IJAMBR 9 (2021) 38-50 ISSN 2053-1818

International Journal of Applied Microbiology and Biotechnology Research
www.bluepenjournals.org/ijambr

Antibiotics: Classifications and mechanism of resistance

doi.org/10.33500/ijambr.2021.09.004

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Article History
Received 11 April, 2021
Received in revised form 11 May, 2021
Accepted 14 May, 2021

Keywords:
Bacterial pathogen, Antibacterial agent, Antibiotic classification, Antibiotic resistance.

Article Type:
Review

ABSTRACT

Since the introduction of penicillin in the 1940s, antibiotics have become one of the cornerstones of modern medicine. Infectious diseases caused by bacterial pathogens represent a greater percentage of public health concern. In clinical medicine, antimicrobial agents are often indicated for chemotherapy of infectious diseases that are bacterial in origin. Since the discovery and subsequent widespread use of antibiotics, a variety of bacterial species of human and animal origin have developed numerous mechanisms that render bacteria resistant to some, and in certain cases to nearly all antibiotics. Thus, it is important to study the classifications and biological mechanisms which made the bacterial pathogens to survive in the presence of these inhibitory agents. Understanding antibiotic classification and how these bacterial resistance mechanisms work from the standpoint of molecular physiology and biochemistry will discourage unnecessary antibiotic prescription as well as identify new targets for potential inhibition of multi-drug resistance and thus restore clinical utility of chemotherapy of infectious disease caused by serious bacterial pathogens.

INTRODUCTION

An antibiotic is a substance produced by a microorganism (Denyer et al., 2004), or a semisynthetic substance derived from a microorganism (Schlegel, 2003) which at a low concentration kills or inhibit the growth of another microorganism (Russell, 2004). Those that kill the microorganisms are called bactericidal while those that inhibit the growth of microorganisms are called bacteriostatic (Walsh, 2003). In September 1928, Penicillin was the first antibiotic to be discovered by an English Bacteriologist, Late Sir Alexander Fleming who accidentally discovered the antibiotic Penicillin from a soil inhabiting fungus *Penicillium notatum* and the clinical trials was conducted on humans in the 1940s. Ever since, antibiotics have become one of the cornerstones of modern medicine and the foundation for the treatment of bacterial infections in humans as well as animals (Adriaenssens et al., 2011).

It was envisaged that with the introduction of antibiotics, infectious diseases especially bacterial in origin will be a thing of the past however, this was later found not to be so as most bacterial pathogens are becoming resistant to antibiotics (Livermore, 2013). The extensive use of antibiotics in the management of bacterial diseases in both human and animal medicine as well as its use in livestock farming as growth stimulators majorly for meat production has been associated with antibiotic resistance which could be intrinsic or acquired (Barbosa and Levy, 2000; Blackman, 2002). Treatment failures associated with antibiotic use in modern medicine is practically due to multidrug resistant bacterial organisms. There is, therefore, the need for scientific base studies on the

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Table 1. Bacterial mechanisms of antibiotic resistance.

Basis of resistance	Mechanism	Bacterial proteins/targets responsible	Antibiotic targets
	Hydrolysis	β-lactamases	β-lactams
		Esterase	Macrolide
		C-P lyase complex	Fosfomycin
Enzyme	Group transfer	Acetyltransferase	Streptogramins, Aminoglycosides,
		Phosphotransferase	Chloramphenicol
		Nucleotidyltransferase	Aminoglycosides, macrolides
		Glycosyltransferase	Lincomycin, clindamycin, aminoglycosides
		Ribosyltransferase	Macrolides
		Thiol transferase	Rifampin
			Fosfomycin
	Redox process	TetX	Tetracyclines
Target modification	Structural alterations/modifications	Penicillin binding proteins	β-lactam antibiotics
		Cell wall precursors	Vancomycin
	Mutations in genes	Ribosomal subunits	Streptomycin
	Amino acid substitutions	RNA polymerase	Rifamycin
		DNA gyrase/topoisomerase	Quinolones
	Methylation	16S rRNA	Aminoglycosides
		23S rRNA	Macrolide
	Mutation	23S rRNA	Oxazolidinones
Reduced permeability	Reduced expression/defective Protein	Porins	β-lactams, fluoroquinolones, aminoglycosides, chloramphenicol
Target protection	Ribosome protection	Ribosome protection proteins	Tetracycline
Efflux	Active extrusion	Membrane proteins	All major antibiotics

Kumar and Varela (2013).

mechanisms of multidrug resistance in order to mitigate the challenges associated with treatment of various infectious diseases caused by recalcitrant bacterial organisms (Bhardwaj and Mohanty, 2012).

The mechanisms for bacterial resistance to antibiotics are diverse and this is due to the chemical nature, composition, and targets of the antibiotics as well as the type of the bacterial organisms as shown in Table 1.

Qualities of an ideal antibiotic

An ideal antibiotic should possess the following characteristics:

i. Selective toxicity: ability to kill or inhibit the growth of harmful bacterial organisms regardless of the site of infection with minimal or no harmful effect on the host
ii. Therapeutic dose: drug concentration required for clinical treatment
iii. Spectrum of activity: broad, narrow, or extended spectrum of activity
iv. Should either be bactericidal, bacteriostatic or both
v. Favorable pharmacokinetics: should reach its target site at effective concentration
vi. Should have a tolerable side effects and little resistance development
vii. Should have a tolerable residue
viii. Should be affordable
ix. Should have a defined Minimum Inhibitory Concentration (MIC)

CLASSIFICATION OF ANTIBIOTICS

Antibiotics have been classified in different ways, but the commonest classification is based on molecular structure, mechanism of action and spectrum of activity (Calderon and Sabundayo, 2007). Antibiotics could also be classified based on the route of administration and

