

Review Article

Antimicrobial Resistance – an Overview

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Introduction

We may soon be facing the end of the "antibiotic era." The initial and seemingly unstoppable success of antibiotics, the fruit of human ingenuity, has been countered by an escalation of resistance mechanisms in bacteria. This crisis has been described as an "unwinnable war." The statistics compiled as a result of surveillance efforts illustrate the emergence of many genera of bacteria that are resistant to all antibiotics.

Antibiotics are compounds that are literally against life. Typically antibacterial drugs interfere with some structure or process that is essential for bacterial growth or survival without harm to the host harboring the infecting bacteria. We live in an era where antibiotic resistance has spread at an alarming rate¹⁻⁴.

What are antibiotics? Where do they come from? How do they work? How do they become resistant to bacteria? How do we find new antibiotics? Can we slow down the development of antibiotic resistant super bugs? (Super bugs are multidrug resistant bacteria, that are difficult to treat with limited drugs available) - these are the questions that arise in our minds.

Bactericidal drugs kill the organism but bacteriostatic drugs only nullify the growth. Most antibiotics in human use are natural products, elaborated by one species of microbe (bacteria or fungi). Over the past 60 - 70 years most antibiotics have been discovered by screening of soil samples for natural products that kill pathogenic bacteria, first on culture plates and then in animal infections⁵.

These include Penicillins, Cephalosporins from fungi and Streptomycin, Erythromycin, Tetracycline and Vancomycin from different strains of filamentous bacteria like Streptomyces. Semi synthetic modifications have produced second and third generation Beta-lactams of both Penicillin and Cephalosporin classes where as total synthesis has created the second generation - Erythromycin, Clarithromycin and Azithromycin. Fluroquinolones like Ciprofloxacin are purely synthetic antibacterial drugs⁵.

Antibiotics can be classified into broad spectrum and narrow spectrum antibiotics. For example,

Tetracycline, a broad spectrum antibiotic, is active against Gram positive and Gram negative bacteria, whereas Penicillin which has relatively narrow spectrum, can be used mainly against Gram positive bacteria. Other antibiotics such as Pyrazinamide have an even narrower spectrum, and can be used merely against *Mycobacterium tuberculosis*.

Targets for main classes of antibacterial drug

Antibiotics fight against bacteria by inhibiting certain vital processes of bacterial cells or metabolism. Based on these processes, we can divide antibiotics into five Major classes

- (1) inhibitors of bacterial cell wall biosynthesis, example - Penicillin and Vancomycin
- (2) inhibitors of bacterial protein synthesis, example - Amino glycosides
- (3) inhibitors of nucleic acid synthesis, such as Fluroquinolones which inhibits DNA synthesis, and Rifampicin, which inhibits RNA synthesis.
- (4) Antimetabolites such as sulfa drugs.
- (5) Antibiotics that can damage the membrane of the cell, such as Polymyxin B, Gramicidin and Daptomycin⁶.

What is antimicrobial resistance?

Antibiotic resistance occurs when an antibiotic has lost its ability to effectively control or kill bacterial growth; in other words, the bacteria are "resistant" and continue to multiply in the presence of therapeutic levels of an antibiotic. Antibiotic resistance evolves naturally via natural selection through random mutation, but it could also be engineered by applying an evolutionary stress on a population⁶.

Antimicrobial resistance is resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive. Resistant organisms (they include bacteria, fungi, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, an increasing risk of spread to others. The evolution of resistant strains is a natural phenomenon that happens when microorganisms are exposed to antimicrobial drugs,

and resistant traits can be exchanged between certain types of bacteria (Table.1). The misuse of antimicrobial medicines accelerates this natural phenomenon. Poor infection - control practices encourages the spread of antimicrobial resistance⁷.

Emergence of MRSA occurred in 1961 followed by emergence of ESBL producing gram negative bacilli in 1983. Vancomycin resistant enterococci (VRE) was reported in 1986. In 2000s emergence of carbapenem resistance was reported⁸.

