International Journal of Scientific Research in Engineering & Technology
Volume5, Issue1 (January-February 2025), PP: 01-09.
www.ijsreat.com ISSN No: 2583-1240

A Comprehensive Review on Antibiotic Resistance

Krishnkant V. Late
Satyajeet College of pharmacy, Mehkar, Maharashtra, India.

To Cite this Article: *Krishnkant V. Late, "A Comprehensive Review on Antibiotic Resistance", International Journal of Scientific Research in Engineering & Technology, Volume 05, Issue 01, January-February 2025, PP: 01-09.*

Abstract: *Antibiotic resistance is one of the most severe public health crises that we face in current medical practice. Every year, at least 2.8 million people get an antibiotic-resistant infection, and more than 35,000 people die. In addition to the potential for serious morbidity and mortality, antibiotic-resistant infections add unnecessary and substantial costs to the healthcare system. The impetus for finding solutions in what has been established as a dire situation is overwhelmingly twofold: the necessity with which it must be addressed gives doctors, patients, researchers, policymakers, and caregivers the means to thoroughly address the subject, and the consequences of inaction catapult researchers into a world of microbial and evolutionary surveillance of unparalleled depth.*

This review article discusses the historical, technical, and futurological aspects of antibiotic resistance, presenting an evidence-based collection of findings on resistance and the various mechanisms of resistance that have evolved as a result of our use and misuse of antibiotics. The social, commercial, and economic implications of antibiotic use and resistance must likewise be addressed through public health policy and the motivation of those in the fields of medicine, epidemiology, and microbiology. Alternative techniques to the use of antibiotics, including vaccine development and phage therapy, are thoroughly discussed as potential solutions to the current impasse.

1. INTRODUCTION TO ANTIBIOTIC RESISTANCE

The development of antibiotic resistance has been identified as a global public health threat. Addressing the issue is particularly critical in the South African setting where late diagnosis and limited diagnostic resources impact appropriate treatment. This is compounded by an emerging older population characterized by risk factors for colonization and infection with resistant microorganisms. Resistance limits treatment options, leading to the use of more toxic or less effective alternative agents that may not be registered in all settings. Defining single or even combinations of agents to guide treatment empirically can therefore be challenging. Clinicians need to understand local epidemiology and take measures to reduce further emergence, transmission, and selection of resistant microorganisms. Practical steps to achieve this include an awareness of the relevance of antibiotic resistance in one's own practice, the control of the driver of resistance, and considering the environmental impact of antibiotic use.

Antibiotic resistance is defined as any organism that is not susceptible to the action of the antibiotic to which that particular species of microorganism is normally susceptible, produced by a selection of a strain capable. This can lead to relapse or reinfection by the same organism. Consequences of antibiotic resistance result in treatment failure, slow patient recovery leading to prolonged and more severe disease, and further complications which may lead to longer hospitalization and/or death. Restricting access to certain therapies has in some cases necessitated depriving patients of a potentially life-saving intervention. A comprehensive overview of infection control management is beyond the scope of this literature review. Instead, attention will focus on impeding the further spread of antibiotic resistance in a clinical setting and at the community level. This review aims to provide general assistance and guidance concerning antibiotic usage for health care professionals subject to final decision pathways for management. Antibiotics have been in use since ancient times and became widely used in the 20th century shortly after the discovery of penicillin. Prior to the 1980s, there was a period of discovery and invention of new antibiotics. The so-called 'magic bullet' antibiotics were being screened at a rapid rate and new agents became available. Over the past three decades, however, this trend tempered. The initial optimism regarding controlling previously antibiotic-resistant bacteria was eventually replaced with a realization of the imperfect nature of previously believed miraculous substances. Antibiotic resistance has become a common problem in daily medical practice, and emerging infectious diseases occur on a regular basis. Such infections have the potential to spread rapidly from patient to patient or from health care provider to health care provider. Public health significantly contributes to the ability of communities to combat emerging infections because the social, behavioral, and environmental determinants of some infections intertwine in ways that are challenging to address across settings. In recognizing this, the public health community can purposefully address these factors at the individual, family, organization, and system levels of intervention to create a multi-tiered approach to improving health outcomes.

1.1. Definition and Scope

Antibiotic resistance is a global threat and public health priority. Resistance to all or most available antibiotic classes is present in all countries. Antimicrobial resistance found globally in bacterial, fungal, viral, and parasitic species of public health importance poses a challenge to the management and prevention of an ever-widening range of infectious conditions and syndromes. We define antibiotic resistance as the loss of susceptibility of a variety of microbes to antibiotic agents, resulting in these drugs becoming ineffective. Not all types of resistance are acquired. Resistance can be either innate or acquired. In the case

of innate resistance, the bacterium is naturally insensitive to a drug; in other words, the drug was never developed for its insensitivity. Acquired resistance results from changes in the microbe's genotype, either by mutation or by horizontal transfer of resistance-originating genes from other microorganisms.

The threat of antibiotic resistance is growing, which is rooted in the modern environment and globalized economies, not confined within political or geographical borders. Community-associated antibiotic resistance incurred from the usage of over-the-counter antibiotics or self-prescription, and hospital-associated antibiotic resistance rooted in irrational prescription or excessive dosing of antibiotics, rampant infection prevention failures, inadequate control measures, and weak oversight of the health system further compound the challenge. That antibiotic resistance is an evolutionary process in response to an antibiotic agent sets a complex problem for the control of this resistance. Either by mutational induction or de novo mutations and enteric or parenteral transmission of resistance genes due to either legit transfer or accidental or serendipitous creation of mobile genetic resistance elements, as and when the resistance develops, bacteria emerge with a repertoire of novel and innovative resistance mechanisms.