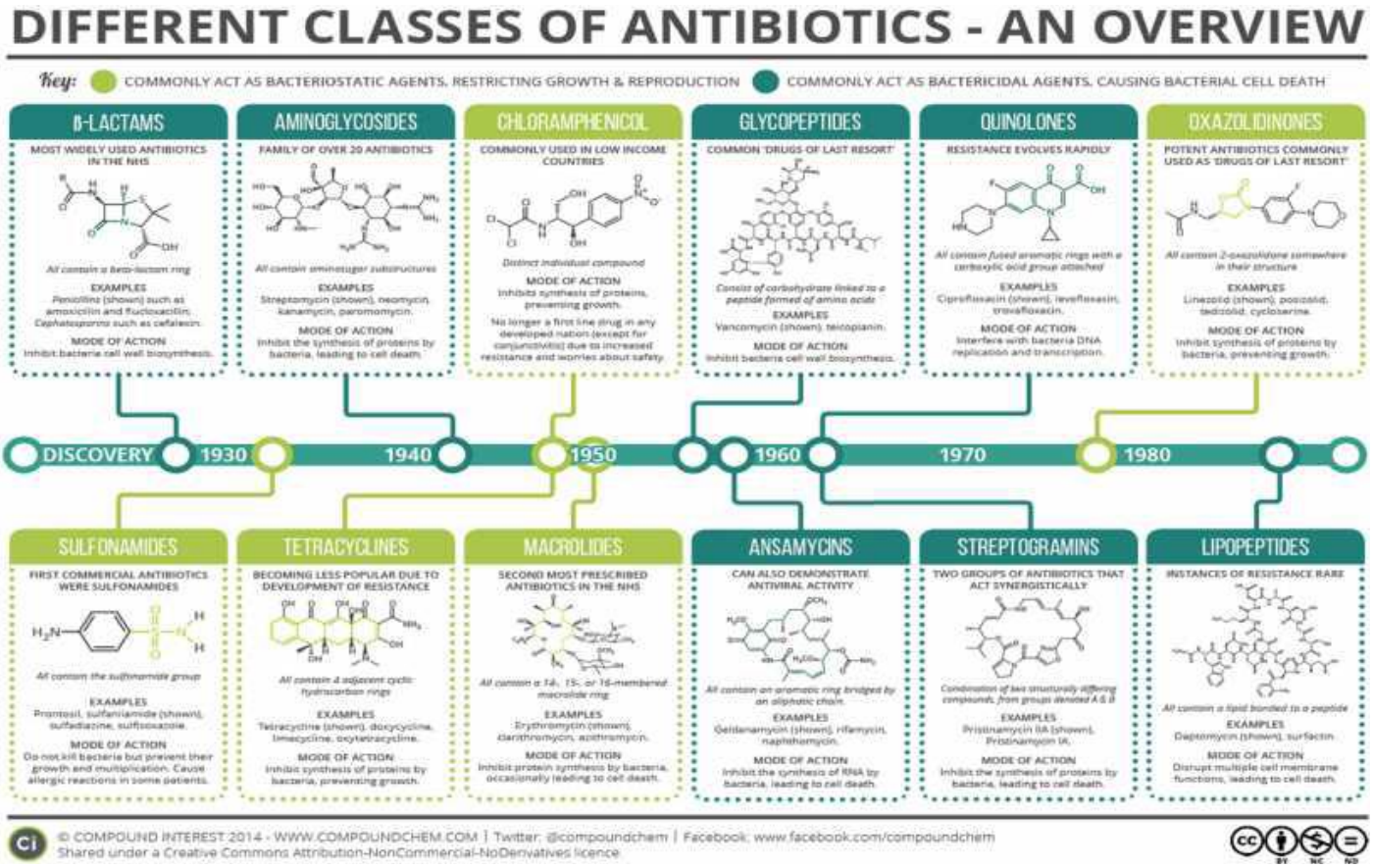

Figure 1. Different classes of antibiotics (Van-Hoek et al., 2011; Frank and Tacconelli, 2012; Adzitey, 2015; Christine, 2016).

whether it kills or inhibit the growth of microorganisms.

Classification based on molecular structure

- Beta-lactams: Penicillins, Cephalosporins, Carbapenems, Monobactams
- Tetracyclines and glycylcyclines: Tetracycline, Tigecycline, Doxycycline, Minocycline, Chlortetracycline, Oxytetracycline
- Chloramphenicol: Chloramphenicol
- Aminoglycosides: Gentamicin, Amikacin, Tobramycin, Netilmicin, Streptomycin, Neomycin, Kanamycin
- Quinolones: Ciprofloxacin, Norfloxacin, Levofloxacin, Moxifloxacin, Gemifloxacin, Ofloxacin, Enrofloxacin
- Macrolides and Ketolides: Azithromycin, Telithromycin, Erythromycin, Clarithromycin
- Lincosamides: Lincomycin, Clindamycin, Pirlimycin
- Streptogramins: Quinupristin/Dalfopristin, Pristinamycin, Virginiamycin
- Glycopeptides: Vancomycin, Teichoplanin, Telavancin, ramoplanin, decaplanin
- Sulfonamides: Sulfadiazine, Sulfamethizole, Sulfamethoxazol, Sulfasalazine, Sulfisoxazole
- Trimethoprim: Trimethoprim
- Polymixins: Colistin, Polymixin B
- Oxazolidinones: Linezolid, Tedizolid
- Lipopeptides: Daptomycin, Surfactin, Mycosubtilin
- Ansamycins: Rifampicin, Rifamycin, Geldanamycin, Streptovaricin, Ansalactam A

Some of these antibiotics are illustrated in Figure 1.

Classification based on mechanism of action

- Interference with cell wall synthesis: beta lactams, glycopeptides
- Inhibition of protein synthesis: macrolides, aminoglycosides, tetracyclines
- Interference with nucleic acid synthesis: quinolones
- Inhibition of metabolic pathways: sulphonamides
- Disorganizing the cell membrane structure or

