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Review of the causes of antimicrobial resistance

Review article

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Introduction

Antimicrobial agents particularly antibiotics have been critical in the fight against infectious diseases caused by pathogenic microorganisms including bacteria, fungi, viruses and protozoa [1]. There usage in clinical medicine for treating infectious diseases has drastically leads to increase in the life expectancy of the human race over the past six decades. This is because the discovery and usage of antibiotics in infectious disease management has helped to reduce the rate of morbidity and mortality caused by infectious disease pathogens in human population. However, in recent years there has been a marked rise in the number and type of antimicrobial resistant organisms [2].

Antibiotic resistance is one of the biggest challenges to the health sector worldwide, and this medical quagmire threatens our ability to effectively manage and treat some infectious diseases. Microbial resistance to antibiotics and/or antimicrobial agents has been documented not only against antibiotics of natural and semi-synthetic origin such as the penicillins, but also against some purely synthetic compounds (such as the fluoroquinolones) or those which do not even enter the cells (such as vancomycin). And unfortunately, the slow pace in the discovery and development of novel antibiotics have not actually kept pace with the emergence and rate at which bacteria develops and mount resistance to some available antibiotics [3].

Some infectious diseases including but not limited to tuberculosis, bacterial pneumonia, septicaemia, gonorrhoea, wound infections and otitis media are now becoming recalcitrant to treat with some available antibiotics because the causative agents of these diseases are fast becoming resistant to some available antibiotic therapy. These antibiotic resistant organisms have developed several novel ways and mechanisms that allow them to ward-off the antimicrobial onslaught of potent antimicrobial agents and/or antibiotics targeted towards them. This article reviews the primary resistance mechanisms.

Antimicrobial resistance as an adaptive response

The number of antibiotics belonging to various families, their varied mode of action and the number of bacteria in which antibiotic resistance has been documented suggests that, in principle, any microbe could develop resistance to any antibiotic. It is also noteworthy that most microorganisms that are antibiotic producers are resistant to their own antibiotic. This phenomenon actually gives impetus to the school of taught that microbial resistance is a natural process of microbial adaptation in their environment [4].

For a microbe to resist the onslaught of antibiotics, it means that a given pathogen continues to live and multiply even in the presence of potent antimicrobial agent(s) capable of killing or inhibiting its growth. Antibiotic resistance is a phenomenon that occurs when bacteria are not killed or inhibited by usually achievable systemic concentration of an antibiotic (drug) with normal dosage schedule and/or fall in the minimum inhibitory concentration (MIC) ranges of the drug in question [5]. Antibiotic resistance occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs or other agents designed to cure or prevent the infection

that the organism causes. Thus, the bacteria survive and continue to multiply causing more harm in the host taking the drug instead of abating the patient's disease condition. Microorganisms harbour resistance genes and/or traits which encode various mechanisms that allow them to resist the killing or inhibitory effects of specific antibiotics directed towards them. These mechanisms also offer resistance to other antibiotics or antimicrobial agents of the same class and sometimes to several different antimicrobial classes. Resistant microorganisms survive exposure to a given antimicrobial agent and continue to multiply in the body, potentially causing more harm and spreading to other animals or people directly or indirectly.

Antimicrobial resistance and selective pressure

Some available antimicrobial agents have been underused or misused in human medicine, agriculture and veterinary practice; and this development have allowed these microbes to develop resistance to these agents through selective pressure [6].

Antibiotic selective pressure can be defined as the impact of antibiotic usage on a population of microorganisms in which the microbes that are resistant to the antibiotic gain (or acquire) a survival advantage over those bacteria that are susceptible to the antimicrobial onslaught of the drug. The advantage gained by the resistant microbes is so unique because it allows them to take over the niche or habitat left by the antibiotic-susceptible bacteria (which were all killed by the antibiotic). The resistant bacteria starts to spread in that particular environment even as it proliferates and ensures a continued reservoir of antibiotic-resistant bacteria. This kind of development allows some chronic infections caused by drug-resistant microbes to persist and cause more harm to the individual. Microbial strains that harbour antibiotic resistance genes are usually more likely to clonally disseminate under some environmental conditions such as antibiotic selective pressure that encourages their dissemination within a given community [7].