II.HISTORICAL BACKGROUND OF ANTIBIOTIC DEVELOPMENT

Antibiotics are considered the standard treatment for bacterial infections and are instrumental in modern medicine. In this section, we provide a comprehensive historical overview of the development and progress made in the field of antibiotics.

The successful development and use of synthetic penicillin in the 1950s marked the beginning of antibiotic development. In 1953, broad-spectrum antibiotics synthesized by Streptomyces antibioticus were discovered. In 1957, it was noted that antibiotics would never be exhausted, such as penicillin, marking a good time in world medicine, and this golden age lasted only 20 short years. By the 1970s, even in a highly consumable field, pessimism about antibiotics had spread due to the exhaustion of conventional antibacterial agents. The lack of funding and returns from the long period of antibiotic research, the few major pharmaceutical companies that are truly serious about research and development of new antibiotics, and the increasingly difficult market and more stringent regulatory requirements have all contributed to a further decline in the research and development of antibiotics.

The use of antibiotics is still high, but the hope experienced in the early 21st century has given way to a profound understanding of these compounds. Antibiotics are drugs that kill bacteria or inhibit their growth and reproduction, and select for the emergence of drug-resistant strains. In recent years, the prevalence of drug resistance has become more and more obvious to people. The widespread use of antibiotics is likely to result in the emergence of resistant strains of bacteria, so antibiotic resistance must be monitored at all times.

III.MECHANISMS OF ANTIBIOTIC RESISTANCE

A comprehensive literature review of antibiotic resistance; Section 3: Mechanisms of Antibiotic Resistance It is important to understand the numerous mechanisms bacteria use to develop antibiotic resistance on the genetic and molecular levels. It is also key to differentiate two processes that can give rise to acquired resistance: bacterial intrinsic characteristics, in which there is no need for the bacterium to be exposed to selective pressure to have increased resistance, and cellular adaptive responses to external pressure such as treatment with an antibiotic. In bacteria exposed to antibiotics, four main processes can lead to drug resistance: mutation of existing genes; horizontal transfer of resistance genes; vertical transfer of resistance genes into anti-infective agents; and a number of targets that may be reached by mutation or resistance. Mutation is one of the most efficient processes giving rise to resistance. Given the large number of cells in infected patients, the mutant bacterial cells would quickly dominate, rendering the antibiotic ineffective. Plasmid-mediated multidrug resistance consumes the selective advantage of carrying the resistance trait because of successive plasmid loss in bacteria. For example, a cephalosporin exhibits a regrowth effect in an in vitro hollow fiber infection model of Staphylococcus aureus. Plasmid-encoded resistance genes are not associated with a selective advantage. They are driven by the horizontal transfer of the gene, normally harbored on a conjugative plasmid, from bacteria that carry the metallo-beta-lactamase in an organizer to bacteria living in other parts of the body. Thus, it would increasingly become difficult to control infections caused by resistant strains. The spread of these genes has been linked to low-quality water sources, where these and a multitude of other bacteria encounter partial concentrations of several antibiotics. Therefore, it is not surprising that many of these organisms possess a resistance gene, which is an excessive genetic condition that runs in unison with bacterial evolution.

3.1. Genetic Basis

This review will focus on three major aspects of antibiotic resistance. It is useful to consider them in consecutive order, as they tend to go hand in hand. This approach corresponds to the common methods of diagnostics and therapeutics, as well as to those from the perspective of counteraction to pathogens acquiring resistance. The first aspect lies in recognizing, on the genetic basis, how certain bacteria become resistant. We must consider the existence of genes that provide resistance and may occur not only on the bacterial chromosome but also – and more frequently – in the form of additional genetic material. Bacteria themselves can transfer it to others of their kind, but the most worrisome is the exchange of resistance genes between completely different types of bacteria.

We can find plenty of recent discussions on possible antibiotic resistance evolutionary paths, describing, for example, the successive accumulation of chromosomal mutations. These can result in phenotypic changes, which not only increase survival in an antibiotic-containing environment but also impact subsequent mutations. Similarly, the occurrence of a mutation in the active centre of a bacterial enzyme targeted by antibiotics may result in changes in the binding of this antibiotic, as well as in a broad range of other chemicals. It could widen the substrate specificity of such an enzyme and potentially lead to resistance when needed. In addition, detailed knowledge of the genetic basis of a specific resistance mechanism provides new ways for the development of

diagnostics directly aimed at dangerous strains. Molecular diagnostics can determine whether a particular resistance gene has been acquired in the treatment process – in which case, the treatment will not protect the life of the patient and will encourage the development of antibiotic resistance.

3.2. Acquired Resistance

When discussing resistance in a clinical context, the term 'acquired resistance' is often used as a direct precursor to 'antibiotics'. By this, it is generally intended to illustrate how bacteria buy time to adapt to and develop resistance to drugs. Bacteria survive antibiotic treatment by acquiring new mechanisms to withstand an antibiotic's action. Resistance can be acquired by the broader bacterial population as a selective pressure of sustained antibiotic usage or from direct exposure to antibiotics. The former often leads to the sudden appearance of resistant strains. Acquired resistance can be brought about by horizontal gene transfer, gain of new genetic material, deletion, or via selection of resistant mutants. Pathogens known to frequently acquire resistance by horizontal gene transfer through drug pressures include members of the genera Salmonella, Neisseria, Haemophilus, enterococci, staphylococci, and Mycobacterium tuberculosis in healthcare-related surroundings.

