Review Paper:

A Comprehensive Overview of Bacterial Antibiotic Resistance: Insights, Methods and Future Prospects

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Abstract

Antimicrobial-resistant bacteria have emerged as a significant contributor to global mortality and morbidity. Upon the initial introduction of antibiotics in the 1900s, it was believed that mankind had triumphed over germs. It was then revealed that the bacteria might acquire resistance to any administered medications. Many pathogenic bacteria possess the ability to develop resistance to specific antimicrobial drugs.

The primary causes of resistance include restricting drug uptake, altering drug targets, inactivating drugs and actively expelling drugs. These processes are inherent to the bacteria or are obtained from other microbes. Gaining further insight into these pathways would result in improved treatment alternatives for infectious disorders and the creation of antimicrobial medicines capable of resisting microbial resistance.

Keywords: Bacteria, Antibiotic Resistance, Review, Antibiotics.

Introduction

The advent of antibiotics led healthcare professionals to believe that the struggle against infectious illnesses had been victorious. With several bacteria developing resistance to various antimicrobial treatments, the conflict appears to have intensified in favor of the bacterium. Contagious illnesses are presently a significant source of illness and death globally. The World Health Organization (WHO) assessed that fewer respiratory illnesses, diarrheal illnesses, Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) and malaria rank among the top ten contributions to deaths and morbidity[3]. The emergence of antimicrobial resistance has substantially increased the prevalence of infectious illnesses and elevated healthcare expenditures.

Despite the extensive array of antimicrobial medicines available for infection treatment, proven resistance to them has emerged against all of them, often quickly after the approval of a new antibiotic. The WHO initiated a Global Action Strategy on antibiotic resistance in 2016 in response to these issues. Antibacterial substances can be categorized into classes according to their mechanisms of action[16]. The primary categories include chemicals that obstruct cell wall construction, disrupt the cell membrane, limit protein synthesis, impede nucleic acid synthesis and interfere with metabolic processes in microorganisms. Given the extensive array of systems, the research should possess enhanced control over living things[9]. Regrettably, inadequate management of antimicrobial drugs has contributed to the significant resistance problem the research currently confronts.

Factors contributing to the escalating resistance issue include heightened utilization of antimicrobial agents by people and pets and inappropriate prescription of antimicrobial treatment. The excessive utilization of several prevalent antimicrobial medicines by doctors arises from the selection of medication being influenced by a mix of affordability and minimal toxicity[4]. Inappropriate prescription of antimicrobial medications occurs, exemplified by the inappropriate initial prescribing of a broad-spectrum agent that is eventually ineffective against the illness's causative organism(s). The peril lies in people's overuse of medicines, resulting in the evolution of resistant microbes. Previous administration of antimicrobial agents increases a patient's susceptibility to infections caused by drug-resistant organisms, with individuals with the most significant exposure to antibiotics frequently being those afflicted with resistant bacteria[6].

Antibiotics have been used for years to treat or prevent livestock production diseases. Animal feed frequently incorporates antibiotics at concentrations varying from sub-therapeutic to full therapeutic doses, with the medicines derived from most antimicrobial families employed in humans. Evidence suggests that administering antibiotics to creatures leads to the emergence of antimicrobial-resistant microbes, which can be transmitted to humans who eat these creatures[13]. The resistant antimicrobial profiles observed in the animals correspond to the kinds and quantities of antibiotics administered. The transfer of antibiotic resistance from livestock to people can occur through multiple pathways, with the straight oral route constituting the predominant method (which includes consuming meat and ingesting excrement via infected food or water). A prevalent path is through direct human-animal contact[11].

The persistent rise in antibiotic resistance has resulted in a reduction in treatment alternatives for patients, along with a corresponding increase in illness and fatality rates. The research sees increasingly serious infections necessitating more comprehensive treatment and prolonged illness durations, frequently resulting in extended hospitalizations[8]. This has significantly escalated the healthcare expenses

related to these types of infections. The method has indicated that an optimistic projection suggests approximately 2.2 million individuals in the U.S. contract antimicrobial-resistant diseases annually, leading to more than 24k fatalities.

The expenses associated with these persistent infections range from roughly $7.2k to over $29.5k per person. Research indicates that the healthcare expenses associated with methicillin-resistant *Staphylococcus aureus* illnesses are over $18.5k per incident in the U.S., approximately €9.2k per case in Europe and above 100000 Swiss francs per incident in Switzerland. Diverse strategies for managing antibiotics have been proposed to mitigate the risk of resistance[19]. One approach entails employing a variety of antibacterial agents. This pertains to utilizing multiple pharmacological agents, either sequentially or simultaneously, ideally employing medications with distinct modes of action rather than administering a single drug.

