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AN OVERVIEW OF MECHANISMS OF ANTIBIOTIC RESISTANCE IN BACTERIA

[1]Jehad Ahmed Alluhaybi*, [2]Hisham Ayidh Alharbi, [3]Ahmed Saeed Alghamdi, [4]Yaser Abdullah Alqurashi, [5]Faisal Fahad Alsharif, [6]Abdullah Ali Alshehri, [7]Muath Abdullah Hadayidi, [8]Yaser Mishal Alharthi, [9]Sami Ali Hasan, [10]Rami Mohammed Dada

[1]Pharmacist, Heraa General Hospital
[2]Pharmacist, Heraa General Hospital
[3]Pharmacy technician, Heraa General Hospital
[4]Pharmacist Assistant, Directorate of Health Affairs in Makkah
[5]Pharmacy technician, Heraa General Hospital
[6]Pharmacy technician, King Abdulaziz Hospital - Jeddah
[7]Pharmacy technician, Heraa General Hospital
[8]Pharmacy technician, Heraa General Hospital
[9]Pharmacy technician, Heraa General Hospital
[10]Pharmacy technician, Heraa General Hospital

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Abstract:

The purpose of this review was to highlight the most significant parts of antibiotic resistance mechanisms. In addition, we endeavored to address the advantages of antibiotics as well as the resistance challenge. We conducted a comprehensive literature evaluation on antibiotics resistance by an electronic search of MIDLINE, EMBASE, and Google Scholar databases up to April 2022. For the purpose of analyzing the mechanism of antibiotic resistance, we picked the most significant papers pertinent to our area of inquiry. The value and importance of antibiotics cannot be overestimated; we rely on them solely for the treatment of infectious diseases, and they must never be considered fundamental products. Antibiotics are essential to the success of cutting-edge surgical procedures, such as organ and prosthesis transplants, in addition to their use in the treatment of communicable diseases. There is little doubt that the situation in regards to antibiotic resistance is dire, despite all good intentions to restrict antibiotic consumption (albeit limited activity). Resistance mechanisms are widespread and cause considerable clinical and monetary concerns for healthcare systems globally. There are no universal solutions to the problem. Even when lives can be saved, decisive actions requiring significant commitment and enforcement are never emphasized. It is crucial that we have a good picture of the amount of different resistance systems that private bacteria may possess.

Corresponding author:
Jehad Ahmed Alluhaybi,
Pharmacist, Heraa General Hospital

QR code

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INTRODUCTION:

Antibiotics in the biosphere are produced by microorganisms as secondary metabolites at a concentration much lower than the therapeutic dosage. Waksman was convinced that antibiotics play "no genuine part in influencing or customizing living processes that take place in nature" [(1)] though there is evidence to the contrary [(2)]. Resistance to antimicrobial agents has become a major source of morbidity and mortality worldwide. Present research study studies [(3,4,5,6)] reveal that antibiotics do have some certain results on the all-natural scene of the bacteria while they presume a totally different function as antibacterial agents in the dose made use of in rehabilitation [(3,4,5,6)].

Antibiotic resistance is 'bacteria changing in manner in which eliminate the efficiency or decrease of antibiotics efficiency [(9)]. These changes are because of bacterial improvement, as well as endanger the solitary greatest therapeutic advance in the background of medication. The quick development of resistant bacteria is happening worldwide, endangering the efficiency of antibiotics, which have actually changed medicine as well as saved wide populations of many infectious diseases [(5,6,7,8)]. Several years after the really first patients were treated with antibiotics, bacterial infections have once more wind up being a danger [(8)]. The antibiotic resistance situation has in fact been credited to the overuse and also misuse of these antibiotics, in addition to an absence of new medicine development by the pharmaceutical market due to reduced monetary incentives and also hard regulative requirements [(9,10,11)].

METHODOLOGY:

We conducted a comprehensive literature evaluation on antibiotics resistance by an electronic search of MIDLINE, EMBASE, and Google Scholar databases up to April 2022. We picked the most significant research connected to our issue for reviewing the mechanism of antibiotic resistance and methods to combat this crisis. Our search was confined to English language and human subjects.

DISSCUSION:

Classification:

The antibiotics are classified on the basis of mechanism of action as described in (Figure 1).

Antibiotics targeting cell wall:

Bacterial cells are enclosed by a cell wall composed of long sugar polymers and peptidoglycan. The peptidoglycan undergoes cross-linking of the glycan strands as a result of the action of transglycosidases, and the peptide chains extend from the sugars in the polymers to form cross linkages, one peptide to another (2,3). In the presence of penicillin-binding proteins, the D-alanyl-alanine segment of a peptide chain is cross-linked by glycine residues (PBPs). This cross-linking reinforces the cell membrane. -lactams and glycopeptides hinder the formation of the cell wall (4).

