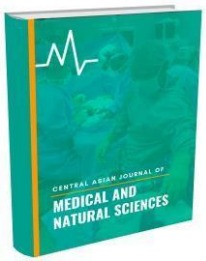

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Article

Harnessing the Immune System in the Fight Against Bacterial Infections: Current Strategies and Future Prospects

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Abstract: The problem of antibiotic resistance, or antimicrobial resistance (AMR), keeps getting worse and spreading to new areas. Because of this, it is harder or even impossible to treat Bacterial diseases, which has caused more people to get sick and die. Even though traditional antimicrobial treatment hasn't worked in the last 20 years, no new class of antibiotics has been made available. This has led to the discovery of a number of new ways to fight these multidrug-resistant infectious bacteria. The purpose of this study is to collect information and think about the methods being used or mentioned as possible replacements for common antibiotics. Methods that aren't often used, like the CRISPR-Cas system, techniques that target the enzymes or proteins that make bacteria immune to medicines, drug delivery systems, and combinations of these, are some of the things that are being done. These different methods could change how hospitals and other medical places treat germs that are resistant to many drugs.

Keywords: Antibiotic Resistance, Alternatives To Antibiotics, Antimicrobial Peptides, Bacteriophages, Antimicrobial-Resistant Enzymes, Biofilms, Antivirulence.

1. Introduction

When bacteria get into the body, the innate immune system is the first to respond. Skin and mucous membranes are examples of physical barriers; neutrophils and macrophages are examples of effector cells; and soluble agents like complement factors and antimicrobial peptides (AMPs) are examples of agents. The host's internal environment is kept secure from outside dangers by the skin and mucous membranes acting as barriers when they come into contact with dangerous bacteria [2]. By identifying microbial compounds called pathogen-associated molecular patterns (PAMPs), skin keratinocytes, for instance, not only establish a barrier that keeps infections out but also initiate the immune system's response [3].

Soluble factors are released in response to PAMP recognition. Among them are AMPs and proinflammatory cytokines, which direct neutrophils, macrophages, and monocytes—effector cells—to the infection site [4]. The blood vessels let neutrophils into the body. They eat germs and make many antimicrobial chemicals to kill them [5]. Pathogens are eaten by monocytes and macrophages, and these cells also release many pro-inflammatory chemicals that make the immune system stronger and activate the adaptive immune system [5, 6]. Even though this review didn't look at them, neutrophils, monocytes/macrophages, and other innate cells (NK cells, dendritic cells, etc.) work together to fight diseases [7].

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Bacterial pathogens can change their metabolism when they interact with the innate immune system, just like immune cells can. This shows that these changes may be a way for the pathogen to respond physically, which can also help the bacteria stay alive by controlling the immune response [8]. Bacteria often change their metabolism through horizontal gene transfer. This helps them notice changes in their environment and has more control over their metabolic pathways, especially in places where the environment is always changing [9]. They have evolved more ways to get important nutrients like glucose, free peptides, lipoic acid, and transition metals [10]. This is because many harmful bacteria have become less pathogenic over time. Also, some bacterial pathogens have amazing ways of figuring out how much oxygen is in their host and reacting to it, switching between fermentation and breathing as needed [11]. These metabolic changes make it possible for many bacterial diseases to get past the body's defense systems and nutritional limits [11].

2. Materials and Methods

The research methodology used in this study follows a comprehensive literature review and data analysis approach. Initially, secondary data sources were gathered from scholarly articles, journals, and credible online repositories, focusing on recent advancements and current challenges in combating antibiotic-resistant bacterial infections. Relevant studies on alternative antimicrobial approaches, such as the CRISPR-Cas system, antimicrobial peptides, and bacteriophage therapy, were identified and systematically analyzed to evaluate their effectiveness against multi-drug-resistant bacteria. Furthermore, to ensure a broad perspective, the review included an examination of past and emerging methods that specifically target bacterial resistance mechanisms. Data were synthesized qualitatively, identifying trends, success rates, and limitations in alternative treatments. This method enabled the identification of gaps within current research and the potential for future innovations in combating bacterial infections. The data interpretation emphasizes integrating alternative therapeutic strategies as a complementary approach to traditional antibiotics, presenting new avenues to address global health threats posed by antibiotic-resistant bacteria.

3. Results

The importance of immune resistance against bacterial infections

The immune system keeps the host from getting sick by using multiple layers of protection that get more specific over time. Pathogens, like bacteria and viruses, can't get into a body because of physical barriers [12]. The innate immune system responds right away, but it is not very specific if a pathogen gets through these defenses. All animals have defense systems that work on their own. The innate reaction is vertebrates' first line of defense against pathogens. If pathogens are able to get past this, the adaptive immune system steps in and protects them [13]. This better reaction is stored in the immune system as an immunological memory after the pathogen is gone. This lets the adaptive immune system launch faster and stronger attacks the next time it comes across this pathogen [14].

