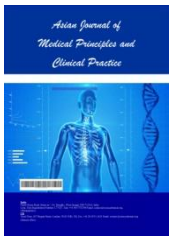

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Implementation of Antimicrobial Stewardship (AMS): An Imperative Step to Reducing Resistance and Improving Infectious Disease Cure Rates

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Commentary

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ABSTRACT

The discovery of penicillin in 1940 by Alexandra Fleming brought a major breakthrough in the management of infectious diseases and further sparked special interest in the research and development of antimicrobial agents. However, in a matter of time, penicillin like the sulphonamide that predates it had to battle the evolution of antibiotics resistance as microbes threw out their strong offensives against this wonder drug. Over the years, we have seen the introduction of several other groups of antibiotics, from streptomycin to chloramphenicol, macrolides, aminoglycosides, ampicillin, and cephalosporins. But we still have had to combat the same problem of resistance against each of these newer agents. In the light of this, we moved towards drug combinations in order to mitigate the effect of resistance especially for the "Hospital Acquired Infections'". These combinations lead to better cure rate or more synergistic results. The sad news however is that treatment cost for infectious diseases continues to skyrocket while microbes

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acquire more virulent and resistant powers. The “cidal and static" actions of antibiotics left microbes with two options. To die or fight back. They choose the latter, hence, our predicament. Antimicrobial stewardship (AMS) seems to be the single most important way left in curbing resistance crises. The implementation of AMS in our various healthcare facilities in line with WHO protocols is an imperative step to improving infectious disease cure rates and stopping the emergence of new forms of bacterial resistance. However, the big question is “to what extent has this important policy been implemented in the healthcare institutions especially in developing countries of the world. There is a serious need for both the private and public healthcare facilities to prioritize AMS and join hands in the global fight against antimicrobial resistance.

Keywords: Antimicrobial; stewardship; resistance; disease; infections; healthcare; health professionals.

1. INTRODUCTION

Many of the diseases affecting man and animals are as a result of microorganisms which invade the body tissues. These diseases also called infections can lead to complications and finally death if not treated. The invent of antimicrobials was a great breakthrough in public health and in the treatment of infectious diseases. These antimicrobials have been in use for some decades and have led to a great reduction in infectious disease morbidity and mortality [1].

The misuse of these antimicrobials has resulted in microorganisms developing resistance them. In past years, this was not much of a problem, as there was continuous production and development of new antimicrobial agents. So, if resistance developed to one, there were always new and better options to use in treatment [2]. However, the production of new antimicrobials has reduced drastically and the increasing resistance to existing antimicrobials is a threat to global health. The development of antimicrobial resistance has been associated with treatment failure, increased health and treatment costs, increased length of hospital stays, and increased mortality and morbidity [3,4].

Around the world, antimicrobial resistant (AMR) organisms are posing a risk to healthcare by endangering already effective treatments, thereby making them ineffective. In Africa, antimicrobial organisms have been identified among several pathogens that cause diseases such as malaria, tuberculosis, typhoid, cholera, meningitis, gonorrhoea, and dysentery [5].

The phenomenon of Antimicrobial resistance has consequently led to the development of antimicrobial stewardship (AMS) program within the healthcare system. AMS can be defined as a coordinated set of efforts that encourages the optimum use of antimicrobials through methods that enhance consistent access to appropriate antibiotic treatment [6]. Antimicrobial stewardship encompasses many actions such as control of antibiotic use, optimizing antibiotic drug regimen including the dose, duration and route of administration.

The terms used to refer to antimicrobial stewardships programs may vary considerably: antibiotic policies, antibiotic stewardship programs, antibiotic control programs, and other terms may be used more or less interchangeably. This stewardship program is an imperative step by the WHO to reduce the increasingly alarming rate of antimicrobial resistance and to improve the treatment of infectious disease.

Doron and Davidson, 2011 identified three goals of antimicrobial stewardship. The first goal is centred on the role of health care professionals in ensuring the most appropriate antimicrobial with the correct dose and duration for a particular infection is gotten by each patient. Optimizing each patients’ therapy also helps in saving treatment costs. Second is the prevention of antimicrobial overuse, misuse, and abuse. Unnecessary and wrong uses of antimicrobials are great drivers of antimicrobial resistance for which antimicrobial stewardship is needed. Third is to significantly decrease the development of resistance to existing antimicrobials.