Whereas the importance of solution resistance needs to be minimized, resistance via replication can have profound effects primarily if bacteria are pathogenic organisms. Bacteria known for their ability to develop resistance through sustained antibiotic exposure include members of the genera Streptococcus pneumoniae, Streptococcus pyogenes, and Haemophilus influenzae in healthcare-associated surroundings. As with sterilizing and tolerance resistance, treated infections can persist long after treatment cessation. Thus, responsible usage of antibiotics is particularly important in the presence of slow-killing chemotherapeutics as the chances of causing resistance are increased. The impact of acquired resistance on the likely clinical outcome of an infected host and control measures employed will differ according to the mode of resistance developed.

IV.EPIDEMIOLOGY OF ANTIBIOTIC RESISTANCE

Globally, there has been an increasing trend in the number of antibiotic-resistant bacteria isolated. Prevalence rates and patterns are variable and depend on local practice; however, rates as high as 47.7% of all infections caused by resistant organisms have been reported. The majority of antibiotic-resistant infections occur in the community, as a result of antibiotic-resistant bacteria that typically live in healthy people without causing disease. People who carry those germs can spread them to other people or can themselves become ill when resistance leaves bacteria that were once treatable with antibiotics in an untreated state.

Recognized as one of the main drivers of antibiotic resistance, the unnecessary use of antibiotics and the prescription of these drugs to patients with suspected viral infections contribute significantly to the emergence of resistance. This is evidenced by the strong positive correlation of antibiotic use and resistance rates; as use increases, more of the bacteria that are treated show resistance. Though this evidence is strong, there are few linear relationships between the use of specific antibiotics and increases in specific resistance rates. On the other hand, there is a strong relationship between the overall resistance rates and the overall use of antibacterials across different classes. Evidence indicates that the majority of antibiotics are prescribed for respiratory tract infections, though these particularly common conditions do not benefit from the use of antibiotics. Resistance, including multi-drug resistance, is particularly common in hospital practice.

4.1. Global Trends

Antibiotic resistance is a global public health crisis that has developed over time due to the misuse, overuse, and lack of innovative antibiotic discovery. Recommendations were made in the 1960s to highlight the gravity of unprescribed use; however, it took many years for international guidelines and public campaigns to develop. The US reports annual warnings in state-by-state profiles detailing substantial rates of resistance to multiple drugs, including carbapenem-resistant bacteria. In India, it is projected that over 50,000 cases of neonatal sepsis are associated with high rates of antimicrobial resistance; stillbirths and deaths are consequently bound to follow. Many other countries have published evidential reports on growth among this health challenge. The World Health Organization has shown the initial steps to publicly approach the issue of antimicrobial resistance to be through proper tendering, spreading knowledge, and understanding among the general public. International resolutions, which aimed to preserve human health and animal safety by collaborating against antibiotic resistance, were promulgated in 1999 and remain effective to the present day.

One of the globally trending causes of resistance resides in multi-drug resistant organisms, which are now emerging in many parts of the world, regardless of economic authority. Their ability to escape the assaults of various antibiotic classes supporting Gram-positive, Gram-negative, and anaerobic bacteria has basically echoed these organisms as a global concern. Few concerns have been heightened with Gram-negative infections spreading beyond country lines. For instance, the NDM-1 Klebsiella originates from New Delhi and has infected persons in various countries. To control the emergence of these organisms, it therefore becomes necessary to accumulate information and data concerning international disease control mandates. In order to better understand antibiotic resistance, comprehensive policies are needed to accumulate knowledge from various international sectors. For instance, cross-border intervention built on established regulations and behavioral principles underpinning the general public, physicians, and patients. Blockading the threat of antibiotic resistance will require diverse and complex methods, including multi-sectoral and cross-border interventions. Resistance population indicators, resistance in ecological niches, and social hunger for resistance should therefore not be overlooked in the development of policy and public awareness of antimicrobial resistance. In 2018, a few global and national panels showed significant discoveries in resistance to antibiotics. Data collation has shown that worldwide, total resistance population indicators were over 40/100,000. Over 27 data collection programs were used; 13 programs were national, and two of these were regional programs. Medical indications were available in 18 programs, with 9 covering public infections. A median of four medical drugs was consumed over the three-year period of data collection. Over 30 resistance

population indicators were reported, including carbapenem-resistant bacteria.

4.2. Impact on Public Health

Antibiotics have literally saved millions of lives since 1943, but the infectious disease that they once successfully treated became resistant to the drugs. Healthcare settings sometimes have a higher prevalence of these resistant organisms, which can result in healthcare-associated resistances. Since then, both healthcare-associated and community infections with resistant bacteria have been on the rise. This has created a series of new public health problems, including a higher incidence of poor patient outcomes, a higher financial burden due to these preventable outcomes, and challenges in treating an infection with fewer antibiotics.

Healthcare-associated infections with resistant bacteria have been found to increase the patient's morbidity and mortality rates, as well as potentially increase the length of time spent in hospitals. It appears that resistance is possibly the cause of the increased morbidity and mortality rates; additional efforts are needed to improve antibiotic use. In order to accurately assess the impact of resistance, surveillance of patients with resistant bacteria is necessary. Similar to other public health data, surveillance can serve as an epidemiological tool that can identify trends. These identified trends can raise public awareness within hospitals, concerning communities, states, and even entire world regions. This is in part due to verifiable surveillance and public awareness. In addition to increased awareness, hospitals are also constantly changing in order to prevent transmission by anyone. Most recently, the studies into resistant bacteria have also used molecular methods to help better understand genes and conjugative or mobile elements. In order to be more effectively used, public health manpower must be better connected. Additionally, essential strategies must be used to prevent community-acquired infections, including vaccinations, handwashing, and practicing infection control standards at home.