The immune system and infection resistance mechanisms

Definition of immune response

The immune reaction is how the body stays safe by fighting off external threats. It includes ways to defend against most germs and very specific ways to deal with a certain problem. This defensive reaction is either very specific, learned through adaptation, general, or natural. This is how the body always defends itself against pathogens, which are often our first line of defense against anything foreign. A few of these natural defenses are the skin barrier, saliva, tears, different cytokines, complement proteins, lysozyme, bacteria, and many cells, such as neutrophils, basophils, eosinophils, monocytes, macrophages, the reticuloendothelial system, natural killer (NK) cells, epithelial cells,

endothelial cells, red blood cells, and platelets [15]. It is the adaptively learned immune reaction that stops germs from getting into the body. Immunoglobulins and cytokines are two things that cells make. It usually looks like this:

- Specialization: A certain pathogen, immunogen, or antigen is the triggering mechanism.
- Heterogeneity: Indicates the generation of millions of distinct immune response (antibody) effectors against millions of invaders.
- Memory: The immune system can not only identify the infection on its second encounter but also mount a more potent and quick reaction. [16,17].

Inflammatory immune responses, which prevent infections from entering the body through the skin, lungs, or stomach, are instances of innate immunity. Macrophages await pathogens in the subepithelial tissues if they manage to pass past the epithelial layers. As they attempt to consume them, these cells will produce cytokines that intensify the inflammatory response [15, 16].

Because of this, active immunity is gained when the immune system reacts to an antigen. Passive immunity is when immune cells or antibodies from a person who has been vaccinated are transferred to another person. Through its ability to distinguish between itself and external antigens, the immune system has developed to preserve homeostasis. Absence of this specificity results in an autoimmune reaction or illness [16, 17].

Mechanism of immune cells in fighting bacteria

Macrophages use reactive oxygen species and lysosomal enzymes to kill the germs they eat. These cells make cytokines, which protect the body by sending more white blood cells to the spot of the infection. The body's natural defense against bacteria is made up of two parts: sending monocytes to inflamed tissue to turn into macrophages and activating neutrophils to eat bugs. They can deliver the antigen to a class of specialist cells that, having taken it in and processed it, have already assembled the immune response. Owing to the release of their grain contents, eosinophils guard against parasite infections [18, 19].

Antibody-dependent cell-mediated cytotoxicity (ADCC): is a method of killing cells in which killer cells expressing Fc receptors locate target cells by using certain antibodies [19].

Affinity maturation: These days, an increase in the average affinity of antibodies is mostly seen after an immune response.

Complement system: Blood proteins function in concert to tear down cell membranes, regulate inflammation, and activate phagocytes. IgG and IgM (the traditional pathway) or components B, D, H, P, I, and C3, which form a distinct pathway known as C3 convertase, can activate the system [20].

Anergy: It is the inability of stimulation with a possible immunogen to elicit an immunological response [20].

Antigen processing: An antigen is changed into a form that lymphocytes can identify. This is the first thing that sets off an immune reaction [21].

Antigen presentation: It's the process by which some immune system cells put antigenic peptides and genes of the major histocompatibility complex (MHC) into their cell membranes so that lymphocytes can recognize them [20, 21].

Apoptosis: Apoptotic bodies are formed and nuclei split apart during planned cell death.

Chemotaxis: Cells move in response to changes in the quantity of chemotactic factor.

Hypersensitivity reaction: An immune reaction powerful enough to cause more tissue damage than the Bacterial or antigen that set off the reaction. Check out allergic bronchial asthma and systemic lupus erythematosus as two examples of type I and type III hypersensitivity responses [22].

Inflammation: Some responses send immune system chemicals and cells to the site of an infection or harm. It got more blood, white blood cells could pass through the endothelium, and the valves were more open [22, 23].

Opsonization: The mechanism facilitates absorption by coating the antigen with opsonins (IgG and C3b) [23].

Phagocytosis: the process by which phagosomes in the cytoplasm are enclosed around an antigenic substance or microbe by cells (e.g., macrophages and dendritic cells) [24].

Immunological tolerance: a state of certain immune system inactivity [24].