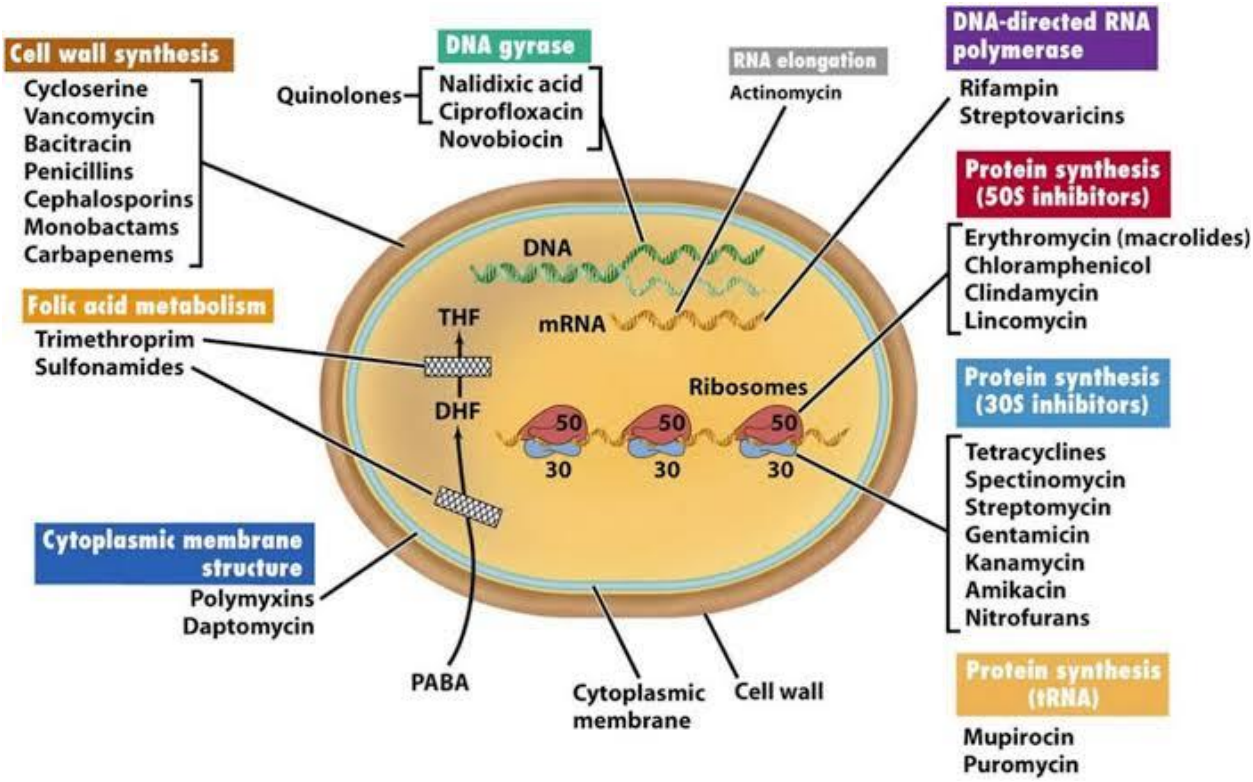

Figure 2. Mechanisms of actions of antibacterials (Talaro and Chess, 2008; Madigan and Martinko, 2006; Wright, 2010).

function: lipopeptides and polymyxins

These are shown in Figure 2.

Classification based on spectrum of activity

- Extended spectrum: antibiotics that have effect against bacterial, rickettsial and protozoan organisms for example, tetracyclines.
- Broad spectrum: antibiotics that are effective against both Gram-positive and Gram-negative bacterial organisms for example quinolones.
- Narrow spectrum: antibiotics that are only effective against either Gram-positive or Gram-negative bacterial organisms for example, macrolides.

Classification based on route of administration

Antimicrobial agents are also classified based on the mode of administration.

- Oral: antibiotics that are administered through the oral cavity.
- Parenteral: antibiotics that are administered through injection.
- Topical: antibiotics that are administered through application on body surfaces.

Classification based on killing effect

- Bactericidal: antibiotics that exert their therapeutic effect through killing the bacterial agents.
- Bacteriostatic: antibiotics that exert their therapeutic effect through inhibiting the growth of bacterial agents (Walsh, 2003).

MECHANISM OF ANTIBIOTIC RESISTANCE

Microorganisms are ubiquitous in nature culminating into local and systemic infections and as a result, the first and second lines of drugs are no longer effective due to repeated administration. The increased use of antibiotics has caused the microorganisms to be increasingly resistant ensuring their survival against the load of antimicrobial agents which are continuously administered. Antimicrobial agents exert their effects by interfering with a specific pathway thereby killing or inhibiting the growth of the target microorganism.

