A Review on Antibiotic Resistance: When Bacteria Fight Back

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***Abstract*—Antibiotics are currently the most effective treatment against bacterial infections, and it has saved millions of lives since it was first discovered. However, due to the overuse and misuse of these medications, the prevalence of antibiotic-resistant bacteria is increasing rapidly worldwide, meaning that almost all modern medical advancements can be jeopardized, thus affecting clinical and therapeutic outcomes. This may lead to treatment failures and death due to infection after surgical and chemotherapy treatments, where antibiotics are given prophylactically. Antibiotic-resistant bacteria are already causing immense clinical and financial burdens to patients and their families. Therefore, understanding some mechanisms of resistance present in bacteria due to resistant genes to combat the mechanism of action of antibiotics is crucial to designing new drugs. This review article discusses the discovered major self-resistance mechanisms of bacteria, the origins of resistance, consequences of multi-drug resistance bacteria as well as new emerging weapons against this complication. Moreover, the action of the human immune system will also be addressed in this article, as it may facilitate the development of the next generation of therapy, known as immuno-antibiotics, which is less susceptible to resistance development due to its indirect involvement in treatment.**

***Keywords*—antibiotics, antibiotic resistance, infection, bacteria, biofilm, innate and adaptive immunity, immuno-antibiotics**

I. Introduction

Antibiotic Resistance (ABR) is reported when a bacterium's possesses the ability to withstand the effects of a particular type of antibiotic by the dissemination of various mechanisms, resulting in its ability to reproduce in presence of antibiotics at clinically achievable levels, thus requiring a higher dosage of antibiotic [1]. ABR has become a growing global threat where the antibiotic will no longer be effective in the treatment of the infectious disease they were initially designed for [2]. This is particularly worrying as bacterial infections are one of the leading causes of illness and death globally and the spread of ABR will jeopardise humanity's ability to treat all infectious bacterial diseases [2]. In 2017 the World Health Organisation (WHO) published a list of 12 families of bacteria that pose substantial threat to humanity. This list distinguishes bacteria into: critical, high and medium priority, according the urgency of need for new antibiotic development (Fig. 1) [3]. Bacteria presented as medium priority have some resistance, but currently many antibiotics still remain effective in eliminating such infections [3]. Presently, it is evaluated that more than 70% of all pathogenic bacteria are resistant to at least one type of industrially obtainable antibiotic, causing 700,000 deaths worldwide per year [4]. It is estimated that by 2050, 10 million deaths per year will result by infections caused by ABR microorganisms, which will cost the global economy $100 trillion [5]. Despite the rapid advances in the emergence and spread of ABR, there has been little change in clinical and agricultural policies to reflect the gravity of this crisis [6]. And in 2022, antimicrobial resistance was placed among the top ten global healthcare threats facing humanity by the WHO, since 'the world is running out of antibiotics' [7]. In 2019, ABR was estimated to directly accountable for 1.27 million deaths worldwide, and contributed to 4.95 million deaths [8].

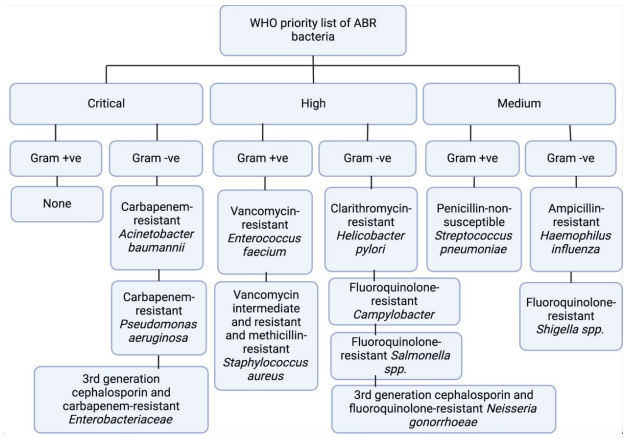

Fig. 1. To encourage research and development of new antibiotics, the WHO groups pathogenic bacteria under three priority categories according to their resistance. Created using Biorender.