Intrinsic resistance

Some bacteria are said to possess innate/intrinsic resistance against antibacterial action put forward by antibiotics. These microbes mount a great ingenuity in devising means or ways of neutralizing the killing or growth inhibitory action of antibiotics directed towards them. This innate form of antibiotic resistance in bacteria shows the different variations in the structure of the cell envelope of the organism, which allows them to mount resistance against drugs. The structural makeup of some bacteria also makes them to be naturally resistant to antibiotics. For example, the cell wall of Gram-negative bacteria contains outer membrane that covers the bacterial cell wall and thus makes it difficult for antibiotics to reach the cell wall of the organism. Innate (natural) resistance is a vertical means by which bacteria acquire resistance; and this usually occurs through spontaneous mutation. In vertical gene transfer, microbes transfer their genetic material or DNA to their progeny during cell division and/or DNA replication. Once a spontaneous mutation leading to the development of resistance genes occur in a bacterium; the resistance genes so developed can be passed on to all the bacteria progeny during cell division or DNA replication. This type of mutation is rare in bacterial population. But when it occurs, the subsequent progeny acquires the resistance genes formed. A spontaneous mutation in the bacterial chromosome imparts resistance to a member of the same bacterial population, and this continues as the organism undergoes DNA replication. This exemplifies how genes or DNA can be transferred amongst microbial populations via a vertical gene transfer mechanism. Intrinsic or innate form of antibiotic resistance can occur by any one of the following route (8):

- Spontaneous mutation in the chromosomal DNA of bacteria.
- Accumulation of several point mutations in bacteria.
- An evolutionary process occurring only under selective pressure such as in the prior exposure of bacteria to antibiotics.

Acquired resistance

Microorganisms develop numerous mechanisms including mutation in order to acquire resistance to antimicrobial agents or antibiotics. Acquired resistance is a type of antibiotic resistance that is acquired by bacteria from their environment or from other drug resistant microorganisms by one of the mechanisms of genetic transfer. Conjugation, transformation, and transduction are typical examples of genetic transfer mechanisms via which microorganisms can transfer their genetic material (i.e. the DNA) from one organism to another. Conjugation is a direct cell-to-cell contact between two bacteria via which the transfer of small pieces of DNA called plasmids takes place. Transformation is a process where parts of a DNA are

taken up by the bacteria from the external environment. Transduction occurs when bacteriophages or phage (i.e. bacteria-specific viruses) transfer DNA between two closely related bacteria [9].

In acquired/phenotypic resistance, the bacteria acquire reduced susceptibility to antibiotics through adaptation to growth within a specific environment (such as undue exposure to antibiotics). Acquired resistance is a horizontal means by which bacteria become resistant to the antibacterial properties of antibiotics. In horizontal gene transfer (HGT), the genetic material or DNA of a given organism can be transferred between individual bacterial of the same species or even amongst individuals of different species. In acquired resistance, the organism acquires new genetic material (especially those that mediate antibiotic resistance) from another organism or from other sources. Acquired resistance can be achieved in bacteria by several routes.

- Resistance can be maintained on horizontal mobile elements like plasmids, integrons and transposons. These mobile genetic elements serve as route through which antimicrobial or antibiotic resistance genes can be passed on from one organism to another through genetic transfer mechanisms such as conjugation.
- Resistance genes can be transferred among bacteria through one of the mechanisms of genetic transfer including transduction, conjugation and transformation.
- Resistance genes can be integrated into the bacterial chromosome or can be maintained in an extra chromosomal state such as plasmids. Susceptible bacteria pick up resistance plasmid from their environment and become resistant to antimicrobial agents afterwards.

Mechanisms for the transfer of resistance genes

Antibiotic resistant bacteria owe their drug insensitivity and ingenuity in developing resistance against our therapeutic regimens to resistance genes which they harbour or possess. These resistance genes can either be inherently (naturally) part of the organism's physiology or it can as well be acquired from other resistant organisms in their environment. It is these resistance genes that resistant bacteria transfer to non-resistant (susceptible) strains of microbes, thus compounding the problem of antibiotic resistance [10].

