



An Insight Review on Antibiotic Resistance and Its Challenges

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ABSTRACT

Antibiotics are antimicrobial substances that target bacterial infections. Currently, antimicrobial resistance to antibiotic agents is a major problem and a great challenge. It develops when the resistance of bacteria to an antimicrobial drug that was originally effective for the treatment. Diagnostic uncertainty, extensive and irrational antibiotic use in humans, animals, and agriculture and lack of awareness are among the factors which aggravate antibiotic resistance. Bacteria can acquire resistance through mutation or through horizontal transfer of genetic information and have developed sophisticated mechanisms of drug resistance to avoid killing by antimicrobial molecules. Those mechanisms are; modifications of the antibiotic molecule, chemical alterations of the antibiotic, destruction of the antibiotic molecule, decreased antibiotic penetration and efflux, changes in target sites, target protection, and global cell adaptations. Even though AMR is a global crisis, the threat posed by these resistant bacteria is exacerbated in developing countries due to sub-optimal hygiene conditions, poor infection prevention and control measures, lack of surveillance and the dearth antimicrobial stewardship programs. Awareness creation on rational use of drugs and understanding of antimicrobial resistance for the community, the implementation of recommended steps, disease prevention (vaccination), new policies to manage the crisis and renewed research efforts to find novel agents and approaches to treating bacterial infections could dramatically reduce these risks. Henceforward, this review article aims at giving insight into antibiotic resistance with special emphasis on its challenge.

Keywords: Antibiotics, Antibiotic Resistance, Bacteria, Challenges

INTRODUCTION

Antibiotics are widely used in human and veterinary medicine for disease prevention and treatment, to control disease spread, to prevent contamination of the food chain, and to increase productivity. Antibiotics either are cytotoxic or cytostatic to the micro-organisms,

allowing the body's natural defenses, such as the immune system, to eliminate them. They often act by inhibiting the synthesis of a bacterial cell wall, synthesis of proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), by a membrane disorganizing agent, or other specific actions.

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Antibiotics may also enter the cell wall of the bacteria by binding to them, using the energy-dependent transport mechanisms in ribosomal sites, which subsequently lead to the inhibition of the protein (Hao et al., 2014; Marshall & Levy, 2011).

Antibiotics were considered a magic bullet that selectively targeted microbes that were responsible for disease causation, but at the same time would not affect the host and multiple varieties of the antibiotics have been used for therapeutic purposes over time. Antibiotics were seen as the ‘wonder drug’ in the mid-20th century. The beginning of the modern “antibiotic era” was synonymously associated with two names Alexander Fleming and Paul Ehrlich. In 1910, Salvarsan was the first antimicrobial agent in the world; a remedy for syphilis that was developed by Ehrlich. Domagk synthesized sulfonamides in 1935. However, these drugs had limitations in terms of safety and efficacy (Aminov, 2010; Zaman et al., 2017).

Alexander Fleming was the first person who cautioned about the potential resistance to penicillin if used too little or for a too short period of treatment. The period from the 1950s to 1970s was thus considered as the golden era for the discovery of novel antibiotics classes (Aminov, 2010; Davies & Davies, 2010). Some studies on bacterial resistance have shown that there is a huge diversity of resistance mechanisms, in which the distribution and interaction is most complex and unknown. The mechanism of resistance may be the evolution of either genetically inherent or the result of the microorganism being exposed to antibiotics. Most of the antibiotic resistance has emerged as a result of mutation or through the transfer of genetic material between microorganisms (Marshall & Levy, 2011).

Several new initiatives are being put in place to halt the alarming trend of resistance to antibiotics and to deal with the ever-increasing number of infections caused by resistant bacteria. Emergence of antibiotics resistance could be the result of the use and misuse of antibiotics both in humans and animals. As a

result, it may lead to increased mortality, morbidity, costs of treatment and loss of production in animals. Even though there were various indications on the misuse of antibiotics by health care providers, unskilled practitioners, and drug consumers, there is still inadequate awareness as well as surveillance on the control and prevention of antibiotic resistance in general and in veterinary practice in particular (Centers for Disease & Prevention, 2013). Therefore, this review article tries to highlight the current status of antibiotic resistance with special emphasis in Ethiopia and its possible mitigation strategies.