V.CLINICAL IMPLICATIONS OF ANTIBIOTIC RESISTANCE

The clinical implications of this emergent phenomenon are numerous, particularly for healthcare providers and patient safety. Antibiotic resistance threatens the cornerstone of modern medicine and, as a result, the ability to effectively treat patients. The history of bacterial pathogens developing resistance has demonstrated that there are times when there were only limited effective antibiotic options against resistant infections. However, in the modern era, the number of effective antibiotics has significantly decreased, and those that remain are considered "last resort" options. Consequently, significant efforts have been made by the healthcare community to prevent, identify, and successfully treat resistant organisms, yet infections persist.

Antibiotic resistance results in an increased number of complications from infections. Patients who are affected by invasive and complicated infections typically require hospital and ICU-level care and surgical interventions. Families and patients experience psychological distress due to compounded physical complications from infections. The emotional and financial strains on affected families and patients are numerous. Clinical practice previously focused on controlling infection, preserving source control, improving outcomes, and preventing further complications. Addressing antibiotic resistance complicates these approaches, necessitating the utility of the limited available antibiotics, the judicious use of surgical and physiologic resources, and the exploration of varied therapeutic responsive alternatives. Diagnostic tools that might identify infected patients more promptly are under active clinical development. Until such novel capabilities are hyper-accurate and considered standard practice in all healthcare settings, all healthcare providers should proceed with a focus on infection management in the context of the local antibiotic resistance trends. Efforts to mitigate these risks through the judicious use of antibiotics and resistance prediction through stewardship and susceptibility management programs are clearly necessary. In this era of increasing antibiotic resistance, it is instrumental that healthcare providers and programs are educated about the dynamic local and/or population-based mechanisms associated with resistance and therapeutic alternative strategies.

5.1. Treatment Challenges

Limited treatment options exist for infected patients, especially for those with infections caused by highly resistant organisms. Treatment of patients with already identified infections by highly resistant pathogens may require the use of higher doses or combinations of drugs, which could lead to higher drug costs, toxicity of therapies, and lower feasibility of outpatient parenteral antibiotic therapy, as severe underlying conditions, increased comorbidity, or immune status depression must be considered. At the same time, the importance of dose adjustment and therapeutic drug monitoring in patients infected by resistant bacteria should be considered in terms of an appropriate antimicrobial regimen that must be tailored to the individual, instead of being based only on clinical guidelines, avoiding high systemic toxicity and ensuring the maximum bactericidal effect at the maximal dosage allowed. Resistant pathogens arise, and they are indeed more difficult to handle due to their limited antimicrobial susceptibility profile; this is unarguably a key clinical problem. Indeed, there is an undeniable and growing number of bacterial strains or strain associations that have been responsible for causing treatment failures with various antibiotics. The sulphanilamide's are an early example of treatment failures caused by microbial resistance, and even with modern antibiotic discovery and drug development efforts, resistance has remained a constant companion and threat throughout history. Moreover, based on the harmful consequences of microbial resistance, these issues are a great concern for healthcare professionals. Finally, drug-resistant infections represent a burden for healthcare resources, with a subgroup of patients needing prolonged hospitalization. For this reason, an increase in direct costs attributable to the use of second- and third-line antibiotics has been reported, highlighting also adverse impacts on the healthcare system and on patient outcomes. For these reasons, a multifaceted approach is crucial for the appropriate use of antibiotics, such as stewardship and training of prescribers, along with the implementation of international, national, or local guidelines aimed at the control of the emergence of resistance. Areas of particular risk should be focused on, including the intensive care setting where antibiotic prescriptions are high and broad-spectrum agents are usually used to cover a

large range of potentially resistant organisms. A need for strategic directions is inevitable, with high-priority actions identifying flagship projects, including research projects and clinical trials to approve new agents and strategies, programs for testing new drugs, the maximization of uptake optimization with pilots of regional, national, and European guidelines, and the use of grants for collaborative research on antibiotic resistance. The resistance threat is a global issue that requires international collaboration for action.

5.2. Increased Mortality Rates

Currently, as pharmaceutical development struggles to keep pace with bacterial resistance, the potential impact of such a problem is feared to result in a 'post-antibiotic' era in the future. In addition to the associated chronic health concerns, there are concerns regarding an increase in the mortality rates because current fatal cases are generally associated with infections due to resistant bacteria. Moreover, a delay in proper diagnosis and effective treatment of the infection increases the probability of severe health outcomes and, in some severe cases, may lead to death. The bloodstream, urinary tract, and respiratory tract infections, especially in cases of severe pneumonia, could result in an increased risk of severe sepsis; hence, in hospitals, they could be more life-threatening. This is of particular concern for those patients who may have other health issues and, thus, may be unable to withstand serious infections of resistant bacteria, which could increase the risk of dying in malnourished children or children who are already ill. However, hospitals and communities in general are tragically influenced by such fatal cases. Families of such cases could be psychologically affected, and the public health instigators have the duty of expressing their concern over the losses of life attributed to antibiotic resistance and also increasing awareness among healthcare providers, patients, and organizational guardians about effective preventive measures. The percentage of severe infections associated with increased mortality risk has doubled owing to the healthcare services accessed, and there is an increased emergence of patients with risk factors susceptible to resistant infections. Subsequent data also showed a significant increase in the proportion of hospitalizations, deaths within the first 30 days, chronic healthcare facilities, and others within the first 30 days. The economic impact of mortality is of pilot importance that also requires attention and prevention.