Conjugation

Conjugation is the form of gene transfer and recombination in bacteria through which genetic materials (DNA) are transferred from one bacterium to another through a direct cell – to – cell contact. It occurs by direct contact between two bacteria; and this contact leads to the transmission of genetically important materials such as plasmids amongst bacterial population. Conjugation is the most important genetic transfer mechanism by which bacteria transfer their antibiotic resistance genes to susceptible bacteria. Conjugation is mediated by a particular kind of circular DNA called a plasmid, which replicates independently of the chromosome.Many plasmids carry genes that confer resistance to antibiotics. When two bacterial cells are in close proximity to each other, a hollow bridge like-structure known as the "pilus" forms between the two bacterial cells. This allows a copy of the plasmid as it is duplicated to be transferred from one bacterium (known as the donor cell) to another bacterium (known as the recipient bacterial cell). This process called conjugation enables a susceptible bacterium to acquire resistance genes to a particular antibiotic from another organism which harbours resistant genes [11].

Transformation

Transformation is a mechanism of genetic transfer in bacteria in which a piece of free DNA (genetic material) is taken up by a bacterium and integrated into the recipient genome. During this process of transformation, genes are transferred from one bacterium to another as "naked" DNA. When bacterial cells die and break apart through cell lysis, DNA can be released into the surrounding environment. Other bacteria in close proximity can scavenge this free-floating DNA and incorporate them into their own DNA. This incorporated DNA can contain advantageous genes such as antibiotic resistance genes and benefit recipient bacterial cells which resultantly become resistant to the antimicrobial agent or antibiotic that the resistant gene codes for [8].

Transduction

Transduction is the transfer of genetic material between bacteria by bacteriophages or phages. Bacteriophages are bacterial viruses. A phage or bacteriophage is a virus that uses bacteria as its host. In transduction, antibiotic resistance genes are incorporated into a phage capsule which is later injected into another bacterium. In the

process of transduction, bacterial DNA is transferred from one bacterium to another inside a virus that infects bacteria. These viruses that infect bacteria are called bacteriophages or phages. When a phage infects a bacterium, it essentially takes over the genetic process of the bacteria to produce more phages. During this process, bacterial DNA may inadvertently be incorporated into the new phage DNA. Upon bacterial death and lyses or breaking apart, these new phage goes on to infect other bacteria in the environment. This brings along genes from previously infected bacterium into the recipient bacterium. These genes might contain advantageous genes such as antibiotic resistance genes, which will leave the recipient bacterium resistant to a particular antimicrobial agent or antibiotic [9].

Resistance by influx-efflux systems

Certain bacteria can often become resistant to antimicrobial agents or antibiotics through a mechanism known as "efflux". Efflux pumps are pumps found in bacteria cells. These pumps help them to export antimicrobial agents and/or antibiotics and other chemical compounds out of the bacterial cell. The antibiotics enter the bacteria through chemical channels called "porins" found on the bacterial cell membranes. However, some resistant bacteria with the influx-efflux mechanisms uses this system to pump out antimicrobial agents from the cell in order to prevent the intracellular accumulation of the drug required to kill or inhibit an important metabolic process in the target bacterium. By actively pumping out the antibiotic and other harmful substances out of the cell, the efflux pumps prevents the intracellular accumulation of the antimicrobial agent that is necessary to exert optimal antibacterial activity inside the bacterial cell. Increased expression of the efflux pump mechanisms in bacteria can result in antibiotic resistance in bacterial population. Bacterial cells have an inherent (natural) capacity to restrict the entry of small molecules (e.g. antibiotics) that destabilizes its internal metabolism and interferes with the normal growth and developmental process of the organism. This is what the cell wall and outer cell membranes in both Gram-positive and Gram-negative bacteria respectively do [12].

The ability of bacteria to restrict the entry of harmful materials into their internal environment is more pronounced in Gram-negative bacteria unlike in Gram-positive bacteria which are devoid of "outer membrane" that the former possesses. The "outer membrane" is a first-line defence mechanism in Gram-negative bacteria, and its absence in Gram-positive bacteria is the reason why Gram-positive bacteria are highly sensitive to antibiotics than their Gram-negative counterparts. This is because there is no form of security or outer covering to protect the peptidoglycan of Gram-positive bacteria as is applicable in Gram-negative bacteria with outer membrane. The "influx - efflux" system in bacteria has to do with the entry and partial accumulation of harmful substances like antibiotics within the cytoplasm of a bacterium and the subsequent exit or removal of these harmful substances from the bacterial cell through efflux pumps. The "efflux system" in bacterial cell pumps out the antibiotics that finally made their way into the cytoplasm of the bacterium, thereby preventing their intracellular accumulation. The most well studied efflux system is in *Escherichia coli* and with this mechanism in place; bacteria can easily mount resistance to antibiotics directed against them.

