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ANTIBIOTIC RESISTANCE PREVENTION AND CONTROL IN HEALTH CARE PRACTICE – A BRIEF REVIEW

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ABSTRACT
Antibiotic resistance occurs when an antibiotic has lost its ability to effectively control or kill bacterial growth and continue to multiply in the presence of therapeutic levels of an antibiotic. Resistance arises through one of three ways includes natural resistance in certain types of bacteria, genetic mutation, or by one species acquiring resistance from another. Resistance can appear spontaneously because of random mutations are more commonly following gradual buildup over time and because of misuse of antibiotics or antimicrobials. All classes of microbes develop resistance includes fungi develop antifungal resistance, viruses develop antiviral resistance, protozoa develop antiprotozoal resistance and bacteria develop antibiotic resistance. The prescriber having rights to prescribe the drug should closely adhere to appropriate right like the right patient, the right drug, the right dose, the right route and the right time. Any bacteria that acquire resistance genes, whether by spontaneous mutation or genetic exchange with other bacteria, have the ability to resist one or more antibiotics. According to the Centers for Disease Control and Prevention Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. Strengthening antibiotic policies, programmes and implementation of infection prevention and control measures in community will plays key role motivating the research community for development of new antibiotics, vaccines, diagnostics tools will shows the better progress in community.

KEYWORDS: Antibiotics, vaccines, random mutations, genes, diagnostics, resistance.

INTRODUCTION
Antibiotics any of a variety of substances, usually obtained from microorganisms, that inhibit the growth of or destroy certain other species. Antibiotics are used to treat or prevent some types of bacterial infection.it will work against killing bacteria or preventing them from reproducing and spreading. Antibiotics are a group of medicines that are used to treat infections caused by germs (bacteria and certain parasites). Parasite is a type of germ that needs to live on or in another living being (host). Antibiotics are sometimes called antibacterials or antimicrobials. Antibiotics can be taken by mouth as liquids, tablets, or capsules, or they can be given by injection. Antibiotics are also available as creams, ointments, or lotions to apply to the skin to treat certain skin infections.[1]

Doses of antibiotics can be provided in several ways

- Oral antibiotics – tablets, capsules or a liquid that you drink, which can be used to treat most types of mild to moderate infections in the body.
- Topical antibiotics – creams, lotions, sprays or drops, which are often used to treat skin infections.
- Injections of antibiotics – these can be administered as an injection or infusion through a drip directly into the blood or muscle, and are usually reserved for more serious infections.

The strategic objectives of Antibiotic resistance includes

- To improve awareness, knowledge and understanding of antimicrobial resistance.
- To strengthen the surveillance and research initiations about the resistance.
- To reduce the incidence of infection.
- To optimize the use of antimicrobial medicines.
- To ensure sustainable investment in countering antimicrobial resistance.

The main types of antibiotics include

- **Penicillins** - for example, phenoxymethylpenicillin, flucloxacillin and amoxicillin.
- **Cephalosporins** - for example, cefaclor, cefadroxil and cefalexin.
- **Tetracyclines** - for example, tetracycline, doxycycline and lymecycline.
- **Aminoglycosides** - for example, gentamicin and tobramycin.
- **Macrolides** - for example, erythromycin, azithromycin and clarithromycin.
- **Clindamycin**.
- **Sulfonamides and trimethoprim** - for example, co-trimoxazole.
- Metronidazole **and** tinidazole.
- **Quinolones** - for example, ciprofloxacin, levofloxacin and norfloxacin.

Types of antibiotics

There are hundreds of different types of antibiotics, but most of them can be broadly classified into six groups. These are outlined below.