VI.PREVENTION AND CONTROL STRATEGIES

To mitigate antibiotic resistance, prevention and control strategies are implemented in healthcare settings. One of the most important responses to tackle the problem of resistance is the development and implementation of antibiotic stewardship programs. These multidisciplinary interventions should aim to optimize the individual and societal outcomes of antibiotic use, reduce the risks associated with antibiotic use, and minimize the selection and spread of antibiotic-resistant microorganisms. Educational campaigns for healthcare professionals and the general public can help to increase knowledge about the correct administration of antibiotics and the adverse outcomes due to the misuse or overuse of such drugs. For healthcare professionals, webinars on the correct use of antibiotics in different pathologies can be delivered, while the general public can be recipients of health campaigns that encourage not to stockpile antibiotics and not to use leftover antibiotics. The effects of such public health campaigns not only help to make the education meaningful both for patients and healthcare professionals but also help to curb antimicrobial resistance. In addition, tangible advances in reducing AMR have been achieved by adding public awareness to governmental agendas.

Infection prevention and control measures, such as hand hygiene, environmental decontamination, contact precautions, and isolation, are strongly recommended to control the spread of potentially resistant microorganisms in the healthcare setting. Multi-modal interventions can improve the rate of hand hygiene compliance among healthcare professionals and have a positive effect on the bacterial load on hands and hand hygiene-related infection rates in patients. Overall, active surveillance on AMR is necessary to monitor resistance levels and patterns within a region. This information is essential to plan clinical activities, to introduce intensified prevention and control programs targeting resistant organisms, and to formulate public health directives in order to stop their spread. Moreover, investment in research is also needed to continuously introduce new antibiotics and counteract the development of resistance. Also, a clear commitment from the health provider is needed to support research, the encouragement of public-private partnerships, and incentive contribution for major international programs. In countries with an initial economic base, cooperation among institutions and multinational companies is necessary in order to conduct research and produce innovative antibiotics at an affordable price for low-income countries that do not have economic resources.

In particular, the initiative should be supported not only by the healthcare workers and their institutions responsible for human and animal health but also by local political authorities, and through the active involvement of the general public. In this framework, the bottom-up approach is fundamental, in which the concept of one health is aimed at conducting interventions involving human, animal, and environmental health. Expert opinion was also sought in order to understand the relevance to society of the antibiotic resistance campaign and to identify the communication media preferred by the general public. In fact, it is important to understand how the information should reach the target population; another aspect that emerged is that the message should be addressed differently to adults and children.

6.1. Antibiotic Stewardship Programs

Antibiotic stewardship programs (ASPs) are now established as a strategic approach to overcome the problem of rising resistance. Key principles are to try and ensure that antibiotics are being used in the best way for individual patients and to minimize misuse. Best practice in the development of an ASP has been defined by multiple international guidelines for a number of healthcare settings, including critical care. An ASP typically has a recognizable structure that includes both non-medical support and medical support. Routine monitoring and reporting of antibiotic use, as well as outcomes, are key components of any ASP approach.

Antibiotic stewardship is a core element of any program to combat antibiotic resistance. The key concept is to optimize

antibiotic use and minimize misuse. Internationally, there is increasing pressure from governments, governmental agencies, and society in general to ensure the responsible use of these medications. Best practice guidelines for the development and implementation of antibiotic stewardship programs (ASPs) in the acute care hospital have been published in multiple jurisdictions and provide a robust framework to implement ASPs. However, there are specific challenges in the implementation of these programs in critical care. These include ensuring education and training of rotating junior doctors, who are often the ones with the most patient contact, connecting and communicating with other units or referring hospitals to ensure continuity of care while ensuring local specific policies are followed. A best practice guide proposed some specific elements of ASPs to ensure they relate to and care for the critically ill. Monitoring and surveillance of ASPs to ensure that the projected improvements are achieved is a fundamental component of not only a fully functioning ASP but also a system to detect changes in resistance or antibiotic use. Data collection can be acted upon directly or through the innate tracking of downstream surveillance efforts. Just as the outcomes and effectiveness of the implementation of novel therapies for resistant pathogens are important in the assessment of those therapies, guidance statements also suggest this continuous monitoring is linked to an ASP. As such, there is no doubt that the research and analysis of data need to be a parallel consideration when planning your ASP.

6.2. Infection Prevention and Control Measures

In general, active preventive measures capable of reducing resistance and spreading are always preferable to reactive solutions in treatments. The implementation of some basic infection prevention and control measures can be helpful in this regard. Prevention and reduction in resistance levels can be achieved with the use of antibiotic stewardship, which in turn can be affected by control measures in a variety of ways. Crucially, infection prevention and control need to adhere to existing guidelines, and all healthcare facilities should work in this direction. Some strategies are considered essential to preventing infections and avoiding the spread of resistance. Hand hygiene, remaining the most important infection prevention strategy, should be universally practiced by all healthcare staff. Sterilization and disinfection protocols, as well as the isolation of infected patients from the susceptible, are essential.

Healthcare workers play pivotal roles in the implementation of these control measures, and a conducive environment for infection prevention and control is necessary. Suboptimal adherence to these measures could result in rates of infection and the spread of resistant bacteria among patients. A limited number of studies have reported how rates of antibiotic use can be detected at the patient and hospital levels. However, infection prevention and control strategies do have an effect as they can lead to low rates of infections and low rates of target infections, which are the result of a transmission process for which antibiotics would be prescribed. The implementation of infection prevention and control measures can reduce adverse events and heavy consumption of antibiotics, resulting in a lower level of resistance development. The implementation of these behavioral practices is full of challenges, both in the resource-poor crowded wards in developing countries and in the well-resourced, space, privacy, and individually oriented customs of high-income countries. While infection control measures have been adapted and implemented in well-resourced high-income country hospitals, there are still service implications in adapting IPC interventions for crowded hospital wards in developing countries. Education and training in infection prevention is a priority, but there are mixed results in the impact of such interventions.

