Resistance to Antibiotics: A Systematic Review

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Abstract **- Antibiotics save human and animal lives. Any time antibiotics are used, they can promote to side effects and resistance. There are generally 2 types of antibiotics that work, or they work by mainly 2 ways to stop the infection either they slow down the development of microbes and destroy their ability to generate and reproduce and spread or they kill the bacteria by damaging the bacterial cell walls. The potentiality of the microbes to withstand or resist the effects of an antibiotic is commonly known as antibiotic resistance. The antibiotics are prescribed anonymously throughout the world, and because of this widespread use, the target designed have been altered, in return making the drugs less effective. Antibiotics aren't useful in viral infections. Antibiotic Resistance is a "one health" problem and associates to the health of people, animals, and the environment. Antibiotic resistance occurs when germs beat the drugs devised to kill them. It does NOT mean the body is resistant to antibiotics. Antibiotic resistance is rising to severely high levels in all parts of the world. New resistance mechanisms are appearing and spreading globally, bullying our ability to treat common infectious diseases. A growing list of infections – such as pneumonia, tuberculosis, blood poisoning, gonorrhea, and food borne diseases – are becoming harder, and sometimes impossible, to treat as antibiotics become less effective. When encountered with antibiotics, bacteria, viruses can mutate over time and that may affect their ability to reproduce, genetic changes (mutations) can occur that enable the microbe to survive.**

Index Terms **- Antibiotic Resistance, Germ Defense, Resistant infections**

INTRODUCTION

Disease; di-ease: It is the disturbance in our ease. Any abnormal situation or condition that affects the normal bodily functions and routine is called a diseased state. Diseases are generally understood to be medical conditions that implicate a therapeutic process associated with a specific set of symptoms. Localized diseases affect peculiar parts of the body; disseminated diseases spread to other parts of the body; and systemic diseases affect the entire body.

Categories of diseases include autoimmune, bacterial, blood, cancer, digestive, heart, nerve (or neurodegenerative), sexually transmitted or thyroid. Diseases may be communicable or non-communicable. Foreign sources that can cause disease include acquired viruses or bacteria, and internal or domestic causes of disease include autoimmune or generic dysfunction. Some diseases are chronic implying that they are continually present and may present symptomatically during a long duration.

The term 'antibiotics' originally refers to a natural compound produced by a fungus, bacteria or any other microbes that is helpful in killing the bacteria which are the cause for the diseases in humans and animals. (1) These are the classes of drugs that slow down and destroy the growth and development of micro-organisms, such as bacteria, fungi and parasites. These are specifically used to treat, prevent, and cure bacterial infections as viral infections do not respond to antibiotics. Antibiotics are one of the most successful forms of therapy and treatment. These have been use for a long run and are most frequently prescribed and suggested. (2)

WHO'S Assistant director- general for health security, Dr. Keiji Fukunda, said: "Effective antibiotics have been one of the pillars allowing us to live longer, live healthier, and benefit from modern medicine unless we take significant actions to improve efforts to prevent infections and also change how we produce, prescribe and use antibiotics." But the efficiency of the antibiotics is now being compromised, because of the growing number of antibiotic resistant bacteria. (3)

Some common side effects of antibiotics include diarrhea, vomiting, nausea, rashes, upset stomach, with certain antibiotics or prolonged use, fungal infections of mouth, digestive tract and vagina. Less familiar side effects of antibiotics include development of kidney stones(while taking

sulfonamides),atypical blood clotting (while consuming some cephalosporins), sensitivity to sunlight (while taking tetracyclines), blood disorders (when taking trimethoprim),and in cases deafness (when taking erythromycin and aminoglycosides). (4)

HOW DOES ANTIBIOTICS WORK?

Antibiotics were discovered by a scientist 'Alexander Fleming' in 1928, and are extensively assigned as the most important medical findings in human history. Antibiotics are used to treat infections caused by the bacteria. Mostly, the bacteria are benign or even helpful for our body, like some help in digestion, fermentation etc, but simultaneously some can and do cause diseases. There are generally 2 types of antibiotics that work, or they work by mainly 2 ways to stop the infection:

1) Either they slow down the development of microbes and destroy their ability to generate and reproduce and spread.
2) Or they kill the bacteria by damaging the bacterial cell walls.

