Jabirian
Journal of Biointerface Research in Pharmaceutics and Applied Chemistry
ISSN: 2584-2536 (Online)
Vol.1(03), July 2024, pp, 26-36
Journal homepage: https://sprinpub.com/jabirian

Research article

Synergistic role of Extended-spectrum beta-lactamases (ESBL) and bacterial structure on antibacterial drugs

Hamadamin Zrar Hamadamin[1]*, *Ahmed Farhan Shallal*[2], *Ibrahim Nazem Qader*[3]

[1,2]*Department of Biology, College of Science, University of Raparin, Rania,46012, Sulaymaniyah, Iraq*
[3]*Department of Physics, College of Science, University of Raparin, Rania,46012, Sulaymaniyah, Iraq*

ARTICLE INFO

Keywords:
Antibacterial drug
Antibiotics
Pharmaceutical science
Drugs
Resistance

Article History:
Received: 03-01-2024
Accepted: 20-07-2024
Published: 25-07-2024

ABSTRACT

The illnesses induced by pathogenic microorganisms, particularly bacteria, are progressively on the rise at a global scale. Antibiotics, whether derived from specific microorganisms naturally or altered chemically, play a vital role in managing bacterial infections. These pharmaceuticals hinder or eradicate bacteria through a variety of mechanisms, which include impeding the synthesis of cell walls or cell membranes, inhibiting the production of proteins and specific metabolites, as well as thwarting the synthesis of nucleic acids. Nevertheless, bacteria have the ability to acquire resistance to antibiotic treatment through various means, such as the generation of specific enzymes like extended-spectrum beta-lactamases (ESBL) to degrade the antibiotic, reducing drug absorption by bacterial cells, and modifying target locations. This analysis functions as an extensive manual on antibiotics, concentrating on their historical context, production, and evolution, the interactions of antibiotics within the human body, the different categories of antibiotics and their modes of action against bacteria. However, the emergence of antibiotic resistance, the factors that contribute to bacterial resistance, the significance of extended-spectrum beta-lactamases (ESBL) and their diverse forms in resistance progression, and prospective strategies for addressing antibiotic-resistant bacterial infections are the focal points of this paper.

Cite this article:
Hamadamin HZ, Shallal AF, Qader IN. Synergistic role of Extended-spectrum beta-lactamases (ESBL) and bacterial structure on antibacterial drugs. Jabirian Journal of Biointerface Research in Pharmaceutics and Applied Chemistry. 2024;1(3):26-3. https://doi.org/10.55559/jjbrpac.v1i3.293

1. Introduction

For millions of years people have been infected by various types of infections, which have bad effects on people's lives [1], the infections are caused by many different microorganisms like bacteria, fungi, and viruses [2]. The development of humanity and finding the new drugs like antibiotics have important role in the treatment of microbial infections. Antibiotics are group of drugs that are used to treat infections caused by pathogenic bacteria that effect on their growth and reproduction, and it has an important role in medicine, antibiotics are naturally produced by microorganisms usually fungi as their normal metabolite this causes the inhibition or kill other microbes [3, 4]. Many infectious microbes usually bacteria make resistance against antibiotics and antibiotics no longer treat the bacteria that have resistance against specific antibiotics [5]. The bacteria develop resistance against antibiotics by producing specific enzymes that inhibit the function of antibiotic drugs like the production of beta-lactamase enzyme that breaks down the beta-lactam ring in penicillin [6]. Extended-spectrum beta-lactamases (ESBLs) are enzymes that are produced by certain bacteria and develop resistance against specific groups of antibiotics [7].

The live with infectious microorganisms is hard for the people that live in the past due to insufficient knowledge and information to search and detect the cause and origin of these infections made the situation worse. However, due to a lack of information to prevent and control the pandemic infections that spread throughout people were unsuccessful for a long period. These problems continued until the microscopic mold was found in the seventeens century that produced metabolic waste that caused an effect on other infectious microbe life [1, 8, 9]. The foundation of antibiotics and the development of bacterial or microbial isolation techniques make scientists work on microbes and bacteria easily and work to find new drugs and treatment routes [10, 11]. After bacteria were isolated and purified in cultures, which helped the scientists to work on them and identify special agents that were produced from the normal metabolic waste of bacteria until the first synthetic antibiotic was produced from bioactive agents of these microscopic organisms, many pharmaceutical companies and laboratories search for this bioactive agents in bacteria and fungi, until twenties century that many antibiotic drugs and classes were discovered, and also many targets are identified to increase line of production [1, 12]. Antibiotic drugs that have a beast effect on treating bacterial infections in the early years of development until the development of antimicrobial resistance cause a major health issue throughout the world, this causes the World Health Organization (WHO) to recommend working and finding new antimicrobial drugs by changing the natural agent to form fully

* ***Corresponding Author:***
Email: hamadamin.zrar1999@gmail.com (*H. Z. Hamadamin*)
https://doi.org/10.55559/jjbrpac.v1i3.293

synthetic and semisynthetic antibiotics to make them have a better effect on infectious microbes [13-15].

The term antibiotic refers to antibiose and was first used by Paul Vuillemin to describe the antagonistic action among distinct microorganisms in his 1890 publication [12, 16], in year 1947 The term antibiotic was first proposed by Selman Waksman who found Streptomycin in his work on the soil, and defined as chemical substances that produced by microorganisms to prevent growth and sometimes to kill other microbes and microorganisms [12]. In the early twentieth century, many natural antibiotics were discovered by many scientists like penicillin, streptomycin, and many other drugs by their working on microbes [17], the antibiotics, for example, are classified into two groups by their effect on bacteria, this antibacterial drugs that kill bacteria called Bactericidal and these that inhibit the growth of bacteria called Bacteriostatic [17], and many diseases were identified that caused by many microorganisms like Cholera, typhoid fever, syphilis, and tuberculosis. The few number of antibiotics had the best effect on microbes a hundred years ago in comparison to these numerous antibiotics that are present today, this is because the bacteria have many mechanisms to resistance against the antibacterials, and this resistance by microbes causes scientists to change the natural antibiotics to produce semisynthetic and synthetic antibiotics in the laboratory [1, 17].

Antibiotics and antimicrobial drugs are widely used and investigated in many fields like microbiology and pharmacology and research about antibiotics has increased exponentially in the last years. This review article acts as a general guideline about antibiotics and focuses on the history of antibiotic discovery and developments, antibiotic interaction mechanism inside the body, many different antibiotic classes mentioned with their mechanism of action against bacteria, and the mechanisms and factors that contribute to antibiotic resistance with the role of ESBL-producing bacteria on antibiotic and future prospect are the aim of this article.

2. Importance of Study

Antibiotics and antibacterial drugs have been widely investigated across wide fields of studies including, microbiology, pharmacology pharmacy, infectious disease, biochemistry, molecular biology, chemistry medicinal, biotechnology, food science technology, immunology, organic chemistry, veterinary, and multidisciplinary sciences. These categories collectively account for more than 75% of research that is published in the Clarivate database. **Figure 1 A** shows the publication articles about antibiotic and antimicrobial agents that are obtained from Clarivate analysis (WoS) from 1970 to 2022, the data shows the exponential increase in the interest of researchers in working in this field in a limited period. Additionally United States and China have a good contribution to this field through their funding agencies "United States Department of Health Human Services", "National Institutes of Health Nih USA" and "National Natural Science Foundation of China Nsfc". Also, this field is recognized universally, various researchers in various countries working on this field throughout the world, typically the United States of America, India, and China, as the countries in East Asia and the Middle East, also European countries have a significant role on working on this field, as shown in **Figure 1 B.**