VII.TECHNOLOGICAL ADVANCES IN FIGHTING ANTIBIOTIC RESISTANCE

Over the past century, antibiotics have revolutionized medicine by significantly reducing the mortality associated with bacterial infections. The arrival of antibiotic resistance has, however, brought about a reversal in these gains with serious public health ramifications. The protracted discovery of new antibiotic classes has led to renewed attention to alternative treatment approaches, such as new antimicrobials, repurposed drugs, and host-directed therapies. Already, there are evident technological advances in the fight against AMR manifested in the development of new rapid diagnostic assays, telehealth consultations, local pharmaceutical formulation facilities, point-of-care interventions, and drugs to treat emerging and enticing bacteria. The following examples show how these advances are being used and what potential they hold in the fight against antibiotic resistance.

Due to the increasing number of bacteria that are resistant to multiple therapies, and the development of new therapies, there has been a resurgence in phage therapy, the therapeutic use of bacteriophages to treat bacterial infections. Numerous recent studies, including clinical trials, have shown that phages can be highly effective against a number of different resistant pathogens. Genome editing using CRISPR has demonstrated advantages for improving antibacterial strategies by killing CRISPR-positive bacteria, suppressing virulence factor expression, preventing or curing biofilm formation, and disrupting persister cell formation. Clinical trials could also occur in parallel, given that the biocompatibility of a macromolecule with a defined function in resistance is reasonably well understood. Furthermore, the observed SNVs are rare at this stage and are likely the consequence of bacterial exonucleases that degrade nucleic acid drugs. Steering away from current resistance mechanisms, advances in CRISPR technology – such as designer nucleases and base editors – present new paths towards editing and targeting genes. CRISPR is a promising field of research for developing new antibacterial strategies in all of the areas covered above. Beyond technical concerns, however, it also raises ethical questions. Because resistance genes are still evolving, the same approach may be effective if a resistance gene is removed while using termination molecules. Although designer nucleases show potential for gene editing, the clinical success of these new technologies depends on the identification of new and relevant antibacterial targets to address unmet therapeutic needs. Many other technological breakthroughs can have uses in a variety of antimicrobial treatment choices because it is difficult to anticipate where and how resistance may evolve. Given the ceaseless feature of resistance, continued investment in such new science is critical to identify interventions that will continue to be effective in the decades to come.

7.1. Phage Therapy

Phages are bacterial proteins that infect specific bacterial species and eliminate them. Phages exist everywhere bacteria exist and seem to be the most effective arms against infections. Numerous antibiotics or antibiotic-like proteins produced by pathogenic bacteria themselves are being tested in laboratory systems. Phages are special because they have host specificity. They are more effective in low bacterial loads in the human system, particularly against urinary tract, lung, and eye infections. Phages may be particularly useful in chronic bacterial infections or in polymicrobial accumulations. The capability of host specificity leads to reduced destruction of normal bacteria, as observed in the case of broad-spectrum antibiotic treatment regimens. Phages are classified into three groups: virulent phages, temperate phages, and satellite phages. The best strategy is to find antibiotics, molecules, phages, or bacteria that can harm both virulent and dormant stages of bacteria. Long phage treatments can lead to the production of phage-resistant mutants; however, these mutants can have disadvantageous survival and proliferation. The use of phages has several advantages over antibiotics. We must consider phages as more precise or more failsafe than antibiotics.

The revival of this field has been prompted by the emergence of antibiotic resistance in numerous multi-drug-resistant infections. Phage therapy was in use during World War II, particularly in Eastern Europe. However, the development of broad-spectrum antibiotics reduced the study and application of bacteriophages to treat bacterial infections. Eventually, the most studied specific cocktail preparation comes from a clinic in Georgia for over a century. The resurgence of phage therapy is mainly due to the situation in Eastern European countries where multi-drug-resistant bacterial infections have been appearing years or even decades before similar cases developed. Various research works try to show the real limitations of phage therapy. Ethical and legal reasons: despite the development of new antibiotics, phage research is still on the rise in Europe and collaborations with industry and academia elsewhere, primarily to establish that phages might be best used as adjuvants with current therapy or to inform current drug development strategies. It is not easy to produce large amounts of phage, and it must be in isolated formats in hospitals. Current regulations in most European countries place restrictions on this. Pharmacological tools and paraphernalia must be removed, and the infection control system has been established for new treatment modalities to complete their mission at the bedside. Regulatory issues also involve a specific form of process engineering, particularly the production aspect, where prerequisite hygienic and safety standards must be practiced more than in any other pharmaceutical production. Furthermore, regulatory issues involve ethical and legal considerations such as human informed consent, compassionate use or treatment, double-blind clinical trials, foster care, parental care, and other forms of clinical support. All of these factors are being addressed in newly launched research initiatives. Moreover, it has been ensured that research involving phage therapy in humans complies with ethical guidelines.

7.2. CRISPR-Cas9 Technology

CRISPR and Cas genes are bacterial defense mechanisms against viral infection, which have been profusely investigated for the development and application of "molecular scissors" for gene editing. CRISPR-Cas systems can easily be manipulated to generate targeted DNA double-stranded breaks with high precision and frequency. Nowadays, a myriad of techniques have been developed to decimate, knock out, or knock in specific bases or target genes directly and reliably in bacterial and archaeal cells, as well as in therapeutically relevant environments, such as biofilms and challenging bacterial pathogens, including strict, resistant gut bacteria persisting in the human body. Currently, the choice of a CRISPR-based antibacterial therapy can be designed and implemented with great precision to exert a bactericidal activity or reprogram the resistant phenotype/reverse resistance.