- Penicillins – widely used to treat a variety of infections, including skin infections, chest infections and urinary tract infections.
- Cephalosporins (such as cephalexin) – used to treat a wide range of infections, but some are also effective for treating more serious infections, such as septicaemia and meningitis.
- Aminoglycosides (such as gentamicin and tobramycin) – tend to only be used in hospital to treat very serious illnesses such as septicaemia, as they can cause serious side effects, including hearing loss and kidney damage.
- Tetracyclines (such as tetracycline and doxycycline)– can be used to treat a wide range of infections, but are commonly used to treat moderate to severe acne.
- Macrolides (such as erythromycin and clarithromycin) – can be particularly useful for treating lung and chest infections, or an alternative for people with a penicillin allergy, or to treat penicillin-resistant strains of bacteria.
- Fluoroquinolones (such as ciprofloxacin and levofloxacin) – broad-spectrum antibiotics that can be used to treat a wide range of infections.

History of the development of antibiotics from past to modern era

The great modern advances in chemotherapy have come from the chance discovery that many microorganisms synthesize and excrete compounds that are selectively toxic to other microorganisms. These compounds are called antibiotics and have revolutionized medicine. The period since World War II has seen the establishment and extremely rapid growth of a major industry, using microorganisms for the synthesis of, amongst other compounds, chemotherapeutic agents.[2]

The first chemotherapeutically effective antibiotic was discovered in 1929 by Alexander Fleming (1881–1955), a British bacteriologist, who had long been interested in the treatment of wound infections. On returning from a vacation in the countryside, he noticed among a pile of petri dishes on his bench one that had been streaked with a culture of Saphyloccocus aureus which was also contaminated by a single colony of mold. As Fleming observed the plate, he noted that the colonies immediately surrounding the mold were transparent and appeared to by undergoing lysis. Fleming isolated the mold, which proved to be a species of Penicillium and established that culture filtrates contained an antibacterial substance, which he called penicillin.

Although it has often been suggested that many bacteriologists must have observed petri dishes that were similarly contaminated and therefore similar in appearance to Fleming's dish, such speculation is undoubtedly false. As subsequent experiments have shown, a highly unusual series of events must have occurred in order to produce the results seen on Fleming's plate: contamination must have occurred at the time the plate was streaked with bacteria (prior growth of either would have prevented growth of the other in the immediate vicinity); the inoculated petri dish must not have been incubated (if it had been the bacterium would have outgrown the mold); the room temperature of the laboratory must have been below 68°F.

Penicillin proved to be chemically unstable and Fleming was unable to purify it. Working with impure preparations, he demonstrated its remarkable effectiveness in inhibiting the growth of many Gram-positive bacteria and he even used it with success for the local treatment of human eye infections. In the meantime, the chemotherapeutic effectiveness of other, non-antibiotic compounds such as sulfonamides had been discovered and Fleming, discouraged by the difficulties in purifying penicillin, abandoned further work on the problem.[3]

Ten years later a group of British scientists headed by H.W. Florey (1898–1968) and E. Chain (1906–1979) resumed the study of penicillin. Clinical trials with partly purified material were dramatically successful. By this time the industrial development of penicillin was undertaken in the United States, where an intensive program of research and development was begun in many laboratories. Within three years, penicillin was being produced on an industrial scale.

Penicillin G proved the most successful and later it became possible to remove the side chain and replace it by a variety of chemical substituents, thereby producing semisynthetic penicillins. For example, penicillin V is resistant to acid and therefore can be administered orally because it is not inactivated in the stomach; ampicillin is also acid resistant and also effective against enteric bacteria; oxacillin is resistant to the action of B-

lactamase, the enzyme produced by certain "penicillin-resistant" strains of bacteria.[4]

This was the first example of a broad-spectrum antibiotic. Other antibiotics with even broader spectra of activity, such as the tetracyclines, were subsequently discovered. The search for new antibiotics remains an empirical enterprise. Antibiotics have proved less effective in the treatment of fungal infections. Antifungal antibiotics, such as nystatin and amphoterecin B are considerably less successful therapeutically than their bacterial counterparts, at least in part because their toxicity is far less selective. There are no known antiviral antibiotics.