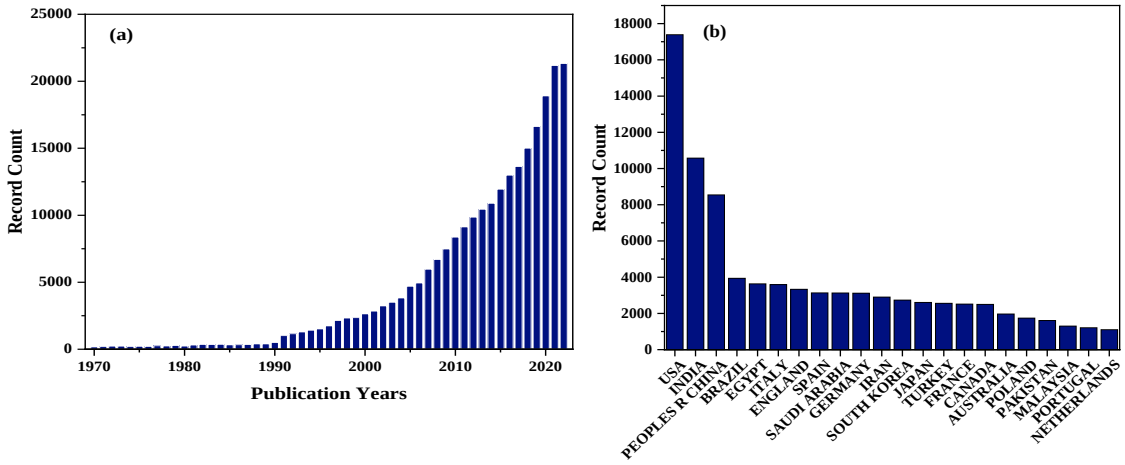

Figure 1. Analyzing published articles on antibiotic and antibacterial drugs in WoS, (A) Publications based on years, (B) Publications based on Countries

3. Bacteria Structure and Types

Bacteria are classified based on gram staining into gram-positive and gram-negative, the gram-positive bacteria contain the cell membrane and are surrounded by a very tough cell wall on the outside, while the gram-negative bacteria contain a cell membrane surrounded by a thin layer of cell wall and cell wall surrounded by lipid membrane or outer membrane, these outer membrane contain porin channels that allow special molecules to enter the cell, the space between cell wall and outer membrane called periplasm, the components of cell wall of gram-positive and gram-negative bacteria shown in **Figure 2** [18, 19]. The cell membrane is a protective layer located beneath the cell wall of bacteria, it controls the movement of important substances like amino acids, proteins, and nutrients that enter and out of the cell and also maintains the internal osmotic pressure and cell wall components are produced here, it contains phospholipid, protein, and carbohydrates [18-20]. The cell wall is a rigid protective layer that surrounds the cell membrane, the cell wall is made up of peptidoglycan, which protects the cell from bursting and gives the shape to the cell, the peptidoglycan contains linear strands of glycan that contain N-acetylglucosamine and N-acetylmuramic acid, that interconnected by short peptides, the peptidoglycan subunits are cross-linked by the action of enzyme called transglycosidase that connect glycans from one peptide to another [18, 19, 21].

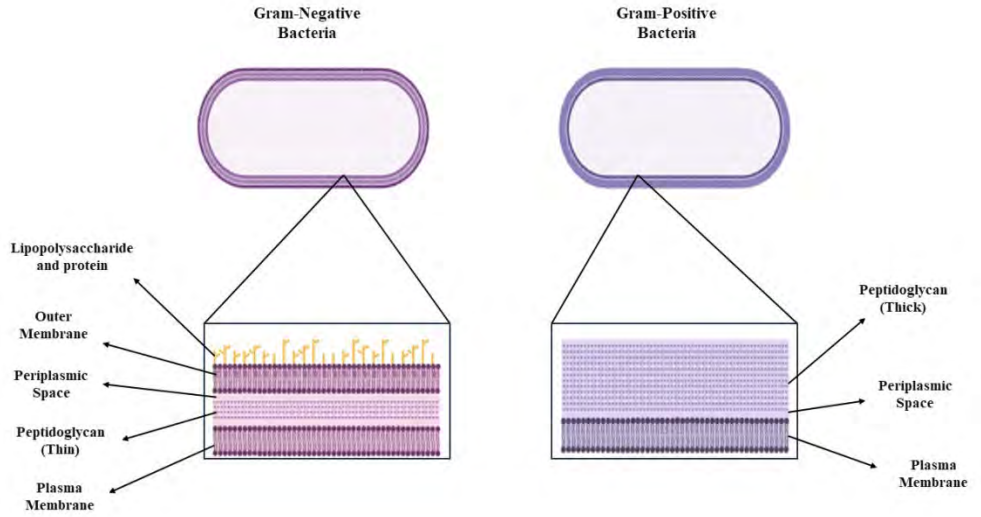

Figure 2. The cell wall structure of Gram-negative and Gram-positive bacteria [18]

4. Discovery and Development of Antibiotic Drugs

The founding and development of antibacterial drugs started after Alexender Fleming's foundation of penicillin from *Penicillium notatum* mold that inhibits the growth of bacteria in his work in 1928. Following the finding of penicillin, many other antibiotics like streptomycin, tetracycline, and chloramphenicol are found in soil microorganisms. This period of antibiotic development is called the Golden Era, antibiotics of this era are natural products and have the best effect on bacteria. After the golden age of antibiotics, the Chemical Era of antibiotics came after the middle of the twentieth century in 1960 and later, in which the structure of natural antibiotics was changed to form semisynthetic and chemically modified antibiotics, antibiotics of this era had a broad-spectrum activity and had a good effect on bacteria. After that antibiotic development entered the Resistance Era in the late twentieth century and at the beginning of the twenty-first century, the antibiotics of this era were target-specific and had a broad spectrum but had low success due to the resistance development by bacteria against antibiotics. The Narrow Spectrum Era was developed from the beginning of the twenty-first century until now, the working antibiotics of this era are continuous to improve and develop the antibiotics that have the best effect on bacteria, and using a combination of antibiotics to treat infections, and developing the new methods of diagnosis, and working to production of narrow-spectrum antibiotics, the results are seen in the future [22]. The discovery and development of antibiotic drugs are shown in **Figure 3.**

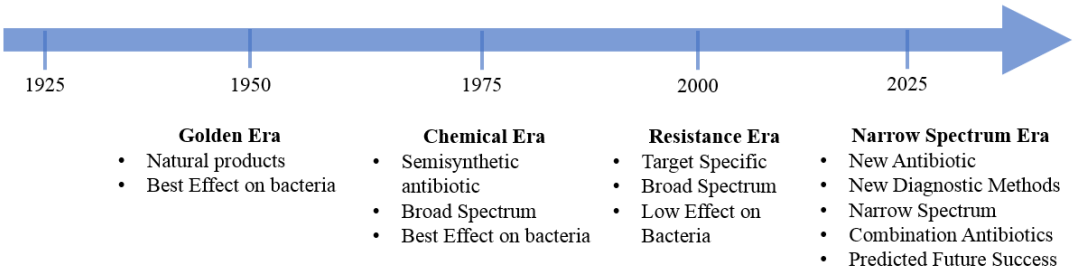

Figure 3. Discovery, development, and characteristics of antibiotics in different eras

5. Antibiotic Production Methods

Many different methods are used in the production of antibiotics, the most widely used methods that are used in laboratories and pharmaceutical companies are shown in **Table 1.**

Table 1: Different methods that are used widely for the production of antibiotics

Method	Types	Advantage
Fermentation	Solid state fermentation	• Nutrient-rich waste materials can be recycled and require less moisture [15].
	Submerged fermentation	• Purification of antibiotic products is easier [15].
	Continuous Fermentation	• Increase the rate of antibiotic production and decrease the time of production [23].
Genetic Engineering	Gene manipulation	• New and effective antibiotics can be manufactured [13].
Metabolic pathway engineering	Metabolic Engineering	• Developing a new efficient drug and drug precursor [24].
Chemical synthesis	Chemical	• Production of antibiotics that are more powerful and complex than natural antibiotics [25].

