A Review on Antimicrobial Resistance and Emerging Strategies to Tackle It

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “A Review on Antimicrobial Resistance and Emerging Strategies to Tackle It” submitted by Thamjeed Mohaimeen (ID: 18346069), of Summer, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human or animal trial.

Abstract

Global health concerns are now significantly attributed to the emergence of antimicrobial treatment resistance. When antibiotics were initially developed in the early 1920s, many people believed that disease had finally been defeated by humans. However, it soon became clear that any antibiotic utilized might not be effective against the bacteria. Almost all pathogenic bacteria appear to be capable of developing resistance to various antibiotic classes. By deepening our knowledge on how the resistance develops, we would be able to maximize the available drug therapy as well as develop novel antimicrobial agents. This review will address epidemiology of antimicrobial resistance, resistance mechanism, existing therapies, recent advancements in this field along with challenges and limitations to counter antimicrobial resistance.

Keywords: Antimicrobial resistance, Antibiotics, Bacteria, Global surveillance, Infectious disease, Treatment.

Dedication

I would like to dedicate this paper to my parents & close ones.

Acknowledgement

I would like to acknowledge and give my warmest thanks to my supervisor Kazi Fatema Rahman for her unconditional support and assistance. Her guidance carried me through all the stages writing my project. I also acknowledge the support received from School of Pharmacy, BRAC University.

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List of Acronyms

AMR - Antimicrobial Resistance

CDC - Disease Control and Prevention

CA- Community - associated

HCA - Healthcare-associated

EARS-Net - European Antimicrobial Resistance Surveillance Network

CAESER - Central Asian and Eastern European Surveillance of Antimicrobial Resistance

LPS - Lipopolysaccharide

HGT - Horizontal gene transfer

CAP - CA-Pneumonia

PCR - polymerase chain reaction

MALDI-TOF - Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry

MDR - Multidrug resistant

MDR-TB - Multi-drug-resistant *Mycobacteria* that causes tuberculosis

CRE - Carbapenem-resistant *Enterobacteriaceae*

EP - Efflux pump

MICs - Minimum inhibitory concentrations

ATP - Adenosine triphosphate

ABC - Adenosine triphosphate binding cassette

RND - Resistant nodule

SMR - Small multidrug resistance

MFS - Major facilitator superfamily

MATE - Multiple drugs and toxic excursion

PBP - Penicillin-binding protein

ESBLs - Extended-spectrum B-lactamases

BLI - B-lactamase inhibitors

MRSA - Methicillin-resistant *Staphylococcus aureus*

GNB - Gram- negative bacteria

UTI - Urinary tract infection

CABP- Community-acquired bacterial pneumonia

EMA - European medicines agency

STD - Sexually transmitted disease

GRAM - Global Research on Antimicrobial Resistance

GLASS - Global Antimicrobial Resistance Surveillance System

ABSSI- Acute bacterial skin and skin structure infections

AMPs – Antimicrobial Peptide

Chapter 01

Introduction

When pathogens such as bacteria, viruses, or fungi become resistant to drugs, this phenomenon is known as antimicrobial resistance (AMR). The rise of microorganisms that are resistant to current antimicrobial treatments is one of the major public health challenges of the 21st century (Prestinaci et al., 2015). As a result of particular drugs' diminished ability to cure specific infectious diseases, future healthcare expenses remain unknown. AMR's proliferation results in serious illnesses, protracted hospital stays, increased healthcare expenses, higher prices for second-line therapies, and frequently unsuccessful treatment (Dadgostar, 2019). The frightening prospect of antimicrobial resistance is especially significant in the domain of bacterial antibiotic resistance. Over two million Americans fall ill each year from infections caused by antibiotic-resistant bacteria, according to the Centers for Disease Control and Prevention (CDC), with at least 23,000 of those cases ending in death (Dadgostar, 2019). Predictive statistical models show that 4.95 million (3.62-5.7) deaths, including 12.7 million (95% UI 0911-171) deaths associated with bacterial AMR, were attributed to bacterial AMR in 2019. Antibiotic resistance weakens a person's natural defenses against illness and increases the risk of complications for immunocompromised patients undergoing operations like chemotherapy, dialysis, surgery, and joint replacement, in addition to lowering their chances of recovering from infection (Dadgostar, 2019). On top of that, people with chronic conditions like diabetes, asthma, and rheumatoid arthritis will experience the effects of antibiotic resistance the most keenly. Some evidence suggests that the COVID-19 pandemic-related global crisis may have made antibiotic use worse (Murray et al., 2022). As a result, services and programs like disease surveillance have been interrupted. The pandemic has also marginalized many public health priorities and programs in various countries. The progress accomplished recently against AMR is in danger as a result of everything put together. This entails feeding the pipeline, making investments in the innovation of novel therapies while being aware that the R&D process for safe and efficient products takes time, and implementing government policy, such as advanced remuneration frameworks, to foster an environment that is conducive to the development of novel products. This review will cover the epidemiology of microbial

resistance, its causes, detection methods, mechanisms of antimicrobial resistance, existing antimicrobial therapies and their drawbacks. The paper will then focus on future improvements to curb AMR effectively.

1.1 Aims and Objectives

This review article focuses on the potential threats that antimicrobial resistance poses and emerging approaches to combat them. The possible causes of antimicrobial resistance, available therapies as well as development of novel antimicrobial agents in this field are discussed in this article. The limitations and challenges global health care is facing to counter antimicrobial resistance are also taken into account.

The purpose of this study is

-To elaborately discuss the causes and mechanisms of antimicrobial resistance.

-To explore currently existing drugs and their drawbacks.

-To discuss newer therapeutic strategies to treat microbial infections.

-To highlight challenges and limitations associated with AMR.

-To outline improvements that can be made to emerging drugs to establish them as widely used antimicrobial therapies.

1.2 Methodology

The information for this review article was taken from original research articles and review papers published in well-reputed peer reviewed journals, indexed in databases which include PubMed, Scopus and Google Scholar etc. Key journals that were consulted were The Lancet, Nature, Frontiers, MDPI. Following the selection of the topic, an outline was created with relevant headings and subheadings. Keywords like antimicrobial resistance, antibiotics, bacteria were applied to search pertinent papers. On the basis of the subject, relevant information was accumulated. Mendeley Desktop was used to generate the bibliography and in-text citation.

Chapter 02

Epidemiology of Global Antimicrobial Resistance

The WHO has expressed concern that a post-antibiotic era is possible in the 21st century in its global report on surveillance for antimicrobial resistance (AMR) (Akova, 2016). Since antimicrobials are used to treat a wide variety of infections, antimicrobial resistance has become an urgent issue for public health. Despite the fact that there were major gaps in surveillance and a lack of effective interventions, the World Health Organization (WHO) was able to identify extraordinarily high rates of resistance for both Community-associated (CA) and healthcare-associated illnesses (HCA). Reports of *E. coli* cases resistant to fluoroquinolones have come in from 92% of WHO's 194 member states and 5/6 of WHO's global regions (Akova, 2016). There is evidence that 86 nations and 5 regions have developed resistance to cephalosporins of the third generation as a result of extended-spectrum cephalosporinase (Akova, 2016). Similar to the prevalence of methicillin-resistant *S. aureus*, *K. pneumoniae* has developed resistance to third-generation cephalosporins and carbapenems. Evidence of an upward trend in antibiotic-resistant bacteria over the past decade has been provided by the CDC's National Healthcare Safety Network as well as the EARS-Net (European Antimicrobial Resistance Surveillance Network) and the CAESAR (Central Asian and Eastern European Surveillance of Antimicrobial Resistance) (Akova, 2016). Antibiotic consumption and resistance rates across countries can be tracked in real time with the help of specialist software, which allows for continual updates as new information becomes available on an interactive map.