Resistance by chemical alteration of antimicrobials

Antibiotics are expected to exert killing or inhibitory effects on their target pathogenic microorganisms when in vivo. However, some resistant microbes have developed mechanisms through which they alter the chemical composition or structural/functional groups of antibiotics so that the antimicrobial agent will be rendered inefficacious for therapy in vivo. Chemical alteration of antibiotics is thus one major mechanism via which bacteria can become resistant to an antibiotic. Some antibiotics need to be activated in vivo before ever they can reduce (bring out) their antibacterial activity against a target pathogen to which they were meant to attack and kill or inhibit its growth. Antibiotics whose functional group are deactivated or altered in vivo by bacteria are usually activated in vivo by being reduced by a specific enzyme or gene; and only then can such drug be able to elicit their biological properties in vivo. For example, antibiotics in the Nitrofuran family such as nitrofurantoin (notable for their usage in treating urinary tract infections, UTIs) are reduced by cellular reductase enzymes encoded by specific genes in the target organism; and any mutation in these genes can eventually lead to a nitrofuran resistance. More so, some pathogens produce enzymes such as beta-lactamase enzymes that alter the chemical structure and/or biological function of some antibiotics. Thus, the chemical alterations of some antibiotics such as antibiotics in the beta-lactam group like

the penicillins and cephalosporins in vivo by antibiotic-degrading enzymes (e.g. beta-lactamases) can inactivate the biological activity of these antibiotics, thereby leading to resistance [13].

Resistance due to target alternations

Microorganisms including bacteria and fungi have specific target site(s) for drug-binding on their cell wall or cell membranes. Antibiotic resistance in bacteria could develop as a result of alteration in any of these target site(s); and this prevents the drug from binding and carrying out its notable antimicrobial activity either in vivo or in vitro. Most pathogens have the ability to alter target sites(s) of antibiotics in their cell. These alterations as aforementioned in the target of the drugs on the organism occur in such a way that the action of the antibiotic on the target pathogen is countered or prevented. Alteration of the penicillin-binding-proteins (PBPs) in bacteria result in antibiotic resistance to some classes of antibiotic especially the beta-lactam drugs such as the penicillins that have high affinity for the PBPs. The penicillin-binding-proteins (PBPs) are transpeptidases which catalyze the cross-linking reaction between two stem peptides N-acetyl muramic acid (NAM) and N-acetyl glucosamine (NAG). And each of these molecules is linked to the peptidoglycan backbone which is the major component of bacterial cell wall.

The reaction that catalyzes the cross-linking of NAM and NAG is known as transpeptidation reaction. This reaction leads to the formation of peptidoglycan layer that gives rigidity to the bacterial cell wall. Penicillin and other beta-lactam drugs exerts their antibacterial activity by binding to the PBPs, thereby preventing the cross-linking of N-acetyl-muramic acid and N-acetyl-glucosamine that will eventually lead to the formation of a very rigid bacterial cell wall. But alterations in this important drug target sites on the pathogen (i.e. the PBPs) can make the organism to resist antimicrobial action from beta-lactam drugs. The alterations in drug target sites could also be mutational in which case a mutation in the target site could prevent the binding of the drug [14].

Resistance due to non-inheritable states of bacteria

Microorganisms including bacteria and fungi have some non-heritable physiological states which are inherent with the organisms; and which aid or assist them to evade antimicrobial onslaughts of antimicrobial agents and/or antibiotics. These physiological states of microbes are not transferable like resistant plasmids and transposons that carry resistant traits and thus could be transmitted from one organism to another. The non-heritable form of antibiotic resistance posed by bacteria to antibiotics has to do with some physiological states in which bacteria exist in, and which are not heritable or transferred by other organisms as aforementioned. These non-heritable physiological states of bacteria include the biofilm states of bacteria, swarming states of bacteria, and the persistence states of microbes. Microbes assume these non-heritable states in order to render bacteria or a community of organisms insensitive to the antimicrobial onslaughts of antibiotics. The physiological states of microbes are expressed in a transient state, and they are reversible and non-heritable in nature. In such states, bacteria are said to be antibiotic tolerant (i.e. they continue to thrive in the presence of potent antimicrobial activity). The persistence state in bacteria is characterized by a state in which bacteria exist in a small fraction of slow or non-growing, antibiotic tolerant cells called persisters. These persisters (which are antibiotic-tolerant states of bacteria) exist in this form and remain insensitive to harmful substances such as antibiotics.