Mechanisms of Bacterial Resistance Acquisition

The fast proliferation of Antimicrobial Resistance (AMR) in bacteria cultures cannot be ascribed to a singular cause[1]. It frequently arises from intricate procedures. It is essential to categorize antibiotics into subgroups according to their distinct mechanisms of action before examining the variables influencing resistance to these compounds.

This review focuses on the categories of medicines most directly associated with the emergence of resistant antibiotics. The primary modes of action of antibiotics involve suppressing various bacterial activities related to cell wall formation, the production of proteins, nucleic acid synthesis and metabolism pathways[15]. The primary causes of resistance include reduced drug uptake, modification of medicine targets, deactivation and medicine efflux pumps' activity (Figure 1). The way of action of various antibiotics is predominantly influenced by their structural characteristics and affinity for specific bacterial components; therefore, comprehending this process is essential for understanding the development of opposition to these illicit substances.

International assessments of resistance to antibiotics: Antibiotics are regarded as "wonder drugs" for combating bacterial infections and their creation and subsequent therapeutic use represent a significant milestone in the history of medicine. Antimicrobials have been used for years for therapeutic purposes and as a prophylactic precaution in other sectors including livestock management and farming[18]. AMR denotes the ability of bacteria and other microbes to resist the effects of a drug against which they were once vulnerable, enabling these pathogens to endure and proliferate. AMR is unavoidable as microorganisms undergo genetic modifications to counteract its detrimental impact. Resilience was first detected in staphylococci, microorganisms and bacteria; after introducing the first industrial antibiotic antibiotics in 1940, ampicillin-resistant *S. aureus* appeared in 1943. Once more, methicillin, a partially synthetic antibacterial similar to penicillin, was released to the marketplace in 1962 to address amoxicillin-resistant *S. aureus.* However, it developed resistance to aureus in the following year.

AMR has become a significant concern as antibiotic-resistant strains can proliferate. Over 72% of pathogenic microbes oppose at least one antibiotic, rendering AMR one of the most serious threats to public wellness, food safety and medical care. The 2018 Antimicrobial Resistance Risks Assessment by the Centers for Disease Control (CDC) indicates that over 2.9 million antibiotic-resistant diseases occur annually in the USA, leading to more than 36.2k fatalities[20]. A survey suggests that a child succumbs to an antibiotic-resistant pathogen every 9 minutes and over 51k infants are projected to perish from sepsis due to microorganisms resistant to commonly used antibiotics.

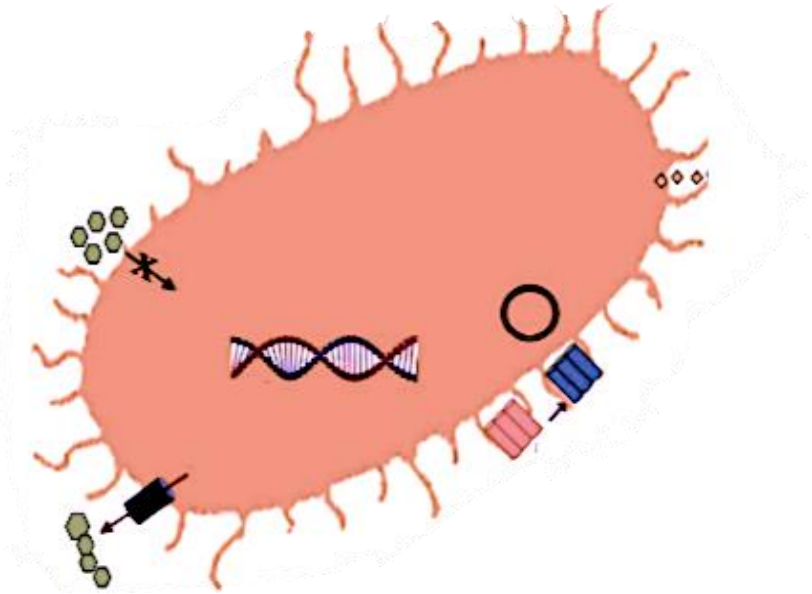

Figure 1: Process of antibiotic resistance in pathogens

Recent research findings on anti-tuberculosis (TB) drug resistance indicate that 3.62% of current TB patients and 19.2% of previously treated TB cases globally are anticipated to exhibit multidrug-resistant (MDR) or Rifampicin-resistant (RR) TB[17]. In 2019, around 559k instances of MDR/RR-TB were documented globally, resulting in 235k fatalities that year. In summary, antibiotic resistance poses a significant threat to civilization, resulting in approximately 750k deaths globally each year, with projections indicating that without effective intervention, millions of deaths will occur by 2040.