Chapter 03

Mechanisms of Resistance

It is possible for microorganisms to develop resistance to antibiotics by one of four major mechanisms: active drug efflux, drug uptake reduction, drug target modification, and drug inactivation. Drug efflux and altering drug targets are examples of acquired resistance mechanisms, while limiting drug uptake and inactivation are examples of natural resistance strategies (C Reygaert, 2018). Processes differ between gram-positive and gram-negative bacteria, which is partly attributable to structural differences between the two types of bacteria (C Reygaert, 2018). Unlike gram-negative bacteria, which routinely employ all four methods of drug uptake restriction, gram-positive bacteria, which doesn't have an LPS outer membrane and the capability to employ some types of drug efflux mechanisms, seldom do so (C Reygaert, 2018). The following Figure 1 illustrates the mechanism of antimicrobial resistance.

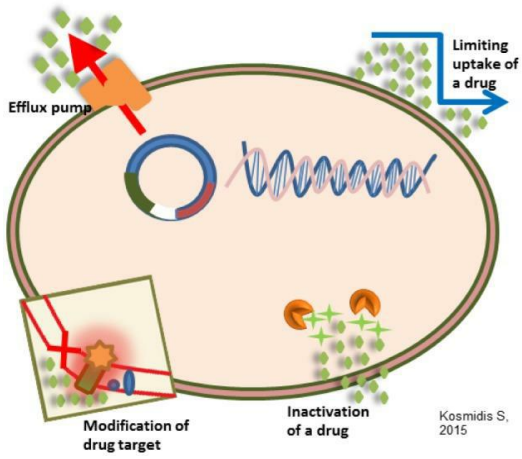

Figure 1 : Mechanism of antimirobial resistance (Reygaert, 2018)

3.1 Classification of Antibiotic Resistance Mechanism

The four most prevalent classifications of antibiotic resistance mechanisms are as follows:

3.1.1 Intrinsic Resistance

Bacteria may evolve intrinsic resistance by altering their structure or constituent elements, allowing them to resist an antibiotic. For instance, bacteria lacking a cell wall are immune to antibiotics such as penicillin, which target the bacterial process responsible for wall formation (Habboush & Guzman, 2022).

3.1.2 Acquired Resistance

Bacteria can conquer the power to resist the antimicrobial action to which they were formerly vulnerable to. Either a new genetic mutation that improves a bacteria's survival or the acquisition of DNA from an already resistant bacterium can result in the development of resistance. *Mycobacterium TB* exhibits rifamycin resistance as an example (Habboush & Guzman, 2022).

3.1.3 Genetic Alteration

The bacterium's DNA may be altered, resulting in unique bacterial components and receptors that evade detection by the antibiotic. Coexisting microorganisms in the same environment may have innate genetic resistance determinants, which would alter their genomes. Examples of trimethoprim resistance include *E. coli* and *Haemophilus influenzae* (Habboush & Guzman, 2022).

3.1.4 DNA Transfer

Horizontal gene transfer allows bacteria to share genetic components and convey resistant DNA to other bacteria (Habboush & Guzman, 2022). They share by

- Transformation (by naked DNA incorporation)
- Transduction (via the phagocytosis process)
- Conjugation (through direct contact)

The below Table 1 presents used antibiotics & the bacteria which developed partial to complete resistance against them.

Table 1 : Antibiotics which are resistant to specific bacteria (Gupta et al.,2011)

Serial No.	Antibiotics	Multidrug resistant bacteria
1	Penicillin	*Streptococcus pneumoniae, Neisseria gonorrhoeae*
2	Cephalosporin	*Escherichia coli, Proteus mirabilis*
3	Methicillin	*Staphylococcus aureus*
4	Fluoroquinolone	*E. coli, Campylobacter*
5	Isoniazid	*Mycobacterium tuberculosisS*
6	Rifampicin	*E. coli, Mycobacterium, S. aureus*
7	Vancomycin	*Lactobacillus, Enterococcus*
8	Sulfonamides	*E. coli, N. gonorrhoeae, Shigella*
9	Chloramphenicol	*E. coli, Shigella, Haemophilus influenzae*
10	Tetracycline	*Shigella, H. influenzae, Vibrio cholerae*
11	Streptomycin	*E. coli, Shigella*
12	Ampicillin	*E. coli, H. influenzae, V. cholerae, P mirabilis*
13	Gentamicin	*aureus, Staphylococcus epidermidis*
14	Erythromycin	*S. aureus, Streptococcus pyogenes*
15	Furazolidone	*Salmonella gallinarum, V cholerae*
16	Polymyxin B	*Acinetobacter baumannii, P mirabilis*
17	Amphotericin B	*Saccharomyces cerevisiae*
18	Ciprofloxacin	*E. coli, Stenotrophomonas maltophilia*
19	Nystatin	*Dictyostelium discoideum*

Chapter 04

Causes of the Antibiotic Resistance Crisis

4.1 Overuse of Antibiotics

As early as 1945, Sir Alexander Fleming predicted that antibiotics will be overused because "people will desire [the drug and]... then will begin a period... of abuse " (Ventola, 2015). Overuse of antibiotics is unquestionably linked to the emergence of resistance. Epidemiological studies have shown that the overuse of antibiotics is directly correlated with the development and spread of antibiotic-resistant bacterial strains. Bacterial genes can be passed down through generations or acquired on mobile genetic elements called plasmids (Ventola, 2015). This type of horizontal gene transfer (HGT) between bacteria has the potential to cause antibiotic resistance to spread among many different bacterial species (Ventola, 2015). A natural defense mechanism against the infection could arise through mutation. Drug-resistant bacteria proliferate when their drug-sensitive counterparts are wiped out by antibiotics. Despite warnings, antibiotic misuse is commonplace around the world. To reduce the widespread use of these medications in the United States will need considerable effort, given how often they are administered. The average number of antibiotics prescribed to U.S. citizens in 2010 was 22.0 standard units (one unit equals one dose, thus 22.0 standard units would be equivalent to 22 pills, capsules, or ampoules) (Ventola, 2015). This number is derived from the total quantity of antibiotics purchased from both retail and hospital pharmacies. Antibiotic use is most prevalent in the Great Lakes and Gulf Coast states, and least prevalent in the Western states. Antibiotic treatment courses are administered at a rate that far surpasses the population in some states, leading to an average of more than two sessions per person annually (Ventola, 2015). The figure below demonstrates antibiotic prescriptions per 1000 people of all ages.

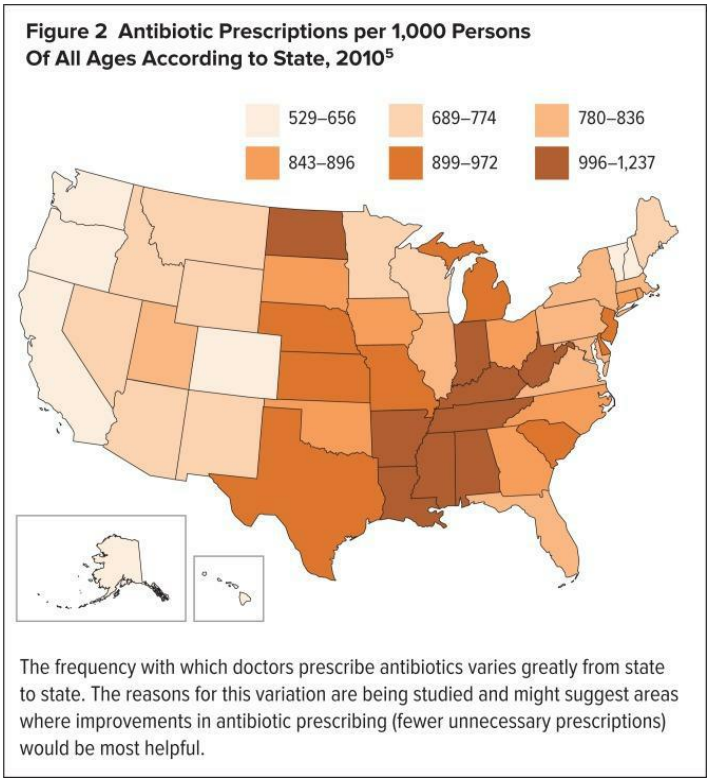

Figure 2 : The number of prescriptions for antibiotics per 1000 people in different states in USA (CDC, 2021)

4.2 Inappropriate Prescribing

When antibiotics are prescribed wrongly, it may foster the development of bacteria that are resistant to them. Depending on the study, healthcare providers are inaccurate 30%-50% of the time in their timing of therapy, agent choice, or antibiotic prescription length of 17,435 patients in the United States hospitalized with CA-Pneumonia (CAP), only 7.6% had a pathogen identified (Ventola, 2015). The Karolinska Institute in Sweden, on the other hand, used molecular diagnostic methods such as polymerase chain reaction and semiquantitative PCR to correctly identify the likely culprit in 89% of CAP cases ((Ventola, 2015). As well as putting patients at risk for antibiotic-related adverse effects, antibiotics that are administered inappropriately have dubious therapeutic value (Ventola, 2015). Low, non-therapeutic antibiotic dosages promote antibiotic resistance through mechanisms such as altered gene expression and chromosomal rearrangements. For instance, *H. influenzae* and other influenza viruses H1N1 virus; influenzae subtype B virus (Ventola, 2015).

