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AN OVER VIEW ON MICROBIAL INFECTIONS AND THEIR ANTIMICROBIAL RESISTANCE

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Abstract

Anti-microbial Resistance (AMR) is the major problem during long term therapy of a particular disease AMR develops when microbes stop responding to the drugs that were previously able to kill them. Both microbial behavior and the way in which people take antimicrobial drugs are responsible for the increase in AMR. This resistance could be very dangerous as it could mean that it is no longer possible to treat some infections, which could lead to severe complications or even death. Scientists are working to develop new treatments to try to counter AMR. People can help by only using medications according to a doctor's prescription and ensuring that they complete the full course of treatment.Antimicrobial resistance has been ascribed to the misuse of these agents and due to unavailability of newer drugs attributable to exigent regulatory requirements and reduced financial inducements. Comprehensive efforts are needed to minimize the pace of resistance by studying emergent micro-organisms, resistance mechanisms, and antimicrobial agents.

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INTRODUCTION:

The discovery of antibiotics may be one of the greatest achievements in medicine. Antibiotic treatments have improved clinical outcomes from infections, leading to the reduction of morbidity and mortality in surgical, transplant, cancer, and critical care patients. With the use of potent broad-spectrum antibiotics, selective pressures have made antibiotic resistance an urgent worldwide concern. Increasing numbers of hospital-acquired infections are now caused by multidrug-resistantpathogens, making treatment progressively difficult and antibiotic choice increasingly limited.[1]Antibiotic treatment is one of the main approaches of modern medicine which is used to combat infections. The "golden era" of antibiotics ranged from the 1930s to 1960s which gave rise to many antibiotics.[2]Unfortunately, this era ended because researchers were unable to maintain the pace of antibiotic discovery in the face of emerging resistant pathogens. Persistent failure to develop or discover new antibiotics and nonjudicious use of antibiotics are the predisposing factors associated with the emergence of antibiotic resistance. [3]

Antimicrobial resistance (AMR) poses a serious global threat of growing concern to human, animal, and environment health. This is due to the emergence, spread, and persistence of multidrug-resistant (MDR) bacteria or "superbugs."[4]MDR bacteria exist across the animal, human, and environment triangle or niche and there is interlinked sharing of these pathogens in this triad. The plausible causes of "the global resistome" or AMR include excessive use of antibiotics in animals (food, pets, aquatic) and humans, antibiotics sold over-the-counter, increased international travel, poor sanitation/hygiene, and release of nonmetabolized antibiotics or their residues into the environment through manure/fecus. These factors contribute to genetic selection pressure for the emergence of MDR bacterial infections in the community. Recently, the global consumption of antimicrobials in livestock has indicated the hotspots of antibiotics use across the continents that will have economic and public health impacts in the years to come. In food animals, antibiotics are commonly used in cattle, chicken, and pigs and it is projected that in 2030 such use will increase up to 67% in the most populated countries of the world.[5]The discovery of antibiotics was a defining moment in the history of mankind that revolutionized medicine and saved countless lives. Unfortunately, these "magic bullets" have been accompanied by these emerging resistant strains of pathogens. Currently, medical experts are raising real concern for a return to the preantibiotic age. After the analysis of the available bacterial genomes, it has been concluded that over 20,000 potential resistance genes (r genes) are present, fortunately; however, the functional resistance determinants in various microbes are far less in number. [6]During the late 1950s and early 1960s, antibiotic resistance to multiple antimicrobial agents was detected, for the very first time, among enteric bacteria namely Salmonella, Shigella, and Escherichia coli. These resistant strains caused huge clinical, economic losses and loss of life, mainly in the developing world. However, in the developed world it was considered a mild health problem restricted to enteric microbes. This misconception changed in the 1970s when it was observed that Neisseria gonorrhoeae and Haemophilus influenzae are resistant to ampicillin, while in the case of Haemophilus it was further reported to resist tetracycline and chloramphenicol as well. Due to the increasing use of antimicrobials, the incidence of resistance accelerated, particularly in the developing world where these drugs were freely accessible without any prescription. Deprived hygiene settings facilitated the transmission of resistance and insignificant health care funds limited access to novel and effective antibiotics.[7] World Health Organization (WHO) have declared antibiotic resistance to be a "global public health concern."[8]