Bacterial survival strategies to combat antibiotics

Wide spread use of a effective antibiotic reduces its lifespan. Clinically significant resistance appears in periods of months to years. A principal mechanism for the rapid spread of antibiotic resistance genes through bacterial populations is that such genes get collected on plasmids⁹ that are independently replicated within and passed between bacterial cells & among species. Furthermore some of these genes that reside on plasmids, may be further segregated within transposons¹⁰ that can actively cut themselves out of one DNA locale, promiscuously moving their antibiotic resistance – conferring genetic cargo. The various mechanisms of antibiotic resistance are listed below (Fig.1)

Table 1. Evolution of Resistance to antibiotics

Antibiotic	Year deployed	Resistance observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins first generation	1960s	Late 1960s
Cephalosporins second generation	1974	1980
Cephalosporins third generation	1980	1983
Quinalones	1983	1990
Carbapenem and monobactam	1984	2000s

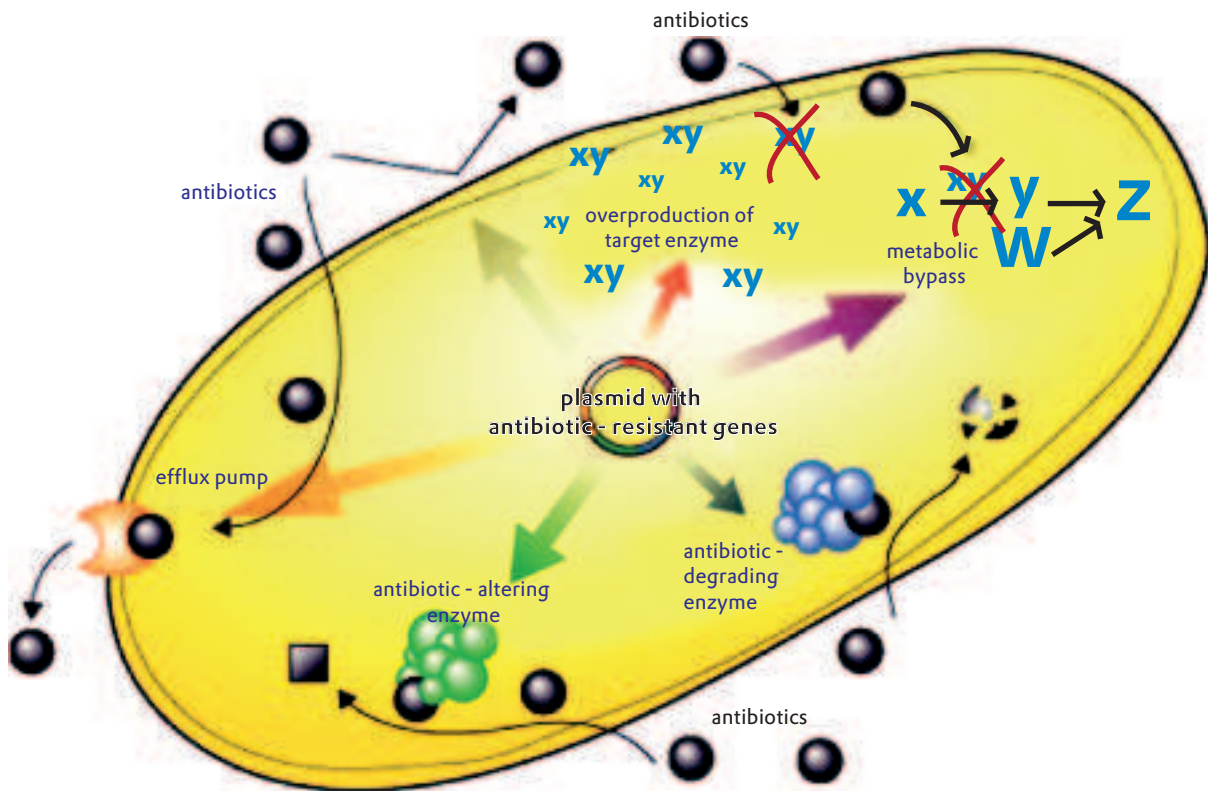


Fig 1: Mechanisms of antimicrobial resistance

Pump out the antibiotic

For antibiotics to be effective they must reach their specific bacterial targets and accumulate at concentrations that can act in some reasonable time frame. For example, the protein synthesis machinery is located in the cytoplasm, so antibacterials that inhibit protein synthesis must pass through the cell membrane. Both gram positive and gram negative bacteria that become resistant to Tetracycline's, commonly over produce related membrane proteins that act as an efflux pump for the drug^{11,12}. As schematized in Fig.1, the drug is pumped out faster than it can diffuse in, so intra bacterial concentrations are kept low and ineffectual.