4.3 Extensive Agricultural Use

Antibiotics are widely used as supplements for growth in cattle all around the world . Antibiotics are used in animal husbandry for both the prevention of disease and the promotion of animal growth. Antimicrobial treatment of livestock has long been thought to increase yields and improve product quality through increased animal lifetime (Ventola, 2015). Drugs given to livestock can affect people when they eat the animals (Ventola, 2015). Antibiotic-resistant bacteria were discovered at alarmingly high rates in the intestinal flora of both farm animals and farmers, raising concerns that they could be passed to people. Meat products sold to the public have been shown, through the use of cutting-edge molecular identification methods, to harbor antibiotic-resistant bacteria that were first found in farm animals (Ventola, 2015). This result can be attributed to the following series of events: Three major problems arise from the widespread use of antibiotics in livestock: 1) Death or repression of susceptible bacteria promotes the growth of antibiotic-resistant bacteria ; 2) resistant bacteria are transmitted to humans via food chain and 3) these bacteria can infect humans, which may have negative health consequences. Antibiotic use in agriculture has repercussions for the microbiome of the surrounding ecosystem (Ventola, 2015). Animals that are administered antibiotics can spread those drugs far and wide through their waste, which ends up in fertilizer, water tables, and surface runoff at rates of up to 90% (Ventola, 2015). Furthermore, tetracyclines and streptomycin are used as insecticides by spraying them onto fruit trees in the southwestern and western parts of the United States (Ventola, 2015). It's true that this method only represents a tiny fraction of all antibiotic use, but the subsequent dispersal can be rather widespread. In addition to exposing microorganisms in the environment to growth-inhibiting substances, this approach alters environmental ecology by boosting the fraction of resistant microbes over vulnerable ones. The development of immunity in children and adults to environmental antigens may be hindered by the use of antibacterial agents sold for hygiene or cleaning purposes. As a result, the immune system may be less adaptable, which could make people more susceptible to diseases that would otherwise be mild. Both developed and developing countries regularly use antibiotics as growth enhancers in cattle. It is estimated that 80 percent of antibiotics sold in the United States are administered to livestock (Ventola, 2015). Cattle that have been treated with antimicrobials are hypothesized to have better overall health, which would lead to higher yields and higher quality meat and dairy products. Antibiotics fed to animals are eventually eaten by humans. It has been known for over 35 years that antibiotic-resistant bacteria

may be found in the intestinal flora of both farm animals and farmers, and that this finding was the first clue that animals kept in factory farms could potentially spread these bacteria to humans (Ventola, 2015). Antibiotics used in farming have an effect on the microbiome of the environment. Animals can distribute the antibiotics they are given through their waste, which ends up in the environment via fertilizer, water, and other surfaces. Pesticides like tetracyclines and streptomycin are applied to fruit trees throughout the west and south of the United States (Ventola, 2015). Antibacterial treatments used for hygiene or cleaning purposes may increase this problem since they may hinder children and adults from establishing immunity to environmental antigens. Because of this, the immune system may be less flexible, raising the risk of serious illness and death from infections that are usually mild (Ventola, 2015).

4.4 Lack of New Antibiotics

The pharmaceutical industry's efforts to develop new antibiotics, a tactic that has been effective in the past to defeat resistant bacteria, have essentially ground to a halt due to financial and regulatory constraints (Ventola, 2015). 15 of the top 18 drug companies abandoned the antibiotic business (Ventola, 2015). The number and variation of research teams have been drastically reduced as a result of pharmaceutical industry mergers. Due to budget limitations brought on by the economic downturn, antimicrobial research has been curtailed in academic institutions (Ventola, 2015). The Figure 3 below depicts the number of new antibacterial drug approval versus intervals of year.

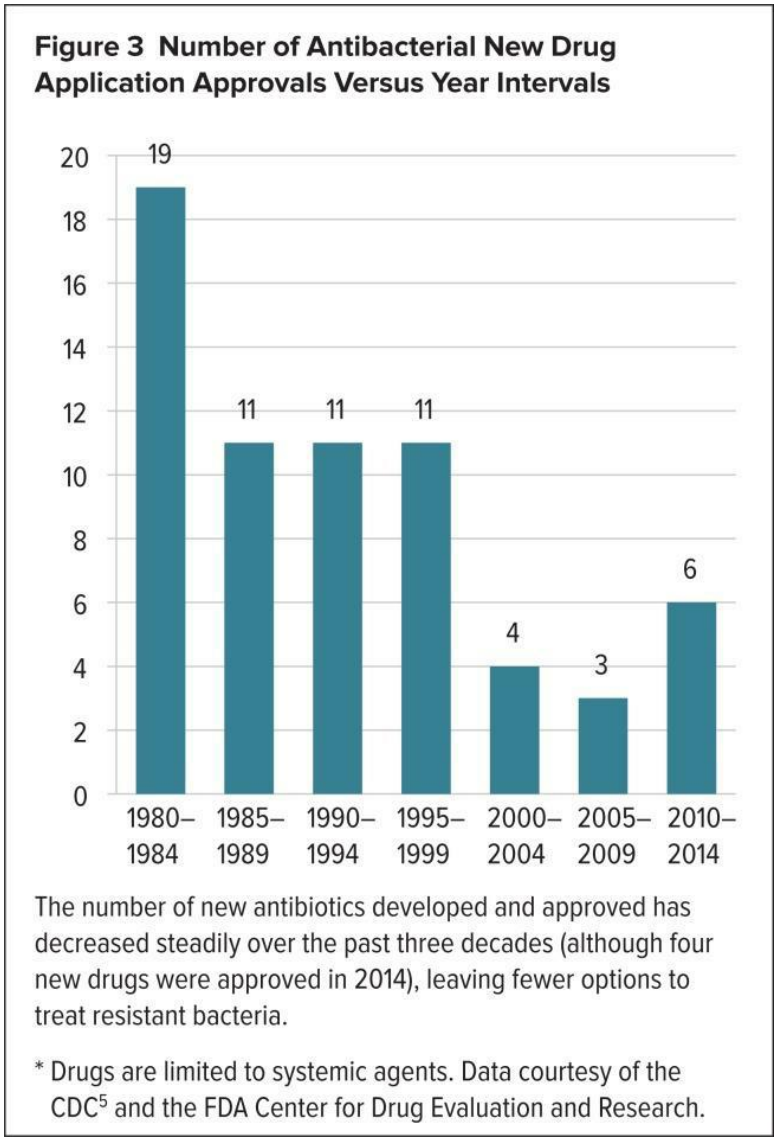

Figure 3: The number of new antibacterial drug approval versus intervals of year (Schrubbe, 2016)

Chapter 05

Detection of Antimicrobial Resistance and Antibiotic Susceptibility Testing

Methods based on measuring bacterial growth while the tested drug is present are the most popular in clinical microbiology because they allow for phenotypic detection of antibiotic resistance (March-Rosselló, 2017). The typical waiting time for results using these more traditional approaches is around 24 hours. This section describes the most common methods for quickly determining an antibiotic's susceptibility. Microarrays, immunochromatographic methods, colorimetric methods, image methods, nephelometry, MALDI-TOF mass spectrometry, flow cytometry, chemiluminescence, bioluminescence, microfluidics, and cell disruption-based methods are just some of the many techniques used to collect the data, all of which are analyzed in detail (March-Rosselló, 2017).