II. Literature Review

A. Benefits of Antibiotics

Antibiotics are medications which eliminate or inhibit the further development of bacterial infections [4]. The discovery of antibiotics has been crucial to advances in medicine, allowing for surgical treatments such as organ

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transplants and open-heart surgery, as well as cancer treatment, to take place, by preventing and treating microbial, mainly bacterial, infections [9]. The risk of microbial infections in patients suffering from chronic diseases such as end-stage renal diseases, diabetes and rheumatoid arthritis, and patients who have had intricate surgeries such as organ transplants or cardiac surgeries are all reduced due to the availability of antibiotics. Thus, antibiotics are a major contributor to the extended expected lifespan across the globe; the expected lifespan in the United States rose from 56.4 years in 1920 to nearly 80 years in 2023 [10]. Antibiotics also reduce death caused by food born and poverty-related diseases such as salmonella, tuberculosis and malaria in developing countries [11].

B. Origins of Antibiotic Resistance

Nowadays, most antibiotics used originate from the phylum *Actinobacteria* and almost 80% of all actinobacterial-derived antibiotics are produced by the soil-dwelling *Streptomyces* [12]. However, previous to the breakthrough leading to the discovery of natural antibiotics and synthetic compounds such as quinolones, salvarsan and sulfa drugs, which are used as chemotherapeutic agents, penicillin, often called the 'wonder drug' at the time, was the first natural antibiotic to be discovered by Sir Alexander Fleming, who also warned of an era which misused and overused antibiotics [4]. Penicillin works by inhibiting cell wall synthesis and was discovered to be effective against Gram-positive bacteria, but the presence of the extra outer membrane in the Gram-negative bacteria offers them intrinsic resistance [13]. It is also ineffective against *Mycobacterium tuberculosis*, which has an outer membrane composed of a variety of lipopolysaccharides, along with fatty acids imbedded wax esters and glycolipids [12, 14].

C. Emergence of Antibiotic Resistance Bacteria in Clinical Situations

Recently, there has been a rise in the chronicity of nosocomial diseases. Among the bacterial pathogens which cause such infections, Gram positive cocci have become predominant within the last two decades due to their ability to accumulate resistant determinants [15]. After the excessive use of penicillin in the 20th Century, currently, more than 95% of *Staphylococcus aureus* isolates are penicillin-resistant globally [4]. Despite the development of penicillinase-resistant semi-synthetic penicillin, methicillin, a second-generation beta-lactam antibiotic, Methicillin-Resistant *Staphylococcus aureus* (MRSA) was reported just two years after its introduction to clinical practice in the United Kingdom [4, 16]. The increasing number of MRSA infections is commonly present in community hospitals, facilities which offer long-term care, as well as tertiary care hospitals, and its main mode of transmission is via the transiently colonized hands of hospital workers [17]. There have been strategies of control put forward, such as precautions regarding contact isolation, including wearing gloves, gowns, and hand antisepsis, and carrier decolonization with topical antimicrobials. These have different extents of success but do seem to slow down the transmission of MRSA [17].

Many MRSA strains require the use of vancomycin, a last-resort glycopeptide antibiotic during treatment. Yet despite this, there has been recorded treatment failures due to decreased susceptibility to vancomycin (vancomycin intermediate *Staphylococcus aureus*, VISA) has been reported in the United States and Japan [18]. MRSA, VISA, and vancomycin resistant *Staphylococcus aureus* are recognized by the WHO to be a serious pathogen of hospital acquired infections, and their pathogenicity and antibiotic resistance pattern poses a significant threat to human health globally [19]. This means that these strains are almost impossible to treat with the limited options left for effective therapy, demonstrating the threat and need for the development of alternative therapies to combat MRSA and other resistant strains of infectious nosocomial pathogens. Presently, it is evaluated that more than 70% of all pathogenic bacteria are resistant to at least one type of industrially obtainable antibiotic and it is estimated that by 2050, 10 million deaths per year will result from infections caused by antibiotic-resistant microorganisms, which will cost the global economy $100 trillion [4]. Thus, highlighting the urgent need for novel treatment methods such as immuno-antibiotics.