Reprogram the target structure

Another resistance strategy focuses not on removal or destruction of antibiotic, but on reprogramming of the target. An example of reprogramming strategy is used by Vancomycin Resistant Enterococci to escape from Vancomycin. In Vancomycin Resistant Enterococci the *van_{HAX}* genes encodes a new path way of enzymes that reduces pyrurate to D-lactate.

Penicillin resistance can arise not only by β lactamase expression, but also by mutation of penicillin binding proteins (PBP) into new PBPs with low affinity for antibiotics. The acquisition by *Staphylococcus aureus* of the *mec_A* gene that encodes a PBP2' protein with low affinity for all β -lactam antibiotics provides the molecular basis for the Methicillin resistant *Staphylococcus aureus* (MRSA) phenotype that is now widely disseminated.

Production of Enzymes

Extended-spectrum β -lactamases (ESBLs) are a rapidly evolving group of β -lactamases which share the ability to hydrolyze third-generation Cephalosporins and Aztreonam yet are inhibited by Clavulanic acid. The presence of ESBLs by Gram negative bacilli carries tremendous clinical significance. The ESBLs are frequently plasmid encoded. Plasmids responsible for ESBL production frequently carry genes encoding resistance to other drug classes (for example, Aminoglycosides). Therefore, antibiotic options in the treatment of ESBL-producing organisms are extremely limited. Carbapenems are the treatment of choice for serious infections due to ESBL-producing organisms, yet carbapenem-resistant isolates have recently been reported⁴.

Carbapenems are β lactam antibiotics, as are Penicillins and Cephalosporins, but differ from these other classes in their exact chemical structure. Carbapenems are the sole β lactam antibiotics with proven efficacy in severe infections due to ESBL producing bacteria and our last effective defense against multi-resistant bacterial infections.

NDM-1 stands for New-Delhi metallo beta-lactamase, an enzyme capable of destroying antibiotics, even powerful carbapenems. The enzyme NDM-1 is encoded for by sections of bacterial DNA known as plasmids, which can be transferred between types of bacteria, hence more than one type of bacteria can

acquire this type of resistance. It is most often seen in *Klebsiella pneumoniae* and *E.coli*.

Most bacteria with the NDM-1 enzyme do remain susceptible to two types of antibiotics, neither of which are ideal for general use - these antibiotics are Colistin (an old and rather toxic antibiotic) and Tigecycline (a newer antibiotic than can only be used in some, not all types of infections). Otherwise bacteria with NDM are resistant to all antibiotics. A few isolates with NDM are completely resistant to antibiotics, including Colistin and Tigecycline.

Acinetobacter baumannii is a nonfermentative, gram-negative, nonmotile, oxidase-negative bacillus, whose natural reservoir still remains to be determined. Nevertheless, it is found in many health care environments and is a very effective human colonizer in the hospital. The combination of its environmental resilience and its wide range of resistance determinants renders it a successful nosocomial pathogen. As such, *A. baumannii* is emerging as a cause of numerous global outbreaks, displaying ever-increasing rates of resistance.

Acquired resistance

Several mechanisms are developed by bacteria in order to acquire resistance to antibiotics. All require either the modification of existing genetic material or acquisition of new genetic material from another source.