5.1 Molecular Techniques

It is possible to use molecular techniques to locate both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), two kinds of genetic material (RNA). The polymerase chain reaction (PCR) is the molecular method with the highest diagnostic value since it not only accurately detects the infectious agent but also serves as the primary tool to profile its genotypes for resistance and virulence (March-Rosselló, 2017). It takes roughly 12 hours to finish all three phases of conventional PCR.

5.2 Microarrays

This technique relies on analyzing images to ascertain if a target molecule has hybridized with a probe that has been mounted on a solid substrate. These probes, which are often oligonucleotides, are connected rather firmly to one another, allowing for the possibility that a high number of resistance genes can be discovered using a microarray (March-Rosselló, 2017). A wide variety of microarrays are sold in stores, including the Check-MDR CT102, Check-MD CT103, and Check-MDR CT103 XL (Check points Health BV) (March-Rosselló, 2017). From the colonies grown on the isolation plates, the microarrays identify a huge number of genes encoding various beta-lactamases (ESBLs, AmpCs, and carbapenemases) (March-Rosselló, 2017).

5.3 Commercial Antibiogram Methods

Commercial antibiogram techniques commonly used in clinical microbiology laboratories have been directly applied to various clinical samples (March-Rosselló, 2017). Commercial strips with an antibiotic gradient have been used to directly create antibiograms from respiratory sample analysis. Mueller-Hinton agar plates are used, and antibiotic strips are inserted before any samples are added (March-Rosselló, 2017). After 24 hours of colony growth on the plates, the minimal inhibitory concentration is determined. According to their research, Boyer et al. discovered an 89% rate of agreement, 1.5% of extremely large mistakes, and 9.6% of moderate to large errors (March-Rosselló, 2017). Overall, Bouza et al. discovered that there were 96.44% agreements, 1.98% major mistakes, and 1.56% minor errors (March-Rosselló, 2017).

5.4 Immunochromatographic Techniques

These methods typically yield results in around 20 minutes (March-Rosselló, 2017). They don't cost much, don't call for any special equipment or expertise, and are easy to come by. The results would seem to indicate that they can be accomplished in just about any laboratory. To combat antibiotic resistance, researchers have identified bacterial enzymes capable of hydrolyzing the drug (March-Rosselló, 2017). Step one of the process is to suspend the bacteria in the diluent. Capillary action transports the bacteria from one end of the strip to the other once a few drops of the diluent have been introduced (which is typically constructed of nitrocellulose) (March-Rosselló, 2017). If an antibody specific to the bacterium's antigen is bound to the test site of the strip, resulting in the appearance of a colorful band, the test is positive. For the detection of OXA-48 and KPC carbapenemases, two immunochromatography systems (Coris BioConcept) have been released with about 100% sensitivity and specificity (March-Rosselló, 2017).

5.5 Colorimetric Methods

Carbapenemases can be detected with a number of different tests, such as the RAPIDEC, CARBA NP kit from bioMérieux or the Rapid CARB Screen® kit from Rosco Diagnostica A/S. With a turnaround time of around two hours and a high degree of sensitivity and specificity, these kits are ideal for rapid diagnosis (March-Rosselló, 2017). In these tests, the bacterium is grown in the presence of the antibiotic. An alteration in the color of the indicator may occur if the bacteria create carbapenemase, which hydrolyzes the antibiotic and alters the pH of the medium (March-Rosselló,

2017). There is no way to tell which type of carbapenemase is being tested for in these particular assays. However, in phenotypic studies, they are able to distinguish between each carbapenemase variant (March-Rosselló, 2017).

Chapter 06

Surveillance of Antimicrobial Resistance

In the case of severe infections, timely administration of potent chemotherapeutic medications is crucial for successful treatment. Unlike some infections, such as tuberculosis (TB), whooping cough, and gonorrhea, which are caused by a single pathogen, the vast majority of infections, such as those affecting the skin and soft tissues, the upper and lower respiratory tracts, the urinary tract, meningitis, and sepsis, are caused by a number of different pathogens (Johnson, 2015). Knowing the likely infectious agents and how they might respond to antibiotics is crucial for making clinical judgments on empirical treatment (Johnson, 2015). Although this knowledge can be gleaned in part through therapists' years of experience, surveillance provides more reliable and unbiased information. The US Centers for Disease Control and Prevention (CDC) define surveillance as the continuous systematic gathering, analysis, and interpretation of health data necessary for the planning, implementation, and evaluation of public health practice, with the prompt dissemination of these data to those who need to know (Johnson, 2015). Surveillance, in a nutshell, is the practice of gathering information for use as needed to guide decision making and policy formulation (Johnson, 2015). According to these definitions, a readily available data source is necessary for surveillance to be effective. Since bacteria isolated from clinical samples are routinely identified and evaluated in microbiology laboratories for susceptibility or resistance, these data provide the important core information for the surveillance of antibiotic resistance. These data, now maintained in the lab's computer system, may, if accessed, pooled, and evaluated, reveal insights about the extent of antibiotic resistance occurring in various bacterial species or isolates from various diseases (Johnson, 2015). It is also possible to track antibiotic resistance as it develops over time and moves between regions. Surveillance requires data collection and analysis to detect and track public health concerns. Furthermore, monitoring should disclose the threat's epidemiology and its consequences on the people. One crucial aspect of surveillance is the timely dissemination of information to stakeholders, since this encourages them to take steps toward mitigating or preventing the public health risk that is being monitored (Johnson, 2015). For the purpose of monitoring antibiotic resistance, microbiology laboratories collect data from antibiotic susceptibility tests performed on bacteria isolated from clinical samples sent in for analysis. These

data can be linked to demographic and clinical information on the patient groups from which the viruses were isolated, shedding light on the underlying epidemiology and aiding the development of sensible treatments that attempt to lessen the burden of resistance (Johnson, 2015). These initiatives play a crucial role in the global effort to combat the threat that antibiotic resistance poses, in addition to being important on a national level (Johnson, 2015). Antibiotic resistance is a global health crisis, hence these activities are crucial on a national and international scale.

Chapter 07

Existing therapies to Combat Antimicrobial Resistance

The emergence of antibiotic-resistant bacteria has made it critical to preserve the efficacy of currently available antibiotics, develop new ones, and investigate other potential therapeutic options (Worthington & Melander, 2013). Many of the disease-causing bacteria that were once treatable with antibiotics are now resistant to them. The gonorrhea-causing bacteria *Neisseria gonorrhoeae* and the staphylococcal species *Staphylococcus aureus*, also known as "golden staph" are examples of bacteria that are now almost completely resistant to benzyl penicillin (Worthington & Melander, 2013). Traditional treatment for these diseases usually involved penicillin. The most serious problem with antibiotic resistance is that some bacteria are now resistant to practically all of the commonly used antibiotics (Worthington & Melander, 2013). Since these bacteria can cause severe illness, this is a major problem for public health. The World Health Organization (WHO) released a fact sheet on AMR bacteria on February 27th, 2017 that includes a comprehensive list of bacteria. Mortality, resistance, and the possibility of treatment are used to categorize pathogens into critical, high, and medium categories (Worthington & Melander, 2013). Gram-negative bacterial infections are a potentially catastrophic event. Enterobacter, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacter make up the ESKAPE group of pathogens (Worthington & Melander, 2013).Carbapenem resistance is a serious problem since these bacteria are resistant to the last line of defense (Worthington & Melander, 2013). *Mycobacterium tuberculosis*, the bacteria responsible for tuberculosis, is now included on this list of pressing global health concerns. They could cause life-threatening complications like pneumonia or blood poisoning (Worthington & Melander, 2013). These bacteria are immune to the most powerful antibiotics used to combat MDR-B, including carbapenems and third-generation cephalosporins. Resistance is linked with increased mortality, which is problematic given the slow pace at which new antibiotics are being produced. This pathogen priority list should be used to prioritize the allocation of resources for research and development (R&D) focused at developing novel, effective antibacterial medications (Worthington & Melander, 2013).