Strategies to stimulate the immune system

There are different ways for internal bacteria to stay alive and grow inside host cells without being killed by phagolysosomes. Depending on the species, bacteria can grow either inside certain parts of cells or in the cytoplasm, which is the empty space inside cells. Our study shows that the cytosol is a place where *L. monocytogenes*, *S. dysenteriae*, *B. anthracis*, rickettsial species, *Burkholderia (B.) pseudomallei*, and *F. tularensis* can all multiply. It takes longer for *B. pseudomallei* and *F. tularensis* to leave the endosome than for *L. monocytogenes*, *S. dysenteriae*, *B. anthracis*, and rickettsiae to leave the early phagosomeal vacuole [25]. As phagosomes carrying F. tularensis develop into late endosomes, they become acidic and then break apart, letting the bacteria enter the cytoplasm [26]. But B. pseudomallei is freed from late endosomes once the phagosome and early endosomes join together [26]. F. tularensis can move back into autolysosome-like vesicles [26] and copy itself in the cytoplasm [26]. Some bacteria use vacuoles, which are hollow sacs, to make copies of themselves. *L. pneumophila* deviates from the endocytic path and grabs vesicles from the endoplasmic reticulum (ER) to create inclusion vacuoles coated with ribosomes. Bacteria can grow in these spots [26]. In order to make room for replication, *C. pneumonia* brings in vesicles made in the Golgi and stops the phagosome from joining with early endosomes [26]. On the other hand, *M. tuberculosis* lives in early endosomes and stops the vesicle from connecting to the lysosome and turning acidic enough to copy [26]. But when the late endosome and lysosome join together, *C. burnetii* grows in acidic spaces that look like phagosomes [26, 27]. *A. enterica S. ssp*. enterica eventually copies itself in late-endosome-like vesicles that take in lysosomal proteins but don't join with the lysosome to keep the germs from being broken down. These vacuoles carrying *S. enterica* float and stick to the nucleated microtubule-organizing center (MTOC) [28, 29]. Figure 1 shows a list of both extracellular and intracellular bacterial diseases, along with the immunity systems that help protect us, which we will talk about next.

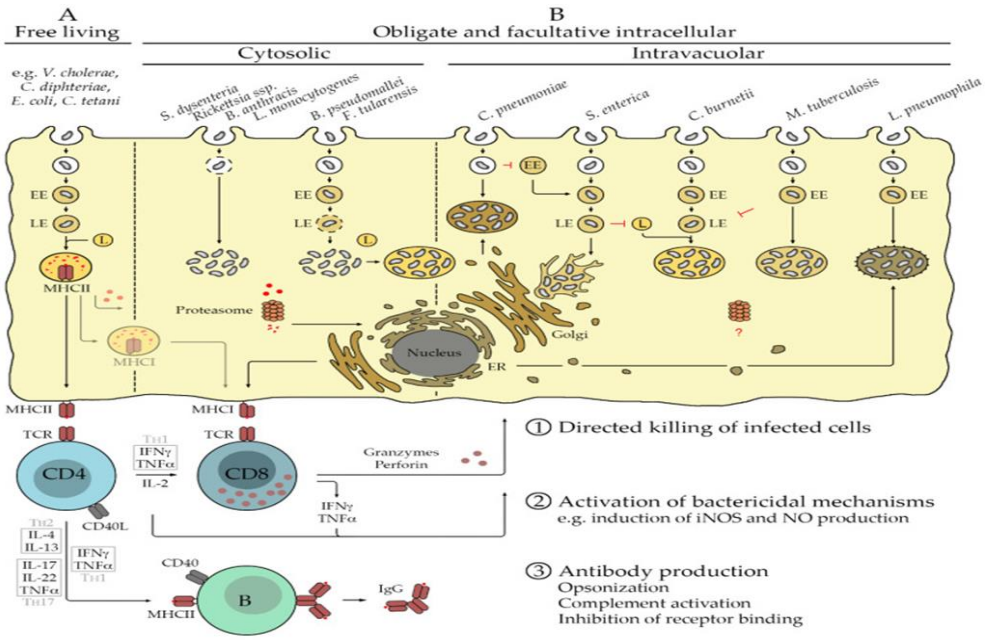

Figure 1: Extra- and intracellular bacteria and immune response

The Critical Demand for New Vaccines Against Antibiotic-Resistant Bacterial Infections

Vaccines are known to play a big part in keeping people from getting infectious diseases and dying or being hospitalized because of them. Vaccines could have avoided about a quarter (21.7%) of the 5.3 million deaths among children under 5 years old in 2019 [30, 31].

Other childhood diseases like diphtheria, pertussis, tetanus, meningococcal disease, pneumococcal sickness, have also been seen to be less common in places where vaccination rates are high [32].

Antibiotics are often used to treat illnesses caused by bacteria. However, a lot of germs have become resistant to antibiotics, which is a very big problem.

In the US and Europe, *A. baumanii*-related infections account for around 2% of all illnesses [33], whereas in the Middle East and Asia, the incidence is twice as much [34]. About forty-five percent of isolates of *A. baumanii* are reportedly not drug-sensitive. High on the priority list are also enterobacteria, enterococci, *S. aureus*, *H. pylori*, *Campylobacter species, Salmonellae, N. gonorrheae, S. pneumoniae, H. influenzae,* and *Shigella* species. The WHO website (accessed May 4, 2022) gives figures on how common diseases caused by resistant germs are around the world. reveals specific U.S. statistics that the Centers for Disease Control and Prevention (CDC) keeps track of and makes public; clear numbers from other countries are sparse [34]. The number of antibiotic-resistant bacterial infections in this nation is impressive. *A. baumanii, C. difficile, Enterobacterales, N. gonorrhea, H. pylori, Enterococci, P. aeruginosa, Salmonella spp., Salmonella Typhi, Shigella, S. aureus, S. pneumoniae,* and *M. tuberculosis* are some of the most common ones. Streptococcus Groups A and B that are not easily killed with antibiotics are also a worry. That's why the CDC has put *M. genitalium* and *B. pertussis* on a watch list [35].