Persistence versus resistance

Before discussing the various aspects of antimicrobial resistance, it would be helpful to distinguish resistance from persistence. If a bacterium is resistant to a certain antimicrobial agent, then all of the daughter cells would also be resistant (unless additional mutations occurred in the meantime). Persistence, however, describes bacterial cells that are not susceptible to the drug, but do not possess resistance genes. The persistence is undoubtedly due to the fact that some cells in a bacterial population may be in stationary growth phase (dormant); and most antimicrobial agents have no effect on cells that are not actively growing and dividing. These persister cells occur at a rate of around 1% in a culture that is in stationary phase [9,10] shown in Fig.1 describe about the difference between persistent and resistant bacterial cells.

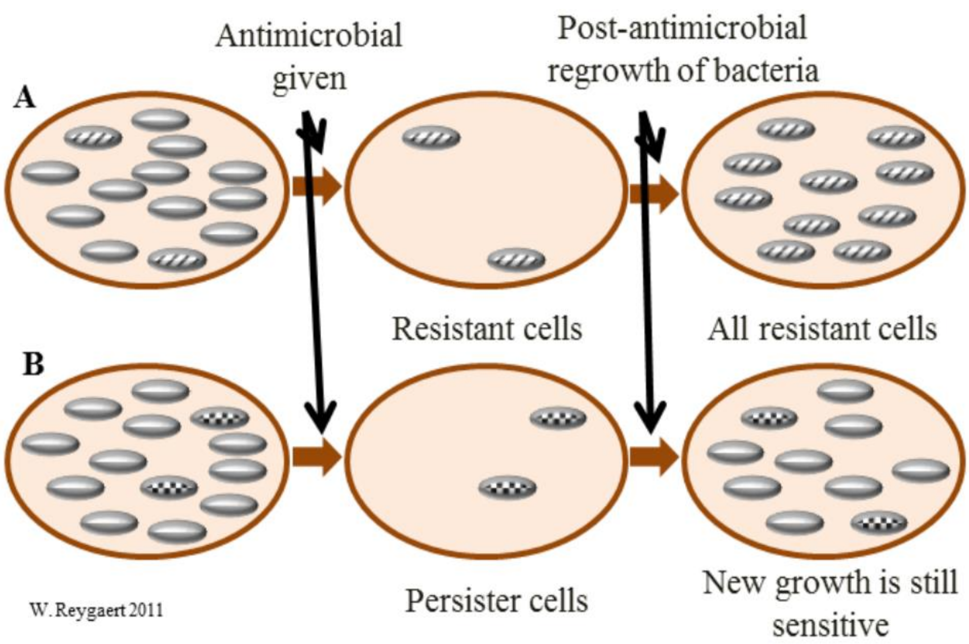

Fig.1:Resistance V/s persistence.

When bacterial cells are exposed to an antimicrobial agent there are two possible scenarios. There may be cells present that are resistant to the antimicrobial agent (A). The non-resistant cells are killed, leaving only the resistant cells. When the resistant cells are regrown, all of the cells in the culture will be resistant. The other possibility is that there may be persister cells (dormant, not resistant) present (B). The non-persister cells are killed, leaving only the persister cells.When the persister cells are regrown, those cells not in a dormant state will still be susceptible to the antimicrobial agent**.**

Origin of resistance

Bacteria as a group or species are not necessarily uniformly susceptible or resistant to any Particular antimicrobial agent. Levels of resistance may vary greatly within related bacterial groups. Susceptibility and resistance are usually measured as a function of minimum inhibitory concentration (MIC), the minimal concentration of drug that will inhibit growth of the bacteria. The susceptibility is actually a range of the average MICs for any given drug across the same bacterial species. If that average MIC for a species is in the resistant part of the range, the species is considered to have intrinsic resistance to that drug. Bacteria may also acquire resistance genes from other related organisms, and the level of resistance will vary depending on the species and the genes acquired [11,12].