2. Factor Accelerating Antibiotic Resistance

Antibiotic resistance is the ability of a bacterium or other microorganisms to survive and reproduce in the presence of antibiotic doses that were previously thought effective against them. The belief in the universal applicability of antimicrobials has resulted in their exuberant use and so to virtually all diseases have resulted in the increasing rates of antibiotic resistance (Nesme et al., 2014).

2.1. Abuse of Antibiotics and Diagnostic Uncertainty

Antibiotic resistance can be more prevalent where antibiotic consumption is found to be higher. Chronic usage of sub-therapeutic doses in a large group of people and animals are among the most important risk factor for the increase of resistance. This occurs when an antibiotic used to treat an infection kills off the bacteria most susceptible to that antibiotic, leaving behind the most resistant bacteria to multiply and spread. Antibiotic use is relatively uncontrolled among the countries where there is no universal health coverage for its citizens (Lessing, 2010; Zaman et al., 2017).

In addition, diagnostic uncertainty is also a key driver of drug misuse and overuse. Antibiotics are often prescribed for self-limiting illnesses, such as colds and influenza, caused by viruses that will not respond to antibacterial drugs. In the absence of a clear diagnosis, physicians often prescribe antibiotics just "to be on the safe side" or to prevent possible secondary bacterial

infections. Patients forget to take medication or may be unable to afford a full course. They tend to consider antibiotics as antipyretics that treat symptoms and stop taking them as soon as they feel better (Grigoryan et al., 2008; Richman, Garra, Eskin, Nashed, & Cody, 2001).

2.2. Agricultural and Other Uses of Antibiotics

The agricultural use of antibiotics also affects the environmental microbiome. Up to 90% of the antibiotics given to livestock are excreted in urine and stool, and then widely dispersed through fertilizer, groundwater, and surface runoff (Bartlett, Gilbert, & Spellberg, 2013). In addition, tetracyclines and streptomycin are sprayed on fruit trees to act as pesticides in the western and southern U.S. This practice also contributes to the exposure of microorganisms in the environment to growth-inhibiting agents, altering the environmental ecology by increasing the proportion of resistant versus susceptible microorganisms (Golkar, Bagasra, & Pace, 2014).

Antibacterial products sold for hygienic or cleaning purposes may also contribute to this problem, since they may limit the development of immunities to environmental antigens in both children and adults. Consequently, immune-system versatility may be compromised, possibly increasing morbidity and mortality due to infections that wouldn't normally be virulent (Michael, Dominey-Howes, & Labbate, 2014).

2.3. Antibiotic Residues and Use of Antibiotics as Growth Promoter

The use of veterinary drugs in food-producing animals has the potential to generate residues in animal-derived products (meat, milk, eggs, and honey) and poses a health hazard to the consumer. There are many factors influencing the occurrence of residues in animal products such as drug's properties and their pharmacokinetic characteristics, physicochemical or biological processes of animals and their products. The most likely reason for drug residues might be due to improper drug usage and failure to keep the withdrawal period (Beyene, 2016).

Concern over antibiotic residues in food of animal origin occurs in two times; one which produces potential threat to direct toxicity in human, second is whether the low levels of antibiotic exposure would result in alteration of microflora, cause disease and the possible development of resistant strains which cause failure of antibiotic therapy in clinical situations. A withdrawal period is established to safeguard humans from exposure to antibiotic added food (Nisha, 2008).

Low levels of antibiotic agents are frequently added to animal feed for growth promotion in livestock mostly in the production of pigs, broiler chickens, turkeys, and feedlot cattle. More recently, molecular detection methods have demonstrated that resistant bacteria in farm animals reach consumers through meat products (APUA, 2010; Bartlett et al., 2013). This occurs when Antibiotic use in food-producing animals kills or suppresses susceptible bacteria, allowing antibiotic-resistant bacteria to thrive and resistant bacteria are transmitted to humans through the food supply, these bacteria can cause infections in humans that may lead to adverse health consequences (Centers for Disease & Prevention, 2013).