6. Drug Interaction Mechanism

When drugs and antibiotics are taken by a patient two mechanisms of drug interaction occur inside the body, which are, pharmacodynamic, and pharmacokinetic. Pharmacodynamics is the interaction between drug concentration and the drug response, while pharmacokinetics is the changing amount of drug concentration in various body parts [26, 27]. Pharmacodynamic interactions are classified into three main interactions, single receptor site, variety receptor site, and general non-specific interaction, but most drugs that are taken interact with the body are in these groups that interact with specific receptors, in which the drug interacts with specific receptors on the surface of the cell membrane, within cytoplasm or nucleus [26]. Pharmacokinetics includes all reactions that the drug goes through from administration or drug intake to absorption, distribution, metabolism, and drug elimination. There are many ways to drug administration, including, oral intake, intravenous, and intramuscular. Drug absorption rates vary according to the route of administration in which these drugs that are taken intravenously and intramuscularly are more easily absorbed into the blood flow than those drugs are taken orally due to the action of gastric acid. Drug distribution is the process of distributing a drug to it is location inside the body, including the drug binding to specific receptors on the cell surface to make the drug go inside the cell. Metabolism includes these reactions that cause the termination of drug activity after the work of the drug is completed inside the body. Elimination is the process of removing drugs from the body in many different ways like respiratory way, kidney, and gastrointestinal tract [26].

7. Antibacterial Families and Classes

Many different classes and families of antibiotics are used widely today including penicillin, macrolides, tetracycline, cephalosporin, aminoglycosides, fluoroquinolones, sulfonamides, and carbapenems. These classes of antibiotics are classified according to their spectrum activity which are broad spectrum and narrow spectrum, and also according to their mechanism of action, which include cell membrane inhibitors, cell wall synthesis inhibitors, protein biosynthesis inhibitors, and nucleic acid inhibitors, these and more are shown in **Table 2** [28].

Table 2. Antibiotic classes, members, spectrum activity, and mechanism of action

Antibiotic classes	Members	Spectrum Activity	Mechanism of Action
Beta Lactams	Penicillin, cephalosporin, amoxicillin, ceftriaxone, ampicillin, ….	Gram-Positive G+ve And Gram-Negative G-ve	Inhibition of cell wall synthesis [29].
Tetracycline	Tetracycline, doxycycline, minocycline, …	G+ve and G-ve	Inhibition of protein synthesis binding to 30S ribosomal subunit [30].
Aminoglycoside	Gentamycin, amikacin, streptomycin, neomycin, …	G-ve and some G+ve	Inhibition protein synthesis binding to 30S ribosome subunit [31].
Fluoroquinolones	Ciprofloxacin, ofloxacin, levofloxacin, …	G+ve and G-ve	Inhibit DNA replication [32].
Macrolides	Erythromycin, azithromycin, clarithromycin, …	G+ve and some G-ve	Inhibition protein synthesis binding to 50S ribosome subunit [33].
Glycopeptide	Vancomycin, teicoplanin, telavancin, …	G+ve	Inhibition of cell wall synthesis [34].
Monobactam	Aztreonam	G-ve	Inhibition of cell wall synthesis [35].
Carbapenems	Imipenem, meropenem, ertapenem, …	G+ve and G-ve	Inhibition of cell wall synthesis [36].
Lincosamides	Clindamycin, lincomycin, …	G+ve	Inhibition of protein synthesis binding to 50S ribosomal subunit [37].
Sulfonamide and Trimethoprim	Sulfamethoxazole, sulfadiazine, sulfasalazine	G+ve and G-ve	Inhibition of folic acid synthesis [38].

7.1 Spectrum activity of antibiotics

According to the spectrum activity of antibiotics, there are two groups of antibacterial drugs.

7.1.1 Broad Spectrum Antibiotic

These groups of antibiotics can kill or inhibit the growth of both gram-positive and gram-negative bacteria, thus called broad in their spectrum activity, including many drugs like tetracycline, and amoxicillin [39, 40].

7.1.2 Narrow Spectrum Antibiotics

These groups of antibiotics are only active against specific groups of bacteria, some antibiotics only have activity against gram-positive bacteria, like penicillin and vancomycin. While other antibiotics have better effects against gram-negative bacteria like aztreonam and gentamycin [14, 39].

7.2 Antibiotic Mechanism of Action

Based on the mechanism of action, antibiotics are classified into many groups, like, cell wall synthesis inhibitors, cell membrane synthesis inhibitors, nucleic acid (DNA & RNA) synthesis inhibitors, protein synthesis inhibitors, and metabolite synthesis inhibitors, which are shown in **Figure 4** [41].

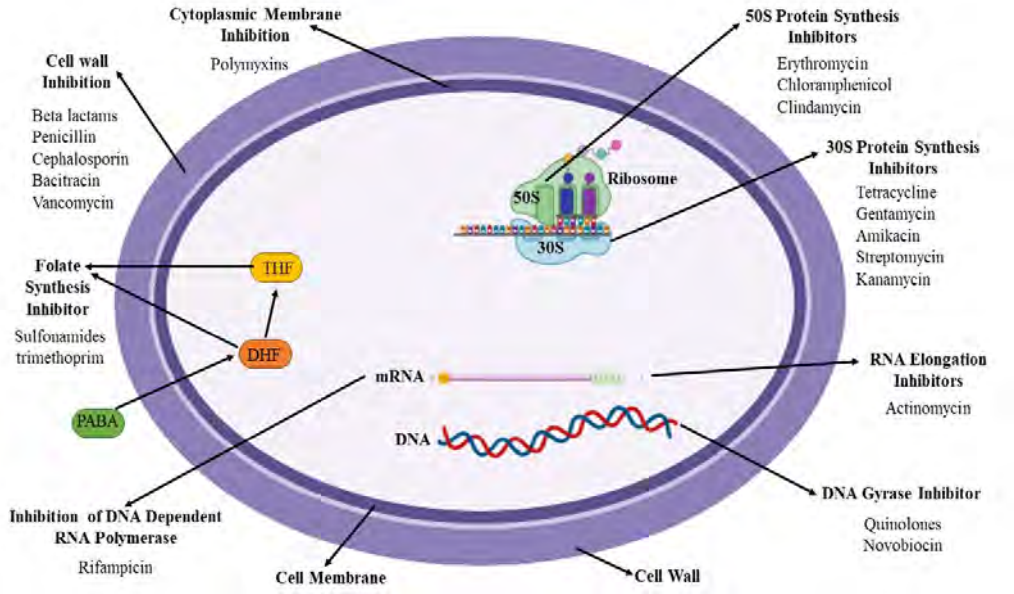

Figure 4. Antibiotic mechanisms of action

7.2.1 Cell Wall Synthesis Inhibitors

The cell wall is the rigid outer protective layer that surrounds bacteria, it protects the cell from bursting in a hypotonic environment and also protects the osmotic pressure of the cell [18, 20]. In the cell wall, the part of the peptide chain has a cross-link with glycine in the presence of penicillin-binding protein (PNB), this linkage strengthens the cell wall. The group of antibiotics that interact with the cell wall and prevent it is production includes the Beta-lactam antibiotic (β-lactam antibiotic) contains the beta-lactam ring in its structure and glycopeptides like the vancomycin family [18, 42].

7.2.2 Cell Membrane Synthesis Inhibitors

The cell membranes of both gram-positive and gram-negative bacteria are affected by antibiotics, the cell membrane of bacteria is located below the cell wall in both gram-positive and gram-negative, but gram-negative have an outer layer made up of lipid and lipopolysaccharides and thus have more barriers and make them resistance to antibiotics. The cell membrane is made up of phospholipids, proteins, and carbohydrates, many antibiotics interact with cell membrane production by interfering with special structures like the polymyxin family [19].

7.2.3 Protein Synthesis Inhibitors

Protein synthesis is an important mechanism to keep bacteria and other organism alive, the information needed for the production of protein is located in genes in the DNA in the nucleus, and this information is copied and transported to the cytoplasm in the form of messenger RNA (mRNA) in a process called transcription, then this information is used to form amino acid chain then to protein by a process called translation, in translation, the ribosome play major role in protein synthesis, which is 70S in bacteria that contain to ribonucleoprotein subunits 30S and 50S. Many antibacterial drugs that prevent protein synthesis interact with one of these ribonucleoproteins [18, 43].

Aminoglycosides and tetracyclines like tetracycline, chlortetracycline, doxycycline, or minocycline are a family of antibiotics that interact with 30S ribonucleoprotein subunit and prevent tRNA from binding the A site on rRNA thus prevent protein synthesis [18, 43].

Oxazolidinones and macrolides are an antibiotic family that prevents protein synthesis that binds to the 50S ribonucleoprotein subunit thus preventing translocation of the ribosome to new codon [18, 43].