Benefits of Antibiotics

Antibiotics have not only saved patients' lives, they have played a pivotal role in achieving major advances in medicine and surgery. They have successfully prevented or treated infections that can occur in patients who are receiving chemotherapy treatments; who have chronic diseases such as diabetes, end-stage renal disease, or rheumatoid arthritis; or who have had complex surgeries such as organ transplants, joint replacements, or cardiac surgery.

Antibiotics have also helped to extend expected life spans by changing the outcome of bacterial infections.

Factors associated with resistance pattern

Overuse

The overuse of antibiotics clearly drives the evolution of resistance. Epidemiological studies have demonstrated a direct relationship between antibiotic consumption and the emergence and dissemination of resistant bacteria strains. In bacteria, genes can be inherited from relatives or can be acquired from nonrelatives on mobile genetic elements such as plasmids. This horizontal gene transfer (HGT) can allow antibiotic resistance to be transferred among different species of bacteria. The Resistance can also occur spontaneously through mutation.

Inappropriate Prescribing

Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria.[5] Studies have shown that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30% to 50% of cases.

Extensive Agricultural Use

In both the developed and developing world, antibiotics are widely used as growth supplements in livestock. An estimated 80% of antibiotics sold in the U.S. are used in animals, primarily to promote growth and to prevent infection.

The antibiotics used in livestock are ingested by humans when they consume food.

Availability of Few New Antibiotics

The development of new antibiotics by the pharmaceutical industry, a strategy that had been effective at combating resistant bacteria in the past, had essentially stalled due to economic and regulatory obstacles Of the 18 largest pharmaceutical companies, 15 abandoned the antibiotic field.[5]

Antibiotic development is no longer considered to be an economically wise investment for the pharmaceutical industry. Because antibiotics are used for relatively short periods and are often curative, antibiotics are not as profitable as drugs that treat chronic conditions, such as diabetes, psychiatric disorders, asthma, or gastroesophageal reflux. A cost–benefit analysis by the Office of Health Economics in London calculated that the net present value (NPV) of a new antibiotic is only about $50 million, compared to approximately $1 billion for a drug used to treat a neuromuscular disease.

Another factor that causes antibiotic development to lack economic appeal is the relatively low cost of antibiotics. Newer antibiotics are generally priced at a maximum of $1,000 to $3,000 per course compared with cancer chemotherapy that costs tens of thousands of dollars. The availability, ease of use and generally low cost of antibiotics has also led to a perception of low value among payers and the public.

In addition, microbiologists and infectious-disease specialists have advised restraint regarding antibiotic use. Therefore, once a new antibiotic is marketed, physicians rather than prescribing it immediately—often hold this new agent in reserve for only the worst cases due to fear of promoting drug resistance and they continue to prescribe older agents that have shown comparable efficacy. Therefore, new antibiotics are often treated as "last-line" drugs to combat serious illnesses. This practice leads to the reduced use of new antibiotics and a diminished return on investment.[6]

When new agents are eventually used, the emergence of resistance is nearly inevitable.[2] However, since bacterial evolution is uncertain, the timeline for the development of resistance is unpredictable. A manufacturer that invests large sums of money into antibiotic development may therefore discover that profits are prematurely curtailed when resistance develops to a new antibiotic. Economic uncertainty related to the Great Recession has also had a restraining effect on the end users of antibiotics. Developed countries with well-funded health care systems have applied austerity measures, while developing countries such as China and India still have a large cohort of population that cannot afford expensive new medicines. As an additional complication, most antibiotics are currently off-patent and are supplied by manufacturers of generic drugs. The result has been access to cheap and generally effective drugs, which is good for the public; however, the downside is that many payers expect all antibiotics to be priced similarly even

new agents that target multidrug-resistant (MDR) pathogens.