Many antibiotics, including penicillin, work by attacking the cell wall of bacteria. Specifically, the drugs prevent the bacteria from manufacturing a molecule in the cell wall called peptidoglycan, which gives the wall with the strength it needs to survive in the human body. Other antibiotics prevent progressful DNA replication in bacteria. A category of antimicrobials called quinolones targets DNA gyrase; an essential enzyme that helps unwind DNA for replication. By eliminating gyrase from the equation, ciprofloxacin and similar antibiotics completely prevent the bacteria from building up. Some antibiotics, including tetracycline, which is used to treat acne, respiratory tract infections and other conditions, prevent protein synthesis. The drugs do this by forbidding key molecules from binding to selected sites on cell structures called ribosomes, where protein synthesis takes place. Without its proteins, the bacteria cannot carry out necessary functions, including asexual reproduction. The choice of antibiotics varies on the type of bacteria. (5)

ANTIBIOTICS DO NOT WORK ON VIRUSES

Since viruses differ from bacteria, they have different way of surviving. Viruses lack cell wall and so are not attacked by antibiotics. Particular antibacterial hinder with the synthesis of the cell wall, impairing the peptidoglycan scaffold within the bacterial wall so that the structural virtue eventually fails. Since mammalian cells have a plasma membrane but lack the peptidoglycan wall structure, this class of antibacterial discriminatorily spots the bacteria with no symbolic negative effect on the cells of the mammalian host. Vancomycin, a glycopeptide antibiotic with a compelling larger structure, also prohibits cell wall construction by interrupting with transglucosylases.

Penicillins and Cephalosporins are the major antibiotics that constrain bacterial cell wall synthesis. They are called Beta-lactams because of the unusual 4-member ring that is common to all their members. The beta-lactams include some of the most competent, broadly used, and well-tolerated assistants available for the treatment of microbial infections. Vancomycin, Fosfomycin and Bacitracin also inhibit cell wall synthesis but are not nearly as influential as the beta-lactam drugs. The way bacteria and humans make proteins is a little bit different. So, antibiotics can specifically stop bacteria from making proteins while leaving the human cells alone. Aminoglycosides like streptomycin and neomycin attach to a smaller piece of ribosomal RNA (rRNA) within the 30S subunit. When they are attached, the ribosome does not read the mRNA correctly and makes mistakes creating the protein. If the protein is not made correctly, it will not be able to do its job.

Tetracyclines, including doxycycline, avoid the binding of aminoacyl-tRNA by intercepting the A (aminoacyl) site of the 30S ribosome. They are competent of preventing protein synthesis in both 70S and 80S (eukaryotic) ribosomes, but they as a substitute bind to bacterial ribosomes due to structural differences in RNA subunits. Plus, tetracyclines are effective against bacteria by exploiting the bacterial transport system and increasing the concentration of the antibiotic within the cell to be undoubtedly higher than the environmental concentration.

Aminoglycoside antibiotics have an attraction for the 30S ribosome subunit. Streptomycin, one of the most commonly used aminoglycosides, hampers with the creation of the 30S initiation complex. Kanamycin and tobramycin also bind to the 30S ribosome and intercept the formation of the larger 70S initiation complex. Unlike bacteria, viruses get into the cell walls and live in, while making copies of

themselves into the bodily cells. It is because of these facts, that viruses are not affected by antibiotics. (6-7)

ANTIBIOTIC RESISTANCE

The potentiality of the microbes to withstand or resist the effects of an antibiotic is commonly known as antibiotic resistance. The antibiotics are prescribed anonymously throughout the world, and because of this widespread use, the target designed have been altered, in return making the drugs less effective. Antibiotics aren't useful in viral infections, as mentioned earlier, although when they aren't needed, they donate in antibiotic resistance as well as unwanted side effects. As a result, we are so dependent on the same kind of antibiotics, since decades that on contrary are giving the bacteria a better chance to grow / develop resistance to drugs as well as progress and evolve.