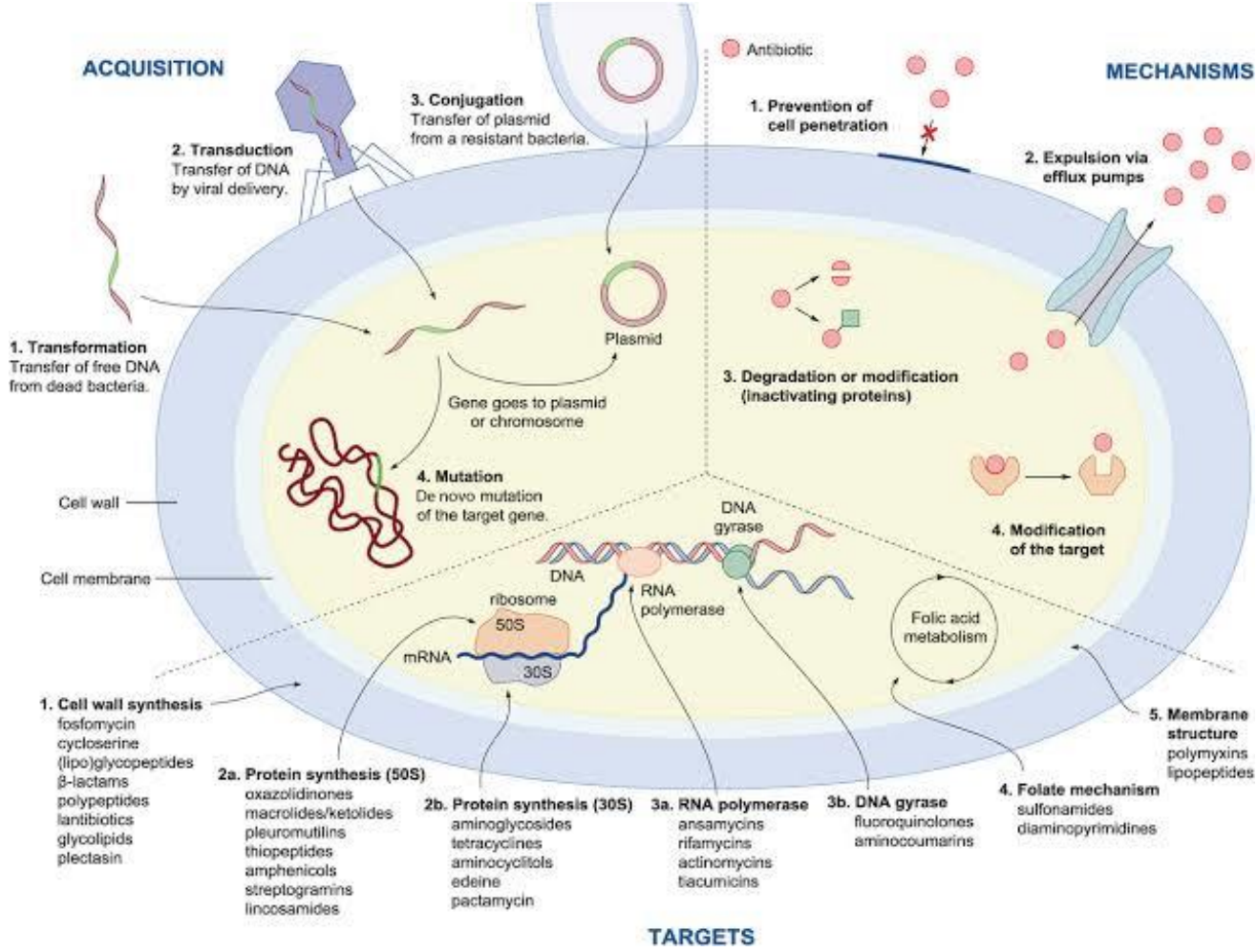

Figure 3. Mechanisms of antibiotic resistance (Chellat et al., 2016).

Therefore, mechanism of resistance majorly depends on which specific pathways are inhibited by the drugs and the alternative ways available for those pathways that the organisms can modify to get a way around in order to survive (Cohen, 2000; WHO, 2014). The various mechanisms of resistance by bacterial organisms are summarized in Figure 3.

TYPES OF ANTIBIOTIC RESISTANCE

Antibiotic resistance is broadly divided into 2 types such as:

Intrinsic or natural resistance: This is sometimes called passive resistance in which some microorganisms naturally do not possess target sites specific for some drugs thereby rendering that drug ineffective when administered or sometimes the microbes will have low permeability to the microbial agents possibly due to chemical nature of the drug or the microbial membrane structure thereby hindering the penetration of the drug into the microbial cells. The low membrane permeability of *Pseudomona aeruginosa* is likely to be the main reason for its innate resistance to many antimicrobials. Other examples include the outer membrane of Gram-negative bacteria, absence of an uptake transport system for antimicrobial and presence of some specific genes by some microbes which aid in mutation (Yoneyama and Katsumata, 2006; Wise, 1999).

Figure 4 shows an overview of the effect of beta lactam (β-lactam) antibiotics on penicillin-binding protein (PBP). Antibiotic A has the ability to penetrate the cell via a membrane-spanning porin protein to reach its target and inhibit peptidoglycan synthesis, Antibiotic B can also penetrate the cell via a porin but could not reach its target PBP in the desired concentration because it is efficiently removed by efflux pump resulting in resistance. Antibiotic

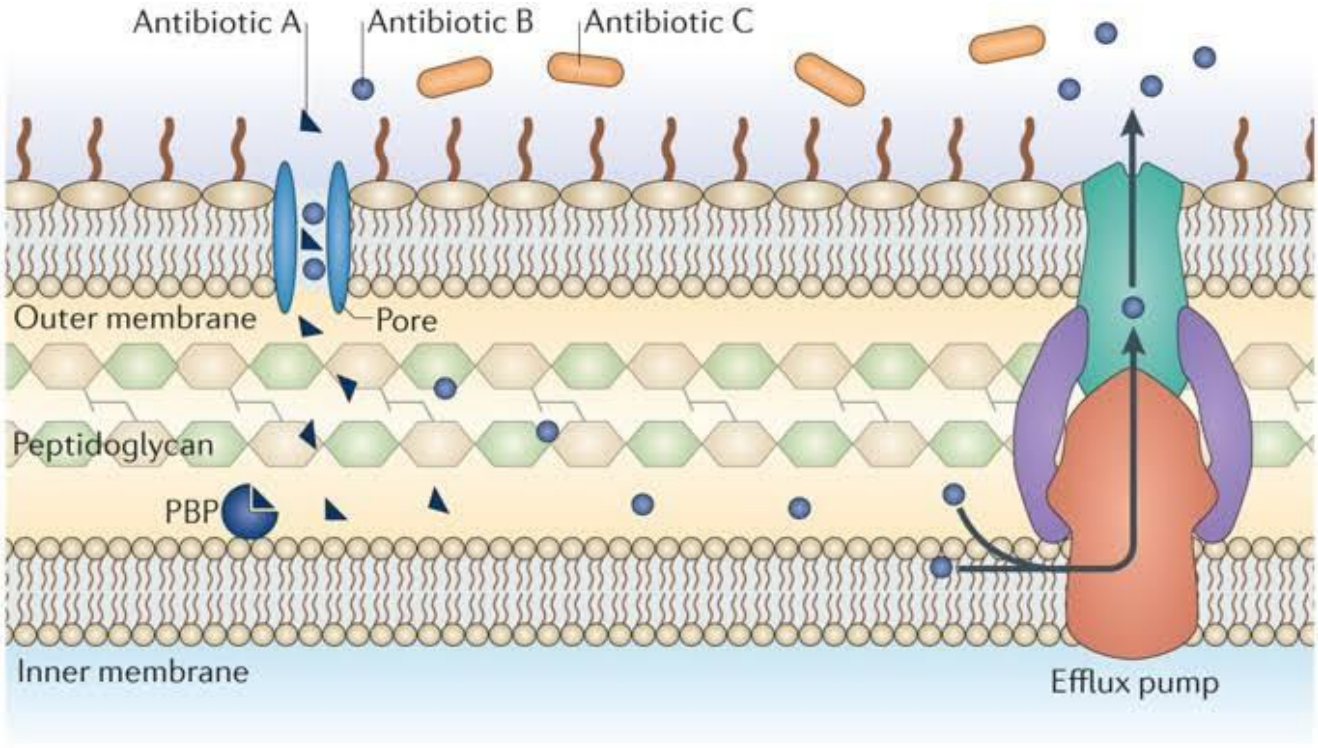

Figure 4. Mechanism of intrinsic antibiotic resistance (Blair et al., 2014).

C on the other hand cannot cross the outer membrane making it unable to access the target PBP thereby conferring resistance.

