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Antibiotic Resistance, Causes and Interventional Measures to Overcome Drug Resistance

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Antibiotic resistance occurs when microbial organisms like bacteria and fungi develop the ability against killing or restrict their growth of them with the drugs designed against them. This means the microbes are not destroyed rather continue to grow and spread infections. Millions of humans and animals are affected by this condition on the challenge with antibiotics in the face of infectious diseases. Transmission of antibiotic-resistant microorganisms between animals and humans and vice versa cause an immense health problem both human and animals in one health perspective around the world through zoonosis. The prevalence of antibiotic resistance in the animal-human interface is a complex phenomenon; it involves multiple transmission routes, vehicles, vectors, hosts, antimicrobial selective pressure, and other ecological factors. Antibacterial resistance involves one health approach through the interaction of different stakeholders such as veterinarians, medical doctors, farmers, agricultural specialists, animal food professionals, environmentalists, and wildlife experts.

The three fundamental mechanisms of antimicrobial resistance are (1) Enzymatic degradation of antibiotics (2) Alteration of bacterial proteins that are antimicrobial targets, and (3) Changes in membrane permeability to antibiotics into cells for effective concentration.

Why antibiotics are essentially used?

Before the discovery of antibiotics, the infections were checked by means of chemotherapy but this chemotherapy is not like the chemotherapy of modern era chemotherapy against cancer. The then chemotherapy means the use of chemicals from the man-made chemicals of biological origin. For example, Diphtheria antitoxin developed from horse serum, different disinfectants from coal tar such as phenol, mercuric chloride as antiseptic,

ammonia,and formaldehyde called hexamethylene-tetramine used as a urinary antiseptic, bismuth salicylate were used as antidiarrhoeal restricting bacterial growth under alkaline conditions in the intestine. But all infections were not cured and the healing may be due to the development of immunity andend of disease course. Sulfa drugs were first used in the 1930 but it was not an antibiotics

In 1928, at St. Mary's Hospital, London, alexander Fleming discovered penicillin and its use of it for effective treatment in the year of 1940s by British and American soldiers. After that several antibiotics were discovered and isolated from fungi (penicillin, Griseofulvin, Erythromycin, Gentamicin, etc), bacteria (bacitracin, Streptomycin, Tetracycline,) and synthetically derived (Chloromycetin, Quinolones). Several antibiotics have been discovered from 1940 to 1970 and their extensive indiscriminate used assisted to develop antibiotic resistance, however antibiotic resistance was reported in the year 1940 by Streptococcus sp. The methicillin-resistant *Staphylococcus aureus* bacterium was reported in 1942 before the extensive use of antibiotics.

Massive antimicrobial agents have been used for the treatment of infections to restrict morbidity and mortality, production of food animals as a growth promoter for early weaning of food animals, for increased body weight gains. Doctors, veterinarians, and paramedical staff used indiscriminately antibiotics for infections and non-infected diseases as well. The amount and frequency of use of antibiotics in food animals are the major determinants of bacterial resistance and transmission to newer hosts. The most common bacterial transmission from animals to humans through mainly food chain are *E.coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *acinetobacter baumannii*, *Pseudomonas aeruginosa,* Streptococcus pneumonia *Salmonella sp*,Yersinia sp, *Campylobacer sp*, *Pseudomonas aeruginosa*, etc

Antibiotic resistance is a global burden

It has been reported that every year millions of human patients and animals suffer from a lack of proper treatment with antibiotics at the verge of bacterial resistance. About one-fifth of the infected patients are dying of improper treatment with antibiotics. The scientific community, veterinarians, and medical doctors are with consensus that antibiotic resistance is a big threat in the treatment regime against bacterial infections worldwide. Although there is a lack of antibiotic-resistant data from many parts of the world. Due to increasing antibiotic resistance

high risk of mortality amongst critical patients both humans and animals. There are several threats that create by antimicrobial resistance (AMR) causing several burdens in human and veterinary productivity. Antimicrobial resistance is also including antiparasitic and antifungal resistance. The AMR causes several burdens in animal and human societies (Ventola, 2015).