This commentary gives an overview on the causes and types of AMS, effects of the AMS on treatment of infectious disease and the role of healthcare professionals in the treatment antimicrobial resistance.

2. CAUSES OF ANTIMICROBIAL RESISTANCE

The inactivation of antimicrobial agents, site alterations of antimicrobials, and a decrease in the accumulation of antimicrobials are the main effects exhibited by the activities of microbes to ensure their survival. No human being created would like to die young but rather aims to reproduce, grow and dissipate as soon as possible and efficiently, this is also applicable to microbes [7]. Microbes adapt to their environment and modify in a way that conserves them, if there is an external force such as antimicrobials to stop them from growing a genetic change may occur which will enable them to survive [8]. There are many ways for antimicrobial resistance to occur which can be Intrinsic, acquired [9], and Human cause.

The majority of human causes of antimicrobial resistance emanate from actions between Health care providers and patients toward antimicrobials. Inappropriate prescription of these drugs to patients is like giving lives to microbes to continue striving, for example, antibiotics and antifungals are targeted to cure bacterial infections and not virus infections. In a situation where a health provider fails to prescribe drugs appropriately here, it may trigger an emergency increase in antimicrobial resistance.

The way health professionals prescribe antibiotics may be quite different from place to place and sometimes it will be difficult to ascertain the right one, a patient can relocate to another hospital in continuation of treatment, and if noticed there will be a total difference in the prescription of drugs or dosage intake, truly this gives room for antimicrobial resistance to emerge.

Lack of information or awareness among health providers with little or no coaching in rural areas leads to the inappropriate prescription of antimicrobials [10]. This increased morbidity and death. WHO "estimates that resistant infections already cause at least 700,000 deaths every year, including 230,000 deaths from multidrug-resistant tuberculosis. Also, by 2050, it is estimated that 10 million people will die annually from drug resistance infection, causing $100 trillion in economic losses if efforts are not drastically scaled up to curtail the misuse of antibiotics globally". Imagine a populated community with untrained health providers or health providers with a lack of information on new emerging antimicrobial resistance, with their regular prescriptions of antimicrobials there will be always an increase in death rates annually and a continual spread of infections within and outside the community Instructions and Compliance work in hand. Patients often miss the dose prescription either by mistake, to enjoy themselves, or because they feel relieved. Antimicrobials are prescribed to kill an entire population of bacteria but when not taken for a full prescription course, the microbes can adapt in the presence of low dosage and automatically form a rigidly resistant population regardless of the dosage [11]. There are still doubts if herbs are the best option for treating infections [12]. Sometimes patients will stop taking their prescribed antimicrobials and believe herbs will hasten the recovery, upon the instructions not to do so while some will be taking both alternatively or simultaneously. Submission to the instructions cannot be overemphasized as it will enhance reducing antimicrobial resistance dominance.

Aside from human causes of AMR, intrinsic and acquired resistance occurs in microbes naturally [9]. Some microbes are naturally resistant to a particular antimicrobial thereby preventing them to reach the site of action (intrinsic resistance), for example, Streptomyces is resistant to streptomycin. This bacterium will continue to thrive and reproduce in the presence of antibiotics even in many dosages.

Gene transfers are always feasible among microbes. Bacteria that have drug-resistant DNA may transfer a fragment of these genes to another bacteria. Non-resistant bacteria receive the new DNA and become resistant to drugs making them multiply and thrive in the presence of antimicrobials. Genes can easily be transferred from one microbe to another either by conjugation, transduction, or transformation. Conjugation involves the physical transfer or cell-to-cell contact as the DNA crosses the sex pilus from donor to recipient, transduction occurs when a virus transfers a gene to mating bacteria while transformation is when DNA is directly acquired from the environment, having been released by another cell [13].

In summary, these causes of antimicrobial resistance have given viruses, bacteria, fungi, and parasites an edge to withstand and withhold to respond to the treatment thereby leading to a severe illness that may lead to death [14]. Realizing these causes of AMR and implementing antimicrobial stewardship is an

imperative step toward reducing resistance and improving infections and disease cure rates.

