

# Antimicrobial Resistance: Causes, Mechanisms of Resistance and Influencing Factors

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**Abstract-** Despite that antimicrobial resistant (AMR) is not a new problem around the world. The number of resistance microorganisms reaches an alarming level increasing morbidity and mortality across different geographical places. World Health Organization (WHO) defined the actual situation of AMR as natural phenomena when the microorganisms adapt and develop their ability to survive and multiply in the presence of antibiotic which was previously susceptible to kill or inhabit this type of organism [1]. Causing diseases agents that were thought to be under control by antibiotics to return in new types of resistance to their therapies.

**Index Terms-** Antimicrobial Resistance (AMR), Antibiotic use, Resistance Strategies, Antibiotic Resistance, Influence factors of (AMR).

## I. INTRODUCTION

Initially AMR appeared in hospital and medical care facilities due the fact that most of antibiotic agents were used. The rapid spread of AMR was detected early in parallel with the first use of antibiotics agents, for example penicillin resistance were confronted early in London Civilian hospital after the introduce of penicillin in 1945 as an antibiotic agent. As well as resistance to other types of antibiotic such as streptomycin was encountered by *Mycobacterium tuberculosis* [2]. Unfortunately, resistance to multiple antibiotic agents was detected among bacteria called, *Escherichia coli*, *Shigella* and *Salmonella* the early 1960s [3]. Such microorganisms causing several clinical problems and cost of lives especially in developing countries where AMR was fueled by increasing antimicrobials use, which were readily available without prescription. In 1970 the frequency of resistance escalated in many different strains, such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*, organisms that cause respiratory and genitourinary disease, respectively [4]. The re-emergence of tuberculosis has happened dramatically in the form of multidrug resistance (MDR) since 1980. The human immunodeficiency virus plays a significant role in developing (MDR) and causing sever and difficult infections to treat by antibiotics agents, sometimes six or seven different type of antibiotics were used to treat one infection caused by (MDR) strains [5].

In the last decades, many studies have discussed the developing of (AMR), factors leading and promoting (AMR), and the international response to the (AMR) as a global threat. In simple way the problem of (AMR) can be summarized as an

equation with two essential conditions; firstly, the chemicals or antimicrobial drugs which kill susceptible microorganism. Secondly, the genetic resistance in organism selected by the chemical components of antibiotic drugs. Therefore, (AMR) emerges only when the two previous conditions come together in host or in environment leading to clinical problem. Selected resistance genes and their host propagate among continuous antimicrobial selection to multiply and spread the problem to other geographical places and new host.

Yearly, millions of kilograms of chemicals and antibiotic drugs are used around the world to treat patients, animals and agriculture. In general, there are around 15 families of antibiotic drugs working on physiological or metabolic targets of bacteria as shown in the below table [6].

Mechanism of action	Antibiotic families
Inhibition of cell wall synthesis	Penicillin; cephalosporins; carbapenems; daptomycin; monobactams; glycopeptides
Inhibition of protein synthesis	Tetracyclines; aminoglycosides; oxazolidonones; streptogramins; ketolides; macrolides; lincosamides
Inhibition of DNA synthesis	Fluoroquinolones
Competitive inhibition of folic acid synthesis	Sulfonamides; trimethoprim
Inhibition of RNA synthesis	Rifampin
Other	Metronidazole

**Table 1: Major antibiotic families and their mechanisms of action [6].**

### The ways in which microorganism resist antibiotics

Microorganism show different strategies to survive in the presence of antibiotic drugs. These strategies can be classified in four major mechanism.

1. Preventing antibiotics to reach their target.

Antibiotics components need an access into microorganism cell to reach their target or the site of action to

perform their treatment function. Chemical agents of antibiotics can enter the bacteria membrane through special channel known as porin channels. This mechanism of resistance based on modifying the permeability of porin channel in different means such as changing size, frequency or selectivity of passage way channels. Usually this mechanism used by gram -negative bacteria to inhabit and reduce the uptake antibiotic agents such as aminoglycosides and beta lactams. Preventing antibiotics components to reach their selected targets, ribosomes and the penicillin-binding proteins, for aminoglycosides and beta lactams respectively. Also, this strategy has been detected in *Enterobacter aerogenes* and *Klebsiella* against imipenem and in some type of gram-negative bacteria against quinolones. As well as *Pseudomonas aeruginosa* against imipenem (a beta-lactam antibiotic) [7].