During the last 70 years, the bacteria's have revealed the capability to become resistant to every antibiotic that has been developed. (8) Dr. Steve Salomon, Director of CDC's (Centers for Disease Control and Prevention) office of antimicrobial resistance told medical news today, that although the antibiotics have transformed modern medicine and have saved millions of lives over the years, and this has been a main driver for antibiotic resistance. The antibiotic resistance in children and other adults, are of particular worry due to alarming rates of antibiotic use.

Once a particular bacterium becomes resistant to an antibiotic, nursing the infection becomes more arduous and, in some cases, medically out of question or simply unfeasible. Dr. Charles Penn, coordinate of antimicrobial resistance at WHO noted, 'the dependence on antibiotics for the modern medical benefits has contributed to drug resistance.' Similarly, now we suppose that many infections are mendable with antibiotics such as tonsillitis, bacterial pneumoniae but some are nowadays becoming untreatable. Abundant and misuse of antibiotics in food producing animals has also been a key player in drug resistance as resistant bacteria can be transmitted to humans through the food we eat. (9)

Antibiotic resistance is rising to severely high levels in all parts of the world. New resistance mechanisms are appearing and spreading globally, bullying our ability to treat common infectious diseases. A growing list of infections – such as pneumonia, tuberculosis, blood poisoning, gonorrhea, and food borne diseases – are becoming harder, and sometimes impossible, to treat as antibiotics become less effective. Where antibiotics can be bought for human or animal use without a prescription, the emergence and proliferation of resistance is made worse. Similarly, in countries without standard treatment guidelines, antibiotics are often over-stipulated by health workers and over-used by the public. Without immediate action, we are proceeding towards a post-antibiotic era, in which common infections and minor injuries can once again kill. (10)

HOW DOES ANTIBIOTIC RESISTANCE TAKE PLACE?

This phenomenon occurs when the bacteria changes in some way that decreases and abolishes the effectiveness of drugs, chemicals or other agents that are prepared to cure and prevent the infections. Since antibiotic resistance occurs as a unit of natural process and phenomenon in which the bacteria progress, it can be slowed down but not fully stopped. Therefore, newer antibiotics will always be needed to cope with the resistant bacteria as well as new tests to follow the evolution of resistance. The arising issue is that manufacturing new antibiotics have become a time consuming, expensive, and lengthy process. (11)

Bacteria, viruses are living organisms that can mutate over time. They reproduce and spread quickly and competently and can accommodate to their environments and change in ways to ensure their survival. When encountered with an antibiotic that may affect their ability to reproduce, genetic changes (mutations) can occur that enable the microbe to survive. This evolution can happen in a number of ways:

- Selective Pressure: In the presence of an antibiotic, microbes that carry resistance genes can survive and clone themselves.
- Mutation: Most microbes reproduce by dividing every few hours and mutations may occur that can help microbes survive vulnerability to antibiotics.
- Gene Transfer: Microbes collect genes from each other that make the microbe drug resistant.
- Societal Pressures: The widespread use of antibiotics in different spheres of society, sometimes when they're unnecessary, creates

selective pressure that favors resistant organisms to develop.

- Inappropriate Use: Improper use of antibiotics can occur, such as when a healthcare provider will prescribe an antibiotic because an adamant patient has asked for it, even without a diagnosis.
- Inadequate Diagnostics: Sometimes broad-spectrum antibiotics are used even when a particular antibiotic might be better because there is incomplete or imperfect information to diagnose an infection. This contributes to selective pressure.
- Hospital Use: Critically ill patients are more sensitive to infections and they unceasingly need antibiotics, but this increased use along with close contact among sick patients creates an environment where antimicrobial-resistant germs can spread easily.
- Agricultural Use: Adding antibiotics to agricultural feed can boost drug resistance. (12)