3. MECHANISMS OF ANTIMICROBIAL RESISTANCE

Worldwide, Infectious diseases are a major cause of morbidity and mortality. With the help of antibiotics, the disease and death rate were curtailed until recent time due to the emergence of antimicrobial resistance. Despite the fact that we have a plethora of antimicrobial agents currently available to choose from treatment of infectious diseases, the advent of antimicrobial resistance has limited their use and resistance to a new drug can occur shortly after it is approved for use [15].

Understanding how antimicrobial agents work is essential for understanding resistance mechanisms [16]. Antimicrobial agents target essential microbial functions with minimal or no effect on host functions. Different antimicrobial agents have different modes of action and they are divided into groups based on their mechanism of action [17]. The main groups of antimicrobials include the following: agents that inhibit the synthesis of cell wall, interrupt the structure of cell membrane, inhibit protein synthesis, inhibit nucleic acid synthesis, and inhibit metabolic pathways/ bacteria enzymes [15].

Microorganisms have developed extensive mechanisms to avoid being destroyed by harmful substances. This is as a result of a Darwinian selection process. These mechanisms include preventing drug entry or export, destroying or modifying antimicrobial by producing harmful enzymes, and changing the antimicrobial target [18].

Antimicrobial resistance can be broadly classified into two [16] which are natural resistance (this may be intrinsic or induced) and acquired resistance. In intrinsic resistance, the common mechanisms are decreased permeability of the outer membrane and the natural activity of efflux pumps. In induced resistance, a common mechanism is also multidrug-efflux pumps. Acquired resistance may be temporary or permanent and can be acquired through various ways such as enzyme inhibition, microbial mutation, and modification of drug target [17].

The main mechanisms of antimicrobial resistance include the following:

3.1 Modification/ Alteration of Drug Target Site

Antimicrobials are designed to bind to their specific targets with high affinity. This causes a disruption in the targets normal activity and the weakening or death the organism. Changes in the targets structure can make binding of the antimicrobial less efficient, thus leading to antimicrobial resistance.

A classic example of this mechanism is the development of resistance to rifampicin. An amino acid substitution in the rpoB gene occurs due to a single point mutation. Having a gene that is similar to the original target is another example of how modification of target site can cause resistance. This can be seen in methicillin-resistant S. aureus (MRSA) where the resistance is conferred by having the staphylococcal cassette chromosome mec (SCCmec) genetic element [19].

3.2 Limiting Drug Uptake

This mechanism of resistance is more common in gram negative than in gram positive bacteria because of differences in structure (absence of lipopolysaccharide (LPS) outer membrane in gram positive bacteria).

The LPS layer in gram negative bacteria serves as a barrier to some molecules and this confers those bacteria with innate resistance to certain groups of large antimicrobial agents. Bacteria such as mycoplasma and other similar organisms that lack a cell wall are intrinsically resistant to all antimicrobials whose mechanism of action involves targeting the cell wall such as β-lactams and glycopeptides. Hydrophobic drugs like rifampicin and the fluoroquinolones have easier access to the mycobacteria cell membrane because of its high lipid content, while hydrophilic drugs have reduced access.

3.3 Drug Efflux

Energy-driven drug efflux systems have been recognized as antibiotic resistance mechanisms. They can be activated by environmental signals or a mutation in a regulatory gene if they are chromosomally located or acquired by bacteria [20].

Resistance to tetracyclines majorly occurs through this mechanism. The drug is ejected via an export protein from the major facilitator

superfamily (MFS). Tetracycline export lowers intracellular drug concentrations, protecting ribosomes within the cell. Tetracycline efflux proteins share amino acid and protein structure similarities with other efflux proteins involved in multiple-drug resistance, quaternary ammonium resistance, and chloramphenicol and quinolone resistance [17].

3.4 Drug Inactivation

Bacteria inactivate drugs majorly by degrading the drug itself or by transferring a chemical group to the drug. β-lactamases are a large class of drug hydrolyzing enzymes and they inactivate the β-lactam drugs which are the largest groups of antibiotics . Tetracycline is another drug that can be inactivated by hydrolysis via the tetX gene. Transfer of a chemical group to the drug is the most common method of drug inactivation. Acetylation is the most widely used mechanism, and it has been shown to be effective against many classes of drugs such as aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones [15].

