Aztreonam<br>Piperacillin–Tazobactam<br>Gentamicin<br>Tobramycin<br>Ciprofloxacin | 4         |
| <i>Enterobacteriaceae</i>  | Meropenem<br>Imipenem<br>Ceftazidime<br>Cefepime<br>Aztreonam<br>Piperacillin–Tazobactam<br>Gentamicin<br>Tobramycin<br>Ciprofloxacin | 4         |
| <i>E coli</i>  | Ceftriaxone<br>Ciprofloxacin  | 5         |
| <i>Acinetobacter</i>   | Imipenem  | 5         |
| <i>Klebsiellapneumoniae</i>  | Ceftriaxone<br>Ciprofloxacin  | 5         |
| <i>Pseudomonas</i><br><i>E coli</i><br><i>Staphylococcus aureus</i><br><i>Acinetobacterbaumani/colcoaceticus</i><br><i>Klebsiella</i><br><i>Citrobacter</i><br><i>diversus/freundii</i><br><i>Proteus mirabilis</i><br><i>Streptococci</i> | Amoxycillin   | 6         |

**Table 2: List of anti-infective agents<sup>[7]</sup>**

| Anti infective Drugs | Developed by               | Year of discovery | Class              | Effective against |
|----------------------|----------------------------|-------------------|--------------------|-------------------|
| Prontosil            | Bayer                      | 1935              | Sulfonamide        | Both              |
| Benzyl Penicillin    | Merck & Co.                | 1942              | Penicillin         | Both              |
| Gramicidin S         | Merck & Co.                | 1942              | Peptide antibiotic | Both              |
| Streptomycin         | Merck & Co.                | 1943              | Aminoglycoside     | Both              |
| Chlortetracycline    | Lederle Laboratories       | 1944              | Tetracycline       | Gram +ve          |
| Chloramphenicol      | Parke Davis & Co.          | 1949              | Amphenicol         | Gram -ve          |
| Erythromycin         | Eli Lilly & Co.            | 1952              | Macrolide          | Gram +ve          |
| Vancomycin           | Eli Lilly                  | 1955              | Glycopeptide       | Gram +ve          |
| Colistin             | Parke Davis                | 1958              | Polymixin          | Gram -ve          |
| Metronidazole        | Rhone-Poulenc laboratories | 1960              | Nitroimidazole     | Both              |
| Trimethoprim         | GSK                        | 1961              | DHFRI              | Gram -ve          |
| Cefalotin            | Eli Lilly & Co.            | 1964              | Cephalosporin      | Both              |
| Nalidixic acid       | George Lesher & Co.        | 1967              | Quinolone          | Gram -ve          |
| Clindamycin          |                            | 1967              | Lincosamide        | Both              |
| Imipenem             | Merck                      | 1985              | Carbapenem         | Gram -ve          |
| Rifaximin            | Salix Pharmaceuticals      | 1987              | Ansamycin          | Gram +ve          |
| Ciprofloxacin        |                            | 1987              | Fluoroquinolone    | Gram +ve          |
| Linezolid            | Pharmacia and Upjohn Co.   | 2000              | Oxazolidinone      | Gram +ve          |
| Telithromycin        | Hoechst Marion Roussel     | 2001              | Ketolide           | Gram +ve          |
| Telavancin           | Theravance                 | 2009              | Lipoglycopeptide   | Gram +ve          |

**Table 3: Relating mechanism of antibiotic resistance in a nutshell<sup>[10]</sup>**

| Anti-biotics  | Mechanism of resistance development |
|---|-------------------------------------|
| Biocides  | Outer membrane alteration           |
| Penicillins and Cephalosporins                          | PBP alteration                      |
| Aminoglycosides, macrolides, fluoroquinolones, biocides | Efflux of antibiotics               |
| Polymyxin   | LPS modification                    |
| Most of the anti-biotics                                | Point mutations                     |
| All anti-microbials                                     | Dysregulation of genes              |

resistance to various antibiotics. While some species of bacteria can be resistant to any one class of an antibiotic using one of the above stated mechanisms; some others might get resistant to numerous antibiotics at a time by means of multiple mechanisms from those stated in Table 3. Multi-drug resistant (MDR) bacteria is one of the most serious issues in the treatment of infectious diseases these days. Some incidences of total drug resistant (TDR) bacteria have also come to light in the last couple of years.

## B: Adaptive resistance

The concept of adaptive resistance has been around for a long time but it is the least studied of all the resistance mechanisms. Though, it might be the one contributing to majority of resistance cases. Adaptive resistance has its roots in Darwin's theory of natural selection where an organism has to struggle for its existence and has to adapt to its changing surroundings faster than other co-inhabitant organisms. Bacteria have a unique ability of adaptation and survival in adverse conditions, leading to their progressive advancement. Various factors that contribute to adaptive resistance are listed in Table 4.<sup>[10]</sup>

## The misuse and abuse of antibiotics and its impact on environment

Antibiotics should be regulated and be used under vigilance to prevent the development of resistant strains. There are guidelines regarding prescribing, dispensing and utilization of antibiotics.<sup>[11]</sup> Antibiotics are abused as growth enhancers in poultry and animal husbandry. For example, tetracycline is used as a growth promoter to improvement production. Antibiotics also enter water reservoirs through effluents from corporate and tertiary care hospitals. This has led to widespread emergence of microbial resistant strains leading to emergence of superbugs like NDM-1. Antibiotics upon getting entry into the food chain, pollute water and food and over time, bacteria adapted to them. In case of cross-resistance, bacteria adapt via multiple mechanisms

**Table 4: Factors that lead to adaptive resistance**

|                                     |
|-------------------------------------|
| Environmental factors               |
| Absence of Oxygen                   |
| Ions and ionic binding              |
| Others                              |
| Social Behaviour of the microbes    |
| Biofilm formation                   |
| Swarming motility                   |
| Presence of Antimicrobial compounds |
| Beta lactams                        |
| Aminoglycosides                     |
| Fluoroquinolones                    |
| Polymixins and other peptides       |
| Biocides                            |
| Others                              |

simultaneously to develop resistance against one or more antibiotics, having a similar mechanism of action. For example, a bacteria which becomes resistant to one of the penicillins might get resistant to other penicillins as well, without any prior exposure to any of them. Globally, APUA is an international agency involved in educating public, professionals and government agencies against the danger posed by indiscriminate use of antibiotics. APUA has been implementing several schemes and programs for creating awareness about the prudent use of antibiotics since the last 4 decades.<sup>[12]</sup>

The advent of antibiotics in the human world was nothing short of a miracle at the time when bacterial infections were taking their toll on human lives.<sup>[13]</sup> Over a period of time, bacteria developed resistance to antibiotics due to their frequent usage. A time might come similar to the period before the discovery of antibiotics due to a severe dearth of newer and more effective antibiotics.<sup>[14-15]</sup> The issue of antimicrobial resistance is one of the gravest concerns for developed and developing countries alike, in terms of increased hospital stay and mortality.<sup>[16-19]</sup>(4)(7).

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**Cite this article as:** Priyendu A, Patel I, Nagappa AN. Antibiotic resistance: A growing concern. *J Pharm Prac Community Med.* 2015;1(1):2-5.