7.2.4 Nucleic Acid Synthesis Inhibitors

Quinolones and fluoroquinolones are a family of antibiotics that interact with an enzyme called gyrase, which is an important enzyme required by bacteria during replication and transcription that prevents positive supercoil of DNA and makes DNA negative supercoil to make DNA easily separate during replication and protein synthesis. The gyrase contains two subunits A subunit which supercoil DNA and release new strand, and B subunit which cause negative supercoil of DNA, these groups of antibiotic interact with the gyrase enzyme and prevent the copy of information in the DNA [18, 44, 45].

7.2.5 Special Metabolite Folic Acid Synthesis Inhibitors

Folic acid is an important metabolite that has many roles in bacteria cell growth and development, sulfonamides and trimethoprim are a family of antibiotics that interact with folic acid metabolism by preventing enzymes that are used in folic acid metabolism like dihydrofolate reductase[18, 46].

8. Development of Antibiotic Resistance

The antibiotics are most widely used drugs worldwide, antibiotics need to enter the bacterial cell to kill or inhibit their growth, antibiotics can enter the bacterial cell through porins on the outer membrane of gram-negative bacteria, and the cell wall of gram-positive bacteria, especially by binding to special molecules and cell surface receptors. However, bacteria use many mechanisms to prevent the action of antibacterial drugs are shown in **Figure 5**, this mechanism of bacteria that is used to

survive from antibiotics is called resistance. The resistance of bacteria may be natural or induced by mutation, the natural resistance for example, bacteria have thick cell walls that prevent the entrance of antibiotics, and resistance may be caused by mutation in the bacterial genome that is code for special receptor, changes in the receptors by mutation make the antibacterial drug not recognize the receptor, thus the antibacterial cannot enter the cell [47, 48].

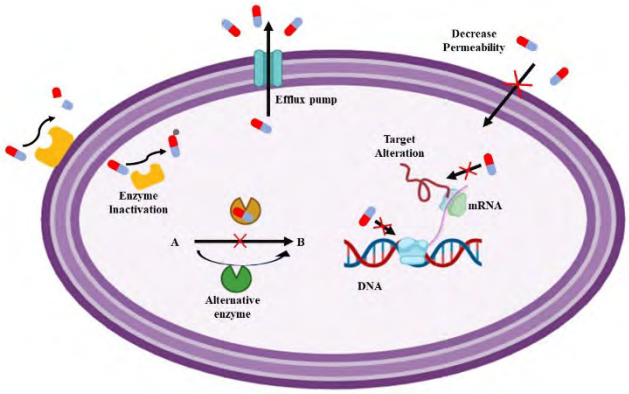

Figure 5. Resistance mechanisms of bacteria against antibiotics

There are many there are many mechanisms of bacterial resistance:

8.1 Alteration of Target Site

This mechanism is used by many bacteria to survive degradation by antibiotics, the target sites and receptors for antibacterial binding are usually changed by mutation of the gene that is responsible for the production of a particular receptor. The target site may be changed on the cell surface to prevent bacteria from entering the cell, or the changing of the target site may occur inside the cell, like alteration receptors of special molecules within the cell like ribonucleoprotein binding sites, or gyrase enzyme target site may be changed, thus preventing the action of antibiotics that act on this target sites and receptors. *Streptococcus aureus* is an example of this bacteria that changes its target site, it changes the mesA gene that is responsible for the production of penicillin-binding protein, by changing this target site most antibiotics like beta-lactams and methicillin cannot bind to this protein in the cell wall of bacteria to inhibit cell wall formation and thus the bacteria survived [49].

8.2 Efflux Pump

The active transporter protein efflux pump that moves molecules against concentration gradient that found in both gram-positive and gram-negative bacteria located in the cytoplasm and outer membrane of gram-negative bacteria and has many important roles in removing toxic substances and antibiotics that enter bacterial cells. When the antibacterial drug enters the cell the efflux pump removes it from the cell, thus bacteria survived from damage by the action of an antibiotic, The efflux pump decreases the permeability of the cell membrane thus lowering drug uptake, for example, gram-negative bacteria like *Salmonella, Shigella*, and *Escherichia coli* resist to tetracycline antibiotic by efflux pump mechanism [50, 51].

8.3 Enzyme Inactivation

When antibacterial drugs enter the bacterial cell the common mechanism that bacteria use to inactivate and degradation of antibiotics is the enzyme inactivation mechanism, in which the bacteria produce an enzyme that breakdown the drug and inactivate it, thus the bacteria produce resistance against the drug and the drug unable to interact with bacteria. Many bacteria both gram-positive and gram-negative produce different enzymes that inactivate antibiotics, the beta-lactamase enzyme is one of the enzymes produced by this group of bacteria that break the beta-lactam ring in penicillin and cephalosporin antibiotics by this change in the structure of antibiotics, it cannot interact with bacteria thus the resistance was produced. *Escherichia coli* is the most common example that produces beta-lactamase enzyme against beta-lactam antibiotics [52].

8.4 Reduce Permeability

The outer membrane of gram-negative bacteria consists of protein, porin canal, lipids, and lipopolysaccharides, while gram-positive have thick peptidoglycan cell walls. Antibiotics need to bind receptors on the surface of the bacterial cell to interact with the bacteria and perform their function, but bacteria change this structure, porin, and receptors on the cell surface, thus bacteria cannot recognize the receptors and antibiotics cannot enter the cell, this process is called reduce permeability in which the drugs have a high concentration in outside of the cell and low concentration in the inside of the cell. *Escherichia coli* can resist many antibiotics by reducing the permeability of drugs like gentamycin, and kanamycin [53].

8.5 Biofilm Formation

Biofilm is a surface polymer that holds a group of bacteria together and makes a protective environment around bacteria, it helps bacteria saving from the host's immune system and antibacterial chemotherapy. This biofilm serves as a physical barrier that decreases antibacterial drug penetration to the bacteria within the biofilm, **Figure 6** shows the effect of the biofilm on antibiotic action. The *Pseudomonas aeruginosa* form biofilm and produce resistance against ciprofloxacin antibiotic [54, 55].

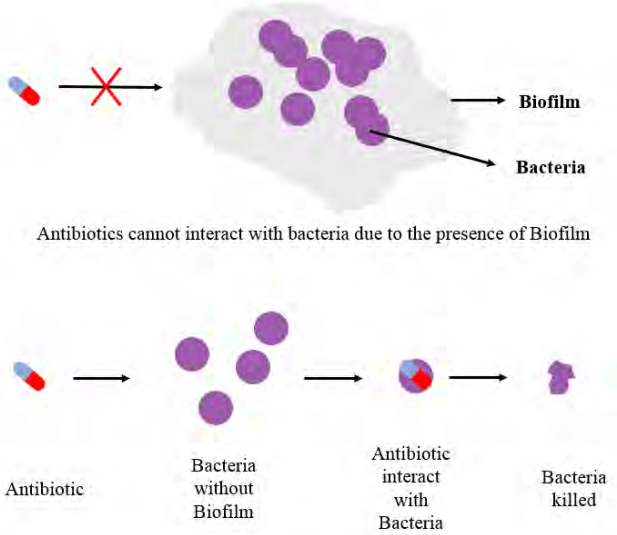

Figure 6. Effect of biofilm on the development of antibacterial resistance

8.6 Horizontal Gene Transfer

Horizontal gene transfer is another method in which bacteria can gain resistance against antibiotics, in this method, the bacteria can acquire a resistance gene from other bacteria by one of the following mechanisms, these mechanisms are shown in **Figure 7** [56].

Conjugation is the process in which genetic material usually plasmid (R plasmid) that contains a resistance gene is

transferred from one bacterium to another of the same genus by direct cell-to-cell contact via pili, thus the bacteria gain the gene that is responsible for antibiotic resistance [56].

Transformation is the process by which bacteria uptake the naked DNA fragment and then incorporate this fragment into their genome by a process called recombination, this DNA fragment may contain resistance genes thus the bacteria integrate this gene into their genome, and then bacteria express resistance genes [56].