Acquired or active resistance: This is the major mechanism of antimicrobial resistance which is as a result of evolutionary processes that made the microbes to develop a counterattack mechanism against a particular antimicrobial or a class of antimicrobials whereby bacterial populations previously sensitive to a particular antimicrobial or a class of antimicrobials become resistant. This type of resistance is usually because of the changes in the genomic structure of the bacterial organism. Resistance may sometimes be acquired through mutation and can be passed vertically to daughter cells. However, horizontal transfer of resistant genes between strains and species are more common. Exchange of genes is possible by transformation, transduction, or conjugation (Yoneyama and Katsumata, 2006; Langton et al., 2005). The mechanisms for acquired resistance include but not restricted to the following ways:

- Reduced uptake of the antimicrobial agent
- Overproduction of the target sites of the antimicrobial agent
- The presence of an enzyme that inactivates the antimicrobial agent
- The presence of an alternative enzyme for the enzyme that is inhibited by the antimicrobial agent
- A mutation in the antimicrobial agent's target, which reduces the binding of the antimicrobial agent
- Post-transcriptional or post-translational modification of the antimicrobial agent's target, which reduces binding of the antimicrobial agent as shown in Figure 5.

β-LACTAM ANTIBIOTIC RESISTANCE

β-lactam antibiotics are a group of antibiotics characterized by possession of a β-lactam ring. The first member being the penicillins was first discovered and reported in 1929 by Alexander Fleming (McGeer et al., 2001). They interfere with proteins essential for synthesis of bacterial cell wall. The β-lactam ring is important for the activity of these antibiotics which results in the inactivation of a set of transpeptidases that catalyze the final cross-linking reactions of peptidoglycan synthesis in bacteria. The effectiveness of these antibiotics relies on their ability to reach the penicillin-binding protein (PBP) intact and their ability to bind to the PBPs (Benton et al., 2007; Wilke et al., 2005).

The mechanism of resistance by bacterial organisms to β-lactams antibiotics is as a result of the hydrolysis of the

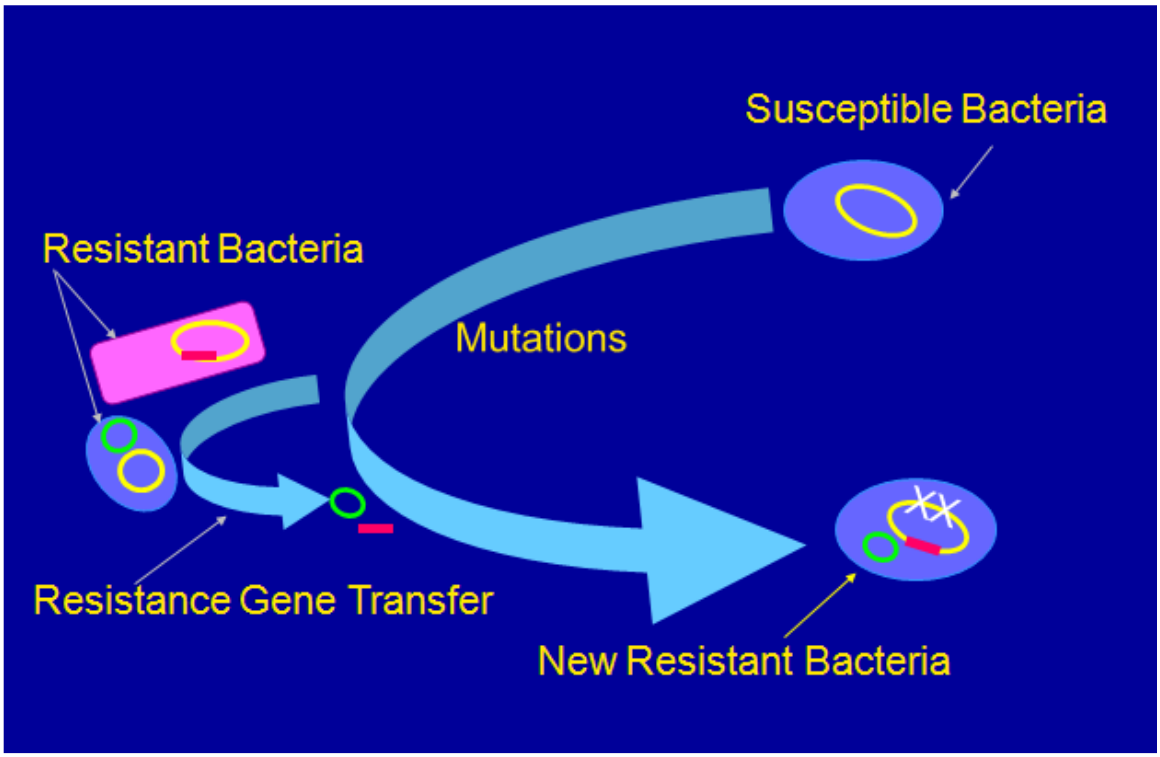

Figure 5. Emergence of acquired antimicrobial resistance (Toma and Deyno, 2015).

antibiotic by β-lactamase enzymes secreted by the bacterial organism or the modification of the PBPs or cellular permeability. β-lactamases constitute a heterogenous group of enzymes which are classified in different ways including their hydrolytic spectrum, susceptibility to inhibitors, genetic localization (plasmid or chromosomal) and gene or amino acid protein sequence. (D'Costa et al., 2011; Wilke et al., 2005; He et al., 2013). The β-Lactam enzyme-mediated resistance arises from the activity of β-Lactamases, enzymes produced by both Gram-positive and Gram-negative bacteria that hydrolyze the β-Lactam amide (Bush, 2018).

TETRACYCLINE ANTIBIOTIC RESISTANCE

Tetracyclines are one of the most used class of antibiotics in both human and animal medicine because of availability, wide safety margin and broad spectrum of activity. Tetracyclines were discovered in 1945 from a soil bacterium of the genus *Streptomyces* by Benjamin Duggar. The first member of this class was chlortetracycline (Sanchez et al., 2004). Tetracyclines exerts their action by inhibiting protein synthesis. This is achieved by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site. They also possess an extended spectrum of activity against atypical organisms such as chlamydiae, mycoplasmas, and rickettsiae, and sometimes protozoan parasites (Roberts, 2005).

There are 3 mechanisms of resistance by bacterial organisms to tetracyclines:

- Efflux of the antibiotics,
- Ribosome protection,
- Modification of the antibiotic.