Economic burden- Normally, the cost of antibiotics is not very much for a single course but a repeated changes of antibiotics due to resistance for a specific infection needs to spend a lot of money. In India, the overall extra cost of antibiotics due to resistance for a common man family may be as high as one year's income, moreover, during the sick period, one cannot work for income generation that also a social burden for common people in society. The increasing AMR may consequently be 1-3% of a nation's GDP by 2030.

Health burden – Health burden is consisting of morbidity and mortality caused by a specific infection. Prolong infections such as tuberculosis, paratuberculosis, brucellosis, typhoid fever which may extend their course from months and years, practically causes normal health issues. Due to prolong disease periods several death may occur and survived animals and humans remain less productive and have reproductive performance. Six microorganisms that are very health burden due to AMR are *Klebsiella pneumonia*, *Salmonella pneumonia*, *E.coli*, *Staphylococcus aureus*, *Acinetobacter Baumannii*, and *Pseudomonas aeruginosa* (Murrey *et al*, 2022)

Production burden- Production from animals are milk, meat, egg, hairs, skin, etc. are goals for animal rearing. Due to increasing in infections on global pollution and microbial transmission along with drug resistance to animals causes a high risk for the occurrence of many diseases. Every disease is a big stress for effective productivity as a result production goes down in quantity and quality. For example mastitis, Johne's disease, and tuberculosis in animals cause a heavy loss in production(milk, meat, wool, etc) as these diseases have few suitable antibiotics and in most cases, aMR persists.

The causes of antibiotic resistance

The bacterial cell can change its genetic materials and genes frequently as per its need and environment. Antibiotics are toxins to bacteria, usually used against different infections but irrational use of antibiotics such as underdoes, overdoses, an environmental pollutant with antibiotics, food antibiotic contaminant, used as a growth promoter, indiscriminate use of

antibiotics, self antibiotic prescription with little knowledge are causes of AMR threat and prolonguse of antibiotics for prophylactic in a susceptible population. There are several methods to recombining their genetic makeup suitable for their smooth living in different environments. The methods are transformation, conjugation, and transduction.

Prokaryotic cells have developed a number of methods for recombining their genetic materials, which in turn, contributes to their genetic diversity. The three most common ways that bacteria diversify their DNA are transformation, conjugation, and transduction. In transformation, the bacteria can receive extracellular DNA, while in transduction genetic materials (DNA) transfer from one bacterium to another bacteria by means of a vector bacteriophage virus. In conjugation, donor bacteria transfer their DNA to recipient bacteria by mating i.e parasexually transfering. Drug resistance is a mobile dynamic where genes can be transferred amongst different taxonomic and ecological groups by means of mobile genes, bacteriophage, plasmid, necked DNA, or transposon (jumping genes)

Therefore, the bacteria can change their activity and physiological functions with changing of their genetic materials. Basically, there are several processes through which they can adapt themselves and become resistant to their toxins (antibiotics). They are (1) limiting uptake of a drug (antibiotic); (2) modifying a drug target; (3) inactivating a drug; (4) active drug efflux(5) Biofilm formation

Besides human medicine who can contribute antibacterial resistance?

In food-producing animals and aquaculture antibiotics are used for growth promoters, prolong use of the antibiotics such as avoparcin, zinc bacitracin, virginiamycin, avilamycin, monensin, salinomycin, lasalocid, etc can cause evolving of resistant strains of bacteria that affect animal and human health. In agriculture, Streptomycin is used in pear, and apple blight caused by *Erwinia amylovora*. This antibiotic causes more drug resistance. Soil is considered as the reservoir of antibiotic resistance genes, as many antibiotics are drained out in soil through water that has been used for human and animal treatment. Drug resistance is much common in six main regions of the world are South East asia, the Western Pacific region, the african region, the North american region, the Mediterranean region, and western Europe.