2. Expulsion of antimicrobial agents

Antibiotic agents must be at high concentration inside the microorganism cell to be effective, the sufficient concentration of antibiotic chemical agents responsible to inhabit or kill bacteria and microorganism. in fact, lab studies and experiment showed that some type of microorganism have a special mechanism known as efflux pump which extrude antibiotic agents outside the cell. Leading to low intracellular concentration or insufficient concentration of antibiotics agents inside the targeted microorganism. in addition to that, some efflux pumps have a selective property to extrude certain type of antibiotics agents such as macrolides, lincosamides, streptogramins and tetracyclines. Whereas other type of efflux pumps referred to multi drug resistance which can extrude many different type of antibiotics agents. This strategy of resistance has been observed in *E. coli* and *Enterobacteriaceae* against tetracyclines and chloramphenicol. Also, *Staphylococci* and *Streptococcus pneumoniae* showed a resistance against macrolides, streptogramins and fluoroquinolones [8].

3. Inactivation of antimicrobial agents

By using this strategy, bacteria can survive and multiply in the presence of antibiotic agents. This mechanism based on chemical reaction destroying the active component of antimicrobial agents by certain enzyme to inhabit the function of antibiotic. One of the most common example for this strategy is beta lactamase enzyme. Hydrolytic deactivation of the beta-lactam ring in penicillin and cephalosporins leading inactivated binding between penicilloic acid and penicillin binding proteins, which completely deactivate the function of antimicrobial agents. This type of resistance has been observed in gram-negative and gram-positive bacteria against aminoglycosides (phosphorylation, adenylation, and acetylation) [9].

4. Modification of antimicrobial targets

This type of resistance based on reprogramming or modifying the special target site to avoid recognition with antibiotic agents. Consequently, no subsequence chemical reaction or inhibition will take place inside the intracellular membrane of microorganism despite the presence of sufficient concentration of antibiotics agents. this mechanism has been observed in different type of microorganism with different type of target modification such as: *Taphylococci* against methicillin and other beta-lactams by modifying the target site of binding proteins to avoid sufficient bind of beta-lactams to destroy cell wall synthesis. Also, other type of modification can be used by *Enterococci* against vancomycin, changing certain component of intracellular wall of organism to decrease chemical binding of antimicrobial agents. in addition to that, genetic mutation of DNA gyrase and RNA polymerase showing antimicrobial resistance against quinolones and rifamycins respectively [10].

The below table summarized the common resistance microorganisms and their mechanisms against antibiotics drugs.

ANTIMICROBIAL CLASS	MECHANISM OF RESISTANCE	SPECIFIC MEANS TO ACHIEVE RESISTANCE	EXAMPLES
Beta-lactams Examples: penicillin, ampicillin, mezlocillin, peperacillin, cefazolin, cefotaxime, ceftazidime, aztreonam, imipenem	Enzymatic destruction	Destroy of beta-lactam rings by beta-lactamase enzymes. Disabling the beta-lactam ring to bind with PBP (Penicillin-binding protein).	Staphylococci against penicillin; Enterobacteriaceae against penicillin, cephalosporins, and aztreonam
	Changing target	Modifying in penicillin binding proteins. Mutational alert in original PBPs or developing of new PBP. Leading inability of the antimicrobial component to bind with PBP and inhibit cell wall synthesis	staphylococci against methicillin and oxacillin
	Reduce effective concentration	Porin channel formation is reduced. preventing beta-lactams to pass	Enterobacter aerogenes, Klebsiella pneumoniae and Pseudomonas

