Title: ANTIMICROBIAL RESISTANCE: An overview

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ANTIMICROBIAL RESISTANCE: An overview

ABSTRACT:
Microbes have emerged on the earth more than 2.5 billion years ago. They play an important role in the survival of human species. Only a few of these organisms cause diseases in humans. Antimicrobials are developed to kill these organisms. However, some of these organisms develop resistance to antimicrobials. These multidrug-resistant bacterial infections encompass serious threat to community and persons in hospital settings. It is associated with significant mortality and morbidity. The demand for developing newer antibiotics increases further escalating financial burden on the health industry. Therefore, optimal use of existing antimicrobials, use of alternative/supportive treatment options (e.g., abscess drainage), increasing immunity, educating health professionals and patients, antibiotic policies by government, infection control measures (e.g., hand washing) should be aimed at prevention of emergence and spread of antibiotic resistance.

Key words: antibiotics, resistance, bacterial resistance, antimicrobials, prevention

INTRODUCTION:

“Knowing is not enough, we must apply, willing is not enough we must do.”

Johan Wolfgang

Microbes play a key role in the biosphere and are very useful to mankind. Only few microorganisms are pathologic causing disease and death in humans. The center for disease control and prevention (CDC) reports that about 26% of human population suffers from infectious disease. The quest to tackle these pathological microbes has become the main aim of health professionals.¹

History

An investigation into the potency of microbial products was carried out in the 19th century by Pasteur and Joubert. In 1928, Alexander Fleming observations
of a mold contamination in one of his bacterial cultures undergoing lysis led to the invention of penicillin. Clinical use of sulphonamides began in the year 1936. However the golden age of antimicrobials started when penicillin was mass produced and available for clinical trials in 1941. More than 100 varieties of antimicrobials were discovered from 1960-1990. William Stuart, general surgeon said, “It is time to close the book on infectious diseases. The war against the pestilence is over.” With the advent of newer antifungal and antiviral drugs, advanced lab investigations for accurate diagnosis, scientist believed that infections would no longer be a problem for human species.

Different antimicrobials have different spectrum of action against the microbes. Some are specific for Gram +ve while some are for Gram –ve. No antibiotic is effective against all the microbes. Some are narrow spectrum while some are broad spectrum. Due to uncontrolled use of antimicrobials, microrganisms developed resistace to the commonly used antimicrobials.

- Penicillinase resistant organisms were first observed in 1948 due to production of penicillanase by microbes. It was followed by gram negative hospital pathogens and also resistance by common community pathogens.
- By 1953, during a Shigella outbreak in Japan, a strain of the dysentery bacillus (Shigella dysenteriae) was isolated which was multiple drug resistant, exhibiting resistance to chloramphenicol, tetracycline, streptomycin and the sulfonamides.
- In 1974 ampicillin resistant H. Influenzae B meningitis was published.
- Later amoxicillin resistant non typable H. influenzae and Moraxella catarrhalis in otitis media were reported.

Not only resistance continued to increase in bacteria, but also in fungi, virus and parasites all over the world. Commonly heard includes Methicillin Resistance Streptococcus Aureus (MRSA), Multi Drug Resistance (MDR), superbugs such as
ND-MBL (New Delhi – MetalloBeta Lactamases), Vancomycin Resistant Enterococci (VRE), Extended-Spectrum Beta-lactamases (which are resistant to cephalosporins and monobactams) ESBL.

**MECHANISM OF ANTIBIOTIC RESISTANCE:**

Microbes employ different ways to develop resistance against different antimicrobials.

1. Enzymatic destruction of drug
2. Prevention of penetration of drug
3. Alteration of drug’s target site
4. Reduced uptake or Rapid ejection of drug – efflux pump.
5. Metabolic bypass
6. Passing of drug resistant gene to progeny and also to other species of microbes.