Beta-lactam antibiotics:

PBPs are the principal targets of -lactam antibiotics. The -lactam ring is expected to imitate the D-alanyl D-alanine segment of the peptide chain that is ordinarily bound by PBP. The PBP interacts with the -lactam ring and is hence unavailable for peptidoglycan production. The destruction of the peptidoglycan layer results in bacterial lysis (4).

Glycopeptides

The glycopeptides bind to the D-alanyl D-alanine component of the precursor peptidoglycan subunit's peptide side chain. The big medicinal molecule vancomycin inhibits cell wall production by preventing the binding of this D-alanyl component to the PBP (5).

Inhibitors of protein biosynthesis

Initially, the information in bacterial DNA is utilized to synthesize messenger RNA (m-RNA), a process known as transcription. The macromolecular structure known as ribosome then synthesizes proteins from m-RNA, a process known as translation. Ribosomes and cytoplasmic components facilitate protein production. The bacterial 70S ribosome is composed of the 30S and 50S ribonucleoprotein subunits. By targeting the 30S or 50S subunits of the bacterial ribosome, antimicrobials limit protein production (6,7).

Inhibitors of DNA replication

Quinilones

The fluoroquinolones (FQ) block the bacterial DNA gyrase enzyme, which nicks double-stranded DNA, creates negative supercoils, and then reseals the nicks. This is important to prevent excessive positive supercoiling of the strands after separation for replication or transcription. Two A subunits and two B subunits make up the DNA gyrase. A subunit performs DNA nicking, B subunit introduces negative supercoils, and A subunit then reseals the strands. The FQs bind to the A subunit with great affinity and inhibit its ability to cut and rejoin DNA strands. After DNA replication, the primary target of action in Gram-positive bacteria is topoisomerase IV, which nicks and separates the daughter DNA strand. Greater affinity for this enzyme may result in increased effectiveness against Gram-positive bacteria. In lieu of DNA gyrase or topoisomerase IV, mammalian cells contain

topoisomerase II, which has a relatively low affinity for FQ and, as a result, negligible toxicity to cells (8,9).

Folic acid metabolism inhibitors:
Sulfonamides and trimethoprim

Each of these medications inhibits specific folic acid metabolic processes. A combination of sulpha medicines and trimethoprim operating at various points along the same biosynthetic pathway exhibits synergy and a decreased rate of resistance mutations. The affinity of sulfonamides for dihydropteroate synthase is greater than that of the enzyme's natural substrate, p-amino benzoic acid. At a later stage of folic acid synthesis, agents such as trimethoprim block the enzyme dihydrofolate reductase (6,11).

Advantage of antibiotics:
Antibiotics have not only saved patients' lives, but they have also played a significant role in achieving major medical advances (6). They have successfully treated infections that can occur in patients receiving chemotherapy; who have morbidities diseases such as diabetes mellitus, end-stage kidney disease, or rheumatoid arthritis; or who have undergone complex surgical procedures such as organ transplants, joint replacements, or heart surgical therapy (6,7,9).
Antibiotics prescribed to prolong life expectancy by modifying the outcome of bacterial infections serve positive purposes (20,21). In underdeveloped countries with inadequate hygiene, antibiotics reduce morbidity and death caused by food-borne and other poverty-related diseases (21).

Since the development in 1937 of the first dependable antimicrobials, particularly the sulfonamides, antibiotics have been plagued by the emergence of specific resistance mechanisms that hinder their therapeutic use. In the late 1930s, sulfonamide resistance was identified for the first time, and the similar systems will continue to operate approximately 70 years from now (13). **Table 1** displays a compilation of commonly used antimicrobials, their methods of action, and resistance mechanisms (14). Alexander Fleming developed penicillin in 1928, and two members of the penicillin discovery team established a microbial penicillinase in 1940, many years prior to the introduction of penicillin as a treatment (13). When the antibiotic was used extensively, resistant strains capable of inactivating the medicine became widespread, and research was conducted to chemically modify penicillin to prevent cleavage by penicillinases (-lactamases). Extremely, the identification of a bacterial penicillinase prior to the administration of an antibiotic can now be valued in light of recent revelations that a large proportion of antibiotic r genes are components of natural microbial populations (15).