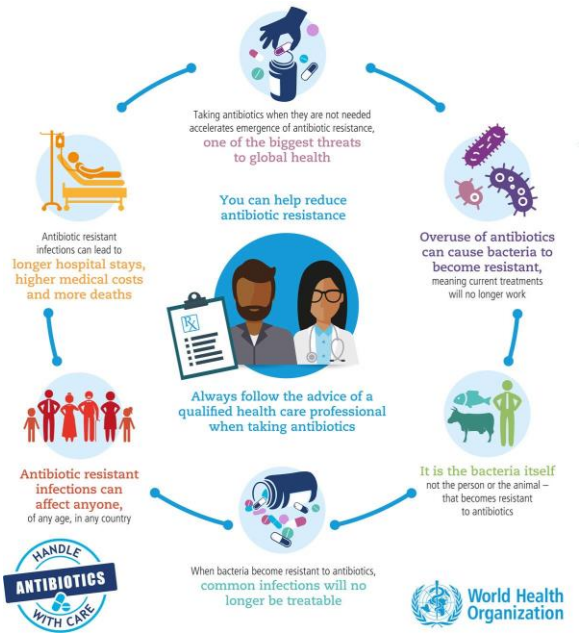

Fig. 1: Ways to reduce Antibiotics Resistance (13)

GERM DEFENSE STRATEGIES

Antibiotics fight germs (bacteria and fungi), but germs fight back and find new ways to survive. Their defense schemes or strategies are called resistance mechanisms. Bacteria develop resistance mechanisms by using directions administered by their DNA. Often, resistance genes are found within plasmids, small pieces of DNA that carry genetic instructions from one germ to another. This means that some bacteria can share their DNA and make other germs become resistant. For instance, Germs restrict access by changing the entryways or limiting the number of entryways. Example: Gram-negative bacteria have an outer layer (membrane) that protects them from their environment. These bacteria can use this membrane to selectively keep antibiotic drugs from entering. (14)

ANTIBIOTIC RESISTANCE THREATENS EVERYONE

Antibiotic resistance has the capacity to influence people at any stage of life, as well as the healthcare, veterinary, and agriculture industries, making it one of the world's most acute public health problems. Each year in the U.S., at least 2.8 million people are infected with antibiotic-resistant bacteria or fungi, and more than 35,000 people die as a result. No one can completely circumvent the risk of resistant infections, but some people are at greater risk than others (for example, people with chronic illnesses).

If antibiotics lose their potency, then we lose the ability to treat infections and control public health threats. Many medical advances are dependent on the efficiency to combat infections using antibiotics, including joint replacements, organ transplants, cancer therapy, and treatment of chronic diseases like diabetes, asthma, and rheumatoid arthritis. (15)

TYPES OF ANTIBIOTIC RESISTANCE

Methicillin-resistant Staphylococcus aureus (MRSA) bacteria commonly seen in hospitals and healthcare settings (hospital acquired or HA-MRSA), but also in among people in close contact such as athletes (community associated or CA-MRSA).

Certain microbes are becoming increasingly resistant to antibiotics:

- Food-borne bacteria responsible for food poisoning such as E. coli, Salmonella, and Campylobacter
- Sexually transmitted bacteria that cause gonorrhea

- Penicillin-resistant Streptococci that cause pneumonia.
- Tuberculosis
- Influenza
- Human Immunodeficiency Virus (HIV)
- Malaria

N. gonorrhoeae causes the sexually transmitted disease gonorrhea. Lack of potent treatments to cure at least 95% of the population with gonorrhea could lead to a notable public health concern. Gonorrhea has evolved resistance to most antibiotics used for its treatment. These bacteria are now resistant to the fluoroquinolone antibiotics like ciprofloxacin (Cipro). The CDC lists drug-resistant Neisseria gonorrhoeae as an "urgent" threat. (16)

RECOGNIZION ANTIBIOTIC – RESISTANT INFECTIONS

Tests may be used to judge which microbe is causing an infection and to which antibiotics the microbe might be resistant (called a “culture and sensitivity”). But often, diagnostic tests can take days to weeks to get results because many of tests need the microbe to grow over a period of time before it can be detected.
Samples may be taken of blood, urine, stool, sputum, tissue, cerebrospinal fluid (CSF), or mucus from the nose, throat, or genitals. Samples may then be stained and examined under a microscope, cultured (allowed to grow), or tested for antibodies, antigens, or genetic material (such as DNA or RNA) from the microorganism to determine the organism responsible for the infection. In many cases treatment decisions are required before test results are known and healthcare providers may suggest broad-spectrum antibiotics when a more specific treatment might be better.

HOW TO TACKLE WITH ANTIBIOTIC RESISTANCE?