Antibiotic resistance in bacteria may be an inherent trait of the organism (e.g. a particular type of cell wall structure) that renders it naturally resistant, or it may be acquired by means of mutation in its own DNA or acquisition of resistance-conferring DNA from another source.³

**Inherent (natural) resistance.**

Bacteria may be inherently resistant to an antibiotic. For example, an organism lacks transport system for an antibiotic; or an organism lacks the target of the antibiotic molecule; or, as in the case of Gram negative bacteria, the cell wall is covered with an outer membrane that establishes a permeability barrier against the antibiotic.

**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 the acquisition of new genetic material from another source.

**Vertical gene transfer**

The spontaneous mutation frequency for antibiotic resistance is on the order of about $10^{-8}$-$10^{-9}$. This means that one in every $10^8$-$10^9$ bacteria in an infection will develop resistance through the process of mutation. In *E. coli*, it has been estimated that streptomycin resistance is acquired at a rate of approximately $10^{-9}$ when exposed to high concentrations of streptomycin. Although mutation is a very rare event, the very fast growth rate of bacteria and the absolute number of cells attained means that it doesn't take long before resistance is developed in a population. Once the resistance genes have developed, they are transferred directly to all the 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: a spontaneous mutation in the bacterial chromosome imparts resistance to a member of the bacterial population. In the selective environment of the antibiotic, the wild types (non mutants) are killed and the resistant mutant is allowed to grow and flourish.

**Horizontal gene transfer**

Another mechanism beyond spontaneous mutation is responsible for the acquisition of antibiotic resistance. Lateral or horizontal gene transfer (HGT) 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 at least three possible mechanisms of HGT, equivalent to the three processes of genetic exchange in bacteria. These are transduction, transformation or conjugation.
Transduction occurs when bacteria-specific viruses (bacteriophages) transfer DNA between two closely related bacteria.

Transformation is a process where parts of DNA are taken up by the bacteria from the external environment. This DNA is normally present in the external environment due to the death and lysis of another bacterium.

Conjugation occurs when there is direct cell-cell contact between two bacteria (which need not be closely related) and transfer of small pieces of DNA called plasmids takes place. This is the main mechanism of HGT.

Mechanisms of horizontal gene transfer (HGT) in bacteria

The combined effects of fast growth rates to large densities of cells, genetic processes of mutation and selection, and the ability to exchange genes, account for the extraordinary rates of adaptation and evolution that can be observed in the bacteria. For these reasons bacterial adaptation (resistance) to the antibiotic environment seems to take place very rapidly in evolutionary time. (Table 1)

The resistant acquired organisms can rapidly give rise to vast numbers of resistant progeny. The mechanism of natural selection favors resistance with ease and also determinants that prevent their own counter selection and resistant strains with enhanced survival ability or virulence.

Increase in drug resistance in microbes is contributed by

1. Heavy antibiotic use – suboptimal dosage, broad spectrum and prolonged use
2. Poor infection control practices
3. Transplantation, dialysis and aggressive therapies
4. Increased international travel
5. Aging populations

Antibiotics proper.
1. Exposure to suboptimal levels of antimicrobials
2. Exposure to microbes carrying resistance genes
3. Prescriptions for non-bacterial conditions
4. Availability of over the counter (OTC) drugs.

**Inappropriate antibiotic usage:**

It is an important contributor for antimicrobial resistance. Doctors contribute by improper prescriptions and antibiotic prescription for viral infections, hospitals/clinics by spread of resistant microbes due to lack of hygiene and sterilization and pharmacist by providing antibiotics without medical supervision. Patients also contribute by antibiotic self treatment and stopping of antibiotic usage after the disappearance of symptoms.