Our current stockpile of antibacterial medications needs to be strengthened in order to retain its potency as the protection it offers is deteriorating. An increase in antibiotic compliance is also essential. Therefore, improvements can be attained by either (i) Developing new drugs to take the place of those that are no longer needed or (ii) By extending the shelf life of current antibiotics (Worthington & Melander, 2013).

7.1 Combinations of Two or More Antibiotics

Combining two or more antimicrobial medications during a therapy plan is one approach of warding off MDR infections. Combination therapy is frequent and vital in many fields of medicine, despite the hazards of drug-drug interactions, which must be taken into account during the drug development process (Worthington & Melander, 2013). It is now believed that combination therapies based on artemisinin are the most effective treatments for malaria (Worthington & Melander, 2013). Similarly, most cancer treatments rely on drug combinations. *Mycobacterium TB* infections are usually always treated with a combination therapy due to the complexity of the bacteria that causes the disease (Worthington & Melander, 2013). They often necessitate the use of many drugs in synergy, sometimes as many as four. With the emergence of more multidrug-resistant bacteria, notably MDR Gram-negative bacteria, monotherapy becomes less effective for treating these infections, and the use of combination medications becomes necessary (Worthington & Melander, 2013). The nephrotoxic polymyxin colistin is typically used in combination with another antibiotic to treat multidrug-resistant Gram-negative infections (Worthington & Melander, 2013). There are three different kinds of antibiotic combination therapy: I) inhibition of targets in various pathways, such as when isoniazid, rifampicin, ethambutol, and pyrazinamide are used together to treat M. tuberculosis infections. ii) Combining the usage of sulfamethoxazole with trimethoprim, (sold as co-trimoxazole in the United Kingdom and under several other trade names worldwide), which inhibits the folic acid manufacturing route at distinct stages, is an example of a multi-target inhibitor (Worthington & Melander, 2013). iii) Alternative methods of inhibiting the same target, such as using streptogramins as an example.

7.2 Antibiotic Adjuvants

Antibiotic adjuvants may maintain the efficacy of present therapies, and synergy and combination of drugs have been shown to be effective against MDR bacteria (Worthington & Melander, 2013). Amoxicillin combined with clavulanic acid is the most well-known and effective such example (Worthington & Melander, 2013). Beta-lactamases inactivate amoxicillin, a powerful beta-lactam antibiotic, whereas clavulanic acid is a weak beta-lactamase inhibitor, making it somewhat antibacterial (Worthington & Melander, 2013). The best-selling medicine of 2001 was Augmentin, a combination of an antibiotic molecule and an antibiotic adjuvant (Worthington & Melander, 2013). Adjuvants for antibiotics are compounds that have little or very little antibacterial activity yet increase the efficacy of antibiotics, hence reducing or preventing antibiotic resistance (Worthington & Melander, 2013). Using adjuvants in conjunction with antibiotics can reduce innate resistance and expand the spectrum of antibiotic activity (Worthington & Melander, 2013). The effectiveness of Gram-positive selective antibiotics against Gram-negative bacterial infections has been well-documented in the medical literature. Given the toxicity of several antibiotics, including colistin, a well-thought-out plan is necessary here. This could be avoided, or at least mitigated, by using antibiotic adjuvants, which improve bacteria's susceptibility to antibiotics and hence boost the effectiveness of the antibiotics at lower doses (Worthington & Melander, 2013). Presently, there are three major types of antibiotic adjuvants available to halt the above mentioned antibiotic resistance processes (Annunziato, 2019).They are, Inhibitors of Beta- lactamase, Inhibitors of the efflux pump and Permeability of outer membrane.

7.2.1 Efflux Pump Inhibitors

It is one of the best-known examples of bacterial systems with the same basic mechanics. Due to their amino acid sequence diversity, they have different affinities for different substrates (Annunziato, 2019). The Ambler classification, based on structural properties, and the Bush and Jacoby classification, based on cross-resistance to multiple antibiotics and efflux pumps, are two alternative classification schemes for B-lactamases (EPs) (Annunziato, 2019). In this type of resistance mechanism, some antibiotics such as macrolides, fluoroquinolones and tetracyclines exert antimicrobial activity inside bacterial cells (Annunziato, 2019). The efflux system has the ability to actively efflux conventional antibiotics, which can result in increased minimum

inhibitory concentrations (MICs) and, in some circumstances, decreased antimicrobial activity (Annunziato, 2019). . In addition to antibiotics, these systems can also extrude non-antibiotic substrates such as heavy metals, detergents (Annunziato, 2019). These transmembrane proteins are expressed by virtually all species, including humans. Sewage pumps fall into five families of her: (i) Adenosine triphosphate (ATP) binding cassette (ABC) superfamily, (ii) Resistant nodule (RND) family, (iii) Small multidrug resistance (SMR) family, (iv) Major facilitator superfamily (MFS) family , and (v) Multiple drugs and toxic compound excursion (MATE) family (Annunziato, 2019). These families are classified based on sequence similarity, substrate specificity, structural folding, and energy source (Annunziato, 2019).

7.2.2 Beta-lactamase Inhibitors

The beta-lactam ring permanently acylates penicillin-binding protein (PBP), a major component of antibiotic activity, due to its electrophilicity (Annunziato, 2019). PBP produces peptidoglycan, which is necessary to maintain the structural integrity of bacterial cell walls. By establishing an inactive open circuit, B-lactamases produced by bacteria can hydrolyze B-lactam-based antibiotics while protecting the cell wall (Annunziato, 2019). The type (and amount) of B-lactamase produced by the microorganism determines the extent and extent of hydrolysis (Annunziato, 2019). Gram-positive bacteria produce their B-lactamase in the periplasm, whereas Gram-negative bacteria produce it in the extracellular space (Annunziato, 2019). This prevents the antibiotic from penetrating the cytoplasmic membrane and reaching its target. Recently, hundreds of β-lactamases have been discovered that have undergone functional characterization studies (Annunziato, 2019). Extended-spectrum B-lactamases (ESBLs) are primarily isolated from *Escherichia coli, Klebsiella pneumoniae,* and *P. mirabilis* and can hydrolyze most B-lactam antibiotics. This is a result of the widespread use of B-lactam antibiotics (Annunziato, 2019). The carbapenemase family of B-lactamases has a broader spectrum and better adaptability than other B-lactam hydrolases (Annunziato, 2019). Most of these enzymes are resistant to inhibition by all commercially available β-lactamase inhibitors (Annunziato, 2019). Due to the growing number of newly discovered B-lactamases, there is an urgent need for potent novel B-lactamase inhibitors that can be used as adjuvants for antibiotic therapy (Annunziato, 2019). Two strategies have been pursued to counteract B-lactamase-mediated resistance to B-lactams. Generation of B-lactamase-stable antibiotics such as cephalosporins and carbapenems that are resistant to hydrolysis by (i) B-

lactamases. (ii) creation of selective B-lactamase inhibitors (BLI) for use in combination with B-lactam antibiotics (Annunziato, 2019). Selecting an inhibitor for use in combination with a particular β-lactam antibiotic is a complex process considering many factors, including: a) the ability of the inhibitor to protect the antibiotic from enzymatic hydrolysis, b) the dose of inhibitor required to ensure this protection, and c) the feasibility and stability of the combination (Annunziato, 2019). In this case, the discovery of clavulanic acid, a secondary metabolite of *Streptomyces clavuligerus*, was an important development in antibacterial research (Annunziato, 2019). This B-lactam has potent antibacterial activity and can inactivate most B-lactamases (Annunziato, 2019). In response, Augmentin (amoxicillin/clavulanic acid) was developed as his first combination B-lactam lactamase inhibitor. After the advent of various combinations, combinations of antibiotic molecules and antibiotic adjuvants have achieved great commercial success (Annunziato, 2019).