2.4. Lack of Awareness and Storage Conditions of Antibiotics

In some developing countries, the knowledge of the farmers concerning antibiotics, withdrawal periods, and dosages was found to be very low. Moreover, the farmers depended more on fellow farmers than veterinarians for antibiotic knowledge, which resulted in the use of the same antibiotics and similar handling practices among farms in close proximity or within the same district. Poor dosing practices, for example, were common when an antibiotic failed to treat an infection (Osei Sekyere, 2014).

The storage conditions of antibiotics are also crucial. The storage environment of the antibiotics is prone to temperature fluctuations which hasten antibiotic decomposition, reducing its concentrations and efficacy, thus promoting resistance in exposed

intestinal bacteria. Furthermore, the antibiotics could easily be accessed and abused in these storage sites, as drugs intended for use in farm animals may be used in humans voluntarily or involuntarily (Laxminarayan et al, 2013).

2.5. The Running Dry Antibiotic Pipeline

The process of novel antimicrobial discovery has slowed to a virtual standstill. Most antimicrobials introduced since the early 1970s have been chemical modifications of previously discovered classes of drugs. The promise of genomics in discovering new antibiotic entities has remained largely unfulfilled to date, it is because; the discovery and development of new antimicrobials is an expensive and time-consuming process. Pharmaceutical companies must prioritize competing projects and antibiotic development has a lower priority than other competing drugs in the portfolio. In the late 1960s, infectious diseases were thought to be conquered, opening the way for a shift in resources to chronic conditions, such as cancer and cardiovascular diseases. The limited duration of antibiotic treatments makes them less profitable than other drugs prescribed for years to treat chronic conditions, such as hypertension and diabetes (Gould & Bal, 2013; Powers, 2007).

Antibiotic development is no longer considered to be an economically wise investment for the pharmaceutical industry. 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 neuromuscular disease. Because medicines for chronic conditions are more profitable, pharmaceutical companies prefer to invest in them. Of the 18 largest pharmaceutical companies in the world, 15 abandoned the antibiotic field (Bartlett et al, 2013; Gould & Bal, 2013; Wright, 2014).

3. Mechanisms of Antibiotic Resistance

Bacteria have evolved sophisticated mechanisms of drug resistance to avoid killing by antimicrobial molecules, a process that has likely occurred over millions of years of

evolution. At least 17 different classes of antibiotics have been produced to date. Unfortunately, for each one of these classes, at least one mechanism of resistance (and many times more than one) has developed over the years. In fact, in some cases these bacteria have been able to develop simultaneous resistance to two or more antibiotic classes, making the treatment of infections caused by these microorganisms extremely difficult, very overpriced and in many instances associated with high morbidity and mortality (Munita & Arias, 2016).

3.1. Genetic Basis of Antibiotic Resistance

The development of antibiotic resistance tends to be related to the degree of simplicity of the DNA present in the microorganisms becoming resistant and to the ease with which it can acquire DNA from other microorganisms. For antibiotic resistance to develop, it is necessary that two key elements combine: the presence of an antibiotic capable of inhibiting the majority of bacteria present in a colony of bacteria carries the genetic these determinants capable of expressing resistance to the antibiotic (Levy & Marshall, 2004). Once this happens, susceptible bacteria in the colony will die whereas the resistant strain will survive. These surviving bacteria possess the genetic determinants that codify the type and intensity of resistance to be expressed by the bacterial cell. The selection of these bacteria results in the selection of these genes that can now spread and propagate to other bacteria. Once gene mutation occurs and causes change in the bacterial DNA, genetic material can be transferred among bacteria by several means. The most common mechanisms of gene transfer are; conjugation, transformation, and transduction (Sefton, 2002).