Antibiotic resistance is quickened 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 lower the consequences and restrict the spread of resistance. Developing or introducing new antibiotics alone cannot help in combating the resistance. In order to prevent this, there should be drastic alterations or modifications in the way antibiotics are prescribed and suggested by the doctors and also consumed by the patients, since it has become a key to antibiotic resistance. (17)

General strategies for tackling with antibiotic resistance:

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 doctor says you don’t require them.
- Always follow your doctor’s advice when using antibiotics.
- Never share or use leftover antibiotics.
- Take an antibiotic exactly as the doctor tells you.
- Do not skip doses. Complete the prescribed course of treatment even if you are feeling better. If treatment retards too early, some bacteria may survive and re-infect.
- Antibiotics should be taken in the right amount and at the right time. A wrong dose of antibiotics makes the drug impotent. Also, extreme intake of drugs may kill the useful bacteria present in our body.
- Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, practicing safer sex, and keeping vaccinations up to date.
- Prepare food hygienically, following the WHO Five Keys to Safer Food (keep clean, separating raw and cooked, cook thoroughly, keep food at safe temperatures, use safe water and raw materials) and choose foods that have been produced without the use of antibiotics for boosting growth or disease prevention in healthy animals.
- Most importantly antibiotics should not be consumed for viral infections. (18)

PRECAUTIONS FOR WOMEN BEFORE TAKING ANTIBIOTICS

- Antibiotics often lead to a vaginal yeast infection. Because antibiotics kill the normal bacteria in the vagina, yeast no longer have competition for food and grow rapidly. Yeast cells begin attacking tissues in the vagina, usually causing one or all of

the following symptoms: itching, burning, and vaginal discharge.

- Antibiotics may reduce the adequacy of birth control pills.
- Certain antibiotics are believed to pose risks during pregnancy. For example, tetracyclines can discolor a growing baby's teeth. Tetracyclines aren't recommended for use after the 15th week of pregnancy.
- As with other medications, some antibiotics may be transferred to a fetus, and some may cause harm. Therefore, should never take antibiotics without the doctor's knowledge if pregnant or nursing.
- Use medications only if actually designated. For antibiotics, this includes treatment of proved infection (urinary tract infection, pyelonephritis, appendicitis, cholecystitis, chorioamnionitis), prevention of increasing infection (asymptomatic bacteriuria), and prevention of early-onset neonatal GBS sepsis.
- If possible, avoid initiating therapy during the first trimester. This is the period of fetal skeletal development and therefore the maximum risk for iatrogenic teratogenicity.
- Select a safe medication, which often means an older drug with a proven track record in pregnancy. Certain antibiotics (streptomycin, kanamycin, tetracycline) are best avoided entirely in pregnancy because of their teratogenicity. (19)

INTERNATIONAL ACTION ON THE ANTIBIOTIC RESISTANCE

The World Health Organization (WHO) has become quite anxious about the rising levels of resistant bacteria in all areas of the world. To provide some global coordination, WHO issued its Global Strategy for Containment of Antimicrobial Resistance, a document anticipated at policymakers that incentive governments to take action to help contain antibiotic resistance.

Developing nations need to focus on eradicating unchecked access to antibiotics and prevention measures such as improving sanitation, cleaning up water supplies and relieving overcrowding. These preventative measures, along with frequent hand washing, would ensure that people get sick less often, and would therefore pass on fewer resistant infections to others.

Industrialized countries need to focus on prevention measures such as limiting antibacterial use, developing vaccines that can protect certain vulnerable populations such as young children, controlling multi-resistant bacteria in hospitals and in the community, and reducing antibiotic use in animal farming and agriculture.

Experts agree that a global system for tracking antibiotic resistance is needed. It would serve as an indicator for recognizing "hot-spots" of resistance and measuring trends that can tell us if our educational programs or other solutions are having positive effects. (19)

CAN THE EFFECTIVENESS OF EXISTING ANTIBIOTICS BE PRESERVED?