Transduction is the process by which bacteriophages (viruses that infect bacteria) transfer genes between bacteria. When a bacteriophage infects bacteria after releasing from it its genome may contain a resistance gene from the lysed bacteria, when it infects another bacteria this gene is injected into the bacteria, thus the bacteria incorporate this gene into its genome and then can express the resistance gene [56].

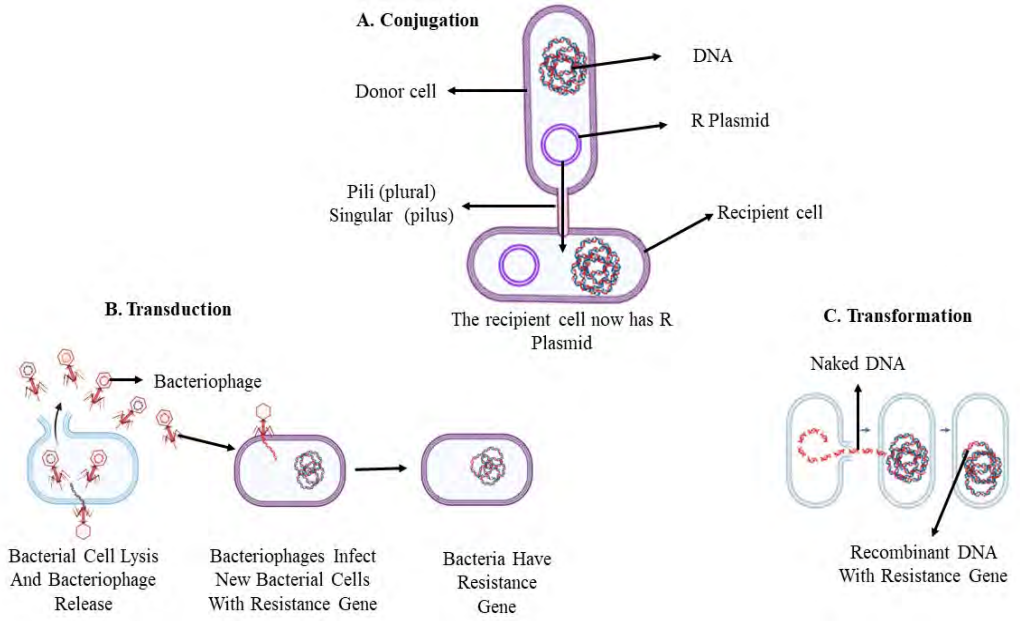

Figure 7. Horizontal gene transfer mechanisms in bacteria, A. Conjugation, B. Transduction, and C. Transformation

9. Factors Contributing to Antibiotic Resistance

Bacterial resistance to antibiotics increases day after day, also the disease caused by bacterial infection increases, understanding and information about these factors that contribute to antibiotic resistance is the best way to control and decrease bacterial resistance against antibiotics. There are many causes and factors in both developed and developing countries that contribute to antibiotic resistance. The following points are the top factors that cause antibiotic resistance.

Insufficient monitoring of antibiotic resistance is the main point, there is no sufficient data in the country that introduces the different types of antibiotics and antibiotic resistance infections, also another point is that the antibiotics that are present in most countries have poor quality and are outdated the using of these antibiotics to treat the bacterial infection, does not treat the infection rather than increases the cause of resistance of bacteria to this drug. Another point is that most patients do not have sufficient information on how to use antibiotics, and many times unnecessary antibiotics are prescribed to the patient, these and more are the major causes of developing antibiotic resistance. Also in most countries, antibiotics are not regulated and are easily available anyone can get it more easily. Also, there is not sufficient research on antibiotics in most countries to determine bacterial resistance against the specific antibiotic for making good solutions to this condition, and antibiotics are used in animal food to prevent infection and increase the growth of animals, which may increase the cause of bacterial resistance, finally, these are the main causes and points of development antibiotic resistance [57], **Figure 8** shows the factors that contribute of antibiotic resistance.

Figure 8. Factors that contribute to antibiotic resistance

10. Molecular Tools for Detection of Antimicrobial Resistance

Many different molecular tools are used for detection of antibiotic resistance genes within bacterial strains and provide fast, accurate and sensitive results, the Polymerase Chain Reaction (PCR), Loop-Mediated Isothermal Amplification (LAMP), DNA Sequencing, and Next-Generation Sequencing (NGS) play significant role in the detection of resistance gene in genome of the microbe [58]. The LAMP technique provide the identification of specific resistance gen in the infectious microbe [59]. The whole-genome sequencing that used to sequence entire

genome of microbe help in the detection of resistance gene in the bacterial population [60], however, molecular tools can be used to monitor the spreading of resistance gene between microbes [61], also the bioinformatics helpful in the prediction of the development of resistance to specific antibiotic through gene mutation [62], other molecular tools like metagenomics can be used to monitor resistance gene variations during antibiotic treatment course [63], thus molecular tools play a significant role in the controlling the pathogenic infections and outbreaks through monitoring the resistance mechanism of infectious microbe.

10.1 Detection of Resistance Genes

The identification of resistance gene play a significant role in treatment of the infection through the detection of specific genes that are responsible for development of resistance and helping the scientists to select and develop effective antibiotic to treat the infection [64]. Many molecular tools are used to detection of resistance gene including:

10.1.1 Real-Time PCR

Real-Time PCR is another molecular technique that can quantify DNA during amplification, by monitoring the DNA amplification and provide the information about the amount of the resistance genes in the sample with more fast and accurate than PCR [65].

10.1.2 PCR

PCR is the most widely used techniques that used to amplify DNA sequences, it is useful in the detection of resistance genes through designing specific primers that are complementary to the resistance gene and amplify it in the sample then the results can be seen by gel electrophoresis [66].

10.1.3 Reverse Transcription PCR (RT-PCR)

RT-PCR is another method for the detection of resistance gene which is found in RNA molecules that cause resistance, RNA is used to form complementary DNA then the PCR is performed on the complementary DNA to amplify targeted resistance gene [67].

10.1.4 Loop-Mediated Isothermal Amplifications (LAMP)

LAMP technique is used to amplify DNA in constant temperature, and multiple DNA polymerases and primers are used to amplify specific DNA sequence that are responsible for bacterial resistance [68].

10.1.5 Next-Generation Sequencing (NGS)

NGS is another molecular tool that can sequence entire genome or specific regions of the DNA like these genes that are responsible for resistance development in the pathogenic bacteria [69].

10.1.6 Multiplexed PCR

This is another molecular tool that can be used to amplify multiple DNA sequences in the same reaction, the primers are designed to bind the specific resistance gene to amplify resistance genes [70].

10.1.7 Microarray

Microarray is another molecular technique in which the hybridization of multiple DNA sequences are used on microarray chip, the sample DNA is labeled and hybridized with chips that contain fragments that are complementary to the resistance gene, it can detect multiple resistance genes in the sample [71].

11. Extended-spectrum beta-lactamases (ESBLs)

Extended-spectrum beta-lactamases (ESBLs) are groups of enzymes that produced by certain group of bacteria and make resistance to broad spectrum antibiotics such as beta-lactam antibiotics like penicillin, cephalosporins, and amoxicillin, that are commonly used to treat infectious bacterial diseases. This ESBL enzymes production which cause resistance against specific antibiotics making the infections caused by ESBL-producing bacteria are more difficult to treatment the infection disease [72, 73]. The ESBL is belong the beta-lactamase enzyme that work against beta-lactam antibiotics and have ability to breaking down or cleavage beta-lactam ring that are present in this type of antibiotics hydrolyze and inactivate these drugs, by this process the bacteria can protect cell wall from action of beta-lactam antibiotics and make resistance against broad spectrum drugs, ESBL-producing bacteria change the composition of the cell wall to prevent the action of antibiotic, the ESBL gene can be horizontally transferred by conjugation between bacteria that are present in the plasmid, the bacteria that gain the resistance gene and can express ESBL enzymes. The bacteria can produce ESBL enzymes including *Escherichia coli*, *Klebsiella pneumoniae*, and many other species belong the family Enterobacteriaceae. The ESBL-producing bacteria can transmit between patients in health-care and throughout the world, the ESBL gene can be detected by polymerase chain reaction (PCR), the carbapenems may use to help treat infection caused by ESBL-producing bacteria [73-75]. There are many types of extended-spectrum beta-lactamases enzymes including:

11.1 SHV

The SHV is a type of beta-lactamase enzyme that produced by *Klebsiella* species usually *Klebsiella pneumoniae*. The gene that code for SHV located in the bacterial chromosome and can be incorporated into plasmid to transport to other bacteria species. The SHV enzyme make resistance to broad spectrum antibiotics such as penicillin's, ampicillin, piperacillin, but do not resist to cephalosporins. HSV beta-lactamase is responsible nearly 20% of resistance in *K. Pneumonia* species [6, 75, 76].