Infection rates with specific bacteria may differ widely and be much higher in some countries than in others, especially in the less developed ones. The evolution of resistant bacterial diseases may follow the same logic. Furthermore, although many other bacterial infections undoubtedly afflict a large number of people globally, their prevalence is unknown. This is due in part to the fact that many of these infectious diseases are not reportable and in part to their underdiagnosis or (re-)emergence. Examples are the growing frequency and geographical spread of rickettsial illnesses worldwide. Major causes of severe meningitis and meningoencephalitis with significant death rates in the Asia-Pacific region are infections with R. typhi (endemic typhus) [36].

Also, there aren't many drugs that work against all types of bacteria that cause disease. In these situations, there aren't many other options. To give you another example, rickettsiae only reacts to a few antibiotics. Doxycycline is the best one to use to treat it. This is why it is rather concerning if doxycycline resistance develops, and there are indications that doxycycline-resistant. Doxycycline allergies are very difficult to treat [36, 37].

Moreover, certain bacteria are considered possible bioweapons, such as *B. anthracis* and rickettsial species (R. prowazekii and R. rickettsii). Antibiotic resistance may be genetically engineered into these particular species, making vaccines against these and many other bacterial diseases critically needed. Most vaccines that have been produced and are in use today are against extracellular bacteria. With the exception of a Q fever vaccine unique to Australia, intracellular bacterial vaccinations are not very frequent [38, 39, 40].

Varieties of Bacterial Immunizations and the Challenges in Vaccinating Against Intracellular Bacterial Agents

These days, bacterial illnesses are protected against by four primary types of vaccinations. Among these are polysaccharide conjugate vaccines, toxoid and subunit

vaccinations, live attenuated bacterial vaccines (LAV), and whole cell antigens (WCA). Furthermore, we will discuss current advancements in new technology and experimental vaccination techniques that could also be effective in immunizing against diseases brought on by bacteria that reside inside cells. The use of nucleotides (DNA, mRNA, viral, and bacterial carriers), bacterial ghosts (BGs), and live recombinant microbes as examples is one. Nanoparticles (NPs) that are related to antibodies or nucleotides are another type. Figure 2 shows a summary of the tried and tested ways to protect against bacterial diseases. These methods are talked about in more detail below [41].

