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The Problem of Pathogenic Resistance and the Relevance of Rational Antimicrobial Therapy in Medical Practice

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Abstract: Since they have prevented infectious diseases from killing millions of people, antibiotics are one of the most significant discoveries of the 20th century. Due to strong selection pressure brought on by the growing use and abuse of antibiotics throughout time, microbes have evolved acquired AMR to numerous medications. Human-to-human contact is the main way that AMR is acquired and spread both inside and outside of medical facilities. Through a variety of drug-resistance mechanisms, a vast array of interrelated healthcare and agricultural factors control the development of AMR. One of the main causes of AMR's introduction and spread has been the unchecked use of antibiotics in animal feed. Antimicrobial-resistant bacteria are now more common than ever before, posing a latent pandemic threat to global public health and demanding immediate action. There are few treatment options for illnesses brought on by bacteria that are resistant to antibiotics, which leads to high morbidity and fatality rates and substantial financial costs. The need for new, innovative antimicrobials to treat illnesses caused by resistant microorganisms is far greater than the availability of these drugs. AMR can be immediately contained by surveillance and monitoring, reducing the use of antibiotics in food animals and over-the-counter medications, providing access to high-quality, reasonably priced medications, vaccinations, and diagnostics, and enforcing the law. If coordinated cooperation is not urgently needed within and across numerous national and international agencies, a postantibiotic period may become more likely than a 21st-century apocalypse. The causes and contributing factors to microbial resistance, as well as important tactics to counteract antimicrobial resistance, are highlighted in this narrative review.

Keywords: Antibiotics, resistance to antimicrobials, resistance mechanisms, resistance drivers, resistance resistance strategies, treatment options.

Introduction. Antibiotics are regarded as the most amazing medical advancement of the 20th century and are the "magic bullets" for combating bacteria. Millions of lives are still saved from bacterial diseases thanks to the development of antibiotics, which has altered the paradigm of treatment. Antibiotics have undoubtedly been a boon to humanity; in addition to their medical applications, they have been used for decades in many developing and impoverished nations for a variety of objectives, such as animal husbandry and production as preventative measures. Microorganisms have acquired antimicrobial resistance (AMR) as a result of their growing use and abuse [1-4]. The concept of antimicrobial resistance refers to the potential of microorganisms like bacteria, viruses, fungi, and parasites to live and continue to proliferate in the middle of treatments designed to kill them. In addition to being challenging to cure, infections brought on by organisms resistant to antibiotics always have a higher risk of serious disease and even death. There are numerous types of antimicrobial agents including antibiotics, antifungal, antiviral, disinfectants, and food preservatives that either suppress the growth and multiplication of microorganisms or kill them. More often used than any other class of antimicrobials, antibiotics are a family of drugs specifically designed to fight bacterial infections and antibiotic resistance [5, 6, 7]. Bacteria try to become resistant to antibacterial medications in order to survive the pressures of environmental selection, making these medications useless. The widespread use of antibiotics, particularly in poor nations, gives bacteria plenty of chance to acquire antimicrobial resistance (AMR), which can have serious repercussions, such as significantly increased morbidity and mortality. The 21st century has seen an unprecedented rise in the incidence and prevalence of bacterial diseases resistant to antibiotics, which poses a concealed pandemic danger to global public health and calls for immediate action. Any nation can experience antibiotic resistance, and people of any age or gender can be impacted. AMR is one of the biggest risks to both global health and food security in the current environment [8-13]. In the context of prophylactic therapeutic procedures and actions, antibiotic resistance can have an impact on human health in terms of both treating and preventing infections. Antibiotic resistance has two effects on human health. First, there are direct treatment-related repercussions, which show themselves as problems and treatment failure. Second, there are indirect effects on prevention that impact the availability of advanced surgical techniques like transplantation, invasive procedures like intubation or catheterization, and effective cancer chemotherapy for immunocompromised patients. The increasing demand for such novel antimicrobials stands in sharp contrast to efforts to create new synthetic and naturally derived compounds for the treatment of illnesses resistant to antibiotics. Since the 1980s, major pharmaceutical corporations have mostly stopped working on the development of antibiotics [14-20]. The article highlights global alliances and collaborations while outlining efforts to address economic obstacles and encourage the development of antibiotics. Lastly, the essay discusses government-led efforts to combat antibiotic resistance, with a particular emphasis on the Middle East. It talks on the proactive steps regional governments, like those in Saudi Arabia and the United Arab Emirates, have made to counter this worldwide menace. A diversified strategy is essential in the face of antibiotic resistance. This article offers insightful information about the intricate world of antibiotic development, the difficulties with regulations, and the teamwork needed to guarantee that antibiotics continue to be useful instruments for preserving public health in the future [21-24].