7.2.3 Outer Membrane Permeabilization

In most cases, antibiotics kill bacteria by attacking the appropriate intracellular targets. To be effective, antibiotics must be able to penetrate bacterial membranes. The outer membrane is an additional barrier that Gram-negative bacteria use to prevent antibiotic penetration (Annunziato, 2019). In fact, the outer membrane of Gram-negative bacteria, which is mainly composed of porins and polyanionic lipopolysaccharides, prevents the invasion of foreign substances such as antibiotics. Some antibiotics are less effective against Gram-negative bacterial infections due to the complex cell wall structure (Annunziato, 2019). Indeed, the complex structure and composition of the membrane wall have a significant impact on bacterial susceptibility to antibiotics. Therefore, it is not surprising that most existing resistant strains often modify their outer membrane proteins to resist the action of specific antimicrobials (Annunziato, 2019). Depending on the chemical composition of the small molecule, the antibiotic penetrates the bacterial cell wall in two ways. (i) Passive transport techniques allow hydrophobic compounds, such as rifampicin and macrolides, to traverse the lipid bilayer (ii) Hydrophilic substances (such as -lactams, fluoroquinolones, and phenicol antibiotics) diffuse through active transport channels using their ability to interact with certain porins (Annunziato, 2019).

7.3 Screening of Previously Approved Drugs

Since toxicology and pharmacology profiles for currently used medications are well-established, repurposing a potential method to finding antibiotic adjuvants has become easier (Worthington & Melander, 2013). An estimated 40% savings in total drug development costs is expected as a result of the removal of a large portion of the toxicological and pharmacokinetic assessment needed for medication approval (Worthington & Melander, 2013). Antihistamines, tranquilizers, antihypertensives, antispasmodics, and anti-inflammatory medications were only some of the many pharmacological classes found to display activity against a broad spectrum of bacteria by systematic testing of permitted "non-antibiotic" chemicals for antibacterial activity (Worthington & Melander, 2013). By using this tack in the hunt for antibiotic adjuvants, it was found that non-antibiotic substances can enhance the antibacterial activity of minocycline. By testing 1,057 different combinations of FDA-approved drugs with the semi-synthetic tetracycline minocycline, researchers found that the latter's activity against *S. aureus, E. coli, and P. aeruginosa* was significantly increased (Worthington & Melander, 2013). Many multidrug-resistant *P. aeruginosa* strains became more sensitive to the antibiotic minocycline after being exposed to benserazide and loperamide, while disulfiram (Antabuse) showed a powerful synergistic effect against *S. aureus,* including a number of MRSA strains. Together, loperamide and minocycline were effective against not only *E. coli* but also *Salmonella enterica, Acinetobacter baumannii, Klebsiella pneumoniae*, and other Gram-negative pathogens (Worthington & Melander, 2013). The membrane permeability of *Escherichia coli* and *Pseudomonas aeruginosa* was found to be increased after exposure to loperamide, which may be the substance's mode of action for its adjuvant function (Worthington & Melander, 2013). In a *S. enterica* Typhimurium-induced mouse model of infectious colitis, the combination of loperamide and minocycline showed efficacy in vivo (Worthington & Melander, 2013). Antibacterial properties have been demonstrated for the NSAID diclofenac sodium, marketed as the topical anti-inflammatory gel Voltaren, in relation to *S. aureus, Listeria monocytogenes, Escherichia coli, and Mycobacterium spp*., including drug-resistant strains (Worthington & Melander, 2013). Diclofenac improved the effectiveness of streptomycin and gentamicin against *Listeria monocytogenes, Escherichia coli, and Mycobacterium spp*. In a mouse model of infection with *Salmonella typhimurium* and *Mycobacterium tuberculosis*, ibuprofen and streptomycin exhibited synergy (Worthington & Melander, 2013). In addition to the NSAIDs already mentioned, the antiplatelet medication

ticlopidine was randomly selected from a pool of 2080 authorized medicines and found to suppress the formation of wall teichoic acid in methicillin-resistant *Staphylococcus aureus* (Worthington & Melander, 2013). It has been shown that certain phenothiazines-based medications have antibacterial capabilities and can be used in conjunction with commonly prescribed antibiotics to treat a wide variety of bacteria, including Gram-positive, Gram-negative ones (Worthington & Melander, 2013). Some clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) have developed resistance to the phenothiazine antipsychotic medication thioridazine, as well as the quinolone antibiotics dicloxacillin and oxacillin (Worthington & Melander, 2013). Thioridazine has been shown to inhibit the transcription of many genes in the VraSR regulon. This includes the genes mecA and PBP2a, among others (Worthington & Melander, 2013). Antibiotic properties of thioridazine against *Mycobacterium TB*, especially those against multi-drug resistant strains, have been recognized for quite some time, though not at clinically important doses (Worthington & Melander, 2013). Subsequent research into the drug's ability to make *M. tuberculosis* more susceptible to commonly used antibiotics found that rifampicin and streptomycin were more effective against multiple *M. tuberculosis* clinical isolates when combined with thioridazine (Worthington & Melander, 2013). When tested in a mouse model of tuberculosis, thioridazine showed synergy with a treatment regimen consisting of rifampicin, isoniazid, and pyrazinamide, as well as a significant reduction in CFU when provided alone, indicating the therapeutic potential of this approach (Worthington & Melander, 2013). *E. coli* can be effectively treated with a combination of the antihistamine promethazine and penicillin G, another phenothiazine (Worthington & Melander, 2013). In contrast, promethazine does not kill bacteria when used alone (Worthington & Melander, 2013).

Chapter 08

Emerging Therapies to Combat Antimicrobial Resistance

8.1 Cefiderocol for Carbapenem-resistant Enterobacteriaceae

The CDC reports that inpatient hospital mortality rates due to infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) species have reached 50%. (Lee & Yeo, 2020). Infections brought on by CRE can manifest in many ways, and are not limited to the aforementioned bloodstream infections, ventilator-associated pneumonia, intra-abdominal abscesses, and urinary tract infections. Therefore, it is critical to create a new class of drugs to combat the spread of bacteria that are resistant to antibiotics. Antibiotics that are effective against illnesses caused by multidrug-resistant Gram-negative bacteria (GNB) were in short supply, so cefiderocol was created in compliance with reduced FDA regulations (Lee & Yeo, 2020). Cefiderocol is a novel parenteral siderophore effective against carbapenem-resistant strains of *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter baumannii, Burkholderia cepacia, and Stenotrophomonas maltophilia*. If other medications are ineffective against a complicated UTI, cefiderocol may be used (Lee and Yeo, 2020). Cefiderocol inhibits the production of microbial cell membranes. Cefiderocol's binding site is a penicillin-binding protein. Cefiderocol enters the periplasmic regions of gram-negative bacteria due to its siderophore-like characteristics, hence enhancing its stability against -lactamases (Rahman & Koh, 2020). In contrast to prior cephalosporins, the siderophore at position C-3 of cefiderocol chelates with iron (ferric form) in the host and is then actively transferred into the bacterial periplasmic region. This "Trojan horse" strategy increases the stability of cefiderocol against efflux pumps and porin channel mutations (Rahman & Koh, 2020). C-3 and C-7 side-chain modifications generate potent antibacterial activity against MDR gram-negative bacteria. The Figure 4 below summarizes the mechanisms and therapeutic uses of novel antibiotic drug, Cefiderocol.