**Strategies to combat drug resistance:**

Till newer antibiotics are discovered, clinicians should use available agents judiciously. Ideally treat all patients with most effective, least toxic, least costly antibiotic for optimal time. Use of narrow spectrum rather than broad spectrum antimicrobials depends on basal resistance status of setting, disease and clinical presentation by the patient. Choose the best drug combination right from beginning considering bacterial killing rate of agents selected. The dosage should be the highest tolerable and not minimally effective. Prescribe loading dose to achieve quick bactericidal concentration and maintain concentration above MBC giving it a continuous infusion. One can de-escalate after receiving culture reports, which reduces use of unnecessary antimicrobials and in turn bacterial resistance. A study by Ivermore and Gootz T D has shown that more than 85% of prescriptions were unnecessary. More than 80% of infections were viral in nature.

Centre for disease control (CDC) of America has advocated four major strategies to prevent antimicrobial resistance in healthcare settings

- Prevent infection
• Diagnose and then treat infections,
• Use antibiotics wisely and
• Prevent transmission.

Steps to combat the problem of antimicrobial resistance to be taken by healthcare professionals and policy makers are as follows:

• Antimicrobial Stewardship\textsuperscript{9,10} is an activity that includes appropriate antibiotic selection, dosing, route and duration of antimicrobial therapy. The goal is to preserve the effectiveness of current antimicrobials by reducing resistance and to improve outcomes associated with antimicrobial use. Benefits from this approach include reduction in health care costs, reduced resource utilization with improved outcomes.

• Track resistance data nationwide
• Use narrow spectrum antibiotics
• Use antibiotic cocktails
• Speed/ promote development of new antibiotics
• Optimal use of existing microbials
• Using alternative treatment options (incision & drainage)
• Reducing the need of antibicrobials by increasing immunity
• Implementation of infection control measures (hand washing)
• Screening & isolation of patients.

Role of patients / concerned family members:

Patients should not take antibiotics for which there is no medical value. Patients should adhere to appropriate prescribing guidelines and take antibiotics until they have finished the course. Patients should discuss the appropriate
medication for illness and avoid overusing or misusing medicines. Strictly follow prescription medication directions and never share or take medicine that was prescribed for someone else. Patients should not save antibiotic for the next time; take all of the medication as prescribed by healthcare provider. If the healthcare provider has prescribed more than the required dose, discard leftover medications after completion of the prescribed course of treatment. Individuals should not share medication with another person.

Summary:

The discovery of antibiotics was a leap in modern medicine. They have been able to stop the growth or kill many different kinds of microorganisms. However, bacteria have proven to be much more innovative and adaptive than we imagined and have developed resistance to antibiotics at an ever increasing pace. Bad practices and mismanagement have only exacerbated the situation. We could soon return to a state of medical health that was as dire as that which occurred prior to antibiotic use. Antibacterial resistance will continue to be a global problem. Optimal use of existing antimicrobial agents, using alternative treatment options, increase immunity thereby reducing the need of antimicrobials, implementing antibiotic polices and infection control measures, screening and isolation could prevent antibiotic resistance. However, with more research, education of the public and well thought out regulations, the problems could be solved. Vigorous and continuous research is required to know microbial pathogenesis such that we could develop strategies to overcome microbes. Otherwise the war between humans and microbes will continue for a very long time to come.
References:

10. Matlow AG, Moriss SK. Control of antibiotic-resistant bacteria in the office and clinic. CMAJ. 2009 May12;180(10):1021-4

Table 1: Antimicrobials displaying their methods of resistance

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Method of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic Class</td>
<td>Effect</td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>reduced uptake into cell</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>active efflux from the cell</td>
</tr>
<tr>
<td>β-lactams, Erythromycin, Lincomycin</td>
<td>eliminates or reduces binding of antibiotic to cell target</td>
</tr>
<tr>
<td>β-lactams, Aminoglycosides, Chloramphenicol</td>
<td>enzymatic cleavage or modification to inactivate antibiotic molecule</td>
</tr>
<tr>
<td>Sulfonamides, Trimethoprim</td>
<td>metabolic bypass of inhibited reaction</td>
</tr>
<tr>
<td>Sulfonamides, Trimethoprim</td>
<td>overproduction of antibiotic target (titration)</td>
</tr>
</tbody>
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