Natural resistance

Natural resistance may be intrinsic (always expressed in the species), or induced (the genes are naturally occurring in the bacteria, but are only expressed to resistance levels after exposure to an antibiotic). Intrinsic resistance may be defined as a trait that is shared universally within a bacterial species, is independent of previous antibiotic exposure, and not related to horizontal gene transfer.[13,14]The most common bacterial mechanisms involved in intrinsic resistance are reduced permeability of the outer membrane (most specifically the lipopolysaccharide, LPS, in gram negative bacteria) and the natural activity of efflux pumps. Multidrug-efflux pumps are also a common mechanism of induced resistance [14, 15].

Acquired resistance

Acquisition of genetic material that confers resistance is possible through all of the main routes by which bacteria acquire any genetic material: transformation, transposition, and conjugation (all termed horizontal gene transfer-HGT) plus, the bacteria may experience mutations to its own chromosomal DNA. The acquisition may be temporary or permanent. Plasmid-mediated transmission of resistance genes is the most common route for acquisition of outside genetic material; bacteriophage-borne transmission is fairly rare. Certain bacteria such as Acinetobacter spp. are naturally competent, and therefore capable of acquiring genetic material directly from the outside environment. Internally, insertion sequences and integrins may move genetic material around, and stressors (starvation, UV radiation, chemicals, etc.) on the bacteria are common causes of genetic mutations (substitutions, deletions etc.). Bacteria have an average mutation rate of 1 for every 106 to 109cell divisions, and most of these mutations will be deleterious to the cell [16, 17]

Mutations that aid in antimicrobial resistance usually only occur in a few types of genes; those encoding drug targets, those encoding drug transporters, those encoding regulators that control drug transporters, and those encoding antibiotic-modifying enzymes . In addition, many mutations that confer antimicrobial resistance do so at a cost to the organism. For example, in the acquisition of resistance to methicillin in Staphylococcus aureus, the growth rate of the bacteria is significantly decreased[18].One huge conundrum of antimicrobial resistance is that the use of these drugs leads to increased resistance. Even the use of low or very low concentrations of antimicrobials (sub-inhibitory) can lead to selection of high-level resistance in successive bacterial generations,may select for bacteria that are hypermutatable strains (increase the mutation rate), may increase the ability to acquire resistance to other antimicrobial agents, and may promote the movement of mobile genetic elements [19].

Causes of Antimicrobial Resistance

At present, the multifaceted etiology of antibiotic resistance has many factors which are at play. These include inadequate regulations and usage imprecisions, awareness deficiency in best practices which steers undue or inept use of antibiotics, use of antibiotics as a poultry and livestock growth promoter rather than to control infection, and online marketing which made the unrestricted availability of low-grade antibiotics very accessible[20,21] Primarily, overuse of antibiotics is the principal cause of resistance evolution, as it was also warned by Sir Alexander Fleming that "public will demand [the drug and] then will begin an era of abuses." Antibiotics kill sensitive bacteria but allow resistant pathogens to remain which then reproduce and thrive through natural selection.

Although overuse of antibiotics is strongly discouraged, there remains over prescription across the globe. Several studies have revealed that treatment indications, agent choice, and antibiotic therapy duration are inappropriate in 30% -50% of the cases. [22,23] Globally, antibiotics are used as a growth promoter in live stock. According to an estimate, about 80% of the antibiotics are sold in the US only for use as growth supplements and to control infection in animals. In another study, a global map of 228 countries was drawn which depicted the consumption of antibiotics in livestock; it was estimated that the total antibiotic consumption was 63,151 tons in 2010.6 van Boeckel et al have also projected a 67% rise in antibiotic consumption by 2030 that would approximately double in Brazil, Russia, India, China, and South Africa block of the rapidly developing and highly populated countries of the world. [24]