Efflux of tetracyclines usually occurs through an export protein that are membrane-associated proteins which code for tetefflux genes and export tetracycline from the cell thereby reducing the intracellular drug concentration. Reduced concentration will result in inability for the tetracycline to disrupt the addition of amino acids to polypeptide chains during protein synthesis in the bacterial organelle and thus the ribosomes within the bacterial cell are intact. Numerous bacteria are now able to resist tetracyclines. Tetracycline efflux proteins have amino acid and protein structure similarities with other efflux proteins involved in multiple-drug resistance, quaternary ammonium resistance, chloramphenicol, and quinolone resistance (Chopra and Roberts, 2001; Medical News Today, 2015).

The mechanism of ribosome protection occurs through the ribosome protection proteins (RPPs) which protect the ribosomes from the effect of tetracyclines. Ribosome

protection proteins are cytoplasmic proteins that confer resistance by binding to the ribosomes, causing an alteration in ribosomal conformation which prevents tetracycline from binding to the ribosome without altering or stopping protein synthesis. They confer resistance mainly to doxycycline and minocycline and confer a wider spectrum of resistance to tetracyclines than is seen with bacteria that carry tetracycline efflux proteins. The most common RPPs are Tet(O) and Tet(M) with over 70% sequence similarity to each other (Connell et al., 2003).

Mechanism of antibiotic modification occurs through enzymatic alteration of the drugs by the microbial pathogens. Some of these genes are coded for by tet(X) and otr(X) genes. The tet(X) gene encodes for NADPH-requiring oxidoreductase, which in the presence of oxygen NADPH inactivates tetracycline, this is however reported only in anaerobic conditions (Roberts, 2005; Chopra and Roberts, 2001).

CHLORAMPHENICOL RESISTANCE

Chloramphenicol is a semisynthetic, broad-spectrum antibiotic with long history of medicinal use. It was derived from *Streptomyces venequelae*. Chloramphenicol binds to the 50S ribosomal subunit and inhibits the peptidyl transferase step involved in protein synthesis (Vazquez, 1964).

The mechanism of chloramphenicol resistance is largely due to inactivation of the antibiotic by a chloramphenicol acetyltransferase which is secreted by the bacterial pathogen. This is seen in Gram-negative and Gram-positive bacteria and usually show little homology. In some cases, decreased outer membrane permeability or active efflux could be responsible for the resistance in Gram-negative bacteria (Wright, 2005).

AMINOGLYCOSIDE RESISTANCE

Aminoglycosides are broad-spectrum class of antibiotics which are characterized by the presence of an aminocyclitol ring linked to amino sugars in their structure and have a broad spectrum of activity against bacterial organisms. Aminoglycoside bactericidal activity is attributed to the irreversible binding to the ribosomes, inhibiting protein synthesis but effects resulting from interaction with other cellular structures and metabolic processes are also known to occur (Peterson, 2008; Shahid, 2007). Streptomycin, which is widely used against *Mycobacterium tuberculosis*, the causal agent of tuberculosis is the first aminoglycoside antibiotic to be discovered in 1943 (Mahajan and Balachandran, 2012).

There are about three mechanisms of aminoglycoside resistance: decreased permeability or reduced uptake which is chromosomally mediated and result in cross reactivity to all aminoglycosides, alterations at the ribosomal binding sites which is through mutation especially in streptomycin since it binds to 30S ribosomal subunits and production of aminoglycoside modifying enzymes which is the commonest resistance mechanism (Mingeot-Leclercq et al., 1999). Modification with aminoglycoside modifying enzymes which make the aminoglycosides to lose their ribosome binding ability and thus no longer inhibit protein synthesis. The widespread resistance is as a result of the availability of more than 50 aminoglycoside-modifying enzymes and most of the genes are associated with Gram-negative bacteria. Depending on their type of modification, these enzymes are classified into three major classes as aminoglycoside acetyltransferases (AAC), aminoglycoside nucleotidyltransferases (ANT), and aminoglycoside phosphotransferases (APH). Efflux systems and rRNA mutations are however involved in few aminoglycoside resistance (Shahid, 2007; Jana and Deb, 2006).

QUINOLONES RESISTANCE

Quinolones are broad spectrum antibiotics and was first discovered in 1962 as nalidixic acid during the development of quinine (Domagala, 1994). Several derivatives have been made available through structure modification, with fluoroquinolones being the most important derivative which contain a substitution of a fluorine atom at position 6 of the quinolone molecule. This modification greatly enhances the activity against both Gram-positive and Gram-negative bacteria as well as anaerobes. These agents exert their antibacterial effects by interfering with DNA replication and transcription in bacteria through inhibition of certain bacterial topoisomerase enzymes, namely DNA gyrase (bacterial topoisomerase II) and topoisomerase IV. These essential bacterial enzymes alter the topology of double-stranded DNA (dsDNA) within the cell. DNA gyrase and topoisomerase IV are heterotetrameric proteins composed of two subunits, designated A and B (Goldstein et al., 2012; Dougherty et al., 2001).

There are 2 mechanisms of resistance by bacterial organisms to quinolones:

- Alterations in drug target enzymes,
- Alterations that limit the permeability of the drug to the target.

In drug target enzyme alteration, the target enzymes are usually altered in domains near the enzyme active sites, and in some cases reduced drug-binding affinity. In Gram-negative organisms for instance, DNA gyrase seems to be the primary target for all quinolones while in Gram-positive organisms, topoisomerase IV or DNA gyrase are the primary targets depending on the fluoroquinolone in

consideration. In almost all instances, amino acid substitutions within the quinolone resistance-determining region (QRDR) involve the replacement of a hydroxyl group with a bulky hydrophobic residue. Mutations in gyrA induce changes in the binding-site conformation and/or charge that may be important for quinolone–DNA gyrase interaction.

Alterations that limit the permeability of the drug to the target usually causes changes in the cell envelope of Gram-negative bacteria, particularly in the outer membrane, have been associated with decreased uptake and increased resistance to fluoroquinolones, though this has not been demonstrated in Gram-positive bacteria (Hooper, 2001; Higgins et al., 2003; Dougherty et al., 2001).

MACROLIDE, LINCOSAMIDE, AND STREPTOGRAMIN (MLS) RESISTANCE

Macrolide antibiotics have a wider spectrum of antibiotic activity than penicillins and are often administered to patients allergic to penicillin (Moore, 2015). Macrolides act by effectively binding to bacterial ribosome thereby prevent the addition of amino acid to polypeptide chains during protein synthesis. Lincosamide antibiotics such as lincomycin binds to 50S ribosomal subunit and inhibit peptidyl transferases during bacterial protein synthesis. Just like the macrolides and lincosamides, streptogramins are group of cyclic peptide antibiotics that act by inhibiting the synthesis of bacterial protein (Gaillard et al., 2016).

