Review Article

Antibiotic resistance: a threat and challenge to society

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Keywords: *Antibiotics, Antibiotic Resistance, Iron Chelation Therapy, Antimicrobial peptides, Antibiotic Nanoparticles*

Abstract

In the past decade there has been a phenomenal rise in the emergence of antibiotic resistant pathogens forcing global agencies like the World Health Organization to take cognisance of the issue. Antibiotic resistance and evolution of resistant pathogens untreatable by a wide class of antibiotics is a real concern for human health and well-being. The present review gives a brief history of antibiotic evolution, discusses the reasons for development of antibiotic resistance and focuses on current development in the research to counteract it.

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Date of Submission: May 31, 2014 **Date of Acceptance:** July 22, 2014 **Date of Publishing:** Aug 3, 2014

How to cite this paper:
Dhawale A, Rath A. Antibiotic Resistance: A Threat and Challenge to Society. Annals of Applied Bio-Sciences. 2014;1: R1-6

INTRODUCTION

Microbes surround the every niche of this planet. As a process of natural selection, these microbes release natural substances for inhibiting other organisms. These substances are called Antibiotics.

An historical overview of antibiotic evolution (Table 1)

Louis Pasteur unknowingly described the first antibiotic in 1877 when he observed that certain bacteria release substances that kill other bacteria. The antibiotics field was initiated when Paul Ehrlich first coined the term 'magic bullet' to designate the use of antimicrobial compounds to treat microbial infections. In 1910, Ehrlich discovered the first antibiotic drug, Salvarsan, which was used against syphilis. [1] In 1928 Alexander Fleming discovered that a mould inhibited the growth of Staphylococcal bacteria and named the substance it produced 'penicillin' (possibly Pasteur's unknown substance.[2] Finally, in 1943, the first TB drug, Streptomycin, was discovered by Selman Waksman who was also the one who coined the term 'Antibiotics'.[3] Protonsil, the first sulpha drug was discovered by the German chemist Gerhard Domagk, who received Nobel prize for Medicine in 1939. [4]

The basic characteristics of antibiotics

Currently, there are about 4000 compounds with antibiotic properties. Antibiotics are used to treat and prevent infections, and to promote growth in animals. They are derived from three sources: moulds or fungi; bacteria; or synthetic or semi-synthetic compounds. They can be used either internally or topically, and their function is to either inhibit the growth of pathogens or to kill them. Antibiotics can thus be divided into bacteriostatic drugs, which merely inhibit the growth of the pathogen, and bacteriocidal drugs, which actually kill the bacteria. However, the distinction is not absolute, and depends on the drug concentration, the bacterial species, and the phase of growth.

Antibiotic resistance (AR)

One of the foremost concerns of modern medicine is antibiotic resistance (AR). Antibiotic resistance may be defined as the phenomenon by which an antibiotic or class of antibiotics are rendered ineffective against a particular organism or group of organisms as those bacterial cells have evolved certain mechanisms to shield them from the bactericidal or bacteriostatic activity of those antimicrobial drugs.[5]

For long it was assumed that the habit of popping pills for every minor ailment was making people resistant to antibiotics. But now there is growing evidence to prove that both medical and non-medical misuse and overuse of antimicrobials is to blame. There are numerous reasons for the occurrence of AR organisms, like unprecedented and uncontrolled use of antibiotics as growth promoters in animal husbandry and aquaculture, use in agricultural products, sub-therapeutic use in poultry and pigs.[6]

Besides overuse and misuse by humans, food chain has been considered the main route for the introduction of animal and environment associated antibiotic resistant bacteria into the human gastrointestinal tract (GIT) where these genes may be transferred to pathogenic and opportunistic bacteria. [7]

Antibiotic contamination is in fact everywhere, contamination of river beds from pharma waste run-offs, use in animal husbandry, aquaculture, agriculture etc. A recent study conducted by experts from UK's Newcastle University and Indian Institute of Technology, Delhi in upper Ganga river, found that in May-June, levels of resistance genes that lead to "superbugs" were about 60 times higher than other times of the year. The time between May-June is the one when millions of pilgrims travel to Rishikesh and Haridwar. [8] Detection of resistant genes in river Ganga and reports of emergence of extremely drug resistant (XDR) strain and totally drug resistant (TDR) strain of Tuberculosis (TB) in cities like Mumbai further highlight the rapid evolution and spread of AR genes. [8,9]