Because of these factors, many large pharmaceutical companies fear a potential lack of return on the millions of U.S. dollars that would be required to develop a new antibiotic. The Infectious Diseases Society of America (IDSA) reported that as of 2013, few antibacterial compounds were in phase 2 or 3 development. In particular, the IDSA noted that unacceptably few agents with activity against emerging, extensively resistant gram-negative bacteria, such as Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii, were being developed. Pharmaceutical companies have also taken a more active interest in developing antibiotics for methicillin-resistant Staphylococcus aureus (MRSA), rather than gram-negative pathogens. The most likely explanation for this imbalance is that MRSA is a major problem worldwide, whereas the market for treating gram-negative organisms is smaller and somewhat more unpredictable given that resistance is rapidly acquired.[7]

Regulatory Barriers

Even for those companies that are optimistic about pursuing the discovery of new antibiotics, obtaining regulatory approval is often an obstacle. Between 1983 and 2007, a substantial reduction occurred in the number of new antibiotic approvals. Difficulties in pursuing regulatory approval that have been noted include: bureaucracy, absence of clarity, differences in clinical trial requirements among countries, changes in regulatory and licensing rules and ineffective channels of communication.

Changes in standards for clinical trial design made by the U.S. Food and Drug Administration (FDA) during the past two decades have made antibiotic clinical trials particularly challenging.

Mechanisms of antibiotic resistance

Antibiotic-resistant bacteria that are difficult or impossible to treat are becoming increasingly common and are causing a global health crisis. Antibiotic resistance is encoded by several genes many of which can transfer between bacteria.

- The inactivation or modification of the antibiotic
- An alteration in the target site of the antibiotic that reduces its binding capacity
- The modification of metabolic pathways to circumvent the antibiotic effect
- The reduced intracellular antibiotic accumulation by decreasing permeability and/or increasing active efflux of the antibiotic

Bacteria can be intrinsically resistant to certain antibiotics but can also acquire resistance to antibiotics via mutations in chromosomal genes and by horizontal gene transfer. The intrinsic resistance of a bacterial species to a particular antibiotic is the ability to resist the action of that antibiotic as a result of inherent structural or functional characteristics.[8]

Prevention of access to target

Reduced Permeability: Compared with Gram-positive species, Gram-negative bacteria are intrinsically less permeable to many antibiotics as their outer membrane forms a permeability barrier. Hydrophilic antibiotics cross the outer membrane by diffusing through outer-membrane porin proteins. Therefore reducing the permeability of the outer membrane and limiting antibiotic entry into the bacterial cell is achieved by the down regulation of porins or by the replacement of porins with more-selective channels.

Increased efflux: Bacterial efflux pumps actively transport many antibiotics out of the cell and are major contributors to the intrinsic resistance of Gram-negative bacteria to many of the drugs that can be used to treat Gram-positive bacterial infections.

Changes in antibiotic targets by mutation

Most antibiotics specifically bind to their targets with high affinity, thus preventing the normal activity of the target.[8] Changes to the target structure that prevent efficient antibiotic binding, but that still enable the target to carry out its normal function can confer resistance. During the course of infection there are often large and diverse populations of pathogens, and if a single point mutation in the gene encoding an antibiotic target can confer resistance to the antibiotic.

Modification of targets

Protection by modification of the target can also be an effective means of antibiotic resistance that does not require a mutational change in the genes encoding the target molecules. In recent years, protection of targets has been found to be a clinically relevant mechanism of resistance for several important antibiotics; for example, the erythromycin ribosome methylase (erm) family of genes methylate 16S rRNA and alter the drug-binding site, thus preventing the binding of macrolides, lincosamines and streptogramins.

Direct modification of antibiotics

As well as preventing antibiotics from entering the cell or altering their targets, bacteria can destroy or modify antibiotics, thus resisting their action.[9]

Inactivation of antibiotics by hydrolysis: The enzyme-catalysed modification of antibiotics is a major mechanism of antibiotic resistance that has been relevant since the first use of antibiotics, with the discovery of penicillinase (a β-lactamase), in 1940.

Inactivation of antibiotic by transfer of a chemical group: The addition of chemical groups to vulnerable sites on the antibiotic molecule by bacterial enzymes causes antibiotic resistance by preventing the antibiotic from binding to its target protein as a result of steric

hindrance. Various different chemical groups can be transferred, including acyl, phosphate, nucleotidyl and ribitoyl groups and the enzymes that are responsible form a large and diverse family of antibiotic-resistance enzymes.