3.2. Biology Basis of Antibiotic Resistance

The development of antibiotic resistance occurs when the gene is able to express itself and produce a tangible biological effect resulting in the loss of activity of the antibiotic (Sefton, 2002). The common biological mechanisms are the following;

3.2.1. Modifications of the Antibiotic Molecule

One of the most successful bacterial strategies to cope with the presence of antibiotics is to produce enzymes that inactivate the drug by adding specific chemical moieties to the compound or that destroy the molecule itself, rendering the antibiotic unable to interact with its target (Munita & Arias, 2016).

3.2.2. Chemical Alterations of the Antibiotic

The production of enzymes capable of introducing chemical changes to the antimicrobial molecule is also the mechanism of acquired antibiotic resistance in both gram-negative and gram-positive bacteria. Interestingly, these microorganisms exert their mechanism of action by inhibiting protein synthesis at the ribosome level. Among the most frequent modifying enzymes involved in biochemical reactions they catalyze include; Acetylation (aminoglycosides, chloramphenicol, streptogramins), Phosphorylation (aminoglycosides, chloramphenicol), and iii) adenylation (aminoglycosides, lincosamides) (Wilson, 2014).

3.2.3. Destruction of the Antibiotic Molecule

The main mechanism of β -lactam resistance relies on the destruction of these compounds by the action of β -lactamases. These enzymes destroy the amide bond of the β -lactam ring, rendering the antimicrobial ineffective. Infections caused by penicillin-resistant *Staphylococcus aureus* became clinically relevant after penicillin became widely available and the mechanism of resistance was found to be a plasmid-encoded penicillinase that was readily transmitted between *S. aureus* strains, resulting in rapid dissemination of the resistance trait. (D'Costa et al, 2011).

3.2.4. Decreased Antibiotic Penetration and Efflux

Decreased Permeability

Most clinical antibiotics have intracellular bacterial targets or, in the case of gram-negative bacteria, located in the cytoplasmic membrane. Therefore, the compound must penetrate the outer and/or cytoplasmic membrane in order to exert its antimicrobial effect. Bacteria have developed mechanisms to

prevent the antibiotic from reaching its intracellular or periplasmic target by decreasing the uptake of the antimicrobial molecule (Hancock & Brinkman, 2002).

Hydrophilic molecules such as β -lactams, tetracyclines, and some fluoroquinolones are particularly affected by changes in permeability of the outer membrane since they often use water-filled diffusion channels known as porins to cross this barrier. The prime example of the efficiency of this natural barrier is the fact that vancomycin, a glycopeptides antibiotic, is not active against gram-negative organisms due to the lack of penetration through the outer membrane (Pagès, James, & Winterhalter, 2008).

Efflux Pumps

Efflux pumps decrease cellular drug accumulation because compounds are pumped out of the inner membrane to the periplasmic space or directly to the external medium. Some efflux pumps are capable of extruding many compounds, including detergents and different antimicrobial classes (Horiyama, Yamaguchi, & Nishino, 2010). Accordingly, in gram-negative bacteria, the resistance nodulation division (RND) family forms a protein tripartite complex with the inner membrane, periplasmic space, and outer membrane, forming an efficient channel to extrude compounds. In contrast, in gram-positive bacteria, the main multidrug efflux pumps belong to the multidrug and toxic compound extrusion (MATE) family (Alvarez-Ortega, Olivares, & Martínez, 2013).

3.2.5. Changes in Target Sites and Target Protection

Bacteria develop antimicrobial resistance by interfering with their target site to avoid the action of the antibiotic. To achieve this, bacteria have evolved different tactics, including protection of the target by avoiding the antibiotic to reach its binding site and modifications of the target site that result in decreased affinity for the antibiotic molecule (Beyene, 2016; Munita & Arias, 2016). These target changes may consist of Point mutations in the genes encoding the target site, Enzymatic alterations of the binding site (e.g.

addition of methyl groups), and/or Replacement or bypass of the original target. Regardless of the type of change, all-cause a decrease in the affinity of the antibiotic for the target site (Floss & Yu, 2005).