The occurrence of resistance in microbes is a natural process. When a resistant strain of bacteria is the dominant strain in an infection, the infection may be untreatable and life-threatening. Examples of bacteria that are resistant to antibiotics include methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant Enterococcus, and multidrug-resistant Mycobacterium tuberculosis (MDR-TB), which is resistant to two tuberculosis drugs, isoniazid and rifampicin. MDR-TB is particularly dangerous because it can give rise to extensively drug-resistant M. tuberculosis (XDR-TB), which requires aggressive treatment using a combination of five different drugs [25]

Prevention against Antibiotic Resistance

Antibiotic resistance occurs when bacteria develop defenses against the antibiotics designed to kill them. This renders the drugs useless against the new resistant strains, allowing resistance to grow and spread to other germs, creating drug-resistant infections that can be difficult to treat.Prevention is the best way to protect against antibiotic resistance. There are many steps that individuals can take to protect themselves and their families:

Wash Your Hands

Our bodies are constantly exposed to millions of germs. Regular hand washing can help fight germs and prevent illness.

Know the Symptoms

Learn how to recognize early symptoms of an infection. If you think you have an infection, or if your infection is not getting better or is getting worse, talk to a healthcare professional.

Queries

Talk to your healthcare professional about the antibiotics they prescribe and learn about possible side effects. Ask about what they are doing to keep their facilities safe and prevent further infections.

Learn the Right Ways to Use Antibiotics

Not all infections need antibiotics. Work with your healthcare professional to make sure you are getting the right antibiotic, at the right dosage, for the right amount of time. Never demand antibiotics if your healthcare professional says they are unnecessary.

Never Share or Use Leftover Antibiotics, Only take antibiotics when appropriately prescribed and administered by your healthcare provider.

Prepare Food Safely

Food such as meat, fruits, and vegetables can be contaminated with bacteria. The Centers for

Disease Control and Prevention (CDC) recommends four simple steps to prepare food safely at home: Clean, separate, cook, and chill

Get Vaccinated

Getting your annual influenza vaccine and keeping up to date on all immunizations can help prevent illness.

Role of Healthcare Professionals on Prevention of Antibiotic Resistance

Healthcare professionals can take several steps to protect patients from drug-resistant infections.

Prescribe Antibiotics Carefully

Make sure to stay up to date on the recommend antibiotics practices and doses. CDC offers many resources for healthcare professionals.

Educate Your Patients

Tell patients about the side effects and risks associated with the antibiotics they are taking. Inform patients about antibiotic resistance and the dangers of misuse.

Take the Antibiotic Stewardship Pledge

Antibiotic stewardship is the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients. NFID and multiple other public health organizations have been working to solve this problem. Help support these organizations and take the Antibiotic Stewardship Pledge.

CONCLUSION:

A problem that has plagued antibiotic therapy from the earliest days is the resistance that bacteria can develop to the drugs. An antibiotic may kill virtually all the bacteria causing a disease in a patient, but a few bacteria that are genetically less vulnerable to the effects of the drug may survive. These go on to reproduce or to transfer their resistance to others of their species through processes of gene exchange. With their more vulnerable competitors wiped out or reduced in numbers by antibiotics, these resistant strains proliferate. The end result is bacterial infections in humans that are untreatable by one or even several of the antibiotics customarily effective in such cases. The indiscriminate and inexact use of antibiotics encourages the spread of such bacterial resistance. Researchers are continually working to discover new antibiotics as a means of overcoming antibiotic resistance. Some potentially effective compounds that have been discovered include certain bacterial toxins and antimicrobial peptides. Novel treatment strategies, such as combining synergistic antibiotics to boost the killing of bacteria, are also under investigation. It may be possible to introduce compounds into bacterial populations that effectively resensitize the bacteria to existing antibiotic drugs.

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