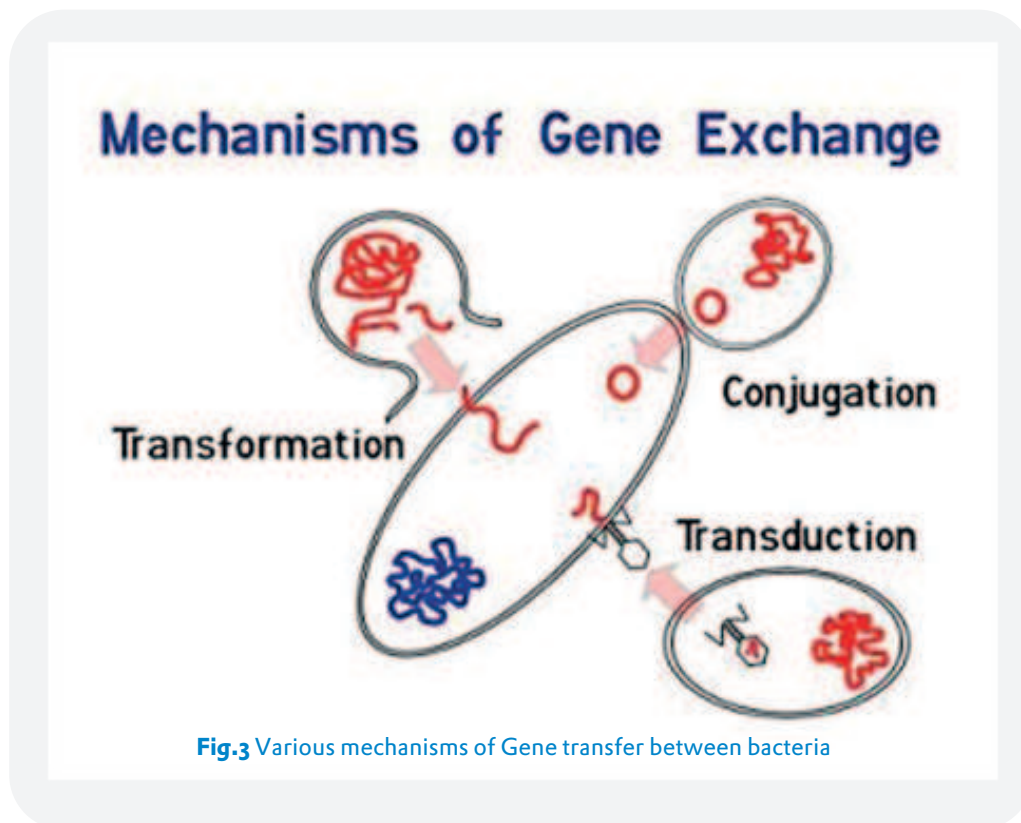
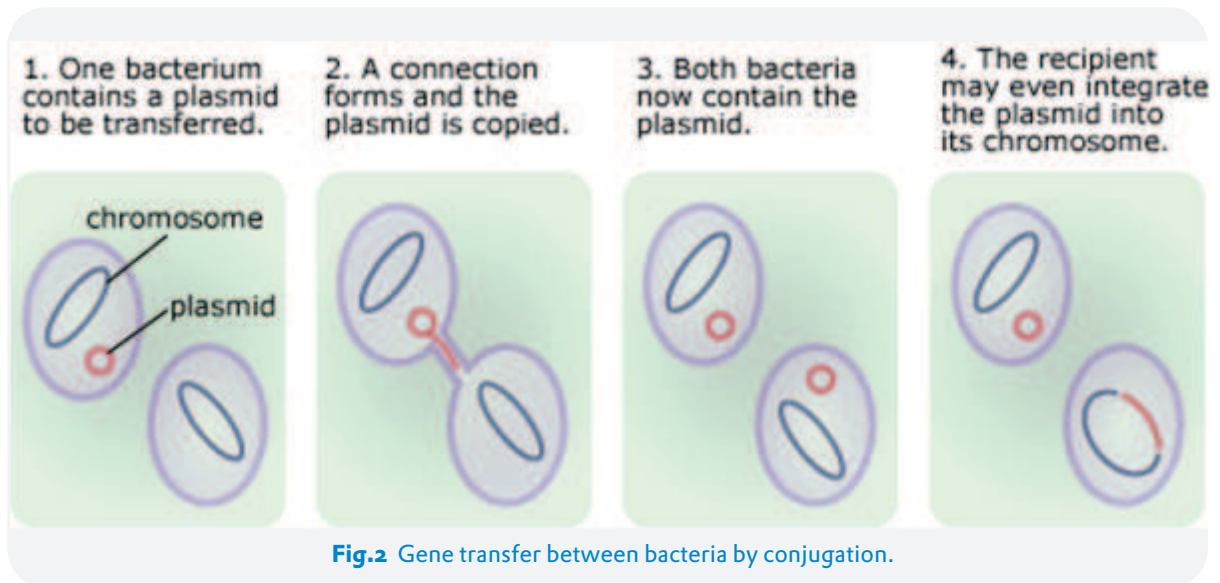
Vertical gene transfer

The spontaneous mutation frequency for antibiotic resistance is the order of about 10^{-8} – 10^{-9} . This means one in every 10^8 - 10^9 bacteria in an infection will develop resistance through the process of mutation⁷. Once the resistance genes have developed, they are transferred directly to all bacteria's progeny during DNA replication. This is known as vertical gene transfer or vertical evolution, the process is strictly a matter of Darwinian evolution driven by principles of natural selection.