Resistance to antibiotics from the past findings

- 1928: discovery of penicillin
- 1940:first identification of a β lactamase
- 1945: 50% resistance to penicillin in Staphylococcus aureus
- 1943: discovery of streptomycin
- 21 January 1950 George Orwell died from an untreatable streptomycin Resistant strain of Mycobacterium tuberculosis

Mechanisms of action of antibiotics

Inhibition of cell wall synthesis

The Beta-lactam ring is the nucleus of penicillins and cephalosporins. These agents inhibit cell wall synthesis

Binding DNA gyrase

The fluoroquinolones – e.g. ciprofloxacin, ofloxacin, norfloxacin, levofloxacin, moxifloxacin are relatively new agents that stop DNA replication by inhibiting DNA gyrase, a bacterial enzyme that is involved in the quaternary folding of double stranded DNA.

Inactivate the antibiotic

The best examples are beta-lactamases produced by many kinds of bacteria. These enzymes open the beta-lactam ring of penicillins and cephalosporins.

Alteration of target sites

- Ribosomal alterations can lead to resistance to any of the agents that bind ribosomes most notably tetracyclines and macrolides.
- Changes in Penicillin Binding Proteins is an important means by which some organisms evade the effects of penicillins and cephalosporins. Methicillin resistant Staphylococcus aureus (MRSA) is a serious problem in hospitals and is the primary example.
- Modifications of folate synthesis enzymes confers resistance to trimethoprim and sulfa drugs.
- Altered DNA Gyrases don't bind fluoroquinolones conferring resistance.[11]

Alterations in Membranes

Gram negative outer membranes contain porins – channels that facilitate transmembrane passage of substances in and out of the cell. Most antibiotics gain access to the inside of bacteria in this way. Alterations in porin structure and number can decrease activity of a wide variety of antibiotics.

Efflux pumps

Several types of bacteria can pump antibiotics out of themselves using energy dependant pumps. This by binding to bacterial cell wall construction enzymes referred to as penicillin binding proteins.

Inhibition of protein synthesis

- Macrolides – e.g. erythromycin, clarithromycin, azithromycin
- Aminoglycosides – e.g. gentamicin, tobramycin, amikacin
- Lincosamides – e.g. clindamycin
- Tetracyclines – e.g. tetracycline, doxycycline, minocycline
- Chloramphenicol

Inhibition of folate synthesis

These two types of compounds are usually used in combination with one another. They inhibit two different steps in bacterial synthesis of tetrahydrofolate which ultimately stops purine synthesis and DNA construction.[10]

relatively recently described mechanism is being more and more reported for more and more types of antibiotics and is gaining in clinical importance.

Spread of Resistance

Bacteria are very promiscuous!! They share genetic elements freely and willingly.

Plasmids are self-replicating, extrachromosomal circular pieces of DNA that facilitate exchange of resistance determinants. Many plasmids carry several different resistance genes making the acquisition of multiple resistances possible with one genetic event.

Bacteriophages are viruses that infect bacteria. They spread genetic material by a process known as transduction.

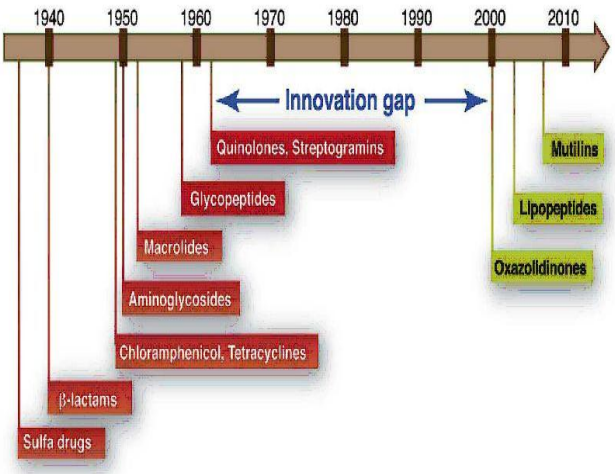

Fig 1: Antibiotic discoveries year wise

Few Ways Pharmacists Can Fight Antibiotic Resistance

- **Counselling Patients in Community Pharmacy Setting**

Community pharmacists are usually a patient's most direct point of contact with respect to their medications.