The main purpose of the presented manuscript is to provide a brief overview of the problem of resistance to pathogens, which is one of the main global problems today, and the relevance of rational antimicrobial therapy in medical practice based on many years of scientific research.

A Chronology of Significant Antibiotic Findings and Resistance. Paul Ehrlich discovered the synthetic prodrug salvarsan and neosalvarsan in 1910 to treat Treponema pallidum-induced syphilis, which can be considered the beginning of the current antibiotic era. Later, salvarsan was gradually supplanted by prontosil, a sulfonamide prodrug that was found by bacteriologist Gerhard Domagk. In the 1930s, American microbiologist and biochemist Selman Waksman is recognized for conducting the first comprehensive analysis of soil bacteria and their capacity to produce chemicals with antibiotic activity [1,3,7,9]. He described an antibiotic as "a compound made by a microbe to destroy other microbes" and discovered several antibiotics from filamentous actinomycetes that live in the soil, including streptomycin, a commonly used antibiotic against tuberculosis. Sir Alexander Fleming, a Scottish physician and scientist, discovered penicillin from a mold called Penicillium rubens in 1928. This marked the beginning of the golden age of antibiotic research, which lasted until the middle of the 1950s. The "Golden Age" of antibiotic discovery is thought to have occurred between the 1940s and the 1960s, and the majority of the antibiotics currently in use were found during that time. Since then, the development of new antibiotics has gradually decreased, and drug-resistant bacteria have evolved in tandem [4-11]. Sadly, vancomycin-resistant strains of coagulase-negative *Staphylococci* (CoNS) were reported in 1979, two decades after the glycopeptide vancomycin was first introduced in 1958 as a rescue medication for treating infections caused by methicillin-resistant *Staphylococci*. Ten years later, vancomycin-resistant *Enterococcus* (VRE) was also described. Vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-intermediate *Staphylococcus aureus* (VISA) were identified in 1997 and 2002, respectively, indicating that vancomycin's effectiveness against *S. aureus* had declined. In order to treat cases of penicillin resistance, cephalosporin, a β-lactam antibiotic, was discovered in 1945 and put into clinical use in 1964. Since then, numerous generations of cephalosporins have been developed, the fifth of which is currently on the market. First of all, it was quite effective, particularly against gram-negative bacteria that produce extended beta-lactamases (ESBLs) [14-21].

Antibiotic Resistance Mechanism. Antibiotics primarily target the microbial cells' biology and physiology in an effort to slow or stop their growth. While some antibiotics target the protein synthesizing machinery by interacting with ribosomal units, which limits the antibacterial activity of certain germs, others break down the β-lactam and glycopeptide components of bacterial cells to destroy their cell walls or cell membranes. These antibiotics that target the cell wall include macrolides, tetracycline, linezolid, aminoglycosides, and chloramphenicol. The other antibiotics that target cells and interfere with the synthesis of nucleic acids include fluoroquinolones (FQ) and rifampin. The remaining antibiotics, such as folic acid analogs, daptomycin, polymyxins, and sulfonamides, disrupt metabolic processes and degrade the membrane matrix [3, 7, 11, 17]. According to research findings, when other antibiotic-sensitive counterparts are exposed to antibiotics, the evolution of antibiotic resistance determinants causes changes in them. Rather than antibiotics, quaternary ammonium compounds, the anionic detergent sodium dodecyl sulfate, ethidium bromide, the DNA-intercalating mutagen acridine, and uncouplers are among the chemically unrelated compounds that bacterial strains become resistant to due to multidrug resistance or related determinants. Therefore, the physiology of bacteria is more affected by multidrug resistance. They also offer resistance to bile acids and other metabolic products produced by the body. Antibiotic resistance is thought to result from certain biological processes in these bacteria that have not yet been determined [11-16].