Horizontal gene transfer

Another mechanism beyond spontaneous mutation is responsible for the acquisition of antibiotic resistance. Horizontal gene transfer is a process whereby genetic material contained in small packets of DNA can be transferred between individual bacteria of the same species or even between different species. There are three possible mechanisms of horizontal gene transfer. These are transduction, transformation and conjugation (Fig 2 & 3).

Conjugation occurs when there is direct cell to cell contact between two bacteria and transfer of small pieces of DNA called plasmids takes place. Transformation is a process where parts of DNA are taken up by bacteria from external environment. This DNA is normally present in the external environment due to the death and lysis of another bacterium. Transduction occurs when bacteria specific viruses (bacteriophages) transfer DNA between two closely related bacteria.



Indeed wider and more indiscriminate use of antimicrobial drugs could actually shorten the cycle time. After the advent of new mighty drugs the proper use of available antimicrobial agents, valuing them as precious and finite resources is essential. As well as efforts to minimize the spread of resistant bacteria through appropriate infection control measures in hospitals would be quite important and may represent a first step in solving the issue of resistant microorganisms¹³.

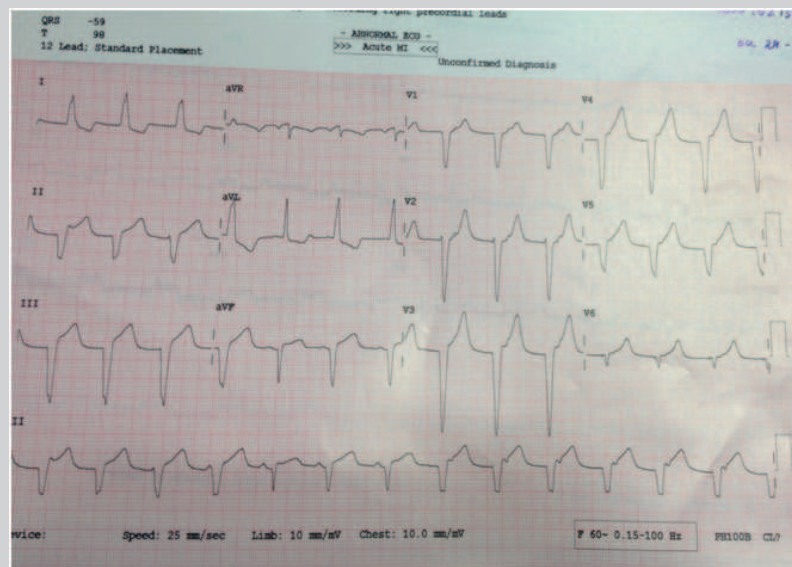
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Diagnose the Condition

50 year old male admitted in the ICU complaints of chest pain and his first ECG showed features of acute IWMI. He was thrombolysed. Next day monitor showed arrhythmia and ECG was taken.



Answer in page: 104

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Eat Chocolates to Stay Slim!

Several studies have already demonstrated the beneficial effects of eating chocolate, particularly in adults: staying slim and reduced risk of cardiovascular disease. Now in a new study published in *Nutrition*, researchers from Granada University's School of Medicine, report that similar benefit is also seen in teenagers. The study was carried out on 1458 adolescents from 9 European countries. The results showed that higher chocolate consumption was associated with lower amounts of total fat and fat around the waist regardless of other factors (including exercise). The beneficial effects are considered to be due to the presence of flavonoids, which exhibit antioxidant, anticlotting, anti-inflammatory and lipolytic effects. These benefits are seen with all types of chocolates and not only with dark ones. (*Nutrition* published online 21 October 2013; DOI: 10.1016/j.nut.2013.07.011; Abstract.)

- Dr. K. Ramesh Rao