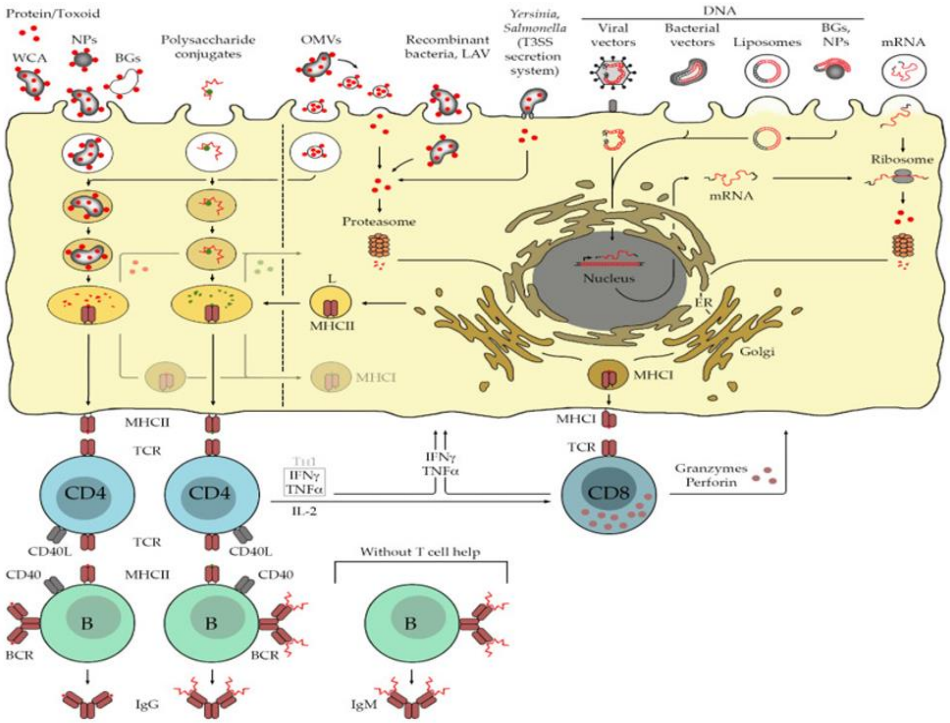

Figure 2: Applied and experimental bacterial vaccines

There are a number of well-known and widely used bacterial vaccines on the market today. These include live attenuated vaccines (LAV), recombinant proteins with toxoids, polysaccharide/protein conjugates, and WCA vaccinations [41, 42]. Getting a vaccine against modified proteins or toxins, bacterial ghosts (BGs), or WCA mostly turns on CD4+ T cells and prepares protein parts for display through MHCII. On top of that, CD4+ T cells help antigen-specific activated B cells make IgG antibodies that bind very well. This makes you remember something. This is the part of the protein that CD4+ T cells recognize when polysaccharide/protein conjugates are present. Without help from T cells, this makes B cells make IgG antibodies that bind the polysaccharide very well instead of IgM antibodies that bind it less well [43]. Most of the time, these methods don't work to activate cytotoxic CD8+ T cells, which are needed for vaccination against germs that live inside cells. Antigens that are acknowledged by CD8+ T cells are primarily cytosolic proteins that have undergone proteasome degradation prior to being presented via MHCI [43, 44]. Getting immunogens into the cytoplasm of host cells is one of the hardest parts of making vaccines work against intracellular bacterial pathogens.

This may be accomplished via the T3SS translocation mechanism present in Salmonella and other bacteria, DNA or mRNA vaccines, viral or bacterial vectors, and OMVs. Both MHCII and MHCI molecules deliver antigens to activate CD4+ and CD8+ T cells in the course of an OMV and LAV immunization. In the meantime, it is unknown how MHCI presents with OMV vaccination. It can be the result of cross-presentation, in which lysosomes combine with vesicles expressing MHCI, or proteins are released from the lysosome into the cytosol [45]. Proteins may be released into the cytosol by LAV. Through the MHCI display route, the proteasome may also be able to break down surface

proteins. Adenoviruses and modified vaccinia virus Ankara (MVA) are the main types of viruses used in vaccines [44]. Adenoviruses copy themselves by putting their double-stranded (ds) DNA sequence into the nucleus of cells that are not active.

When virus-made mRNA products get to the inside of affected cells, ribosomes read and process them [43]. On the other hand, MVA has a duplication cycle that is only found in the cytoplasm and a dsDNA genome. Proteins are only expressed in the cytoplasm of infected cells. This has also been seen with bacterial vectors that carry plasmid DNA with eukaryotic expression cassettes to help make immunogens. You can also raise the production of proteins in the cytosol by putting mRNA or DNA straight into target cells. DNA has to go to the nucleus of the target cell to be copied, but mRNA goes straight to the cytoplasm to be translated into proteins. Virus drivers speed up this process most of the time [45, 46]. And last, one experimental method to introduce proteins into the cytosol of target cells is to use recombinant attenuated bacteria, such as Salmonella, which contain a T3SS translocation mechanism. With this technique, proteins may be injected directly and actively into the cytoplasm of the target cells. Making a recombinant vaccination usually requires knowledge of the immunogenic components of the pathogen, with the exception of WCA and LAV [46].

Antibiotic resistance and existing challenges

The spread of antibiotic resistance

An antibiotic stops the growth of bacteria when it works well with its target. There are only two things that need to happen for this interaction to happen: the antibiotic must be able to recognize the target, and there must be enough of the antibiotic at the target to effectively stop its activity [47]. At that point, all resistance mechanisms either change the target or make it harder for the free drug to get to the target. It's important for antibiotics to get through different layers of bacteria in order to do their job. Isoniazid works by being turned on by an enzyme inside the cell. Genes that code for transporters, targets, or proteins that turn on the pre-antibiotic can be changed to make the cells resistant. These ways of fighting the active antibiotic are called "passive mechanisms of resistance" since they don't change the antibiotic itself. Most of the time, HGT does not give resistance when mutated genes are transferred. One exception is changes in topoisomerases in *Streptococcus pneumoniae*. This means that clonal growth is the main thing that causes mutation-acquired antibiotic resistance to spread [48, 49]. Apart from these processes, the amount of active antibiotic can be decreased by means of its modification by enzymes that inactivate antibiotics or by its efflux through multi-drug efflux pumps. Considered "active mechanisms of resistance," these components can be introduced in another host to impart resistance, meaning that HGT or clonal expansion can both disseminate this kind of resistance. As Qnr quinolone resistance factors, things that change the target or keep it from being affected by antibiotics can also be seen as "active mechanisms of resistance" that can be passed on through HGT [50]. Along with these well-known things that make bacteria resistant to antibiotics, new study has shown that a number of things that are important for bacteria's basic biological processes may also make them less able to fight off antibiotics [51].Since antibiotics have been used in the wrong way, more people have genes that are not affected by antibiotics.