Superbugs are microorganisms, such as bacteria and fungi, that have demonstrated resistance to antimicrobial drugs used to treat them. In actuality, superbug-caused infections have little to no accessible treatment. The acronym "ESKAPE" stands for *"Enterobacterales, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter.*" Currently, methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *enterobacterales* (CRE), carbapenem-resistant *Klebsiella pneumoniae (CRKP), ESBL-producing enterobacterales, vancomycin-resistant Enterococcus (VRE*), multidrug-resistant *Pseudomonas aeruginosa*, and multidrug-resistant Acinetobacter are among the most common superbugs in the world. Only after the extensive and prolonged usage of antibiotics to treat their ailments have multidrug-resistant bacteria surfaced [7-12]. For instance, after decades of antitubercular medication treatment, M. *tuberculosis* evolved into MDR-TB, a significant superbug that is now widespread in both developing and undeveloped nations. Gram-positive (e.g., *Staphylococcus epidermidis, Clostridium difficile*, and *Streptococcus pneumoniae*) and gram-negative (e.g., *Burkholderia cepacia, Stenotrophomonas maltophilia, Campylobacter jejuni, Citrobacter freundii, Enterobacter spp., Haemophilus influenzae, Proteus mirabilis, Salmonella spp.,* and *Serratia spp.*) bacteria are referred to as superbugs because they have been shown to be resistant to the majority of antibiotics. Because treatment options for these bacteria are severely limited, superbug infections increase the likelihood of morbidity and mortality. Additionally, these infections are linked to high treatment costs and prolonged hospital stays [20-24].

Negative Impacts of Resistance to Antibiotics. Since bacteria are becoming more resistant to conventional antibiotics, antibiotic resistance has become a global public health concern that necessitates the development of new medications. Resistance to new antibiotics is thought to be likely to develop and may shorten the time that these drugs are effective. Based on their clinical relevance and degree of resistance, the World Health Organization (WHO) has designated the following diseases as "ESKAPE": (A: *Acinetobacter baumannii, P: Pseudomonas aeruginosa, K: Klebsiella pneumoniae* or C: *Clostridium difficile, E: Enterococcus fecium, S: Staphylococcus aureus or Stenotrophomonas maltophilia,* and *E: Enterobacteriaceae*) [5-9]. Humanity as a whole is impacted by antibiotic resistance, which affects all facets of health, including wildlife, humans, and the environment. In fact, antimicrobials are often advised to treat viral infections in humans and animals and to increase meat consumption in the food industry. Antibiotics are released into the soil and water in large quantities by animal dung, industrial effluent, treatment plants, and organic wastes used for fertilization and irrigation of agricultural areas. When antimicrobial medications are discharged into the soil and aquatic environments, they encourage the development of bacteria that take antifungal medications and the spread of genes that are resistant to antibiotics [11-17]. When antibiotics fail to treat infectious diseases, a number of human-related factors (such as the therapeutic and non-therapeutic use of antibiotics and the disposal of antibiotic formulations into the natural ecosystem) cause resistance in the natural microbial flora, which in turn has an impact on human health. Since traditional antibiotics were unable to control the increasing number of bacterial infections in the human population, antibiotic resistance has become a serious health concern. Additionally, dose-related problems, inaccurate clinical disposal, and ignorance of the quantity of antibiotics required to treat illness have all contributed to the emergence of antibiotic resistance [7, 9, 10, 21, 22, 23, 25].

Antibiotic Resistance's Impact on Drug Development: The Difficulties. Current scientific and clinical developments in drug development address various therapeutic issues and are linked to therapeutic success. In order to address the public health emergency and the problem of antibiotic resistance in the population, numerous discoveries and advancements in antibiotics are in the works. The primary targets of significant antibiotic-based treatment approaches are both biofilm and planktonic infections. Antibiotics work to prevent bacteria from surviving or growing, including by preventing the production of vital proteins, DNA, and RNA, as well as the formation and upkeep of the cell wall. Many drugs are derived from compounds that microorganisms have been using for thousands of years to combat one another [1-4]. The assault tools that germs develop in this battle have sparked defense reactions because bacteria have evolved the innate ability to adapt and avoid the harmful effects of many conventional medications. To get rid of multidrug-resistant (MDR) bacteria, antibiotics may be required as a "last resort" or in large or numerous dosages. Microbe resistance makes treating microorganisms that live in biofilms more difficult and often calls for intensive physical removal of the biofilm, such as via vigorous exfoliation, in addition to high dosages of antibacterial medication. Cost issues for medication research and treatment have arisen as a result of the elevated risks of side effects, antibiotic resistance, and outcome failure [7-11]. Antibiotic research is no longer seen by the pharmaceutical industry as a wise investment. Since antimicrobials are often therapeutic and only taken for short periods of time, they are not nearly as helpful as drugs that treat major conditions like diabetes, mental disorders, asthma, or stomach reflux. Large pharmaceutical firms have hampered and negatively impacted medication development, which requires millions of US dollars to create new antibiotics for the future, because of severe antibiotic and multidrug resistance. A small number of antibiotics are in phase 2 or phase 3 of development, according to publications from the Infectious Diseases Society of America (IDSA) (2013) [12-19].