11.2 TEM

TEM is another type of beta-lactamases that produced by Escherichia coli. It can hydrolyze penicillin's and cephalosporins first generation but unable to breakdown oxyimino cephalosporin. The TEM variant called TEM-3 can hydrolyze extended spectrum cephalosporin. TEM can transport between species of bacteria [6, 75, 76].

11.3 CTX

CTX is a new family of beta-lactamases that can hydrolyze cefotaxime antibiotic. It is found in *Salmonella enterica* serotype *Typhimurium, E. coli*, and other species of Enterobacteriaceae. The gene that code for CTX are located in the chromosome of ESBL bacteria, CTX have many variants based on their nucleotide sequences, it can be acquired by horizontal gene transfer between bacteria from one species to another through plasmid [6, 75, 76].

11.4 OXA

OXA is another type of beta-lactamases that can hydrolyze oxacillin antibiotic. It is found in *Pseudomonas aeruginosa* and also can found in many other Gram-Negative bacteria like *E. coli*. OXA can be transported between bacterial species [6, 75, 76].

11.5 PER

PER is another beta-lactamase enzyme that can hydrolyze penicillin's and cephalosporins. It is found *in P. aeruginosa, S. enterica* serotype *Typhimurium and Acinetobacter*. It can be transported to other bacteria like *E. coli, K. pneumoniae, Proteus mirabilis*, and *Vibrio cholerae* [6, 75, 76].

11.6 GSE

Another type of beta-lactamase is GSE that found in *K. pneumonia*, and it can hydrolyze penicillin and cephalosporin antibiotics but do not breakdown carbapenems. It can be transported between bacterial species [6, 75, 76].

12. Alternative Approaches to Antibacterial Therapy

The increase in bacterial infections day after day, and the development of bacterial resistance against many antibiotics that are present today and only a few drugs have a good effect on bacterial infection, it makes scientists explore and work to find new and effective treatments that are more effective than antibiotics in treating microbial infections. These new methods for antibacterial therapy completely differ from traditional antibiotics that work on specific receptors and target sites like cell wall and cell membrane inhibitors, nucleic acid and protein synthesis inhibitors, and folic acid synthesis inhibitors, these new methods that are now under development are more specific and effective against resistance bacteria [77]. The following are these new approaches to antibacterial therapy.

12.1 Anti-Virulence

Anti-virulence is the method used to prevent the production of virulence factors of bacteria like toxins, cell invasions, and adhesion factors, in this method, the anti-virulence factors that cause disease are identified, and then these virulence factors are inactivated by using inhibitors that interact with this factors to prevent the action or neutralize of this virulence factors, thus the bacterial infection have a low effect, this mechanism is not bacteriostatic or bactericidal is a virulence blocker, thus the bacterial infection is limited and has low effect [77-79].

12.2 Bacteriophage

Bacteriophage is another method that is used to treat a bacterial infection, bacteriophage is a type of virus that only infects specific bacteria without affecting cells in the human body thus it can be used to treat the bacterial infection in combination with antibiotics or alone, bacteriophages are isolated and purified to ensure safety, and then the phage dosage is determined depending on bacteria and phage interaction and the severity and condition of disease, then the phage therapy is administrated to the patient, finally the phage interacts with bacteria and causes lysis of bacteria, this method has many advantages like very specific, narrow spectrum, very safe, easy to administration, less expensive, and low side effect [77, 80].

12.3 Nanoparticle

Nanoparticles are small molecules of about 1-100 nm, they can interact with bacteria in various ways, they have antibacterial properties that can be used to prevent bacterial infections either itself or in combination with antibiotics, the drugs can be loaded to nanoparticles through conjugation, adsorption, and encapsulation, the chemical composition of nanoparticle make it has many delivery systems and can easily go to the site of infection, it has many advantages like solubility, can remain in circulation for a prolonged duration, and can be easily released, there are many types of nanoparticles like gold, copper, carbon, silver, zinc, and titanium oxides, that can be used with antibiotics to treat many bacterial infections, the nanoparticles have many effects on the bacterial cell like production of reactive oxygen species, release of metal ions, and the destruction of the bacterial cell membrane, thus the using nanoparticles with the antibiotics play important role in resistance bacterial infection treatments [77, 81-83].

13. Conclusion

Bacteria are involved in the pathogenesis of numerous diseases that impact human health. Antibiotics are pivotal in the management of bacterial infections by employing a range of mechanisms. Nonetheless, the development and spread of bacterial resistance, which occurs through various pathways, exert a substantial influence on the management and prevention of these infections. Failure to address bacterial resistance could lead to deterioration in the overall well-being of the human population. Advocating for increased research efforts and the advancement of novel strategies for treating bacterial infections are crucial in addressing this pressing concern.

References

1. Mohr, KI. History of antibiotics research. In: Current topics in microbiology and immunology. 2016. p. 237–72. https://doi.org/10.1007/82_2016_499
2. Bartlett, JH. Microorganisms. In: Elsevier eBooks. 2013. p. 291–315.
3. Waksman SA. What is an Antibiotic or an Antibiotic Substance? Taylor & Francis. https://doi.org/10.1080/00275514.1947.12017635
4. Barber, M, Garrod, LP, O'grady, F., Antibiotic and chemotherapy. 1971(3rd Edition).
5. Frieri M, Kumar K, Boutin A. Antibiotic resistance. Journal of Infection and Public Health. 2017;10(4):369–78. https://doi.org/10.1016/j.jiph.2016.08.007
6. Jacoby GA, Medeiros AA. More extended-spectrum beta-lactamases. Antimicrobial Agents and Chemotherapy. 1991 ;35(9):1697–704. https://doi.org/10.1128/AAC.35.9.1697
7. Doi Y, Iovleva A, Bonomo RA. The ecology of extended-spectrum β-lactamases (ESBLs) in the developed world. Journal of Travel Medicine. 2017 ;24(suppl_1):S44–51. https://doi.org/10.1093/jtm/taw102
8. Durand GA, Raoult D, Dubourg G. Antibiotic discovery: history, methods and perspectives. International Journal of Antimicrobial Agents. 2019 ;53(4):371–82. https://doi.org/10.1016/j.ijantimicag.2018.11.010
9. Clardy J, Fischbach MA, Currie CR. The natural history of antibiotics. CB/Current Biology. 2009;19(11):R437–41. https://doi.org/10.1016/j.cub.2009.04.0011
10. Pahlow S, Meisel S, Cialla-May D, Weber K, Rösch P, Popp J. Isolation and identification of bacteria by means of Raman spectroscopy. Advanced Drug Delivery Reviews. 2015;89:105–20. https://doi.org/10.1016/j.addr.2015.04.006
11. Stewart EJ. Growing unculturable bacteria. Journal of Bacteriology. 2012;194(16):4151–60. https://doi.org/10.1128/JB.00345-12
12. Pegadraju, H., et al., RECAPITULATION OF ANTIBIOTIC RESISTANCE AND MRSA.
13. Katz L, Hutchinson CR. Chapter 14. Genetic Engineering of Antibiotic Producing Organisms. In: Annual reports in medicinal chemistry. 1992. p. 129–38. https://doi.org/10.1016/S0065-7743(08)60412-1
14. Melander RJ, Zurawski DV, Melander C. Narrow-spectrum antibacterial agents. MedChemComm. 2018 ;9(1):12–21. https://doi.org/10.1039/C7MD00528H
15. Subramaniyam, R. and R.J.I.J.S.N. Vimala, Solid state and submerged fermentation for the production of bioactive substances: a comparative study. 2012. 3(3): p. 480-486.
16. Nicolaou, K.C. and S.J.T.J.o.a. Rigol, A brief history of antibiotics and select advances in their synthesis. 2018. 71(2): p. 153-184.