3.3.6. Resistance Due to Global Cell Adaptations

Bacteria have developed sophisticated mechanisms to cope with environmental stressors and pressures in order to survive the most hostile environments through years of evolution. Bacteria need to compete for nutrients and avoid the attack of molecules produced by other rival organisms in order to survive. Inside a particular host, bacterial organisms are constantly attacked by the host's immune system and it is crucial to adapt and cope with these stressful situations. Thus, bacterial pathogens have devised very complex mechanisms to avoid the disruption of a pivotal cellular process such as cell wall synthesis and membrane homeostasis. Development of resistance to daptomycin (DAP) and vancomycin (low-level in *S. aureus*) are the most clinically relevant examples of resistance phenotypes as a result of a global cell adaptive response to the antibacterial attack (Diaz et al., 2014).

4. Control and Mitigation Strategy of Antibiotic Resistance

4.1. Responsible Use of Antibiotic

The antibiotic usage is a serious global concern in food animals associated with food safety and public health. All countries in the world should use antibiotics in food animals more carefully and rationally. Sensible use of antimicrobials is an integral part of good veterinary practices. It is an attitude to maximize therapeutic efficacy and minimize the selection of resistant micro-organisms. The judicious use of antimicrobials is the optimal selection of drug, dose, and duration of antimicrobial treatment along with the reduction of the inappropriate and excessive use of antimicrobial agents. Thus, rational and targeted use of antimicrobials should be there in order to maximize the therapeutic effect and minimize the development of antimicrobial resistance (Beyene, 2016; Weese et al., 2006).

4.2. Prevention of Infectious Diseases

Implementation of appropriate disease prevention measures should be given continuously in order to decrease the need for antibiotics, to minimize infection in food animal production and improve animal health. This can be attained through improved hygiene, biosecurity measures both on humans and animals and preventing disease by using vaccines. Vaccines have been a key role in disease prevention for many years since they have many promising attributes such as low cost, ease of administration, efficacy, multiple agent efficacy (viruses, bacteria, mycoplasma, and parasites) and safety (worker, animal, environmental, lack of food residue) (Moges et al, 2014).

4.3. Adopt Antibiotic Stewardship Programs

Antibiotic stewardship programs guide all prescribers in administering antibiotics correctly and involves making a commitment to use antibiotics only when needed, choosing the proper drug and administer the medication at the appropriate dose and duration in every case (Centers for Disease & Prevention, 2013; Lushniak, 2014). Successful implementation of an antibiotic stewardship program requires an interdisciplinary team, system innovation, educational intervention and feedback provided to health care workers (Luyt, Bréchet, Trouillet, & Chastre, 2014).

4.4. Improve Diagnosis and Diagnostic Tools

Perhaps eliminate diagnostic uncertainty is the most effective way to reduce the inappropriate use of antibiotics. Identifying antibiotic-resistant infections can be challenging, so the selection of antibiotic treatments is often empiric. Empiric use of antibiotics could be reduced through the implementation of more rapid, accurate diagnostic methods. In the past, accurate diagnosis of infectious diseases using traditional methods required multiple laboratory-based tests that take days or weeks to complete (Michael et al, 2014; Spellberg et al., 2016).

However, within the past decade, slow, traditional methods based on phenotypic characteristics (e.g., growth on defined media,

colony morphology, gram staining, and biochemical reactions) have started to give way to newer diagnostic techniques, such as real-time multiplex polymerase chain reaction (PCR) and matrix-assisted, laser desorption/ionization, time-of-flight mass spectrometry (Luyt et al., 2014). Such molecular diagnostic techniques detect the unique nucleic acid or biochemical composition of the microbe at the point of care, enabling rapid pathogen-specific identification and treatment (Bartlett et al., 2013).