Antibiotics - past, present and future

Pre-antibiotic era: In the pre-antibiotic era, comprehension of germs and infectious illnesses was insufficient. The treatment methods and prevention of dissemination for these infectious illnesses were ineffective, often nearing epidemic proportions, leading to the deaths of millions. The breakout of the plague serves as an example of the dire circumstances faced by individuals in the pre-antibiotic era. The disease is caused by Yersinia bacteria, transmitted via contaminated livestock fleas[12]. It has been accountable for several pandemics in the past, such as the 'Justinian afflict,' which claimed nearly 110 million lives, the 'Black Mortality in the 14th century, resulting in more than 52 million fatalities in the European Union and the worldwide epidemic from 1898 to 1940, which led to approximately 15 million diseases. Influenza can be effectively treated with medicines.

In 1678, the finding of minuscule living things, termed 'animalcules,' laid the foundation for antibiotic research. In 1873, *Penicillium glaucum* possessed an inhibitory impact on microbial proliferation, allowing to cure a nurse's injuries with *P. glaucum* extracts; this led to the realization that bacteria are accountable for infections[7]. The findings of these two influential microbe researchers have propelled microbiology and the advancement of antibiotics into the contemporary day.

The early era of antibiotics: The inaugural antibiotic, mycophenolic acids, was extracted from *P. glaucus* and suppresses the proliferation of the bacteria. In 1909, a study identified Salvarsan (arsphenamine), the inaugural synthetic arsenic-based antibiotic, active versus *Treponema pallidum*, the etiological agent of disease.

Neosalvarsan was less hazardous and more efficacious in the management of syphilis than its predecessor Salvarsan. Due to the higher risk variables associated with arsenic, both medications were supplanted by Prontosil, a general-purpose antimicrobial sulfuric acid noticed in 1935, primarily utilized for treating wounded troops during World War I.

The finding established another milestone in the history of antibiotic study. A bacteriostatic effect is observed against various bacterial species by preventing the dihydropteroate synthetase (DHPS) protein in the folic acid route, thereby obstructing bacterial nucleic acid synthesis[2]. However, sulfuric acid was ultimately supplanted by the antibiotic as microbes developed resistance to the drug pronto due to changes in the DHPS enzyme. In 1930, the mold *Penicillium notatum* hindered the growth of the bacterium *Staphylococcus aureus* colony.

The fungus secreted a substance that inhibited microbes and they successfully isolated the active component, naming it 'penicillin,' the first real antibacterial. Yet, the research identified the structure of antibiotic G, the first antibiotic utilized in bacterial infections, in 1938, enabling effective purification and large-scale manufacture. The introduction of penicillin as a medicine in 1944 marked a significant advancement in antibiotic development. The study revealed the structure of amoxicillin using X-ray crystallography research in the same year, enabling its classification as the inaugural member of the B-lactam category of naturally occurring medicines[10].

Penicillin, antibiotics, mono bacteria and carbohydrates are classified as B-lactam antibiotics due to their shared B-lactam ring structure and standard antibacterial mode of action. B-lactam impedes the formation of cell membranes in Gram-positive microbes. Specific Gram-negative bacteria can synthesize β-lactamase proteins that degrade the drug's β-lactam rings, thereby conferring resistance to the germs. Semi-synthetic penicillin instruments, such as methicillin, oxacillin, ampicillin and penicillin derivatives, exhibited broad-spectrum activity against multiple Gram-positive and Gram-negative microbes.

Although ampicillin remains in medical usage, staphylococci resisted amoxicillin in 1962, rendering it obsolete in clinical applications. Methicillin-resistant *Staphylococcal aureus* (MRSA) was identified as the inaugural "superbug" in mankind[5].