Table1: Modes of action and resistance mechanisms of commonly used antibiotics [14]

Antibiotic class	Example(s)	Target	Mode of resistance
β-Lactams	Penicillins (ampicillin), cephalosporins (cephamycin), penems (meropenem), monobactams (aztreonam)	Peptidoglycan biosynthesis	Hydrolysis, efflux, altered target
Aminoglycosides	Gentamicin, streptomycin, spectinomycin	Translation	Phosphorylation, acetylation, nucleotidylation, efflux, altered target
Glycopeptides	Vancomycin, teicoplanin	Peptidoglycan biosynthesis	Reprogramming peptidoglycan biosynthesis
Tetracyclines	Minocycline, tigecycline	Translation	Monooxygenation, efflux, altered target
Macrolides	Erythromycin, azithromicin	Translation	Hydrolysis, glycosylation, phosphorylation, efflux, altered target
Lincosamides	Clindamycin	Translation	Nucleotidylation, efflux, altered target

Antibiotic class	Example(s)	Target	Mode of resistance
Streptogramins	Synercid	Translation	C-O lyase (type B streptogramins), acetylation (type A streptogramins), efflux, altered target
Oxazolidinones	Linezolid	Translation	Efflux, altered target
Phenicols	Chloramphenicol	Translation	Acetylation, efflux, altered target
Quinolones	Ciprofloxacin	DNA replication	Acetylation, efflux, altered target
Pyrimidines	Trimethoprim	C_1 metabolism	Efflux, altered target
Sulfonamides	Sulfamethoxazole	C_1 metabolism	Efflux, altered target
Rifamycins	Rifampin	Transcription	ADP-ribosylation, efflux, altered target
Lipopeptides	Daptomycin	Cell membrane	Altered target
Cationic peptides	Colistin	Cell membrane	Altered target, efflux

Resistance to antibiotics is caused by:

Monitoring resistance aims to prevent medical failures caused by excessive levels of bacterial resistance to antibiotics. Resistance is often a continuous attribute, and there can be intermediate, moderate, and severe levels of resistance. Intermediate resistance, sometimes known as "tolerant," is the capacity to endure medication concentrations below that recommended therapeutic (**Figure 1**) (12).

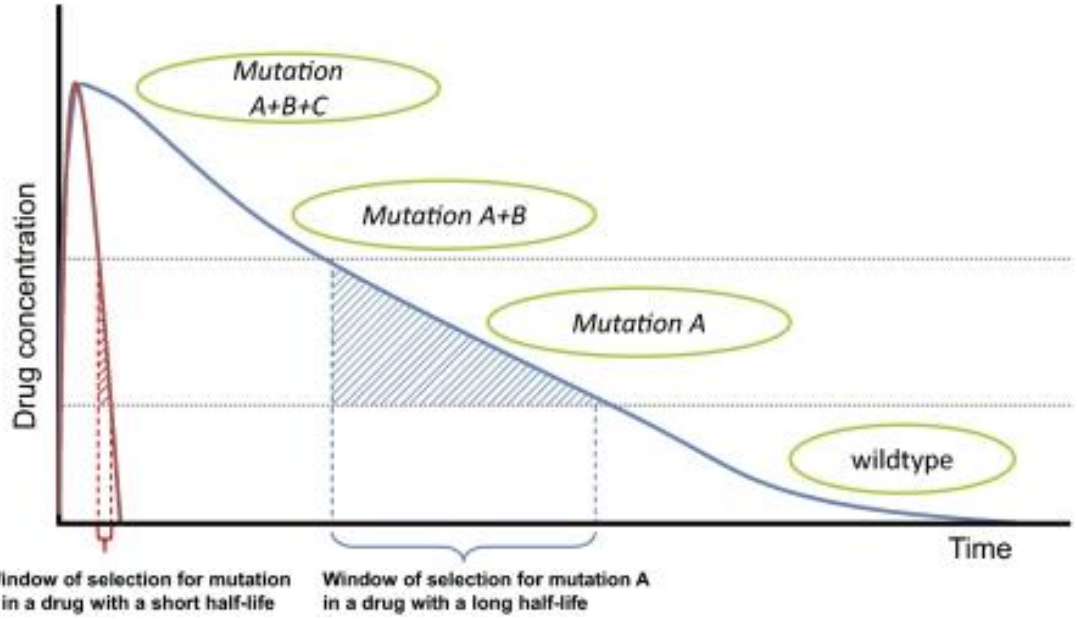

Figure1: Hypothetical path to drug resistance. Solid curves show drug concentration in a treated patient for two drugs with different half-lives; concentrations wane when treatment ceases. In this schematic, wild type parasites can survive very low concentrations, with mutations A, B, and C conferring the ability to survive ("tolerate") successively higher drug concentrations [(12)].

The genetics, biochemistry, and biology of several components of bacterial cell activity, in addition to the molecular mechanism systems of resistance to prescription antibiotics, have been fully investigated (**Table 1**). Antibiotic activity and also resistance research has made substantial contributions to our understanding of cell structure and function. Resistance treatments are commonly diffused in the

bacterial world and have been elucidated for a variety of commensals (19) and microorganisms; the majority can be shared via a number of unique genetic transfer systems. Several resistance types that illustrate the difficulty of maintaining effective antibiotic activity in the face of the biochemical and genetic diversity of microorganism's merit special mention.