4.5. New Approaches to Treating Bacterial Infections

About 99% of the microorganisms that are a potential source of new antibiotics cannot be grown in a laboratory environment and therefore remain uncultured. Accordingly, the pharmaceutical industry has instead favored screening large libraries of synthetic molecules for antibiotic activity to overcome these problems. New strategies in antibiotic discovery, such as resistance and virulence inhibition, new targets, new culturing techniques, and novel drug combinations, are expected to preserve natural products as a continued source of new antibiotics (Ling et al., 2015; Wright, 2014).

New sources of natural antibiotics, such as samples from marine bacteria, tropical rain forests, myxobacteria, and extremophilic bacteria, are actively being investigated (Sengupta, Chattopadhyay, & Grossart, 2013). In January 2015, the discovery of *Teixobactin*, the first of a new class of antibiotics, was reported. The key to this discovery was the use of a new technique (the isolation chip, or “iChip”) to grow the previously impossible-to-culture microbe that produces teixobactin, *Eleftheria terrae*. The use of the iChip allowed this microbe to be grown in the laboratory in soil, its natural environment. Teixobactin has been reported to have excellent activity against gram-positive bacteria, including resistant strains (Ling et al., 2015).

5. Clinical and Economic Impact of Antibiotic Resistance

In 2013, the Centers for Disease Control (CDC) in the USA emphasized that the human race is now in the “post-antibiotic” era. The

World Health Organization (WHO) published the first global surveillance report on antibiotic resistance (ABR) in 2014 to show the clinical impact of resistant bacteria in WHO regions across the world. The report attributed 45% of deaths in both Africa and South-East Asia to multi-drug resistant (MDR) bacteria. It further revealed that *Klebsiella pneumoniae* resistant to third-generation cephalosporins was associated with elevated deaths in Africa (77%), the Eastern Mediterranean region (50%), South East Asia (81%) and Western Pacific region (72%) (Njougang et al., 2015).

Several resistant bacteria have been increasingly involved in infectious diseases in humans, specifically, *Enterococcus species*, *Staphylococcus aureus*, *K. pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*. They are collectively termed ESKAPE and recently gained further global attention by being listed by the WHO as priority antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. The particularity of these bacteria is their ability to develop high-level resistance to multiple drugs, thereby limiting therapeutic options and increasing morbidity and mortality. The threat posed by these resistant bacteria is exacerbated in developing countries due to sub-optimal hygiene conditions, poor infection, prevention and control measures, lack of surveillance and the dearth antimicrobial stewardship programs (Årdal et al., 2016).

The economic impact of increasing numbers of untreatable infectious diseases will become significant, as larger numbers of productive individuals are lost from the workforce for increasing periods of time and decreased productivity in animals, higher costs for treatment and healthcare. Additionally, the increasing burden of caring for those suffering will place additional loads on their families and community, as well as the wider health care systems. The flow-on effects of this loss of labor and increased load on health services will reduce the national outputs of most countries compared to current levels and will have rippling societal and cultural impacts (Perovic, Britz, Chetty, & Singh-Moodley, 2016).

CONCLUSION AND RECOMMENDATION

Antibiotics are extensively used both in human and animal health practices in developed and developing countries of the world mainly for treatment and control of various diseases. However, the use, misuse, and overuse of these medicines contributed favorable conditions for the emergence, occurrence, and development of antibiotic-resistant bacteria. Even though the effect of antibiotic resistance is magnificent, there is still inadequate surveillance and far little attention on the rational use of drugs to minimize antibiotic resistance. Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics. Despite the alarming and increasing threat posed by emerging antibiotic-resistant bacteria worldwide, the implementation of recommended steps, disease prevention (vaccination), new policies to manage the crisis, and renewed research efforts to find novel agents and approaches to treating bacterial infections could dramatically reduce these risks. In conclusion, the following recommendations are forwarded:

- Applying disease preventive approach and improving hygiene is very important rather than the use of antibiotics.
- Antibiotic treatment should be administered after isolation, identification, and conduction of the drug sensitivity test.
- The use of antibiotics as growth promoters should be prohibited.
- Narrow spectrum antibiotics should be the first choice when antibiotic therapy is justified.
- Research needs to be developed on the best ways to mitigate the development of antibiotic resistance

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