The golden era of antibiotics: In 1940, a study initiated a new era in the discovery of antibiotics by isolating tyrothricin off the soil bacterium *Bacillus brevis*, which efficiently killed Gram-positive bacteria. Gramicidin has shown significant toxicity in people and is presently restricted to topical use. In the 1942s, the study investigated the antimicrobial abilities of soil bacteria, particularly Streptomyces spp. The study developed the Waksman paradigm to illustrate bacterial species exhibiting antagonistic interactions. The study identified numerous significant medicinal products through the research including actinomycin, neomycin, erythromycin, clavacin and fumigation.

Numerous antibiotics, such as actinomycin B, streptomycin and neomycin, remain in clinical utilization today. During that prolific era, nearly 22 families of antibiotics were identified from numerous varieties of bacteria and fungi. By Waksman's base culture tactics, countless pharmaceutical companies commenced employing rational screening for the discovery of novel compounds based on the proven

mechanisms that operate of antibacterial[14]. Regrettably, only a few novel antibiotic classes have been discovered and identified; no additional categories have been found in the past 50 years.

The rapid and straightforward advancement of various medicines over a short duration led to their excessive utilization. This and a stagnant antibiotic research stream since the 1972s have contributed to limited antibiotic development in clinical studies. Since the 1985s, about 1250 antimicrobial peptides, known as AMPs, have been identified from various sources including insects, plants and mammals; however, none has ever been used as medicines.

In summary, most of the drugs were produced during the heyday of antibiotic studies and after this era, primarily derivatives of pre-existing medicines were commercialized.

Present situation: Currently, antibiotics are being created in limited quantities, with only 5 of the 25 pharmaceutical businesses that engaged in antibiotic research during the 1980s, remaining engaged today. Most of the biggest drug manufacturers have since withdrawn from antibiotic exploration, which younger companies and the field of biotechnology companies now assume. A 2019 database indicates that merely 2 of the 50 novel antibiotic options in clinical studies for the US market were developed by major pharmaceutical firms while the remainder were pursued by research institutions and small to medium-sized enterprises.

Antibiotic-resistant bacteria are the primary source of this problem. In the initial phase of antibiotic utilization, resistant bacteria were present; a continuous influx of experimental medicines provided alternative treatments, making it straightforward to change therapies once resistance to a particular antibiotic emerged. The influx of antibiotics significantly diminished in the 1982s.

The most recent discovery and market introduction of a new antibiotic class occurred in 1988, whereas the last category of broad-spectrum representatives, namely fluoridation, was identified in 1982. Since then, there has been a scarcity of innovation in the field, with only a limited number of novel antibiotic classes in research that can effectively address existing levels of AMR.

Companies are encountering financial and regulatory obstacles due to resistance and insufficient comprehension of antibiotic production against resistant bacteria has led to substantial investment in scientific research, prompting pharmaceutical firms to reduce or to cease antibiotic growth. Researchers suggest the research is rapidly approaching a 'post-antibiotic era.' Antibiotic innovation is progressively on the rise once more.

In recent years, there has been an increase in investment in antibiotic research and illness diagnosis tools. Partnerships between colleges and biopharmaceutical businesses, such as new drugs, are advancing the development of novel antibiotics and diagnostics.

Investigations are ongoing into alternatives to antimicrobial agents including bacteriophages (viruses that eradicate bacteria) and peptides that fight bacteria. Notwithstanding these techniques' significance, their applications have specific limitations and have not yet been converted into medical equipment. They are a valuable adjunct to other medications and/or medicines.

Future approaches: Scientists are exploring innovative ways to re-conceptualize resistance, sickness and prevention dynamics. Whole Genome Sequencing (WGS) is a fundamental technique in drug development, facilitating the rapid identification of resistance mechanisms and the modulation of resistant bacteria. A promising approach is the recently identified Quorum-Quenching (QQ) technology, which interferes with microbial cell-to-cell interactions to inhibit infection by bacteria. Infection-causing or viral phage therapies have recently acquired prominence due to their superior efficacy compared to antibiotics, as they are non-toxic to host living things, particularly gut microbiota, reducing the risk of infectious diseases.

Phages have been utilized to combat infections with bacteria before antibiotics. They are now being re-evaluated as a viable option. Transformed monoclonal antigens represent the most rapidly growing category of biotechnology-derived compounds in clinical trials, facilitated by swift advancements in genetic decoding. Monoclonal antibodies or white blood cell infusions that target germs, hold potential for pathogen treatment, albeit at a substantial expense. A cohort of researchers employed X-ray crystallography to elucidate the three-dimensional structures of ribosomal pieces from *Staphylococcus aureus*, revealing distinctive structures characteristic of this type of bacteria that might help the development of ecologically friendly, novel, recyclable pathogen-specific pharmaceuticals.