The emergence of resistant pathogens untreatable by antibiotics is a major health concern. Several organizations, including World Health Organization (WHO), Centre for Disease and Prevention (CDC) and European Union (EU) have all stressed the need to control the spread of resistance. At the 2013 World Economic Forum (WEF) at Davos, WHO director general Margaret Chan warned that bacteria are becoming so resistant to common antibiotics that it could mean *'the end of modern medicine as*

Table 1. Overview of Antibiotics Evolution

Sr. no.	Year	Description
1.	Late 1800s	Germ theory of Disease- Theory linking the bacteria and microbes to the cause of various infections was accepted worldwide. As a result scientist began to search for drugs that could kill the disease causing bacteria.
2.	1890	German Doctors:- Rudolf Emmerich and Oscar Low made an effective medication-Pyocyanase from microbes.-First antibiotic to be used in hospitals, however drug didn't work well.
3.	1928	Sir Alexander Fleming observed that colonies of the bacterium *Staphylococcus aureus* could be destroyed by the mold *Penicillium notatum.* The milestone in the History of Antibiotics.
4.	1935	German chemist Gerhard Domagk discovered first sulpha drug:- Protonsil. It has broad activity against gram positive *cocci* but not *enterobacteria*. Gerhard Domagk received Nobel prize for Medicine in 1939.
5.	1942	Howard Florey and Ernst Chain invented process for manufacture of Penicillin G Procaine. Along with Fleming they received Nobel Prize for Medicine for their work on Penicillin in 1945. Penicillin was then sold as prescribed drug
6.	1943	American microbiologist Selman Waksman made drug Streptomycin He found out over twenty different antibiotics. He was rewarded by Nobel Prize for Medicine in 1952.
7.	1955	Lloyd Conover patented Tetracycline in US. It was used as broad spectrum antibiotic in US. This antibiotic was the most prescribed antibiotic at that time in US.
8.	1960-1990	Emergence of various antibiotics
9.	2003	Bacteria resistant to carbapenems were first detected in the U.K. Initially number was low until 2007 which was increased uptil by 2010. The start of the era of Multidrug resistant organisms.

we know it'. India is one of the few countries where deadliest form of tuberculosis is found.

How to meet the challenge of AR?

1. Sensitizing people about antibiotic use and misuse. The casual attitude towards antibiotic use must stop.
2. Development of globally applicable protocols for wise use of antibiotics.
3. Identification of novel organisms secreting antimicrobial compounds.
4. Understanding the mechanism and entities involved in AR so that measures can be developed to counteract them.

Strategies to counteract AR

1. Iron Chelation Therapy :

Iron is an essential cofactor for many bacterial processes. Hence iron chelators and iron competitors can be used as antibacterial agents. Use of iron chelators has been applied to *A.baumannii*. It is an important cause of nosocomial infection. It is responsible for hospital acquired pneumonia and bacteria with a high death rate. Since this bacterium has developed resistance against various antibiotics, it is an ideal model for study of AR. Deferiprone is a synthetic bidentate iron chelator that has antimicrobial activity against several bacterial species, however, this showed only modest activity

against *A. baumannii*. [10] Gallium (Ga+3) is a transition metal with a similar atomic radius and valence to iron (Fe+3), which allows it to compete with Fe3+ for binding to iron-requiring enzymes, proteins, and microbial siderophores. The antimicrobial activity of gallium was higher in serum compared to iron-rich growth media, probably due to the presence of transferrin, which sequesters free iron. This study also showed that gallium treatment resulted in lower bacterial loads in the lungs of mice infected intranasally with *A. baumannii*, indicating that gallium maintains activity *in vivo*.