These genes can be found in hospitals and in the surroundings besides being found in hospitals [52, 53]. The first thing that doesn't make sense about this enrichment is how ecologically connected things are. For instance, a resistant gene found in a type of bacteria that only grows underground probably won't be passed on to a disease that affects people. This is also true for gene exchange groups; being a part of these communities makes it more likely for microbiome members to share a resistant element [54]. The presence of an already-acquired resistance gene in the community is the second thing that makes it hard for a new resistance gene to be passed on. This is called the "founder effect." If there is already a resistance gene in the community, the drug that the gene makes bacteria resistant

to will not stop the growth of bacteria that carry the gene. Because of this, new genes that are resistant to the same antibiotic will not be acquired if there is no selective pressure. The costs of being fit are a third thing that stops the spread of a certain resistant gene [55]. Getting resistant can come with a fitness cost that is sometimes unique to the gene or trait in question [56, 57]. The populations will only keep the resistance elements that don't cost too much in terms of fitness or for which it's easy to make compensatory changes [58]. The resistance gene can be better maintained and then spread if it is linked to other factors that can be co-selected. These factors could be other resistance genes, factors that affect virulence, or factors that give an ecological benefit [58].

Alternative and innovative strategies

Antibiotic resistance in bacteria is being driven worldwide by a number of processes, both inherent to the biology of a pathogen and recently identified, by increasing selection pressure from the misuse and abuse of antibiotics in the medical, veterinary, and agricultural sectors. Now days, at least four pathways of bacterial drug resistance are well known (Figure 3).

Enzymatic degradation of antibiotics, for example, bacteria making β-lactamases that break down medicines in the β-lactam class;

Modification of the antibiotic target, This means that the target moves, making it impossible for the drug to attach to the place where it works.

Control of drug entrance via modification of the membrane and porin molecules in the bacterial cell wall;

Activation of efflux pump systems those things can push medicines out of the cell before they can reach their targets.

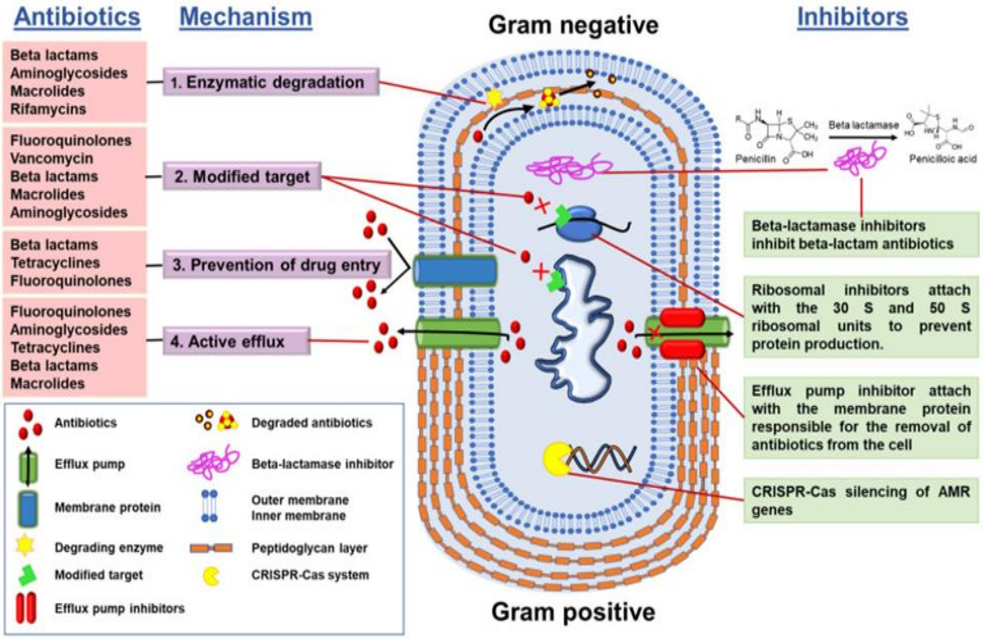

Figure 3: Classes of antibiotics, mode of action, and inhibitors.

The prescription of two or more antibiotics at the same time is called antibiotic combination therapy. The goal is to get synergistic action that may be better for treating patients. When two antibiotics are mixed in the right amount, they work better together. This is known as "antibiotic synergy." A few of the mixtures are antibiotic + antibiotic, antibiotic + pesticide, antibiotic + small drug, and antibiotic + enzyme inhibitor. Remember that this idea of a combination has been tried for many years to try to find one that works from in vitro to in vivo and finally to clinical combination. The aminoglycoside and β-lactam plus β-lactamase inhibitor mixtures are two that have worked [59].

Antibiotic Combinations

Antibiotic Combination with β-Lactamase INHIBITORS

Some medicines, like sulbactam, clavulanic acid, and tazobactam, can make β-lactam antibiotics work again against diseases that are resistant to them. This is because they work with β-lactam antibiotics. A β-lactam/β-lactamase inhibitor (BLBLI) combo is what this kind of mix is called. Bacteria that are resistant to newer β-lactam antibiotics (carbapenem resistance) or combinations of antibiotics that do not use carbapenem have been helped by new Bis antibiotics like avibactam, relebactam, taniboractam, tazobactam, vaborbactam, enmetazobactam, and zidebactam [63]. For example, the aztreonam-avibactam mix works well against NDM (New Delhi metallo-beta-lactamase), VIM (Verona Integron-encoded metallo-β-lactamase), and germs that make IMP (inactivate imipenem). It is also used in hospitals to treat Enterobacteriaceae (recently called Enterobacterales) that carbapenem doesn't work on. In contrast to avibactam, metallo-β-lactamases do not break down aztreonam [64]. The reason for this is that carbapenem antibiotic-degrading metallo-β-lactamases are very common. Also, when fourth-generation broad-spectrum cephalosporins like cefepime are mixed with enmetazobactam, their effectiveness is recovered [65].