Mechanisms of resistance

Antimicrobial resistance pathways are classified into four primary categories: (1) restricting medication absorption, (2) altering drug targets, (3) eliminating drugs and (4) active drug outflow. Innate resistance involves restricted uptake, drug deactivation and medication efflux, while acquired resistance pathways include medication target change, deactivation and efflux.

Due to structural changes, there is heterogeneity in the processes employed by Gram-negative bacteria compared to Gram-positive organisms. Gram-negative microbes typically employ all four primary mechanisms. In contrast, Gram-positive microbes less frequently utilize drug absorption limitation due to the absence of an exterior membrane and lack of capability for specific drug efflux processes. Figure 2 depicts the overarching causes of resistance to antibiotics.

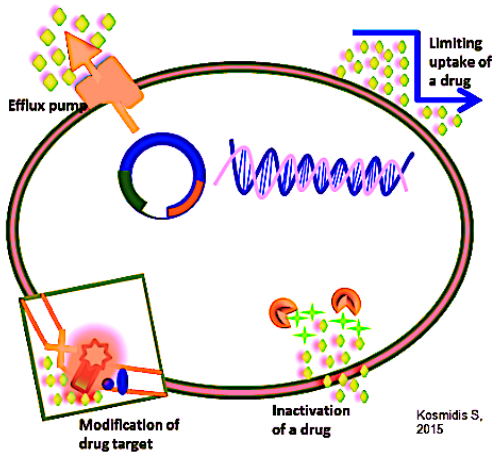

Figure 2: Antibody resistance analysis

Limiting drug uptake: As previously stated, there exists an inherent disparity in the capacity of bacteria to restrict the absorption of antimicrobial drugs. The architecture and activities of the layer in Gram-negative microbes create a barrier to specific types of chemicals. This confers intrinsic resistance to particular categories of substantial antibacterial drugs in those bacteria. The mycobacteria possess an exterior membrane characterized by a high amount of lipids, facilitating the entry of hydrophobic medications as the drug and fluoridation, while hydrophilic medicines encounter restricted access.

A prevalent occurrence in bacteria colonization is the development of a biofilm by a colony of bacteria. The biofilms have a dominant living thing, such as the one found in the lungs, or comprise of a diverse array of living things, as shown in the biofilm ecosystem of the gut's natural flora. Creating a biofilm by bacteria and viruses shields the germs from the body's immune response and offers protection against antimicrobial substances.

The viscous, adhesive nature of the biofilm matrices, composed of protein, polysaccharides and DNA from resident microbes, hinders the penetration of antimicrobial agents into the bacterium. Very elevated doses of the medications are required for efficacy. The bacterial cells within the biofilm are typically sessile, exhibiting a reduced metabolic rate and delayed cell division; thus, antimicrobials aimed at proliferating bacterial cells are mainly ineffective. A significant fact regarding biofilms is that the close closeness of microbe cells facilitates the transfer of genes horizontally. This indicates that disseminating antibiotic-resistant genes is more facile among these infection groups.

Alteration of pharmacological targets: The bacterial cell has numerous components that can serve as targets for antimicrobial medicines and there are various targets that bacteria can alter to confer resistance to these drugs. A route of resistance to ß-lactam medicines, predominantly employed by Gram-positive microbes, involves modifications in the structure and quantity of Penicillin-Binding Proteins (PBPs). PBPs are transpeptidases that participate in synthesizing peptidoglycan within the cell wall. An alteration in the number of PBPs, either an increase in those exhibiting diminished drug binding capacity or a decrease in those with standard drug enforceable, affects the volume of drugs that can be associated with that target. A structural alteration diminishes the drug's binding capacity or completely obstructs drug binding.

Resistance to medications that disrupt the metabolism, occurs through mutations in enzymes such as dihydropteroate synthase (DHPS) and dihydrofolate reducer (DHFR) which are integral to the folate biosynthesis pathway and through a surplus of resistance DHPS and DHFR enzymes, specifically sulfonamides (SM) targeting DHPS and trimethoprim targeting DHFR. SM and trimethoprim bind to their corresponding catalysts as they are structurally related forms of the organic substrates. These medicines exert their effects by inhibiting competitiveness by binding to the active sites of the kinases. Modifications in these enzymes typically occur at or around the active site, causing structural alterations that hinder the binding of drugs while permitting an organic substrate to bind.