17. Aminov RI. A brief history of the antibiotic era: Lessons learned and challenges for the future. Front Microbiol. 2010;1. http://dx.doi.org/10.3389/fmicb.2010.00134
18. Kapoor G, Saigal S, Elongavan A. Action and resistance mechanisms of antibiotics: A guide for clinicians. J Anaesthesiol Clin Pharmacol . 2017;33(3):300. http://dx.doi.org/10.4103/joacp.joacp_349_15
19. Epand RM, Walker C, Epand RF, Magarvey NA. Molecular mechanisms of membrane targeting antibiotics. Biochim Biophys Acta Biomembr. 2016;1858(5):980–7. http://dx.doi.org/10.1016/j.bbamem.2015.10.018
20. Newton BA. Mechanisms of antibiotic action. Annu Rev Microbiol. 1965;19(1):209–40. http://dx.doi.org/10.1146/annurev.mi.19.100165.001233
21. Vollmer W, Blanot D, De Pedro MA. Peptidoglycan structure and architecture. FEMS Microbiol Rev. 2008;32(2):149–67. http://dx.doi.org/10.1111/j.1574-6976.2007.00094.x
22. Brown ED, Wright GD. Antibacterial drug discovery in the resistance era. Nature. 2016;529(7586):336–43. http://dx.doi.org/10.1038/nature17042
23. Maxon WD. Continuous fermentation: A discussion of its principles and applications. Appl Microbiol. 1955;3(2):110–22. http://dx.doi.org/10.1128/am.3.2.110-122.1955
24. Lee SY, Kim HU, Park JH, Park JM, Kim TY. Metabolic engineering of microorganisms: general strategies and drug production. Drug Discov Today. 2009;14(1–2):78–88. http://dx.doi.org/10.1016/j.drudis.2008.08.00
25. Wright PM, Seiple IB, Myers AG. The evolving role of chemical synthesis in antibacterial drug discovery. Angew Chem Int Ed Engl. 2014;53(34):8840–69. http://dx.doi.org/10.1002/anie.201310843
26. Corrie K, Hardman JG. Mechanisms of drug interactions: pharmacodynamics and pharmacokinetics. Anaesth Intensive Care Med. 2011;12(4):156–9. http://dx.doi.org/10.1016/j.mpaic.2010.12.008
27. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci. 2004;93(11):2645–68. http://dx.doi.org/10.1002/jps.20178
28. Yanling J, Xin L, Zhiyu L. The antibacterial drug discovery. In: Drug Discovery. InTech; 2013. https://doi.org/10.5772/52510
29. Page MGP. Beta-lactam antibiotics. In: Antibiotic Discovery and Development. Boston, MA: Springer US; 2012. p. 79–117. https://doi.org/10.1007/978-1-4614-1400-1_3
30. Zakeri B, Wright GD. Chemical biology of tetracycline antibioticsThis paper is one of a selection of papers published in this Special Issue, entitled CSBMCB — Systems and Chemical Biology, and has undergone the Journal's usual peer review process. Biochem Cell Biol. 2008;86(2):124–36. http://dx.doi.org/10.1139/o08-002
31. Becker B, Cooper MA. Aminoglycoside antibiotics in the 21st century. ACS Chem Biol. 2013;8(1):105–15. http://dx.doi.org/10.1021/cb3005116
32. Pham TDM, Ziora ZM, Blaskovich MAT. Quinolone antibiotics. Medchemcomm2019;10(10):1719–39. http://dx.doi.org/10.1039/c9md00120
33. Dinos GP. The macrolide antibiotic renaissance. Br J Pharmacol. 2017;174(18):2967–83. http://dx.doi.org/10.1111/bph.13936
34. Yim G, Thaker MN, Koteva K, Wright G. Glycopeptide antibiotic biosynthesis. J Antibiot (Tokyo). 2014;67(1):31–41. http://dx.doi.org/10.1038/ja.2013.117
35. Freischem S, Grimm I, López-Pérez A, Willbold D, Klenke B, Vuong C, et al. Interaction mode of the novel monobactam AIC499 targeting penicillin binding protein 3 of Gram-negative bacteria. Biomolecules. 2021;11(7):1057. http://dx.doi.org/10.3390/biom11071057
36. Armstrong T, Fenn SJ, Hardie KR. JMM Profile: Carbapenems: a broad-spectrum antibiotic: This article is part of the JMM Profiles collection. J Med Microbiol. 2021;70(12). http://dx.doi.org/10.1099/jmm.0.001462
37. Spížek J, Řezanka T. Lincosamides: Chemical structure, biosynthesis, mechanism of action, resistance, and applications. Biochem Pharmacol. 2017;133:20–8. http://dx.doi.org/10.1016/j.bcp.2016.12.001
38. Sköld OE, Swedberg G. Sulfonamides and trimethoprim. In: Antimicrobial Drug Resistance. Cham: Springer International Publishing; 2017. p. 345–58. https://doi.org/10.1007/978-3-319-46718-4_24
39. van Saene R, Fairclough S, Petros A. Broad- and narrow-spectrum antibiotics: a different approach. Clin Microbiol Infect. 1998;4(1):56–7. http://dx.doi.org/10.1111/j.1469-0691.1998.tb00338.x
40. Kaur, S.P., R. Rao, and S.J.I.J.P.P.S. Nanda, Amoxicillin: a broad spectrum antibiotic. 2011. 3(3): p. 30-7.
41. Hash JH. Antibiotic mechanisms. Annu Rev Pharmacol. 1972;12(1):35–56. http://dx.doi.org/10.1146/annurev.pa.12.040172.000343
42. Sarkar P, Yarlagadda V, Ghosh C, Haldar J. A review on cell wall synthesis inhibitors with an emphasis on glycopeptide antibiotics. Medchemcomm. 2017;8(3):516–33. http://dx.doi.org/10.1039/c6md00585c
43. McCoy LS, Xie Y, Tor Y. Antibiotics that target protein synthesis. Wiley Interdiscip Rev RNA. 2011;2(2):209–32. http://dx.doi.org/10.1002/wrna.60
44. Cambau E, Guillard T. Antimicrobials that affect the synthesis and conformation of nucleic acids: -EN- -FR- -ES-. Rev Sci Tech. 2012;31(1):77–87. http://dx.doi.org/10.20506/rst.31.1.2102
45. Gilbert P, Allison D, Lambert P. Antibiotics that act on nucleic acids and protein biosynthesis. In: Molecular Medical Microbiology. Elsevier; 2002. p. 599–608. https://doi.org/10.1016/B978-012677530-3/50247-6
46. Fernández-Villa D, Aguilar MR, Rojo L. Folic acid antagonists: Antimicrobial and immunomodulating mechanisms and applications. Int J Mol Sci. 2019;20(20):4996. http://dx.doi.org/10.3390/ijms20204996
47. Schwarz S, Cloeckaert A, Roberts MC. Mechanisms and spread of bacterial resistance to antimicrobial agents. In: Antimicrobial Resistance in Bacteria of Animal Origin. Washington, DC, USA: ASM Press; 2019. p. 73–98. https://doi.org/10.1128/9781555817534.ch6
48. Todar, K.J.T.s.o.t.o.b., Bacterial resistance to antibiotics (page 3). 2011. 4.
49. Lambert P. Bacterial resistance to antibiotics: Modified target sites. Adv Drug Deliv Rev. 2005;57(10):1471–85. http://dx.doi.org/10.1016/j.addr.2005.04.003
50. Webber MA. The importance of efflux pumps in bacterial antibiotic resistance. J Antimicrob Chemother. 2003;51(1):9–11. http://dx.doi.org/10.1093/jac/dkg050
51. ALTINÖZ, E., E.M.J.I.J.o.I.R. Altuner, and Reviews, Antibiotic resistance and efflux pumps. 2019. 3(2): p. 1-9.
52. Wright G. Bacterial resistance to antibiotics: Enzymatic degradation and modification. Adv Drug Deliv Rev. 2005;57(10):1451–70. http://dx.doi.org/10.1016/j.addr.2005.04.002
53. Delcour AH. Outer membrane permeability and antibiotic resistance. Biochim Biophys Acta Proteins Proteom . 2009;1794(5):808–16. http://dx.doi.org/10.1016/j.bbapap.2008.11.005
54. Stewart PS, William Costerton J. Antibiotic resistance of bacteria in biofilms. Lancet . 2001;358(9276):135–8. http://dx.doi.org/10.1016/s0140-6736(01)05321-1
55. Stewart PS. Mechanisms of antibiotic resistance in bacterial biofilms. Int J Med Microbiol. 2002;292(2):107–13. http://dx.doi.org/10.1078/1438-4221-00196
56. von Wintersdorff CJH, Penders J, van Niekerk JM, Mills ND, Majumder S, van Alphen LB, et al. Dissemination of antimicrobial resistance in microbial ecosystems through horizontal gene transfer. Front Microbiol. 2016;7. http://dx.doi.org/10.3389/fmicb.2016.00173
57. Sifri Z, Chokshi A, Cennimo D, Horng H. Global contributors to antibiotic resistance. J Glob Infect Dis. 2019;11(1):36. http://dx.doi.org/10.4103/jgid.jgid_110_18