III. Materials and Methods

The research was conducted from scholarly sources, including Google Scholar, the National Center for Biotechnology Information (NCBI), the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the National Institutes of Health (NIH). The search was limited to papers published in English over the past 20 years that were focused on the following keywords for research: "antibiotic", "antibiotic resistance", "immune system", "infection", "bacteria", "innate immunity", "adaptive immunity". Multiple antibiotic mechanisms of action and bacterial mechanisms of resistance have been investigated in detail; these include major classes of antibiotics, including aminoglycosides, peptides, β-lactams, and lincosamides, amongst others. The molecular mechanisms of resistance may be categorized into three main groups: (1) reduction of intracellular antibiotic concentrations, (2) target bypass by altering target, and (3) inactivation of the antibiotic. Studies were included within the following criteria: (a) focused on antibiotic resistance in humans, (b) were published in peer-reviewed journals. Non-English studies and studies mainly focused on animals were excluded. The figures were created using Biorender.

IV. Results and Discussion

A. Mechanisms of Action of Different Antibiotics and the Corresponding Mechaniams of Resistance

Knowledge of different antibiotics' inhibitory and killing effects can impact our understanding of the major mechanisms which grant bacteria resistance [20].

Presently, scientists have obtained knowledge of antibiotics targeting almost every process that takes place in a bacterial cell. These can be classified into several major groups, based on their mechanisms of action (Fig. 2) [21]. Nowadays, the conventional methods of combatting diseases are focused on modifying existing antibiotics, whereas previously, it has been producing new antibiotics, as production was directly proportional to emerging resistant strains [22]. If the bacterial cell already possesses the genes to survive the presence of antibiotics before it is exposed to a particular antibiotic, it is said to possess intrinsic resistance. Acquired resistance is when a bacterium gains newly acquired genetic material that can mediate survival in the exposure to antibiotics [15] (Table I).

TABLE I. MAIN CLASSES OF ANTIBIOTICS USED IN CLINICAL THERAPY, THEIR MECHANISMS OF ACTION AND MECHANISMS OF RESISTANCE

Antibiotic classes (and examples)	Clinically used antibiotics		
	Antibiotic mechanism of action	Bacterial mechanism of resistance	Ref.
Aminoglycosides (streptomycin, gentamicin and kanamycin)	Cause misreading during translation and/or truncated proteins due to corrupting the 30S ribosomal subunit of 16S rRNA.	Use of aminoglycoside-modifying enzymes such as nucleotidyltransferases, acetyl-transferases and phosphotransferases; 16S ribosomal methylases; mutations in the 16S rRNA gene and decreasing influx and/or increasing efflux.	[23, 24]
β-lactams (penicillin, monobactams and carbapenems)	Inhibits penicillin-binding proteins, therefore preventing peptidoglycan crosslinking.	Synthesis of β-lactamases; reducing cell membrane permeability and increasing efflux; altering penicillin-binding proteins.	[20, 25]
Cationic peptides (colistin)	Binds to lipid A in lipopolysaccharideto induce cell membrane permeability.	Altering or removing lipid A.	[20]
Glycopeptides (vancomycin)	Prohibit production of peptidoglycan by inhibiting synthesis as it binds to D-alanyl-D-alanine in the peptide chain.	Gram-negative bacterial cells have intrinsic resistance due to less permeable cell membrane. Gram-positive bacterial cells change and hydrolyse peptidoglycan precursors.	[26]
Lincosamides (clindamycin)	Aim at 23S rRNA of the 50S, disrupting translation, leading to truncated proteins.	Production of methyltransferases to alter 23S rRNA; expressing proteins that inactivate lincosamides and efflux.	[20]
Lipopeptides (daptomycin)	Limit production of ATP by inserting into the cell membrane, causing depolarisation.	Increase thickness and positive charge in the cell wall.	[20, 27]
Macrolides (azithromycin, erythromycin)	Inhibits translocation of peptidyl-tRNA, by binding to the 50S ribosome subunit, leading to truncated protein production.	Modifying ribsomal target by producing rRNA methyltransferases which methylate 23S rRNA; mutations in the 23S rRNA; increasing efflux; protecting ribosomes using ATP-binding cassette F (ABC-F) proteins.	[28]
Oxazolidinones (linezolid)	Prohibit the production of a functional 70S subunit by binding to 23S rRNA of the 50S subunit.	Altering the 23S rRNA by enzymes such as methyltransferases; protecting ribosomes using ABC-F proteins; horizontal gene transfer.	[29, 30]
Phenicols (chloramphenicol)	Prohibit translation by binding to the A site of the 50S ribosomal subunit.	Mutations in the 23S rRNA of the 50S ribosomal subunit; use of acetyltransferases and efflux to inactivate enzymes; decreasing outer membrane permeability; target site modification.	[31, 32]
Rifamycins (rifampicin)	Bind to RNA polymerase to limit DNA-dependent RNA transcription.	Mutations in the efflux of quinolones or proteins that protect DNA gyrase and topoisomerase IV.	[20]
Streptogramins (dalfopristin)	Inhibits peptide bond formation by as aminoacyl-rRNA cannot bind to ribosomal A site.	Mutations in 23S rRNA; use of acetyltransferases to inactivate streptogramins; increasing efflux.	[33]
Sulfonamides (sulfamethizole)	Inhibits dihydropteroate synthase therefore halting dyhydrofolate acid synthesis.	Producing distinct dihydropteroate synthases which are less sensitive to sulfonamides due to mutations in the sul1 and sul2 genes.	[34, 35]
Tetracyclines (tetracycline and tigecycline)	Prohibit the aminoacyl-tRNA from binding to the acceptor on the mRNA-ribosome complex.	Inactivating tetracyclines by enzymes; protein mediated ribosome protection and modification; increased efflux.	[36, 37]