Gene editing procedures that rely on CRISPR tools to precisely target and remove or alter bacterial genes have proven to be efficacious as they amend the genes and molecular/cellular processes that promote antibiotic resistance. Due to their power and specificity, these gene editing tools offer very promising therapeutic and clinical applications, particularly when targeting life-threatening MDR pathogens. There is an appropriate concern about the potential transfer of genes that inadvertently encode undesirable pathways or structures. Importantly, CRISPR technologies have extensively been applied to investigate the mechanism of antibiotic resistance and gene exchange, so they are expected to offer great insights into the functions of bacterial genes linked to resistance. Unfortunately, the translation of these robust tools from the laboratory bench to the clinical settings is currently at its infancy and has many challenges. Moreover, the eventual undesired side effects and the ethical and regulatory constraints pertinent to these approaches are not fully addressed, nor their implications thoroughly investigated so far.

VIII.ECONOMIC BURDEN OF ANTIBIOTIC RESISTANCE

Antibiotics need to be used rationally to fight antibiotic resistance. The economic burden of antibiotic resistance is important due to the unpredictability and magnitude of a proper cost estimation, and because the growing trends suggest a high impact of antibiotic-resistant bacteria. We could consider two economic levels of consequences: (i) the direct costs that influence the expense of hospitalization due to the use of broad-spectrum antibiotics or the prolongation of the antibiotic continuum therapy, and the additional costs of alternative treatments if needed; and (ii) the societal consequences of resistance, which are not yet fully known, such as increased costs of disease management, changes in the national insurance systems, and primary working days and human health. The emergence and spread of highly resistant bacteria could generate inequalities as well as social and economic vulnerabilities in the member states. Resistance is a particularly heavy burden for less well-off countries, even given the evidence of economic benefits linked to the wise use of antibiotics. The cost of comprehensive programs to prevent antibiotic resistance is substantial. Because of this, decision-makers and funding bodies need to know whether these programs represent good value for money, that is, whether the potential benefits they generate in economic and budgetary terms justify the investment costs.

We could summarize three reports that made a quantitative analysis on the economic burden of antibiotic resistance. A study performed in 2014 showed that antibiotic resistance in only nine countries cost 174,500 lives in 2012. These people could

have been saved in their countries if health policies that improve infection control and monitor antibiotic prescription had been in place. The cost to the healthcare systems amounts to 66,000,000. Similarly, it was estimated that sick persons took 7 million unnecessary additional sick days for flu and upper respiratory infections, which are usually treated with antibiotics, whereas those infected by resistant bacteria took significantly longer periods of leave for illness, with 4 days on average, which means a total of 37 million extra sick days. The costs associated with caring for the affected patients are an average of 10,000 or even more for their cure, because treatments often have to be more aggressive and tend to make them live less time than others who are not grappling with resistance. It was estimated the cost of fighting resistant organisms in England and Wales to be 804 million pounds or more, which represents 1% of its own budget of nearly 176 billion pounds. The estimated cost attributable to the resistant infections is 28 million.

IX.ETHICAL CONSIDERATIONS IN ANTIBIOTIC USE

While most of this review is dedicated to the scientific and clinical aspects of antibiotic use, it is essential to consider the ethical implications of the use of antibiotics. There is a moral responsibility for a healthcare provider to use an antibiotic only when it is indicated and to provide the patient with the information to give informed consent for the use of a given antibiotic. There is little question that society benefits when antibiotics are used judiciously. The question is to what extent the needs of the individual patient can be mitigating factors with regard to the broader impact of unnecessary use of an antibiotic. The duty to preserve antibiotics through individual practice and stewardship activities is acknowledged, but it is also concluded that patient needs should balance the physician's responsibility as a global steward of these medicines.

This conclusion is rooted in the recognition that antibiotics are necessary for the short-term health interests of individual patients, but it also reflects concern regarding equitable availability of antibiotics. However, in low-resource settings, it is worth arguing whether immediate health benefits are more important than antibiotic stewardship. It is not unusual to see pharmaceutical companies signify an ethical dimension to their activities. While it can be argued that essential drugs should be provided for all people, other priorities of developing world healthcare are also noted; it is further argued that, due to the potential for ecological disaster, increased exposure to antibiotics and poor resistance testing could exact a heavy genetic cost to the world as a whole. Pharmaceutical marketing regulations also touch upon ethical concerns. There is evidence that the pharmaceutical industry influences prescribing behavior through the provision of gifts or sponsorship. Better training in ethics should be given as part of basic training in recognition of the influence of pharmaceuticals on healthcare. Research has suggested that ethical training could be shaped by two theoretical approaches. The first is the consequentialist approach, which takes into account the consequences of actions or policies and their net effects on the population at large. The second approach is more deontological, where an act is judged from the perspective of whether it is wrong or right in itself. Others argue that more pragmatic learning approaches are lost since ethical reasoning involves the exercise of practical wisdom, such as that found in record-keeping and prescription. Ethical considerations in stewardship, therefore, provide useful practical elements in how we approach antibiotic resistance. Clearly, the idealized scenario would be for the patient and the healthcare worker to participate in an ethical dialogue of judgment and accountability. In our current era, whether ethical frameworks can provide a basis for antibiotic prescribing has many gaps, with no concrete instrumentation. Antibiotics have been portrayed to many as good; the only way to change that, with all humility and patience, would be the engagement of stakeholders.