		through the outer membrane to bind with the PBP of Gram-negative bacteria, a change in the number or shape of porin channels can reduce beta lactam concentration.	aeruginosa against imipenem
Glycopeptides Example: vancomycin	Modifying target	Modifying the structure of molecular cell wall precursor components reduce binding of vancomycin, allowing cell wall synthesis is to continue.	Enterococci against vancomycin
Aminoglycosides Examples: gentamicin, tobramycin, amikacin, netilmicin, streptomycin, kanamycin	Enzymatic modification	Modifying enzymes sites on the aminoglycoside molecule so that the ability antibiotic to bind with ribosome and halt protein synthesis is greatly reduced or lost entirely.	Gram-positive and Gram-negative bacteria against aminoglycosides
	Reduce effective concentration	Change in number or shape of porin channels reducing the concentration of aminoglycosides pass through the outer cell membrane to bind the ribosomes of gram-negative bacteria).	Gram-negative bacteria against aminoglycosides
	Modifying target	alteration of ribosomal proteins or of rRNA. Decreasing the ability of aminoglycoside to successfully bind and inhibit protein synthesis	Mycobacterium spp against streptomycin
Quinolones Examples: ciprofloxacin, levofloxacin, norfloxacin, lomefloxacin	Reduce uptake	changing in the outer membrane diminishes uptake of antibiotic or activation efflux pump to pump out quinolones before intracellular concentration of antibiotic reach sufficient level to inhabit DNA metabolism.	Gram negative and staphylococci (efflux mechanism only) against various quinolones
	Changing target	Reprogramming DNA gyrase sequence reducing the capability of quinolones to bind this enzyme and delay with DNA processes	Gram negative and Gram-positive against various

**Table 2: Resistance Microorganism against different types of antibiotics and their respective mechanisms [11]**

## Factors promote the spread of AMR

Generally, there are a wide variety of factors working simultaneously to increase the spread of antimicrobial resistance. Different major fields of our routine life are responsible to spread AMR globally, such as hospitals and medical facilities, veterinary and use of growth factors in food producing animals, water treatment and agriculture.

In many developed countries the misuse and excessive use of antibiotics lead to increase the acquired resistance of antimicrobial agents. The absence of medical regulations allowing people to purchase antibiotics drugs directly without any prescription by qualified physicians or general practitioners. The incorrect diagnosis of infection would lead to over prescription promoting the excessive use of antibiotics drugs especially when the clinical indicators of viral infection are approximately the same as bacterial infections.

On the other hand, in long term hospital setting the prolong and extra use of antibiotics drugs would be the essential factor to develop and spread of AMR between patients and medical staff. Certain medical cases such as patients with susceptible immunosuppressed, cancer patients, transplant recipients and elderly patients have significant opportunity to obtain and spread antimicrobial infection especially when the control infections procedures are not correctly followed.

In the last years, the environment as one of the significant factors to spread AMR has been widely recognized. Soil generally work as a reservoir of antimicrobial resistance genes, while most antibiotics originated from microorganism living and multiply in soil. Unfortunately, these microorganisms are intrinsically resistant to the derived antibiotics.

Water play a considerable role in dissemination of bacteria between different geographical locations. A huge amount of chemical antibiotics drugs is released in waste water of municipal because of incomplete metabolic process inside human body or due to miss use of antibiotics drugs. Regarding this situation, available data from labs and experimental studies showed that antimicrobial resistance genes and antibiotic resistance microorganisms can be detected and observed in wastewater sample. Recently, many studies showed that there is a high concentration level of antibiotics chemical containing tetracycline, sulphonamide and their resistance bacteria genes in the same location of wastewater treatment plants [12] [13].

The interaction between people and animals develop potential effects on human health situation. However, a major ratio of total antimicrobial agents used outside the field of human medical application. Using of antibiotics drugs in food producing animals and in aquaculture as a growth factors and as a disease treatment consider as substantial contributor to develop and rapid spread of antibiotic resistance problem [14]. The first effect of using antimicrobial agents in growth promoting sector was early discovered by the 1940s [15]. This situation become as integral part of modern trend of animal rearing to achieve commercial benefit including early weaning, increase animal mass and as a cheap source of feeding [16]. Sub-standard growth generated by unsanitary condition usually compensated by adding chemicals and antibiotics agents to animal food. In fact, many chemical and antibiotic components are used in food producing animals, such as flavophospholipol and macrolide tylosin, leading to rapid growth rate, prevent diseases and reduce morbidity of premature

animals [17]. Consequently, the effect of using antimicrobials agents in food producing animals and as a growth promoting factor have been detected in several studies. For example, using of glycopeptide avoparcin found to be related to the selection of vancomycin-resistant enterococci [18].

Finally, many direct evidence of spread AMR between animals and people have been proved. Spread of MRSA directly between infected animals to people has been detected by Catry et. al 2010 [19]. Moreover, transfer of MRSA from human medical facilities and hospital to animals has been reported by Holmberg et. al 1984 [20]. As well as, transfer of salmonella and of campylobacter from food producing animals to community is established and spread whether the microorganism resistance to antibiotics or not [21].

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