4. ROLE OF HEALTHCARE PROFESSIONALS IN PREVENTION OF ANTIMICROBIALRESISTANCE AND IMPLEMENTATION OF ANTIMICROBIAL STEWARDSHIP

The roles of healthcare workers in the prevention of antimicrobial resistance cannot be overemphasized. This is because they are involved directly or indirectly with patient care. Health care professionals such as Infectious disease practitioners, pharmacists, nurses, clinical microbiologists, infection Control practitioners and Hospital Epidemiologists, clinical microbiologists and hospital administrators

4.1 Physicians

Infectious disease physicians play an important role in the prevention of AMR. One of the most important roles is appropriate prescription of antibiotics. As antibiotic use is the major cause of antimicrobial resistance, attention must be paid to proper prescription of these antibiotics. Research has shown that a large amount of antibiotics are prescribed when not needed, or the choice, dose and duration of antibiotic is inappropriate [21]. For example, many antibiotics are prescribed for viral infections or are without adequate diagnostic investigations carried out [22]. Physicians should also educate their patients about antimicrobial resistance, and why an antibiotic may or may not be needed for their disease condition.

In an antimicrobial stewardship program, the infectious diseases-trained physicians should devote a portion of their time to the program's design, implementation, and operation. They should also ensure that therapeutic guidelines, antimicrobial restriction policies, or other measures are based on the best evidence and practice [23].

4.2 Pharmacists

Pharmacists have a vital role to play in the prevention of AMR by reducing the unnecessary use of antibiotics [24] and implementation of AMS. Many antimicrobial stewardship programs started as cost-saving measures led by the pharmacy department of hospitals. Therefore, pharmacists are often the implementer for antimicrobial stewardship programs.

The major roles of a clinical pharmacist involved in antimicrobial stewardship program includes creating guidelines and promoting the optimal use of antibiotics, educating physicians, other healthcare professionals, patients and the public, review of prescriptions containing antimicrobials and giving feedbacks to providers, and reducing infection transmission.

In promoting optimal use of antimicrobial agents, pharmacists should ensure that the uses of antimicrobial agents result in optimal patient outcomes, strategies should be put in place to prevent medication errors and adverse drug reactions, and restricted antimicrobial-use procedures should be developed. The transmission of infections can be reduced by implementing quality control practices of drug products from manufacturing to dispensing, encouraging routine administration of healthcare workers, and active participation in the infection prevention and control committees [25].

4.3 Nurses

Nurses also have important roles to play in key areas of antimicrobial stewardship just like other healthcare professionals [26]. Nurses spend the highest amount of time with patients and can help prevent AMR by practicing standard prevention precautions such as engaging in

proper hand washing and other infection control measures, medication administration, ensuring proper documentation of patient treatment, and promoting the use of prescribing guidelines.

4.4 Clinical Microbiologists

The laboratory unit plays a vital role in preventing antimicrobial resistance by ensuring timely and accurate reporting of susceptibility test results. This can help reduce the unnecessary use of broad-spectrum antimicrobials and reduce resistance. They can also promote antimicrobial stewardship by providing data on antimicrobial resistance rates from susceptibility tests done. This can help the antimicrobial stewardship team in determining which specific antimicrobials should be restricted or reviewed [22].

5. CONCLUSION

Antimicrobial resistance remains a global public health concern and posses a serious threat to the healthcare system and pharmaceutical industries. In this article, we have been able to discuss the concept, causes and mechanisms of antimicrobial resistance and relevance in clinical practice. The increasing number of resistant strains of microorganisms has been recognized as one of the biggest threats to success in the management and treatment of bacterial, fungal and viral infections. Interestingly, antimicrobial stewardship program (AMS) was developed and put in place to combat the problem of resistance and optimize benefits of antimicrobials in the treatment of infectious diseases. It is therefore imperative that relevant stakeholders and all healthcare providers make concerted efforts to ensure the implementation of AMS in their various practice centers and facilities. Doctors, pharmacists and nurses are strategically positioned in the control plan of AMS as they provide direct medical and pharmaceutical care to patients. There is need for greater commitment to rational drug prescribing and dispensing especially in the management of infectious diseases; and health care providers should continue to educate patients and care givers on the need for medication adherence, avoidance of self medication and abuse. With the implementation of antimicrobial stewardship program, the problem of antimicrobial resistance can be curbed resulting in a general decrease in the rate of treatment failure and reduction in overall cost of care.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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