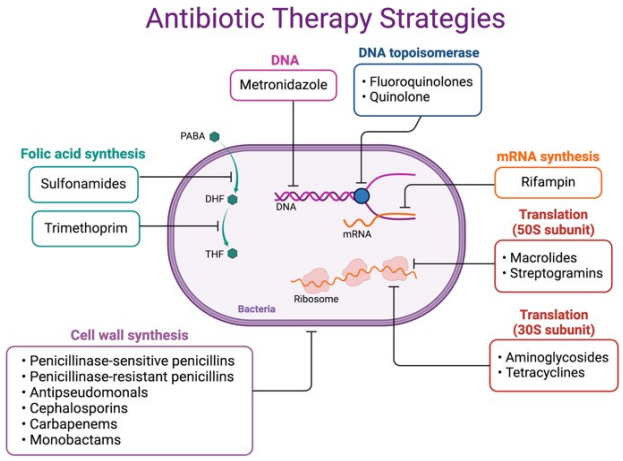

Fig. 2. Locations targeted by different classes of antibiotics. Antibiotics are cytostatic or cytotoxic to bacteria, which then gives time for the immune system to eliminate pathogenic bacteria. Created using Biorender.

B. Bacterial Mechanisms of Resistance

The mechanisms of ABR are classified into four groups: intrinsic resistance, acquired resistance, genetic changes in DNA, and horizontal gene transfer [13]. There is a global increase in the level of resistance to the antibiotics frequently used in the treatment of urinary tract infections, sepsis, hospital-acquired infections, diarrhea, and sexually transmitted infections [4].

In the US alone, following an analysis of the IMS Health Midas database, it is estimated that 22.0 standard units of antibiotics were prescribed per person in 2010, based on estimates of the number of antibiotics sold in retail and hospital pharmacies [11]. The level of antibiotic consumption has been proven by epidemiological studies to have a direct relationship with the increasing emergence and distribution of resistant strains of bacteria [4].

Moreover, the English surveillance programme for antimicrobial utilization and resistance report estimated that total number of severe antibiotic resistant infections in England rose by 2.2% in 2021, compared to 2020, thus is equivalent to 148 sever antibiotic resistant infections a day in 2021 [38]. Carbapenemase-producing Gram-negative bacteria, which causes severe antibiotic resistance, was more prevalent in the more deprived 10% of the country (6.0 per 100,000 people), compared to the least deprived 10% (2.8 per 100,000 people). However, fortunately antibiotic use in England fell by a positive 15.1% between 2017 to 2021; a step to slow the emergence of ABR resistance.

Intrinsic resistance, the simplest form of resistance, is largely present in Gram-negative bacteria, which have a relatively impermeable cell wall due to its double-membrane structure, this enables them to have an inherent resistance to numerous antibiotics that function against Gram-positive bacteria [39]. Moreover, changes to the cell wall structure, including loss of porin or altering the phospholipid and fatty acid content of the cytoplasmic membrane, can affect a drug's ability to penetrate the cell, which plays a part in the emergence of antibiotic resistance [20]. Changes in a bacterium's susceptibility are either primary or secondary. Resistance can occur through spontaneous mutation, which can occur without the presence of a drug. Resistance obtained through this method is encoded in the bacterium's chromosomes and will not be transmitted to the bacterial species. The possibility of resistance occurring in this way is low [20].