Combination of Antibiotics with Biocides

Arms and antibiotics and killer bacteria In concert Though it seems like it would be beneficial, antibiotics and biocides (disinfectants, antiseptics, and preservatives) used together haven't received much study [66]. A study looked at what happens when you mix antibiotics and biocides with P. aeruginosa. It used three antibiotics and seven biocides that all worked in different ways. The results showed that the effects could range from working together to working against each other [67]. Since the way antibiotics and biocides work together in the body showed a lot of promise for stopping AMR with present drugs, more research should be done to see what effects this combination might have on evolution.

Medicinal Plants and Phytochemicals

Different ways for plants to protect themselves from getting infections have evolved over time. Phytochemicals, which are natural substances found in plants' fruits, seeds, roots, leaves, and stems, are used in these methods [68, 69]. Plants also make many different kinds of chemicals with different shapes and sizes. Each of these helps the plant fight germs in a different way [70]. How effectively compounds from plants could function as potential medications interests scientists and those in the pharmaceutical business. They have investigated many plant oils and extracts as potential agents to change antibiotic resistance and fight bacteria [71]. Screening programs employ computational, ethnopharmacological, and random approaches for this sort of novel drug discovery [72].

Small Molecules-Improved Chemical Entities (ICE)

The foundation of modern antibiotic medicines are natural substances and their semi-synthetic derivatives, such as aminoglycosides, tetracyclines, macrolides, and β-lactam antibiotics. But the spread of germs that are resistant to multiple drugs is currently threatening the effectiveness of these medicines. Luckily, genetics and cutting-edge technology make it possible to look at old chemical scaffolds again, bring natural product projects back to life, and finally find new ideas. Modern direct-acting small molecules might be whole novel medications with distinct targets and modes of action, or they can be improved versions of previously developed antibiotics. AMPs, which are both natural and manufactured, are the newest small molecules. Natural chemicals and inhibitors, like LpxC and LpxA, are the other two groups [73, 74].

Essential Oils

When EOs touch Gram-negative bacteria, they mostly damage the cell wall and stop the efflux pump, which can lead to some AMR [75, 76]. Stopping the production of the peptidoglycan layer in bacterial cell walls by binding to PBPs in the case of Gram-positive

bacteria is another known way they work [77, 78]. New discoveries in genomics and proteomics have shown that EOs can stop biofilm development and quorum sensing (QS) production, as well as raise the expression of oxidative stress proteins [79]. When used alone, with other antibiotics, or in combination, eos was successful at killing a variety of pathogens, including multidrug-resistant (MDR) bacteria [78, 79, 80]. We need to do more in-depth research to find and name new EO chemicals that could be used in clinical practice one day. Cinnamon bark [81, 82], lavender [82], peppermint [83], and tea tree oil are EOs that have been studied a lot [81, 82, 83]. Among the other investigated essential oils are black pepper, lemongrass, eucalyptus, and palmarosa [84]. Moreover, it appears essential in the modern world to employ antibiotics as growth boosters in the production of livestock and aquaculture. In such cases, EOs are "green" and hold promise as substitutes for the antibiotic growth promoters that are presently used by cattle and aquaculture businesses [85]. The ability of essential oils to preserve food is also widely known; in fact, several EOs have been studied as food preservatives to extend the shelf life of fruits, vegetables, dairy products, meat and meat products [86]. Combining EOs with nanoparticle technology could help, to some extent, increase their chemical stability and solubility [87]. EO efficacy may be maximized and toxicity may be reduced by nanotechnology, allowing nano-encapsulated EOs to be delivered to the desired place. It is becoming more and more crucial to know how the components of crude essential oils interact, discover new ones, and get EOs scientifically recognized as antibacterial agents [86, 87].

RNA Silencing

RNA silence is a way that could be used to make new medicines as well. In 1985, RNA silence was first talked about. Scientists have found a link between it and the control of many genes. To stop translation, the method uses cis and trans sequences that can be undone by meeting up with regulatory areas on a single m-RNA (antisense sequence). To make things even better, cis-antisense sequences are sometimes copied from the opposite strand at the same DNA location or close to regulatory regions on a single RNA. Trans sequences come from genetic sites that are far away and make up most of a normal antisense sequence. Genes that make synthetic antisense sequences might be able to stop the translation of enzymes that help bacteria fight drugs. By using RNA silencing, one can make very sensitive antimicrobial screens, find out how strong those targets are, and find new chemicals that kill germs [88].