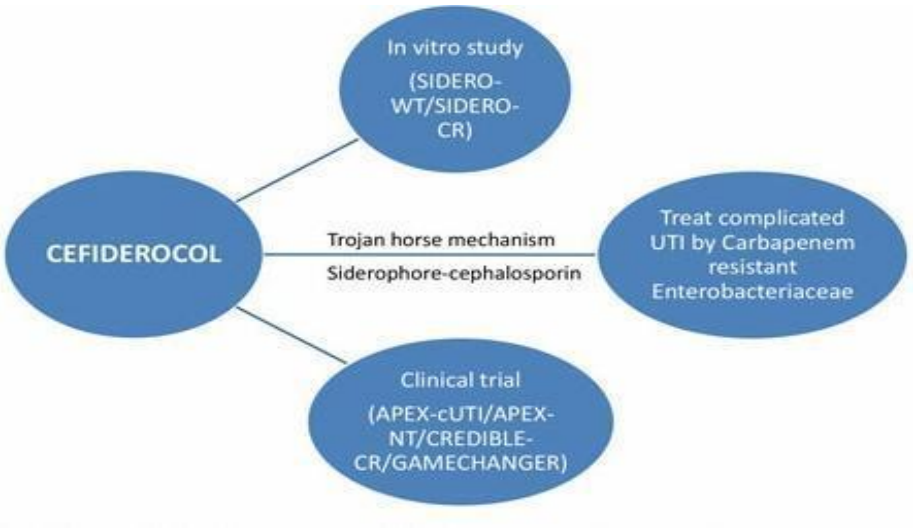

Figure 4 : Cefiderocol, novel antibiotic active against carbapenam resistant gram negative bacteria (Chatterjee et al., n.d.)

8.2 Omadacycline for CABP and ABSSSI

Tetracycline antibiotics, such as omadacycline (Nuzyra), are aminomethylcyclines. It inhibits the synthesis of the 30S ribosomal subunit in bacteria (Andrei et al., 2019). Omadacycline is a kind of tetracycline antibiotic that differs structurally from others at the C9 and C7 positions of the central tetracycline rings (Andrei et al., 2019). These adjustments allow for stable ribosome protection mechanisms and the efflux pump associated with tetracycline antibiotic resistance. Community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) are two conditions for which the FDA approved omadacycline in October 2018. (Andrei et al., 2019). The EMA has not yet given its approval as of now. IV and oral administrations are daily once-use only (Andrei et al., 2019).

8.3 Protomanid for Multidrug Resistant Tuberculosis

Pretomanid Nitroimidazoles are a new class of antibacterial drugs that includes protomanid (Andrei et al., 2019). The Food and Drug Administration (FDA) approved its use in combination with bedaquiline, which inhibits the adenosine triphosphate (ATP) synthase of the TB mycobacteria, and linezolid, the first synthetic antibiotic of the oxazolidinone class, to treat drug-resistant TB (lung tuberculosis) in August 2019. (Andrei et al., 2019). By preventing the conversion of hydroxymycolate to ketomycolate, protomanid prevents the formation of cell walls.

Protomanid produces respiratory toxicity of the bacterial cell under anaerobic conditions by releasing reactive nitrogen species. EMA has not yet approved this drug.

8.4 Zoliflodacin for Multidrug-Resistant *N. gonorrhoeae*

The *N. gonorrhoeae* bacterium, which is known to be resistant to fluoroquinolones and third-generation cephalosporins, is a high-priority pathogen (Terreni et al., 2021). We really need new antibiotics that can overcome this resistance. *N. gonorrhoeae*, the bacteria responsible for gonorrhea, can cause infertility, ectopic pregnancies, and neonatal blindness in rare but serious cases (Terreni et al., 2021). Long periods of time can pass after a woman has been infected with the STD gonorrhea without any outward signs of illness. Infections caused by *N. gonorrhoeae* that are resistant to penicillin and cephalosporin antibiotics, for which azithromycin is typically only used as a last resort, have increased significantly in recent years (Terreni et al., 2021). The latest numbers from the CDC (Centers for Disease Control and Prevention) show that there were more than 500,000 new cases of gonorrhea in the US in 2018. As stated by (Terreni et al., 2021). Phase III testing of zoliflodacin, developed by Entasis Therapeutics and the Global Antibiotic Research and Development Program, is currently underway as a treatment for multidrug-resistant *N. gonorrhoeae* (Terreni et al., 2021). This is the first antibiotic with a spiropyrimidinetrion structure. By attaching to a particular location, it inhibits type II bacterial topoisomerase in a way that is unique from fluoroquinolones. The way that zoliflodacin inhibits microbial biosynthesis differs from the other treatments now on the market in that it halts the creation of fused circular DNA, a necessary component of biosynthesis, and the cleavage of the covalent gyrase complex (Taylor et al., 2018). Targeted antibiotic therapy benefits greatly from knowledge of the minimum inhibitory concentration (MIC) and the drug's pharmacokinetic characteristics (Terreni et al., 2021). The MIC50 represents an antibiotic's "intrinsic action," but the MIC90, which is derived from more comprehensive, multi-center investigations, highlights the various resistance mechanisms of the species in question (Terreni et al., 2021). Multidrug-resistant *Neisseria gonorrhoeae* and Gram-positive and Gram-negative troublesome bacteria with MICs between 0.002 and 0.25 g/mL are killed by zoliflodacin (Terreni et al., 2021). And its frequency resistance is really low. The following Figure 5 illustrates the comparison of MICs with other available antibiotics.

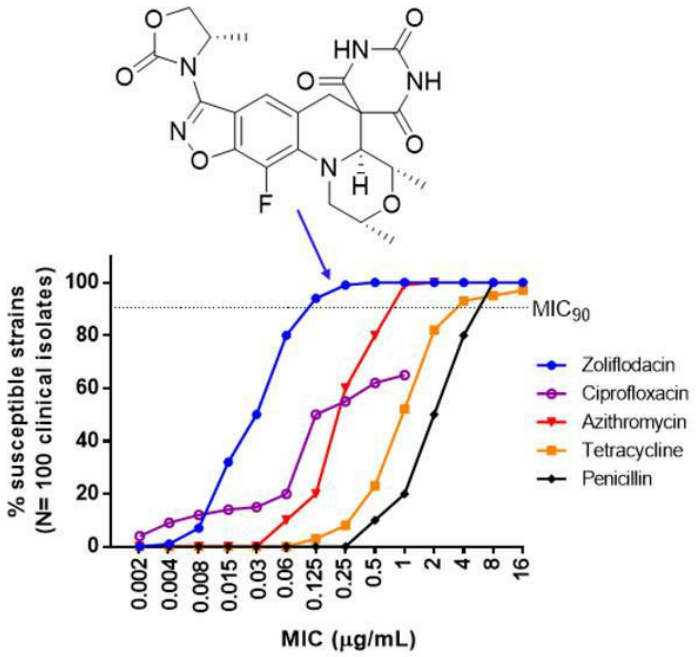

Figure 5 : Comparison of MICs with other available antibiotics (Bradford et al., 2020)

8.5 Fourth-Generation Fluoroquinolones (Delafloxacin) for ABSSSI

Acute bacterial skin and skin structure infections (ABSSSI) has high rates of morbidity and mortality are linked to these diseases. This is caused by numerous varieties of bacteria, both Gram-positive and Gram-negative. Gram-positive and Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Escherichia coli*, commonly cause surgical site infections. Nevertheless, *S. aureus* is the most harmful pathogen for ABSSSI globally (Terreni et al., 2021). Methicillin-resistant *Staphylococcus aureus* (MRSA) infections in particular are a major public health concern. As a result, there are increased mortality rates and higher healthcare expenses related to treating these conditions. Delafloxacin, commonly known as Baxdela®, was developed to treat (ABSSSI) which was approved by the FDA in 2017 for the treatment of (Terreni et al., 2021). Delafloxacin is one of the antibiotic fluoroquinolones. The inhibition of the enzymes necessary for bacterial DNA replication, transcription, repair, and recombination—bacterial topoisomerase IV and DNA gyrase (topoisomerase II)—leads to antibacterial action. demonstrates concentration-dependent bactericidal activity (Hori et al., 2022).