58. Moran RA, Anantham S, Holt KE, Hall RM. Prediction of antibiotic resistance from antibiotic resistance genes detected in antibiotic-resistant commensalEscherichia coliusing PCR or WGS. J Antimicrob Chemother. 2016;dkw511. http://dx.doi.org/10.1093/jac/dkw511
59. Abramova A, Berendonk TU, Bengtsson-Palme J. A global baseline for qPCR-determined antimicrobial resistance gene prevalence across environments. Environ Int. 2023;178(108084):108084. http://dx.doi.org/10.1016/j.envint.2023.108084
60. Zankari E, Allesøe R, Joensen KG, Cavaco LM, Lund O, Aarestrup FM. PointFinder: a novel web tool for WGS-based detection of antimicrobial resistance associated with chromosomal point mutations in bacterial pathogens. J Antimicrob Chemother . 2017;72(10):2764–8. http://dx.doi.org/10.1093/jac/dkx217
61. Roeber F, Jex AR, Gasser RB. Impact of gastrointestinal parasitic nematodes of sheep, and the role of advanced molecular tools for exploring epidemiology and drug resistance - an Australian perspective. Parasit Vectors . 2013;6(1). http://dx.doi.org/10.1186/1756-3305-6-153
62. Macesic N, Polubriaginof F, Tatonetti NP. Machine learning: novel bioinformatics approaches for combating antimicrobial resistance. Curr Opin Infect Dis. 2017;30(6):511–7. http://dx.doi.org/10.1097/qco.0000000000000406
63. Munk P, Andersen VD, de Knegt L, Jensen MS, Knudsen BE, Lukjancenko O, et al. A sampling and metagenomic sequencing-based methodology for monitoring antimicrobial resistance in swine herds. J Antimicrob Chemother. 2017;72(2):385–92. http://dx.doi.org/10.1093/jac/dkw415
64. Fluit AC, Visser MR, Schmitz F-J. Molecular detection of antimicrobial resistance. Clin Microbiol Rev. 2001;14(4):836–71. http://dx.doi.org/10.1128/cmr.14.4.836-871.2001
65. Tao C-W, Hsu B-M, Ji W-T, Hsu T-K, Kao P-M, Hsu C-P, et al. Evaluation of five antibiotic resistance genes in wastewater treatment systems of swine farms by real-time PCR. Sci Total Environ. 2014;496:116–21. http://dx.doi.org/10.1016/j.scitotenv.2014.07.024
66. Aminov, R.I., et al., Detection of tetracycline resistance genes by PCR methods. 2004: p. 3-13.
67. Wada M, Lkhagvadorj E, Bian L, Wang C, Chiba Y, Nagata S, et al. Quantitative reverse transcription-PCR assay for the rapid detection of methicillin-resistant Staphylococcus aureus. J Appl Microbiol. 2010;108(3):779–88.
68. Ota Y, Furuhashi K, Nanba T, Yamanaka K, Ishikawa J, Nagura O, et al. A rapid and simple detection method for phenotypic antimicrobial resistance in Escherichia coli by loop-mediated isothermal amplification. J Med Microbiol. 2019;68(2):169–77. http://dx.doi.org/10.1099/jmm.0.000903
69. Veenemans J, Overdevest IT, Snelders E, Willemsen I, Hendriks Y, Adesokan A, et al. Next-generation sequencing for typing and detection of resistance genes: Performance of a new commercial method during an outbreak of extended-spectrum-beta-lactamase-producing Escherichia coli. J Clin Microbiol. 2014;52(7):2454–60. http://dx.doi.org/10.1128/jcm.00313-14
70. Strommenger B, Kettlitz C, Werner G, Witte W. Multiplex PCR assay for simultaneous detection of nine clinically relevant antibiotic resistance genes instaphylococcus aureus. J Clin Microbiol. 2003;41(9):4089–94. http://dx.doi.org/10.1128/jcm.41.9.4089-4094.2003
71. Frye JG, Jesse T, Long F, Rondeau G, Porwollik S, McClelland M, et al. DNA microarray detection of antimicrobial resistance genes in diverse bacteria. Int J Antimicrob Agents . 2006;27(2):138–51. http://dx.doi.org/10.1016/j.ijantimicag.2005.09.021
72. Ghafourian, S., et al., Extended spectrum beta-lactamases: definition, classification and epidemiology. 2015. 17(1): p. 11-22.
73. ur Rahman S, Ali T, Ali I, Khan NA, Han B, Gao J. The growing genetic and functional diversity of extended spectrum beta-lactamases. Biomed Res Int. 2018;2018:1–14. http://dx.doi.org/10.1155/2018/9519718
74. Senok AC, Khanfar HS, Bindayna KM, Botta GA. Extended spectrum beta-lactamases (ESBL) in Escherichia coli and Klebsiella pneumoniae: trends in the hospital and community settings. J Infect Dev Ctries. 2009;3(04). http://dx.doi.org/10.3855/jidc.127
75. Shaikh S, Fatima J, Shakil S, Rizvi SMD, Kamal MA. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi J Biol Sci. 2015;22(1):90–101. http://dx.doi.org/10.1016/j.sjbs.2014.08.002
76. Saliu E-M, Vahjen W, Zentek J. Types and prevalence of extended–spectrum beta–lactamase producing Enterobacteriaceae in poultry. Anim Health Res Rev. 2017;18(1):46–57. http://dx.doi.org/10.1017/s1466252317000020
77. Theuretzbacher U, Piddock LJV. Non-traditional antibacterial therapeutic options and challenges. Cell Host Microbe. 2019;26(1):61–72. http://dx.doi.org/10.1016/j.chom.2019.06.004
78. Mühlen S, Dersch P. Anti-virulence strategies to target bacterial infections. In: Current Topics in Microbiology and Immunology. Cham: Springer International Publishing; 2015. p. 147–83. https://doi.org/10.1007/82_2015_490
79. Ogawara H. Possible drugs for the treatment of bacterial infections in the future: anti-virulence drugs. J Antibiot (Tokyo). 2021;74(1):24–41. http://dx.doi.org/10.1038/s41429-020-0344-z
80. Principi N, Silvestri E, Esposito S. Advantages and limitations of bacteriophages for the treatment of bacterial infections. Front Pharmacol. 2019;10. http://dx.doi.org/10.3389/fphar.2019.00513
81. Gao W, Thamphiwatana S, Angsantikul P, Zhang L. Nanoparticle approaches against bacterial infections. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2014;6(6):532–47. http://dx.doi.org/10.1002/wnan.1282
82. Jelinkova P, Mazumdar A, Sur VP, Kociova S, Dolezelikova K, Jimenez AMJ, et al. Nanoparticle-drug conjugates treating bacterial infections. J Control Release. 2019;307:166–85. http://dx.doi.org/10.1016/j.jconrel.2019.06.013
83. Yuan P, Ding X, Yang YY, Xu Q-H. Metal nanoparticles for diagnosis and therapy of bacterial infection. Adv Healthc Mater. 2018;7(13). http://dx.doi.org/10.1002/adhm.201701392