Discussion. The history of antibiotics has been a complicated one, with significant changes in both the historical and global evolutionary contexts. A medical revolution was ushered in with the discovery of antibiotics, which gave doctors powerful instruments to fight bacterial infections. However, as bacteria evolved defenses against the medications' effects, the extensive and frequently careless use of antibiotics sparked a rapid and alarming increase in antibiotic resistance. Reducing the overuse of antibiotics and looking for more focused methods to precisely target infections are urgent challenges in our day and age. To maintain the effectiveness of antibiotics, research must be focused on determining the possible causes of antibiotic resistance so that early warning systems and preventative measures can be developed [3-9]. Furthermore, pharmaceutical companies are currently concentrating more on developing treatments for Gram-negative infections than for methicillin-resistant Staphylococcus aureus (MRSA). The most likely explanation for this discrepancy is that, although MRSA is a major problem on a worldwide scale, the market for treating Gram-negative bacteria is smaller and somewhat more surprising because of how quickly resistance spreads. It takes a lot of time and money to find new antibiotics and develop them into medications. It takes between 800 million and 1 billion dollars to create a new drug, and it frequently takes over a decade for it to make it to the lab. Given how urgently we must now address antibiotic resistance, looking at alternatives to antibiotic therapy is a novel tactic [11-14]. Researchers and medical professionals are looking closely into the growing threat posed by drug-resistant microorganisms. The treatment of antibiotic resistance has recently evolved through the use of a variety of treatments, such as combinatorial medicine approaches, bio-nanotechnology techniques, and others. The antimicrobial resistance epidemic now poses a severe danger to the clinical efficacy of the currently available medicines and their prescribed therapies. Because it impacts the social, economic, medical, and ecological sectors, the problem has multiple dimensions. In the absence of the development of new generations of antibiotic medications, appropriate use of presently available antibiotics is necessary to ensure the long-term availability of a viable treatment for infections [1, 11, 12, 13-17]. When fighting bacterial antibiotic resistance, it is crucial to take into account the safety, effectiveness, and economic feasibility of popular alternative medicines in contrast to antibiotics. In the end, it relies on the particular treatment and the bacterial illnesses that are being addressed. Phage treatment, which uses viruses called bacteriophages to infect and kill bacteria, is one such alternative therapy. High specificity for bacterial strains, possible reduced toxicity in comparison to antibiotics, and the capacity to adjust to changing bacterial resistance are only a few benefits of phage therapy. However, it has issues with scalability in commercial manufacturing and regulatory approval, which may limit its broad use. The use of probiotics, which are good bacteria that can aid in reestablishing the body's microbial balance, is another alternative therapy [15-19]. The antimicrobial pipeline was inadequate to meet clinical needs due to a number of issues, especially with regard to antibiotics. These restrictions were mostly caused by difficulties and obstructions in the process of developing antibiotics, including. Lastly, the healthcare industry is better prepared to fight antibiotic resistance while guaranteeing responsible antibiotic use by utilizing AI to its fullest potential and integrating the most recent advancements. Global collaboration and creative solutions are crucial to ensuring that antibiotics continue to be effective in protecting public health in the face of the growing threat of antibiotic resistance [19-24].

Conclusions. Evolution of antimicrobial resistance of bacteria is a continual phenomenon occurring either by new chromosomal mutations or acquisition of drug-resistance genes through HGT. The progressive rise of AMR during the preceding two decades has generated considerable risk for worldwide public health and is now appraised as the top health concern in the 21st century, seriously limiting therapeutic choices. MDR bacteria are regularly discovered in many common infections such as respiratory, urinary, sexually transmitted, or tuberculosis infections globally.

Although there have been several attempts to address the issues of antibiotic resistance and the necessary interventions up to this point, there hasn't been much concerted action, particularly in terms of political will at the national and international levels. Antimicrobial-resistant infections are on the rise, which means that within a few years we may experience severe medical, social, and economic setbacks. All of our modern medical accomplishments, including major surgery, organ transplantation, treating preterm infants, and cancer chemotherapy, will be lost unless immediate, strong, worldwide action is taken.

Future research attempts must prioritize novel medication design, examine alternate antimicrobial techniques like phage therapy, and look into the environmental components of antibiotic resistance. The adoption of the One Health concept, which acknowledges the interconnection of human, animal, and environmental health, will be crucial in confronting antibiotic resistance holistically. Lastly, by utilizing AI to its fullest and integrating the most recent advancements, the healthcare industry is better prepared to fight antibiotic resistance while guaranteeing appropriate antibiotic use. Since antibiotic resistance is a serious concern, international collaboration and creative thinking are necessary to guarantee that antibiotics continue to be effective in protecting public health.

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