In India, animal antimicrobial resistance transmission occurs through meat, milk, eggs, fish, and aquaculture food.

Effect of antibiotic resistance

The most untoward effect of AMR are many, some are as follows

- Therapeutic output with resistant infectious agent leading to a chronic problem
- The adverse effect of long use of antibiotics damaging liver, ear, kidney,immune system, etc
- Increase morbidity and mortality with resistant microbial infection
- Recurring infection after treatment
- Increased transmission of resistant bacteria to many newer hosts
- Extended health and treatment cost with an infection
- Complicated and prolonged stay in hospital or under treatment
- Reduced productivity and Reproduction performance
- Development of a resistant variety of bacteria strains eg MRSA (Methicillin-resistant Staphylococcus aureus, MDR-TB (Multidrug resistant-tuberculosis), Resistant acinetobacter sp, VRE (Vancomycin-Resistant Enterococci), Klebsiella pneumoniae carbapenemase (KPC)

Diagnosis of antibiotic resistance

(1) Isolation and Identification of bacteria from patient's sample. application of antibiotics with regular antibiotic on the patient with no response against the diseases even up to an extended period of treatment

(2) **Cultivation and drug sensitivity test**: The standard method for identifying drug resistance is to be taken from a sample of the wound, blood, urine, milk, nasal discharge, fecal samples and expose resident bacteria to various antibiotics. If the bacterial colony continues to divide and thrive despite the presence of a normally effective drug, it indicates the microbes are drug-resistant.

(2). Molecular diagnosis- Bacterial antibiotic-resistant genes can be transferred to next generations. New resistant genes and vectors of transmission are identified on a regular basis. This can be done by PCR amplification of target DNA and the amplicon is confirmed

by gel electrophoresis, probe hybridization techniques, or DNA sequencing. Standard PCR with amplicon sizing by gel electrophoresis.

Management and prevention of antibiotic resistance

- **Introduce new therapeutic approach**- lack of suitable antibiotics in the face of antibacterial resistance use drugs more prudently, selective drug use and reduce the use of resistant drugs gradually improve resistance, although its speed is very slow
- **Development of newer antibiotics** which can block the resistance mechanism or they attack newer target or changed the mechanism of action
- **Development of rapid diagnostics** that can help in the prescription of newer /changed drugtherapy
- **Phage therapy**- it is a potential source of therapy against resistant bacteria. Phage can penetrate into bacteria by destroying the bacterial protoplasm, particularly in *Pseudomonas aurugenosa* and *Fusobacterium nucleatum*, *Streptococcus* sp., *Proteus mirabilis*., *Listeria* sp.,*E.coli,* etc. Phage PB-1, T4 etc can be used even in complicated infections (Gonzalez and Chalap,2020)
- Development of a conjugate vaccine that can demolish bacterial diseases, particularly for Hemophilus influenza, Pneumococcus sp. (Levy and Marshall, 2004)
- Avoid infections with AMR by means of cleanliness and use of disinfectant for hand wiping, instrument, and mask for environment aerosol inhalation
- Prescribe and dispense antibiotics when it is actually needed avoid indiscriminate use of antibiotics for human-animal and agriculture.
- Use of another system of drug therapy when essentially needed such as Ayurvedic drug, Homeopathic drug,
- Avoid biofilm formation through cleanliness and preventing attachment of biofilm on the biological and inert surfaces
- **Use of nanoparticles** along with antibiotics- Nanoparticles help to reach antibiotics in aneffective concentration to the target tissues. Infections with *Pseudomonas aurugenosa*, *E.coli, acinobacterium Baumann* can be checked by application of nanoparticles and antibiotics as a synergistic effect.

- Avoíd antíbíotícs as growth promoters for anímal productíon and aquaculture
- Regular vaccínatíon agaínst ínfectíon ín endemíc areas and stríct bíosecurítγ measures needed
- Íntegrated awareness wíth antíbíotíc resístance to socíetγ, veterínarγ and aquaculture stakeholders

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