Inactivation of Drugs: Bacteria deactivate pharmaceuticals primarily through two mechanisms: the breakdown of the drug itself or the transfer of a group of chemicals to the medication. B-lactamases constitute a substantial category of drug-hydrolyzing enzymes. Tetracycline can be deactivated by hydrolysis, mediated by the text gene. The inactivation of drugs through the movement of a chemical component predominantly involves the transfer of acetate, phosphoryl and adenyl compounds. A significant number of transfers have been found. Acetylation is the most often employed method and is recognized for its application against antibiotics, chlorine dioxide, streptogramins and fluorescent compounds. Phosphate and adenylation are primarily used against amino acids.

Pharmaceutical efflux: Bacteria contain chromosomally transcribed genes for efflux pumps. Specific genes are continuously stated, while others are triggered or overproduced in response to specific outside factors or the presence of an appropriate substrate; high resistance typically results from a mutation that alters the transport channels. Effective pumps generally expel hazardous substances from bacterial cells, with many of these pumps capable of transporting diverse molecules. The resistance capacity of several compressors is affected by the accessible carbon supply.

Most bacteria exhibit a variety of pumps that regulate efflux. Bacteria possess five primary families of efflux pumps that are categorized by structure and power source: the ATP-Binding Cassettes (ABC) relatives, the multidrug and toxic increase the extrusion relatives, the tiny multidrug-resistant group, the primary facilitator superfamily, as well as the resistance-nodulation-cell dividing group. Most of these outflow valve families consist of single-component valves that facilitate the movement of substrates through the cell membrane.

The family comprises of multi-component motors, predominantly located in Gram-negative microbes, that operate with periplasmic membrane-fusing proteins and outer membrane proteins to expel substrates over the entire cell exterior. Instances exist where other export family members collaborate with various cellular components to function as multicomponent exchangers in Gram-negative microbes. The group's first member functions as a tripartite pump to expel macrolide antibiotics.

Consequences of antibiotic resistance for specific bacteria: It is essential to ascertain the number of resistance mechanisms specific bacteria possess. A notable and significant instance of this is MRSA. The escalation in expenses associated with infections caused by MRSA has already been reported. The elevated costs are influenced by prolonged hospital stays, a rise in required tests and augmented medical and rehabilitative services rendered. The research must consider the effects of MRSA on mortality and morbidity, particularly substantial increases in illness sequelae.

The Methicillin-susceptible *Staphylococcal aureus* (MSSA) and MRSA strains share numerous virulence characteristics including surface molecules that facilitate colonization and release compounds that enable invasion and harm to host cells. These factors of virulence facilitate the bacteria in inducing many forms of illnesses. MRSA is notorious for causing infections of the skin and associated tissues, facilitating its transmission from one individual to another, particularly in hospital environments.

The death rate for cases of MRSA is believed to be 2-4 times greater than that for MSSA variants. Moreover, MRSA bacteria are often multidrug-resistant, constraining existing antibiotic treatments' efficacy. Numerous bacteria such as *Escherichia coli* and *Klebsiella pneumonia*, possess similarly broad weapons and are developing resistance to most existing antibiotic drugs.

Conclusion

Bacteria are highly versatile and adaptable organisms. To survive, they must be adept at managing harmful toxins. Free-living bacteria must possess the capability to endure harmful assaults and waste byproducts from other organisms. Bacteria infecting people include mechanisms to resist antimicrobial substances. The significant rise in antibiotic resistance necessitates the development of strategies to combat these infections. Regrettably, there is no straightforward (or inexpensive, likely) solution to this predicament. The research should rethink the approach to designing new antimicrobial drugs or to explore natural compounds for insights into potential solutions in this battle.

The processes outlined above are as diverse as the microorganisms themselves. These antibiotics encompass nearly all existing antibiotics and further mechanisms for resistance likely remain uncharacterized. The prognosis for combating germs appears grim. The Infectious Infections Society of America advocated the approval of 19 new antibiotics by 2030. Eight new medications received approval in 2020. However, only one of these constitutes a novel antibiotic. The average wait time for authorization for these medications was 6.4 years and the price per dose varies from approximately $2.3k to $4.7k. The research must exert considerable effort and must act swiftly to identify solutions for this urgent issue.

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