Horizontal Gene Transfer (HGT) has a critical role in the spread of both known and unidentified resistance genes [30]. Resistant genes can be inherited from relative bacteria species or passed between different species, where such genes are transferred on mobile genetic elements, such as plasmids [11]. Although horizontal gene transfer is much more probable between bacteria that are phylogenetically related, it sometimes even disregards the barrier between pathogens and environmental (non-pathogenic bacteria) in a fixed domain of microorganisms [40]. Transfer of resistance genes to pathogenic bacteria associated with humans is prompted by stressors including antibiotics, metals and biocides [41]. However, the transfer of genetic material from and to potential human pathogens in environmental conditions can be encouraged by environmental stressors [20]. Therefore, a human pathogen that has received resistant genes will have a higher chance of spreading that gene between commensal bacteria and pathogenic bacteria than if there is the transfer of genes to an alternative pathogen from environmental bacteria [30].

Secondary resistance mechanisms develop when an antibiotic is present, and they are extrachromosomal, including the use of plasmids [42]. A single plasmid can contain genes that lead to resistance to many different antibiotics [30]. Plasmids are most often transferred between bacterial cells by transduction and conjugation. Transduction occurs when the transfer of plasmids from the donor to the recipient cell is meditated by bacteriophages. DNA enters the bacterial cell after the bacteriophage attaches to a receptor of its plasma membrane. Lysogeny can occur when phage DNA is integrated into the bacterial chromosome (prophage) [43].

Furthermore, conjugation can happen between bacteria of different species and genera that are phylogenetically very different. This is because conjugation occurs through direct contact between the two bacteria via strands of proteins produced by them [30].

Due to these mechanisms, the 2022 Global Antimicrobial Resistance and Use Surveillance System report accentuated that the median reported rates in 76 countries for MRSA was 35% and 42% for third-generation cephalosporin-resistant *Escherichia coli*. In 2020, one fifth of urinary tract infections caused by *Escherichia coli* showed reduced susceptibility to common antibiotics, including ampicillin, co-trimoxazole, and fluoroquinolones [8].

C. Biofilm and Antibiotic Resistance

In addition to bacteria's well-known ability to carry HGT, which allows them to transfer antibiotic-resistant genes, bacteria can also produce biofilms to withstand antibiotics [44]. 80% of chronic and recurrent microbial

infections in humans are caused by biofilms, and those with MDR bacteria can bring about higher mortality and morbidity rates. An example of this can be seen in the biofilm-forming *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, which often infect patients suffering from cystic fibrosis or assisted ventilation [45]. Infections of these bacteria are almost impossible to treat because these bacteria are also notorious for obtaining MDR [44]. Biofilms provide protection to residing bacteria from altered pH, water potential, lack of nutrients, and mechanical and cutting forces [44].

Biofilms are highly structured, static populations of microbes encased in extracellular polymeric substances that gather and grow on biotic or abiotic surfaces, often medical implants (Fig. 3) [46]. Bacteria in a biofilm are clustered by a self-producing Extracellular Matrix (ECM), which contains polymers produced by bacteria, including extracellular DNA (e-DNA), Exopolysaccharides (EPS), proteins, and amyloidogenic proteins [47]. Residing in a biofilm community has many advantages for bacteria, such as collective recalcitrance, which enables the survival of pathogenic biofilm in a high concentration of antibiotics [44]. Recalcitrance can be accomplished through multiple mechanisms, such as Hypermutability (HPT) and can result in a greater population of MDR bacteria [48]. A biofilm can even be considered as a 'reservoir of antibiotic-resistant genes' [46]. The metabolic activity of bacteria in a biofilm is different compared to plankton form. Increased rates of exopolysaccharides, activation of inhibition of specific genes correlated to biofilm formation, and a slower growth rate are examples of such changes [47].