Intrinsic opposition:

Intrinsic resistance refers to the presence of genes in bacterial genomes that have the potential to produce a resistance phenotype, i.e. proto- or quasi-resistance. Since the turn of the millennium, the frequent use of genome-wide mutagenesis techniques and rapid microbial genome sequencing has revealed a huge number of potential/intrinsic genetic functions in bacteria that can cause resistance phenotypes. Gene amplification is a typical inherited mechanism for increased antibiotic resistance, particularly for resistance to sulfonamides (22) and trimethoprim.

Antibiotic resistance in Gram-positive Bactria:

However, the problem is still under control Staphylococcus aureus and Enterococcus spp. are the Gram-positive bacteria that currently provide the greatest challenges in terms of antibiotic resistance. Methicillin-resistant Staphylococcus aureus (MRSA), which has existed for five years, is the very first significant player in the antibiotic resistance issue, demonstrating worldwide dissemination and a substantial impact on medical outcomes versus methicillin-susceptible S. aureus (24,25,26). The MRSA phenotype is a result of the expression of modified penicillin-binding proteins (PBPs) encoded by the flat genetics, which modify the characteristics of the native staphylococcal PBPs and are resistant to conventional b-lactams. MRSA is a key factor in human infections in a number of nations in Europe, the Americas, and the Asia-Pacific region, where MRSA prevalence is high (27,28,29). In some countries, however, aggressive infection control projects have proven effective at preventing MRSA transmission (e.g., in the Netherlands) (27) or at reducing an already established MRSA endemicity (e.g., in the United Kingdom) (27,30), demonstrating that infection control can be very reliable at limiting MRSA transmission. However, there are still a number of antibiotics with activity against MRSA, including glycopeptides (e.g. vancomycin and teicoplanin), linezolid, tigecycline, daptomycin, and some new b-lactams, such as ceftaroline and ceftobiprole, which are active against the PBPs responsible for the methicillin-resistant phenotype (31). Resistance to any of these medications has been recorded, but the rates of resistance are generally extremely low (32,33,34), and XDR or TDR MRSA strains have not been routinely reported.

Resistance to antibiotics in Gram-negative pathogens:

An uncontrolled outbreak of Gram-negative microorganisms Currently, the antibiotic crisis is significantly worse than with Gram-positives. In Gram-negative bacteria linked to HAIs, such as Pseudomonas aeruginosa, Acinetobacter spp., and Enterobacteriaceae (mainly Klebsiella pneumoniae), the occurrence of XDR as well as TDR phenotypes has been often observed (35). However, MDR Gram-negatives are also prevalent in the area, including Escherichia coli producing extended-spectrum beta-lactamases (ESBLs) (35), and Neisseria gonorrhoeae resistant to fluoroquinolones, penicillin, azithromycin, tetracycline, and expanded-spectrum cephalosporins. P. aeruginosa was probably the first pathogen to show MDR and XDR phenotypes, with the development of stress-resistance to all kinds of anti-pseudomonal drugs save polymyxins (likewise called Colistin-Only Susceptible-COS- stress). MDR and XDR pressures of P. aeruginosa are identified as agents of high-risk clones, such as ST111, st175, and st235 (35).

COCLUSION:

The value and importance of antibiotics cannot be overestimated; we rely on them solely for the treatment of infectious diseases, and they must never be considered fundamental products. Antibiotics are essential to the success of cutting-edge surgical procedures, such as organ and prosthesis transplants, in addition to their use in the treatment of communicable diseases. There is little doubt that the situation in regards to antibiotic resistance is dire, despite all good intentions to restrict antibiotic consumption (albeit limited activity). Resistance mechanisms are widespread and cause considerable clinical and monetary concerns for healthcare systems globally. There are no universal solutions to the problem. Even when lives can be saved, decisive actions requiring significant commitment and enforcement are never emphasized. It is crucial that we have a good picture of the amount of different resistance systems that private bacteria may possess. MRSA is a major and exceptional example of this. The increase in expenditures associated with MRSA infections was previously mentioned. These increased costs are attributable to an increase in the length of healthcare facility stays, the number of examinations necessary, and the number of medical and rehabilitation services offered. We must also consider the impact of MRSA on morbidity and mortality,

including considerable increases in illness problems. The introduction of these novel substances into scientific methods is not predicted to occur before three to five years. In the absence of these new medications, the only options currently available for addressing the problem of antibiotic resistance consist of enhancing practices aimed at reducing the spread of microorganisms and optimizing the available antimicrobial treatment programs for the most effective dosing schedules.

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