To preserve the potency of existing antibiotics, overall antibiotic use must be decreased. Physicians, pharmacists, and the general public must avoid careless use of these valuable drugs. Antibiotics must be prescribed only for bacterial infections and in the proper dose for the correct amount of time. Narrow spectrum drugs should be chosen by doctors whenever possible to avoid wrecking populations of beneficial bacteria along with the disease-causing bacteria. In addition, non-therapeutic uses of antibiotics in farm animals and agriculture should be eliminated. (20)

CONCLUSION

Antibiotic Resistance (AR) is one of the most urgent threats to public health. AR is a “one health” problem and associates to the health of people, animals, and the environment. Each year in the United States, at least 2.8 million people are infected with antibiotic-resistant germs—at least 35,000 die. Antibiotic resistance occurs when germs beat the drugs devised to kill them. It does NOT mean the body is resistant to antibiotics.

Antibiotic resistance can affect people at any stage of life. Infections caused by resistant germs are difficult—sometimes impossible—to treat. In many cases, these infections require protracted hospital stays, additional follow-up doctor visits, and the use of treatments that may be expensive and potentially noxious to the patient. Healthy habits can protect us from infections and aid us stop germs from spreading.

Getting recommended vaccines, keeping hands and wounds clean, and taking good care of chronic conditions, like diabetes. Antibiotics save human and animal lives. Any time antibiotics are used, they can promote to side effects and resistance. Antibiotics do not work on viruses, such as colds and the flu. Talk to the healthcare provider or veterinarian about whether antibiotics are needed. Antibiotic resistance has been found in all regions of the world. Modern trade and travel mean AR can move easily across borders. It can spread in places like hospitals, farms, the community, and the environment. Tell the healthcare provider if we have recently traveled to or received care in another country.

REFERENCE

[1] Retrieved by: https://www.rxlist.com/antibiotic_resistance/drugs-condition.html

[2] Retrieved by: https://www.medicalnewstoday.com/articles/282357

[3] Retrieved by: https://www.frontiersin.org/articles/10.3389/fmicb.2015.00034/full

[4] R. Velez, E. Sloand, "Combating antibiotic resistance, mitigating future threats and ongoing initiatives". J Clin Nurs (March) (2016)

[5] Retrieved by: https://www.health.qld.gov.au/news-events/news/antibiotics-viruses-cold-flu

[6] Sojib Bin Zaman et al. "A review on antibiotic resistance: Alarm bells are ringing". Cureus (2017), 9(6).

[7] Retrieved from: https://accesspharmacy.mhmedical.com/

[8] Karen Bush et al. Tackling Antibiotic Resistance. Nature Reviews Microbiology. 2011; 9. 894-896.

[9] R. Wesgate, P. Grasha, J.Y. Maillard. "Use of a predictive protocol to measure the antimicrobial resistance risks associated with biocidal product usage". Am J Infect Control, 44 (April (4)) (2016), pp. 458-464.

[10] Retrieved by: https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance

[11] Alemayehu REta, Abebaw Bitew Kifilie, Abeba Mengist, "Bacterial Infections and their Antibiotic Resistance Pattern in Ethiopia: A systematic Review", Advances in Preventive Medicine, vol. 2019, Article ID 4380309, 10 pages, 2019.

[12] Retrievedby:https://www.medicinenet.com/antibiotic_resistance/article.htm#what_is_antibiotic_resistance

[13] https://www.un.org/sustainabledevelopment/blog/2018/01/un-health-agency-finds-high-levels-antibiotic-resistance-worlds-common infections /misuse_overuse_infographic_fa_171023/

[14] Retrieved by: https://www.cdc.gov/drugresistance/about/how-resistance-happens.html

[15] Dan I. Anderson et al, "Antibioitic Resistance & its cost: is it possible to reverse resistance?". Nature Reviews Microbiology. 2010, 8; 260-271.

[16] Retrieved by: https://www.drugs.com/article/antibiotic-resistance.html

[17] N Taneja, "Antibiotic Resistance in the environment: The Indian Scenario", IJMR, 2019.

[18] F. C. Tenover, "Mechanisms of antimicrobial resistance in bacteria," American Journal of Infection Control, vol. 34, no. 5, pp. S3–S10, 2006.

[19] Retrieved by: https://apua.org/what-can-be-done

[20] S. J. Leopold, F. van Leth, H. Tarekegn, and C. Schultsz, "Antimicrobial drug resistance among clinically relevant bacterial isolates in sub-Saharan Africa: a systematic review," Journal of Antimicrobial Chemotherapy, vol. 69, no. 9, Article ID dku176, pp. 2337–2353, 2014.