CRISPR-Cas System

A lot of the time, CRISPR-Cas (clustered regularly interspersed short palindromic repeats-CRISPR-associated protein) keeps bacteria safe from plasmids, phages, and other foreign genetic material [89, 90]. It does this through processes that are stored in DNA, RNA, or DNA itself. CRISPR-Cas is a tool for changing DNA [90, 91] that could lead to new ideas, such as medicines that are made to fit a person's specific needs. These gene-editing techniques can lower or get rid of antibiotic resistance in bacteria by changing genes in a big, focused, and specific way [89, 90, 91, 92]. They can also find new ways to treat MDR diseases. CRISPR-Cas systems can tell the difference between good and bad bugs. They might also be able to make bacteria more sensitive to an antibiotic by taking out plasmids that carry genes for antibiotic resistance or by taking out AMR genes from bacterial populations and markers that make bacteria harmful [93].

Antimicrobial Peptides (AMP)-Including AMP + Antibiotics Combination

One way to make new antibiotics that work well is to use AMPs, which can be used by themselves or with other antibiotics [94, 95]. There are 10 to 50 amino acids in AMPs found in nature. They have a cationic charge overall and are amphipathic. AMPs have the same or even better antimicrobial action than traditional antibiotics [95, 96]. AMPs are everywhere and can be found in nature in many places. For the most part, AMPs are part of the natural immune system in many land and water animals. In nature, AMPs that come

from bacteria are part of the cell defense system that helps bacteria fight off harmful invaders like bacteriophages and other molecules. This process changes inflammation and makes killing pathogens more effective [97]. Bacterial AMPs also give bacteria "space" in complex microbial groups that share the same biological niches [98, 99]. AMPs kill a lot of different germs, both Gram-positive and Gram-negative [100]. They work like regular antibiotics. Once AMPs enter a bacterium's cell wall, they kill it even more by targeting protein production, nucleic acids, and/or ending the production of the cell wall and membrane [99, 100].

Nanoparticle Based Strategies

NPs are particles that are between 1 and 100 nm in size [101]. NPs are being used more and more to stop bacteria from growing. They are being used to coat medical products, stop bacteria from growing on implantable devices, and deliver antibiotics. They can also be used indirectly as antibacterials [102]. Some bulk metals are known to kill both Gram-positive and Gram-negative bacteria. Other metals, on the other hand, only work when they are in the NP form [101, 102].

Three things may happen at the same time that NPs kill germs, but we don't fully understand how they do it yet. A few of these are the release of metal ions, oxidative stress, and non-oxidative processes [103]. Breaking down the outer membrane of bacteria and/or damaging the cell wall are some of the specific things that happen during these processes. Nanoparticles interact with parts inside and outside of cells, photocatalysis creates reactive oxygen species that damage bacterial structures, DNA synthesis stops, enzymes stop working, and energy transfer stops [104].

Utility of Monoclonal Antibodies against Pathogens

Treating infectious diseases is becoming more and more interesting with monoclonal antibody (mAb) therapy. Indeed, mAbs are an important and very specific way to study drugs. When you compare them to regular polyclonal antisera, they have the best tolerance and survival. In general, mAbs made to fight bacterial diseases go after surface-exposed antigens or released toxins that antibiotics don't yet target and probably won't be affected by current resistance mechanisms [105]. Since therapeutic antibodies have possible benefits over broad-range antibiotics, they are being studied as an alternate strategy in the fight to combat the worldwide danger of antibiotic resistance [106]. Beginning in the early 1900s, antibodies have been used to treat human illnesses. The narrow spectrum, adverse responses, and varying efficacy across lots made antibiotics quickly the preferred choice [107]. Molecular biology tools have made it possible to create therapeutic mAbs that are more effective, safe, and pure. This has made it possible for antibodies to be successfully used in the clinic [105, 106]. At the time, antibodies are mostly used to treat illnesses that aren't caused by bacteria. Only a few antibodies have been allowed to treat infections caused by bacteria [108].

4. Conclusion

Particularly, antibiotic resistance, or AMR, keeps emerging and expanding uncontrollably. This is related to several parameters rather than being a single problem. The local, national, and international levels of AMR need coordinated efforts and diverse partnerships. To effectively manage the use and sale of antibiotics for both people and animals, strong government resolve may be needed to create laws, make sure they are followed, and give regular educational updates based on scientific data. Antibiotic advertising that is unethical has to be stopped, and plans to stop overuse or improper use of antibiotics have to be put into place. Several new strategies have been investigated to improve antibiotic effectiveness by means of new targets and mechanisms such as editing, silencing, and inactivation of resistant genes. Crucially, the majority of the cutting-edge substitute techniques do not lead to antibiotic resistance. Thankfully, a lot of new directions are being investigated in order to counteract existing and new resistance, even

though it will take some years before we can assess their effectiveness both separately and in conjunction with the efforts of governments, institutions, and regulatory bodies.

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