Biofilm formation is another non-heritable state of bacteria formed by microbes, and which allows them to be resistant to antimicrobial agents. Biofilms are organized microbial structures that consist of layers of microbial cells associated with either a biotic or abiotic surface. In biofilm states, bacterial cells of several species are embedded in a self-produced exo-polysaccharide matrix that is usually made up of lipopolysaccharides [15].

Drivers for antimicrobial resistance

The use of antibiotics is the single most important factor leading to antibiotic resistance around the world. Since simply using antibiotics creates resistance in the microbial world, it is therefore vital that we only use them wisely especially in the area of infectious disease management. Non-resistant bacteria multiply, and upon proper drug treatment, the non-resistant bacteria die. Nevertheless, drug resistant bacteria multiply as well during this process of treatment, but upon drug treatment, the drug resistant bacteria continue to multiply and spread within the host. Some common and life-threatening infectious diseases such as TB are becoming difficult or even impossible to treat because of drug-resistant bacteria. Microbial infections

caused by resistant microorganisms are often difficult to treat, and such infections usually require high cost and sometimes toxic alternatives to get rid of them from the body. Moreover, patients infected with drug-resistant bacteria often spend long time in the hospital; and long hospitalization makes such individuals prone to acquiring nosocomial (hospital-acquired) infections. Antimicrobial resistance makes it difficult and more expensive to treat many common microbial infections as aforementioned; and this causes delays in effective treatment or, in worst cases, inability to provide treatment at all – since the resistant organisms are often not susceptible to some commonly available antimicrobial agents or antibiotics. a more expensive drug or antibiotic may be used in such cases, and this increases the cost of therapy.

Summary

This review article has outlined the concerns with antimicrobial resistance and the primary mechanisms by which microorganisms acquire or enact resistance. New antimicrobials and renewed efforts are required to reduce the provenance of antimicrobial resistant microbes in society.

Clonal dissemination of microbes refers to the spread of specific clones of an organism throughout a particular community. To prevent antibiotic selective pressure amongst bacterial populations and other microbes, it is critical to restrict and limit as much as possible antimicrobial usage especially for non-clinical purposes such as is obtainable in agricultural practices. Maintaining proper personal and environmental hygiene as well as good infection control practices in both the hospital and community settings are all important for the containment of antibiotic-resistant bacteria. Antibiotic resistance in microbial pathogens should be timely and accurately detected as they emerge in order to avoid there spread within a given locality.

However, the prevention of the problem through the rational use of available drugs is vital. While the development of resistant strains of microorganisms is inevitable (since the process is part of microbial adaptation in the environment), the slack ways that antibiotics are administered and used in the hospitals and outside the hospital environment (especially in veterinary practice, livestock production and poultry production) has no doubt greatly exacerbated the rate at which drug resistant microbes emerge and spread.

Some measures that can be used to control antibiotic resistance in both the community and hospital environment are as follows:

- Development of novel drugs and new ways of fighting bacterial related infections.
- Hand washing as a measure of infection control.
- Review of antibiotic use in hospitals.
- Updating of clinicians, nurses, pharmacists, and even patients on rationale antibiotic use.
- Good personal hygiene in both the hospital and in the community.
- Restriction of the use of human medicine in livestock and animal feeds.
- Patronage of over-the-counter (OTC) drugs by patients for self medication without doctor's prescription should be discouraged.
- Patients should always endeavour to take full course of their drugs when under any medication.
- Continuous multidisciplinary research into the phenomenon of antibiotic research.

In short, a holistic multidisciplinary action is therefore needed to curb the emergence and spread of antibiotic resistant bacteria in society.

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