Additional resistance is also acquired by biofilm matrices, which allows them to withstand the presence of antibiotics and other selection pressures, leading to the emergence of multidrug-resistant bacteria and totally drug-resistant bacteria [49]. Furthermore, biofilms attached to implants, catheters, and other medical devices cause nosocomial infections. These can originate from pathogenic bacteria such as *Escherichia coli*, *Proteus mirabilis*, or *Klebsiella pneumonia*, which can become MDR [46]. Biofilm-forming *Neisseria gonorrhoeae* residing on genital mucosa brings about chronic infections. Due to its exceptional ability to resist all recommended antibiotics used to treat the infection, it is labeled as a high priority by the WHO [50].

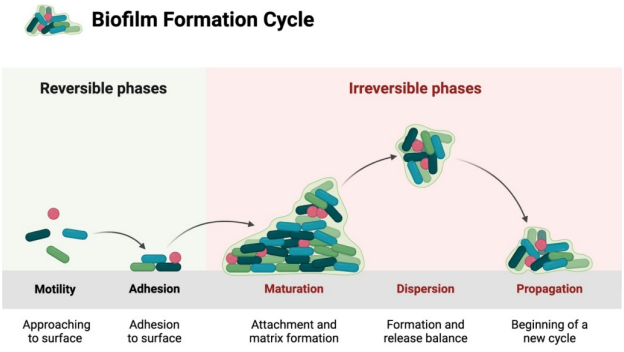

Fig. 3. Regulated process during formation of a biofilm.

D. Immuno-Antibiotics as an Alternative Therapy

1) An overview of the innate and adaptive immunity

To understand the mechanism of action of immuno-antibiotics, the functioning of the immune system must first be acknowledged. The first line of defense against bacterial infection in the human body is the immune system – the multitude of cells that use chemical processes to protect organs such as the skin, respiratory system, digestive tract, heart and other areas against threats posed by microorganisms (bacteria, fungi and parasites), viruses, cancerous cells and toxins [51]. Most immune cells in the human body are produced from the bone marrow after infancy; phagocytes, basophils, dendritic cells, mast cells, eosinophils, natural killer cells, and innate lymphoid cells are major players in eradicating a bacterial infection [52, 53].

Dendritic cells are the most influential Antigen-Presenting Cells (APCs) in initiating a T cell response. Although they can also phagocytose bacterial pathogens, they contain fewer lysosomes and, therefore, are weaker at breaking the bacteria down than macrophages [54].

Adaptive immunity, which consists of antigen-specific T cells, and B cells, can preserve a memory of previous infections, thus preventing reinfection in the body and limits the spread of the resistant bacteria in a community [54]. Distinctive T-Cell Receptors (TCR), present on every T cell plasma membrane, require APCs such as dendritic cells, macrophages, B cells, fibroblasts, and epithelial cells to recognize specific antigens in the bacteria. T cells are activated when their TCRs are in contact with a specific epitope of bacteria bound to class II major histocompatibility complex (MHC) molecule on the APC's surface, leading to secretion of cytokines (Fig. 4) [55, 56]. It also stimulates the differenciation of T cells into cytotoxic T cells ($CD8^+$) and T helper cells ($CD4^+$ Th). The former carries out clonal expansion to form effector cells, which release perforin and granzymes, which stimulate apoptosis of pathogen-infected host cells, and some become memory cells and remain in the body to initiate a secondary immune response [54, 55]. The latter's main role is moderating an immune response by directing other types of cells to perform specific tasks. Th1, 2, and 17 are the most common Th-cell response induced by an APC. The Th1 response is apparent when IFN-γ is released, which stimulates the immunity to intracellular bacteria as well as the anti-bactericidal activities of macrophages [49]. Th1-derived cytokines also play a role in the B cell differentiation in order to make opsonizing antibodies to aid the activity of phagocytes. The Th2 response is signalized by the production of the cytokines IL-4, 5, and 13, which contribute to the development of B cells that release the Immunoglobulin E (IgE) antibody [49, 57].

The complexity of the immune system may make it difficult for the bacteria to escape its efforts of elimination. This means that apart from developing new antibiotics, immuno-antibiotics may also be an effective cure against antibiotic-resistant bacteria.

Therefore, any mutation in the antigen or pathogen-associated molecular patterns, which escapes recognition

by pathogen recognition receptors and presentation by MHC molecules, will be favoured by strong pressure by natural selection [58].

Intracellular bacteria infect host cells and use it as a factory to produce progeny bacteria. These host cells must be recognized and destroyed by cytotoxic T cells [49].