- **Make Sure Everyone Knows How Important Immunizations Are**

All 50 US states plus the District of Colombia have statutes permitting pharmacists to administer vaccines at some level and many of those statutes are evolving to keep pace with changing patient attitudes towards pharmacists and immunizations.

- **Prevent Unnecessary Antibiotic Use for Non-Bacterial Infections**

As many as 1 in 10 health care providers prescribe antibiotics for almost every patient they see presenting with cold or bronchitis, so it should come as no surprise that many patients just assume that antibiotics will cure any ailment.

Prevention and control

Antibiotic resistance is accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Steps can be taken at all levels of society to reduce the impact and limit the spread of resistance.

Individuals

To prevent and control the spread of antibiotic resistance, individuals can:

- Only use antibiotics when prescribed by a certified health professional.
- Never demand antibiotics if your health worker says you don't need them.
- Always follow your health worker's advice when using antibiotics.[15]
- Never share or use leftover antibiotics.
- Prevent infections by regularly by washing hands, preparing food hygienically, avoiding close contact with sick people, practising safer sex, and keeping vaccinations up to date.[12]

Policy makers

To prevent and control the spread of antibiotic resistance, policy makers can:

- Ensure a robust national action plan to tackle antibiotic resistance is in place.
- Improve surveillance of antibiotic-resistant infections.
- Strengthen policies, programmes, and implementation of infection prevention and control measures.
- Regulate and promote the appropriate use and disposal of quality medicines.
- Make information available on the impact of antibiotic resistance.

Health professionals

To prevent and control the spread of antibiotic resistance, health professionals can:

- Prevent infections by ensuring your hands, instruments and environment are clean.
- Only prescribe and dispense antibiotics when they are needed, according to current guidelines.[13]
- Report antibiotic-resistant infections to surveillance teams.
- Talk to your patients about how to take antibiotics correctly, antibiotic resistance and the dangers of misuse.
- Talk to your patients about preventing infections (for example, vaccination, hand washing, safer sex and covering nose and mouth when sneezing).

Healthcare industry

To prevent and control the spread of antibiotic resistance, the health industry can:

- Invest in research and development of new antibiotics, vaccines, diagnostics and other tools.

Agriculture sector

To prevent and control the spread of antibiotic resistance, the agriculture sector can:

- Only give antibiotics to animals under veterinary supervision.
- Not use antibiotics for growth promotion or to prevent diseases.
- Vaccinate animals to reduce the need for antibiotics and use alternatives to antibiotics when available.
- Promote and apply good practices at all steps of production and processing of foods from animal and plant sources.
- Improve biosecurity on farms and prevent infections through improved hygiene and animal welfare.[14]

CONCLUSION

Antibiotic resistance is a natural phenomenon and bacteria have been showing resistance to the medicines because changing of its gene pattern. Pharamcist should interact with the physician and deliver the information about genomics, structural biology, Microbiology, antibiotics practice guidelines in community. identification of new tagets for drugs binding causative factors will helpful for preventable Pattern. The Pharmacist should aid the discovery and development of new agents that can neutralize existing resistance mechanisms. Awaring the community about use antibiotics when prescribed by a certified health professionals and Never share or use leftover antibiotics. The spread of resistant infections reduced through proper sanitation, including handwashing and disinfecting between patients and should encourage the same of the patient, visitors, and family members and Strengthening antibiotic policies, programmes, and implementation of

infection prevention and control measures in community will plays key role motivating the research community for development of new antibiotics, vaccines, diagnostics tools will shows the better progress in community.

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