Chapter 09

Challenges and Limitations of AMR Resistance

9.1 Limitations in AMR Surveillance

AMR Surveillance provides significant obstacles. For a more accurate estimation of the AMR burden, it is essential to define the scientific measuring framework correctly. The Big Data Institute at Oxford University and the Institute of Health Metrics and Evaluation at the University of Washington developed the Global Research on Antimicrobial Resistance (GRAM) project in response to this rallying cry (Schnall et al., 2019). The GRAM research will be the first of its kind to analyze the incidence, prevalence, excess mortality risk, and overall disease burden caused by significant antibiotic-resistant microorganisms on a global, national, and, if feasible, subnational level (Schnall et al., 2019). Consequently, decision-makers will have access to vital data that will permit them to compare the effects of AMR to those of other global health concerns (Schnall et al., 2019). For meaningful AMR burden evaluations, data input quality and availability are crucial. Existing worldwide monitoring networks are scattered and inadequate; hence, the United Nations has recently recommended measures to solve this important issue (Schnall et al., 2019). The WHO's most recent call for joining in its Global Antimicrobial Resistance Surveillance System (GLASS) garnered only 70 signatories, of which less than 50 submitted AMR rates (Schnall et al., 2019). Because they are varied, self-reported, and based on a small number of isolates from a small number of surveillance sites, the data are inconsistent.

9.2 Challenges in Developing New Antibiotics

Global health is also facing the challenge of developing new antibiotics. Regulatory, commercial, and scientific setbacks are primarily to blame for the dearth of new antibiotics Livermore et al., 2011). Conventional methods of discovering antibiotics were abandoned in the 1990s in favor of a strategy combining genetics with high-throughput screening of existing chemical libraries (Livermore et al., 2011). Compound libraries were systematically skewed against antibiotics in order to find targets and the molecules that bind to them, despite the fact that this meant underestimating the capacity of these molecules to penetrate bacteria, inhibit efflux, and avoid mutational resistance (Livermore et al., 2011). However, despite the success of this approach, no

antibiotic discovered by it has been used in clinical practice, and numerous big pharmaceutical corporations have given up on antibiotic research (Livermore et al., 2011). New antibiotic compounds are being discovered by a plethora of start-up companies, some of which are funded by venture capital, nonprofit organizations, or the government. Their advancement into Phase III, however, is reliant on financial commitments from large pharmaceutical corporations, which are understandably wary due to the adverse regulatory climate and the low expected return on investment (Livermore et al., 2011).As of September 2017, 48 novel antibiotics were under development from Phase I to Phase III (Antibiotics currently in global clinical development, 2018). Despite the fact that this information was first reassuring, additional study showed a more somber perspective. Given the development success rates of antibiotics, only 20 to 30 percent will result in a commercially viable medicine (Payne et al., 2007; Thomas et al., 2017). Second, the majority of these antibiotics do not possess a unique mode of action, but rather are adaptations of existing antibiotic groups (Antibiotics currently in global clinical development, 2018). Third, just 38% of the antibiotics in development are anticipated to be active against ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacter*) which have been considered high priority for over a decade (Boucher et al., 2009; Thomas et al., 2017). These concerns, coupled with the unpredictability of the efficacy and safety of expedited/LPAD pathway approvals, give little room for optimism for the future of antibiotics.

Chapter 10

Future Prospects of AMR Resistance

Concerns about the rise of antibiotic resistance have prompted the rapid adaptation of already available drugs and the parallel development of novel medicines (Mandal et al., 2014). Antibiotic resistance can be defeated with the help of three immanent pipelines: phages, synthetic chemical compounds converted into antibiotics, and antimicrobial agents from natural sources (Mandal et al., 2014). There are limitations on the ability to identify and purify natural product-based antimicrobial agents (AMPs, phytochemicals, efflux pump inhibitors, LPS inhibitors, myxopyronin, and archaeons) (Mandal et al., 2014). Producing effective compounds by isolating them from their natural sources or by rationally altering derived chemicals can cut production costs. Extracts from plants that have been chemically produced after being modified are expected to become the most effective antibacterial medications in the near future (Mandal et al., 2014). The major issue of multi-drug resistance can be minimized by developing innovative drugs that focus on bacterial pathogenicity. Antibiotics can have their structure altered by constructing robust structures from preexisting ones. Metallic antibiotics are useful in this context (Mandal et al., 2014). Effectiveness & toxicological studies should be conducted simultaneously on the mechanisms of action, interactions of frequently used antibiotics and in vivo effects (Mandal et al., 2014). Finding reliable approaches for isolating and purifying newer, safer and more effective natural antimicrobial drugs against MDR bacteria is a major challenge. AMPs will be more effective against multidrug-resistant infections if their structure, function, and mechanism of action are understood (Mandal et al., 2014). Phages have the potential to be of great value in the treatment of bacterial infections in humans. The combination of antibiotics to attack phages is a potential future treatment (Mandal et al., 2014). Major pharmaceutical companies should conduct large-scale clinical trials to combat the spread of phages (Mandal et al., 2014).

An alternative, more innovative kind of stewardship is the development of drugs that do not fuel the spread of resistance (Spellberg et al., 2013). Infections may be cured, for instance, by doling out monoclonal antibodies (a cutting-edge upgrade from the more than a century-old serum therapy) or white cells that specifically target bacteria (Spellberg et al., 2013). The host's reaction to the microbe, as proposed by Casadevall and Pirofski in their damage-response hypothesis of

microbial pathogenesis, is more important than the germ itself in determining the emergence of clinical signs, symptoms, and infection consequences (Spellberg et al., 2013). Therefore, infections should be addressed by focusing on targets within the host rather than the microbiota itself. As a matter of fact, recent preclinical studies suggest it may be possible to create medications that attempt to limit the inflammatory response to infection or restrict microbial development by limiting their access to host resources rather than killing them (Spellberg et al., 2013). As an example, *Acinetobacter baumannii* was resistant to a novel class of antibiotics (LpxC inhibitors) that block the synthesis of gram-negative lipopolysaccharide but failed to kill the bacteria in vivo (Spellberg et al., 2013). Monoclonal anti-inflammatory antibodies are an additional example; these probiotics compete with microbial growth by sequestering host resources (such as iron) that would otherwise be available to the germs. Although these medications alone may not be able to reduce antibiotic resistance, their usage in conjunction with normal therapy may be beneficial (Altoni et al., 2019).

In 2021, the United Kingdom introduced a new method of paying pharmaceutical companies for novel antibiotics based on the NHS's and society's perceived value of those drugs (Davies & Oxlade, 2021). The National Health Service (NHS) in England is conducting a groundbreaking policy research experiment to evaluate the feasibility of paying for antibiotics on a subscription basis rather than on a per-use basis. This so-called "Netflix model" aims to incentivize businesses to invest in the potent antibiotics patients need while allowing clinicians to practice appropriate stewardship to optimize patient benefit. Infectious disease is a major global concern, and the selection process was made to emphasize solutions that specifically address this unmet need in the United Kingdom and an infectious area of critical concern on a global scale (Davies & Oxlade, 2021). In addition, the supplier's commitment to antimicrobial and environmental stewardship, as well as its effective surveillance procedures, were weighed heavily during the procurement process.

Chapter 11

Conclusion

AMR poses a grave threat to worldwide public health. Although AMR is receiving more attention on a global scale, our knowledge of its impact, distribution, and causes at the population level is still severely limited. A wide variety of context-specific epidemiological study methodologies must be used in order to fully comprehend the impact of AMR on communities as well as the factors influencing its emergence and spread among the population. The world needs our combined efforts in continued use of antibiotics in clinical settings and advanced efforts for AMR detection, prevention, and management. Global health actions are being developed in order to mitigate the danger of AMR. Even though several new inventions are showing promise, this is insufficient to overcome the resistance. Antibiotic consumption needs to be monitored by defining targets and observing the effects of stewardship programs designed to maximize antibiotic use and reduce antimicrobial resistance. These programs are centered on promoting the enhancing hygiene and sanitation, minimizing use of ineffective antibiotics and discovering innovative medicinal approaches. On top of that, we need to invest more on research to maximize available antimicrobial drug therapies as well as development of novel antimicrobial agents and the invention of new technologies to prevent the spread of AMR. Overall, AMR endangers the sustainability of public health care, it is imperative that preventative steps are taken to mitigate its effects. With the application of the appropriate efforts, the future of AMR could be significantly improved.

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