The mechanism of resistance by microbial pathogens to MLS antibiotics could be intrinsic or acquired. Intrinsic resistance to MLSB (including streptogramin B) antibiotics in Gram-negative bacilli is due to low permeability of the outer membrane to these hydrophobic compounds. There are 3 mechanisms of acquired resistance by bacterial organisms to MLS antibiotics in Gram-positive bacteria:

- Post-transcriptional modification remains the most frequent mechanism of resistance which occur as a result of modification in the transcription process of 23S rRNA by the adenine-N6-methyltransferase which alters a site in 23S rRNA which is common to the binding of MLSB antibiotics resulting in cross-resistance to MLSB antibiotics (MLSB-resistant phenotype).
- The presence of efflux proteins which actively pump out these antibiotics from the cell or the cellular membrane, causing about two-fold reduction in the minimal inhibitory concentration (MIC) of these antibiotics which in turn make the ribosomes free of antibiotics resulting in MLS resistance. This mechanism is more frequent in gram-positive populations and is usually associated with *mef*(A), *msr*(D), and *vga*(A)genes.
- Mechanism of resistance through modification or hydrolytic effect of enzymes. In this case resistance is achieved through streptogramin B hydrolysis or through modification of the antibiotic by adding an acetyl group (acetyltransferases) to streptogramin A, this is also found in structurally related drugs (Rezanka et al., 2007; Echols, 2012).

GLYCOPEPTIDE RESISTANCE

Glycopeptides are made of a cyclic peptide of 7 amino acids, hence the name glycopeptides. Glycopeptide of clinical interest include vancomycin and teicoplanin (Kang and Park, 2015). Their antimicrobial activity is due to binding to D-alanyl-D-alanine side chains of peptidoglycan (peptidic backbone) which prevent the cross-linking of the peptidoglycan chain and are largely effective against most Gram-positive microorganisms which are likely to have a bigger layer of the peptidoglycan. Traditionally, vancomycin was generally accepted because it was thought to be the drug of choice in the treatment of methicillin-resistant *Staphylococcus aureus* infection (MRSA) but the emergence of vancomycin-resistant organisms limited the acceptance of vancomycin.

Resistance to glycopeptides especially vancomycin is encoded by the *van*(A) gene that results in the production of a novel D-Ala-D-Ala ligase resulting in the rebuilding of the peptidoglycan side chain to express D-alanyl-D-lactate type which has less affinity for glycopeptides. Other proteins in this gene cluster that are necessary for conferring resistance include *Van*(H) and *Van*(X) and *Van*(B) (Bush, 2013; Finch, 2011).

SULFONAMIDES RESISTANCE

Sulfonamides are one of the oldest class of antibiotics in therapeutic medicine with extended spectrum of activity in that sulfonamides are active against both Gram-positive and Gram-negative bacterial organisms as well as fungi and some protozoan parasites (Miller-Hjelle et al., 2004; Zessel et al*.,* 2014). Sulfonamides are p-amino-benzoic acid (PABA) antagonists. Sulfonamides achieve bacteriostatic effect by competitively blocking the PABA which is an important compound in bacterial folic acid synthesis thereby reducing bacterial growth and preventing DNA synthesis (Varagić and Milošević, 2009).

The mechanism of resistance associated with sulfonamides is mediated by drug-resistant forms of dihydropteroate synthase (DHPS). In Gram-negative bacilli, resistance generally arise from the acquisition of either of the two genes *sul*(1) and *sul(*2) which are the encoding forms of dihydropteroate synthase that are not inhibited by the drug. *Sul* (1) gene is linked to other resistant genes in class 1 integrons, while *sul*(2) is located

on small non conjugative plasmids or large transmissible multi-resistance plasmids (Langley et al., 2013; Lambert, 2005).

TRIMETHOPRIM RESISTANCE

Trimethoprim is an antifolate antibiotic that is mostly used in combination with sulfamethoxazole. Trimethoprim inhibits bacterial dihydrofolate reductase (DHFR) which is an important enzyme that play a major role during the formation of tetrahydrofolic acid (THF) thereby preventing the synthesis of bacterial DNA (FDA, 2016).

Mechanism of trimethoprim resistance is clustered around the enzyme dihydrofolate reductase (DHFR). Resistance could be achieved either through overproduction of the host DHFR, mutations in the structural gene for DHFR or acquisition of a gene (dfr) encoding a resistant DHFR enzyme. The acquisition of dfr gene which encodes a resistant DHFR enzyme is the commonest resistant mechanism in clinical isolates (Langley et al., 2013; Lambert, 2005).

POLYMYXIN RESISTANCE

Polymyxin is an old class of non-ribosomal cyclic lipopeptide antibiotics discovered in the year 1947. Polymyxins are considered the final option of antibiotic therapy for multidrug resistant bacteria (Rice, 2006; Li and Nation, 2006). Polymyxins act by attacking the cytoplasmic membrane of both Gram-positive and Gram-negative bacteria and the outer membrane of Gram-negative bacteria. Polymyxins bind to phospholipids in the cytoplasmic membrane of bacteria causing complete loss of membrane integrity leading to leakage of cytoplasmic contents and finally resulting in cell death.

Mechanism of resistance is usually by the modification of the phosphate esters linked to the diglucosamine components of lipid A (CDCP, 2013; Goldstein et al., 2012). Multidrug efflux pumps also play an important role in polymyxin resistance. The AcrAB efflux pump encoded by acrAB operon can give *Klebsiella pneumoniae* and *Escherichia coli* resistance to polymyxin (Padilla et al., 2010; Warner and Levy, 2010).

OXAZOLIDONE RESISTANCE

Oxazolidones are synthetic antibacterial agents that are effective against Gram-positive microorganisms. They are one of the most recent class of antibiotics approved for use. Oxazolidone are protein synthesis inhibitors, they act by binding to the P site of the ribosomal 50S subunit of bacterial organisms which prevent the formation of 70S initiation complex which is a prerequisite for bacterial reproduction. It is a drug of choice in managing surgical infections since they easily penetrate and accumulate in the tissues like bone, lung, haematoma and cerebrospinal fluid (Bozdogan and Appelbaum, 2004).