X.FUTURE DIRECTIONS AND RESEARCH PRIORITIES

The concurrent rise of multi-drug resistant and extremely drug resistant infections necessitates a paradigm shift. In an environment marked by fear of a "post-antibiotic era," it is critical that we look beyond micron-level details of resistance and towards the development of innovative solutions. Thus far, progress in the development of alternative treatments to antibiotics has been slow, but it is clear that a broad research agenda is needed to address the deficiencies in a range of fields that make the rise of resistant strains inevitable. Addressing antibiotic resistance will require the research community to integrate not only public health and microbiology, but also to inject an understanding of pharmacology and interdisciplinary research reflecting root causes of resistance and its component pathways. Work in the area of alternative therapeutics has been limited in scope and strategy; we would benefit from more broad and speculative research in this area that allows for the exploration and combination of diverse solutions. Monitoring through our epidemiology and surveillance has been vastly improved in recent years, though as resistance itself changes and becomes more diverse, we in turn need a more diverse array of strategies to detect it. The global scope of antimicrobial resistance, combined with a lack of consistent infrastructure for compliance with global recommendations, inclined us to place a particular emphasis on further international cooperation.

In the realm of sociopolitical and public health policy, it is obvious that antibiotic prescription behavior is a major variable in the rate of resistance that we observe. Unsurprisingly, many public health campaigns have been initiated at a national and international level to encourage doctors to restrict the type and quantity of antimicrobial agents they prescribe. While they have had moderate success, there is a general perception among healthcare workers and the general public alike that such campaigns are a considered and proportionate response to the issue of medical antibiotic resistance. In an environment in which such resistance is taken as a fait accompli, with tales of pan-resistant superbugs being shared widely from developing countries, the urgency and severity of the situation is lost upon a public no longer fearful of bacterial pathogens. Studies showed that those who more directly "experience the impact of antibiotic resistance" are more likely to be resistant to and support regulations and efforts to combat antibiotic resistance. (Chukwu et al.2021)(Strumann et al.2020)(D'Ambrosio et al.2022)(Ashiru-Oredope et al.2021)(Pierre et al., 2024)(Adekanye et al.2020)(Babatola et al.2021)(Zeb et al.2022)(Jacopin et al.2020)

REFERENCES

1. *Chukwu, Emelda E., David A. Oladele, Christian A. Enwuru, Peter L. Gogwan, Dennis Abuh, Rosemary A. Audu, and Folasade T. Ogunsola. "Antimicrobial resistance awareness and antibiotic prescribing behavior among healthcare workers in Nigeria: a national survey." BMC infectious diseases 21 (2021): 1-12. springer.com*
2. *Strumann, Christoph, Jost Steinhaeuser, Timo Emcke, Andreas Sönnichsen, and Katja Goetz. "Communication training and the prescribing pattern of antibiotic prescription in primary health care." PloS one 15, no. 5 (2020): e0233345. plos.org*
3. *D'Ambrosio, Francesco, Federica Di Spirito, Alessandra Amato, Mario Caggiano, Roberto Lo Giudice, and Stefano Martina. "Attitudes towards antibiotic prescription and antimicrobial resistance awareness among Italian dentists: what are the milestones?." In Healthcare, vol. 10, no. 8, p. 1585. MDPI, 2022. mdpi.com*
4. *Ashiru-Oredope, Diane, Susan Hopkins, Sagar Vasandani, Eno Umoh, Olaolu Oloyede, Andrea Nilsson, John Kinsman, Linda Elsert, and Dominique L. Monnet. "Healthcare workers' knowledge, attitudes and behaviours with respect to antibiotics, antibiotic use and antibiotic resistance across 30 EU/EEA countries in 2019." Eurosurveillance 26, no. 12 (2021): 1900633. eurosurveillance.org*
5. *Pierre, J., Carelli, D., and Peters, B. G. "The four worlds of politics and administration in the EU: How institutional arrangements shape the struggle against antimicrobial resistance." Journal of European Public Policy (2024). tandfonline.com*
6. *Adekanye, Usman O., Abel B. Ekiri, Erika Galipó, Abubakar Bala Muhammad, Ana Mateus, Roberto M. La Ragione, Aliyu Wakawa et al. "Knowledge, attitudes and practices of veterinarians towards antimicrobial resistance and stewardship in Nigeria." Antibiotics 9, no. 8 (2020): 453. mdpi.com*
7. *Babatola, Adefunke O., Joseph O. Fadare, Oladele S. Olatunya, Reginald Obiako, Okezie Enwere, Aubrey Kalungia, Temitope O. Ojo, Taofiki A. Sunmonu, Olufemi Desalu, and Brian Godman. "Addressing antimicrobial resistance in Nigerian hospitals: exploring physicians prescribing behavior, knowledge, and perception of antimicrobial resistance and stewardship programs." Expert review of anti-infective therapy 19, no. 4 (2021): 537-546. strath.ac.uk*
8. *Zeb, Shah, Mariam Mushtaq, Muneeb Ahmad, Waqas Saleem, Ali A. Rabaan, Bibi Salma Zahid Naqvi, Mohammed Garout et al. "Self-medication as an important risk factor for antibiotic resistance: a multi-institutional survey among students." Antibiotics 11, no. 7 (2022): 842. mdpi.com*
9. *Jacopin, Eliott, Sonja Lehtinen, Florence Débarre, and François Blanquart. "Factors favouring the evolution of multidrug resistance in bacteria." Journal of the Royal Society Interface 17, no. 168 (2020): 20200105. royalsocietypublishing.org*