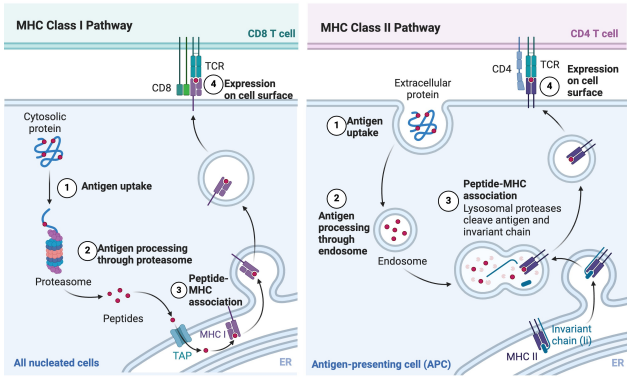

Fig. 4. Shows that the epitope peptides of the antigen that are taken up by APCs through the process of phagocytosis and pinocytosis are recognized by T cells. Both a microbial structure and self-component are required in order for T cells to recognize infected cells.

Two different properties of the MHC make it difficult for bacteria to escape immune responses. Firstly, MHC complexes re polygenic; they contain multiple MHC class I and II genes, so everyone possesses a set of MHC molecules with a variety of peptide-binding specificities. Secondly, the MHC is polymorphic, as there are different ranges of each gene within the human population; so much so that the MHC genes are the most polymorphic genes currently known [59]. This shows how the immune system can be a much more reliable and promising tool against bacteria than antibiotics.

2) An overview of immuno-antibiotics

Improved host immune system activity and immune optimization has been associated with the additional antibiotic effects on bacteria, including antibiotics' ability to impact virulence factors and other immune mechanisms which alter host response [60].

Volk *et al.* [61] have shown that there was increased IL-1 and decreased IL-10 production when β-Lactam adjunctive therapy was combined with standard antibiotics to patients suffering from MRSA bacteraemia. Although the attempted vaccine development for *Staphylococcus aureus* was unsuccessful, the novel combination of virulence factor antibiotics with standard therapeutics as an immunologic-based therapy appears propitious.

Following new progress in the understanding of Methyl-D-Erythritol Phosphate (MEP) pathway and the isprenoid and riboflavin biosynthesis pathways, Dual-Acting Immuno-Antibiotics (DAIAs) were introduced [4]. The study by Eberl *et al.* [62] showed that new immunotherapies are being developed that utilize the relationship between unconventional T cells and bacterial metabolic activities. This method combats bacteria on two fronts: directly targeting bacteria by interfering with the biosynthesis of vital metabolites, and indirectly stimulating the immune system to target the invading bacteria, thereby making it difficult for bacteria to develop resistance [62]. It may even be possible that due to the specific stimulation of immuno-antibiotics to Vγ9/Vδ2 T cells, the medicine can offer long-term protection against this pathogen and possibly even against other pathogens that produce the same type of unconventional T cell ligands [62, 63].

Alternatively, immuno-antibiotics could target the lumazine synthase (RibE or RibH) and riboflavin synthase (RibC) catalysed final two steps of the riboflavin biosynthesis pathway. A pathway presents in almost all bacteria and fungi, but not humans [62]. However, side effects of the therapy must be minimized, as these involve the immune system overacting, leading to systematic or local tissue damage [60].

V. Conclusion

The global crisis caused by of emergence of antibiotic-resistant bacteria is rapidly endangering all the health benefits brought by the discovery of antibiotics. Despite actions taken by some members of the WHO, the use of antibiotics in healthcare, veterinary care, and agriculture is still increasing, putting a huge economic burden on healthcare systems due to extended hospital stays and making infection control more difficult. This proves that coordinated efforts from multiple countries to regulate the overuse of these drugs, as well as renewed research efforts to discover new strategies to treat bacterial infections, are greatly needed. However, clinical research is gradually increasing our understanding of the mechanisms of antibiotics and their corresponding mechanisms of resistance. This information, combined with information on the impacts of new drugs on the host immune system, is vital to the development of new methods to combat bacterial pathogens. The idea of immuno-antibiotics presents a possibility of stimulating the host immune systems as well as inhibiting bacterial activity seems to be a promising approach to antibiotic potentiation.

Conflict of Interest

The author declares no conflict of interest.

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