The synthetic nature of oxazolidones made it not to have a natural prototype therefore, natural pool of resistant gene to facilitate the development of clinical resistance is nearly impossible. However, resistance of bacterial agents to linezolid which is an oxazolidone is generally due to mutations in domain V of 23S ribosomal RNA. Resistance occurs rarely and develop slowly because of the presence of multiple copies of redundant rRNA genes in bacterial genome (Toh et al., 2007; Franceschi et al., 2004).

LIPOPEPTIDE RESISTANCE

These are cyclic lipopeptides with potent antimicrobial activity against Gram-positive bacteria and consist of acyl side chains and peptides of various kinds. Daptomycin is the most used member of this class. They act by binding to bacterial membranes and causes rapid membrane potential depolarization thereby inhibiting protein, DNA and RNA synthesis resulting in cell death. The antibacterial activity of daptomycin is dependent on its ability to bind to calcium and membrane components with subsequent dissipation of the cytoplasmic membrane potential (Schneider et al., 2014).

There is no definitive report on the mechanism of daptomycin resistance, though reduction of diffusion of daptomycin due to the thickening of cell walls induced by vancomycin has been proposed (Boucher and Sakoulas, 2007; Cui et al., 2006). Resistance through mutation in *S. aureus* has been found in mprF gene (lyslphosphatidylglycerol synthetase), yycG gene (histidine kinase), rpoC and rpoB genes (subunits of RNA polymerase) (Friedman et al., 2006). The relationship between these mutations and reduced daptomycin susceptibility is yet to be scientifically substantiated.

ANSAMYCIN RESISTANCE

Ansamycins are macrocyclic polyketides class of antibiotics obtained from *Streptomyces* and *Bacillus* species, they were first isolated in 1959 and was introduced into therapy in 1962. Rifampicin (RIF) as ansamycin derivative is the first-line agent in the treatment of tuberculosis, leprosy and various biofilm-related infections (Kang et al., 2012; Wilson et al., 2011).

Ansamycins are a very important class of antibiotics as they have been demonstrated to have extended spectrum of activities against bacterial, viral and tumorigenic organisms. The antimicrobial mechanism of action of ansamycins is due to their ability to inhibit bacterial RNA polymerase (RNAP) thereby preventing the initiation of

transcription (Wrona et al., 2008; Brandt and Blagg, 2011; Song et al., 2015). Mechanism of resistance is mostly due to mutation in the *rpoB* gene, which is usually very frequent and for this reason, rifampicin is almost exclusively used in combination with isoniazid and only recommended in tuberculosis and emergencies. Other mechanisms of resistance reported include duplication of the target due to mutation in rpoB gene as in *norcadia spp*, action of RNAP-binding proteins; RbpA which confers basal levels of RIF resistance to *Streptomyces coelicolor* and *M. tuberculosis*, modification of cell permeability by decreasing the permeability of the membrane barriers (Maguire and Wild, 2008; Newell et al., 2006; Hu et al., 2000; Siddiqi et al., 2004).

MULTIDRUG RESISTANCE

Multidrug resistance (MDR) is a major setback in clinical medicine as most of the infectious diseases which are treatable are becoming untreatable due to resistance. MDR could be primary or secondary; primary resistance occurs when the pathogen has never come in contact with the drug of interest in a given host while secondary resistance arises when a pathogen has been exposed to a drug of interest in a given host (Khalilzadeh et al., 2006). WHO reported a number of resistant infectious diseases such as *E. coli* against antibiotics like cephalosporin and fluoroquinolones, *K. pneumoniae* against cephalosporin and carbapenems, *S. aureus* against methicillin, *Streptococcus pneumoniae* against penicillin, Nontyphoidal *Salmonella* against fluoroquinolones, *Shigella* species against fluoroquinolones, *Neisseria gonorrhoeae* against cephalosporin, and *M. tuberculosis* against rifampicin, isoniazid, and fluoroquinolone causing common infections (Nikaido, 2009; WHO, 2014).

Infectious diseases caused by bacteria, fungi, virus, and parasite such as typhoid, pneumonia, tuberculosis, hepatitis, HIV, influenza, malaria and yeast infections are associated with high morbidity and mortality indicating MDR as a serious worldwide challenge to public health (Bennett et al., 2010).

Mortality caused by antibiotic resistance is alarming and it has been envisaged that the mortality rate will keep increasing worldwide to more than 50 million by 2050 (Abat et al., 2017). In MDR, bacterial organisms can withstand the antimicrobial activities of antibiotics through three distinct but related mechanisms: resistance, persistence, and tolerance (Levin-Reisman et al., 2019). Resistance is the ability of a bacterial organism to survive and grow in the presence of adequate concentrations of antibiotics (Levin-Reisman et al., 2019; Brauner et al., 2016). Persistent bacteria refer to bacterial organisms that possesses cells known as persister cells which are cells that survive antibiotic activities at a concentration equal to or lower than the MIC (Windels et al., 2019). Tolerant bacterial organisms are organisms with high metabolic activities that can survive transient exposure to high concentrations of antibiotics (Brauner et al., 2016).

FUTURE DIRECTIONS

Even with the tireless efforts of scientist in discovering new therapeutic agents and repositioning the already developed drugs all aiming at mitigating the effects of MDR, little or no result was achieved. Therefore, good sanitary measures and hand washing practices are important steps towards ensuring infection free society (Wang and Barrett, 2007). Highly restricted or prudent use of antibiotics by clinicians, veterinarians, farmers, and individuals will make a head way in tackling multidrug resistance (Niederman, 2005). Reintroduction of Phage therapy which entails the use of bacterial viruses (bacteriophages or phages) to infect and lyse bacteria to treat or prevent infection is also of paramount importance (Carlton et al., 2005; Salmond and Fineran, 2015). Regulation of antibiotic use in clinical medicine and livestock industry and adequate surveillance will greatly reduce the spread of MDR bacteria (Medina and Pieper, 2016), the use of statins which are lipid-lowering molecules with pleiotropic effects has shown promises in managing recalcitrant bacterial infections caused by the genera *Staphylococcus*, *Streptococcus*, *Enterococcus*, and *Moraxella* (Jerwood and Cohen, 2008). The exclusive use of pre and pro biotics in animal farming as a substitute for antibiotics should be highly encouraged and the concept of drug repositioning can be adopted to reposition some of the antibiotics that less sensitive or insensitive to the bacterial organisms they were originally manufactured for.

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