2. Antimicrobial peptides

Antimicrobial peptides are small molecular weight proteins containing 12 to 50 amino acids which have antimicrobial activity against variety of bacteria, viruses and fungi. They are mostly positively charged proteins having amino acids like arginine, lysine and histidine in higher proportions and are amphipathic in nature and hence can cross the lipid bilayer of target cells and enter the aqueous intracellular environments. [11,12] They are key elements of the immune system of higher organisms. They can be used as antibacterial agents. [12] Several antibacterial peptides have been studied *in vitro* and *in vivo* against *A. baumannii*. The cecropin A–melittin hybrid peptides have demonstrated in vitro bactericidal activity against multidrug- and colistin-resistant *A. baumannii* strains and showed local efficacy in an experimental model of peritoneal sepsis caused by a pandrug resistant strain.[13,14,15] However, the peptide exhibited a short half-life after administration, limiting its systemic efficacy. Several peptides derived from frog and toad skin and their analogs have also been studied. The brevinin-2- related peptide and six cationic a-helical frog skin derived peptides showed good activity (MIC 4–128 mg/ml) against multidrug-resistant strains of *A. Baumannii* and had low haemolytic activity[16,17]. However, more studies are needed to better understand their antimicrobial activity.

3. Antimicrobial activity of nanoparticles

Nanoparticles are the particles with the size range of 1-100 nm. Antimicrobial activity of various heavy metal nanoparticles have been well documented. Recently, synergistic effect of antibiotics and nanoparticles has been studied. In one such study; antibiotic nanoparticle resulted in a 0.2–7.0 (average, 2.8) fold-area increase in antibacterial activity, which revealed that nanoparticles can be effectively used in combination with antibiotics in order to improve their efficacy against various pathogenic microbes. [18]

However despite the use of these techniques there are many resistant pathogens today like methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococcus* (VRE), and extended spectrum β-lactamase (ESBL) producing *Klebsiella pneumoniae* and *Escherichia coli* or pan-drug resistant Gram negative bacteria like *Acinetobacter baumannii* and *Pseudomonas aeruginosa which have posed a major challenge*.[19, 20]

One novel strategy that has been tried is to reconvert the antibiotic resistant microbes to wild type using Bacteriophage Therapies.

4. Bacteriophage Therapies

Bacteriophages are viruses that infect, and in some cases lyse, bacterial cells. Phage therapy, or more precisely, therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections, is one approach that has great potential as a solution to the serious worldwide problem of drug-resistant bacteria.[21] While they were administered as antibacterial agents as early as 1919, before the discovery of antibiotics, inadequate understanding of phage biology and genetics reduced the efficacy of phage therapy.[22,23,24]

Bacteriophage therapy has also been used for controlling metallo-beta-lactamase producing, multidrug resistant *Pseudomonas aeruginosa* infection in Catfish.[25]

Conjugation is the main mode of horizontal gene transfer that spreads antibiotic resistance among bacteria. It mainly takes place by the formation of sex pili between donor and recipient strain. By targeting this mode of gene transfer one can stop or reduce the spread of gene transfer.

A) By means of Filamentous Phages

Bacteriophages were first observed to inhibit the conjugation several decades ago. [26] Filamentous phages are a family of single stranded DNA phages that attach to the tip of conjugative pilus. M13 phages attach to F pilus, which retracts and brings

the phage into contact with the host cell co receptor TolA. The interaction between phage and TolA co receptor leads to transfer of the phage genome into the cell. M13 phage reduce the fitness of cells which reduces the population of F+ cells over time. M13 phage also cause pilus retraction, so the F+ cells might not be competent as donors. Phage minor coat protein g3p mediates infectivity. It has been observed that overexpression of the N-terminal domains of g3p blocks contact with the recipient cell through physical occlusion of the F pilus or TolA thus inhibiting conjugation and infection by Ff phage.[27]

B) By inhibiting the conjugative DNA Relaxase:
Relaxases are essential for conjugative transfer and act by cleaving DNA strands and forming covalent phosphotyrosine linkages. Bisphosphonates inhibit relaxase activity and conjugative DNA transfer.In in vitro studies bisphosphonates have been found to inhibit F plasmid conjugative relaxase at even nanomolar concentrations.[28]

CONCLUSION:

It is important to understand the mechanism and entities involved in AR so that newer measures can be developed to counteract it. The immediate need is to develop novel and effective strategies to prevent it from acquiring catastrophic proportions.

Acknowledgements

None

Funding

None.

Competing Interests

None declared.

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