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Antibiotic Resistance in Pathogenic Bacteria: Mechanisms and Solutions

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Annotation: The increasing resistance of pathogenic bacteria to the range of antibiotics produced through natural and synthetic methods is a major and catastrophic health problem around the globe. Currently, the appearance of broad-spectrum resistance in pathogenic bacteria, which curbs the clinical performance of universal antibiotics like vancomycin due to emerging vancomycin-resistant Staphylococcus aureus or extended-spectrum beta-lactamase (ESBL)-positive Pseudomonas aeruginosa strains, poses crucial healthcare challenges like raised therapy expenses, higher death rates, amplified incapacities and longer hospital stays, particularly in developing countries. Moreover, challenges like global warming or the frequent transport of travelers or livestock and goods globally drastically contribute to worldwide sharing of antibiotic-resistant bacteria populations that include resistance against an extensive range of antibiotics.

The continued appearance of different mechanical resistance structures in pathogenic bacteria like genetic material alterations via mutation or obtaining conjugative genetic elements carrying resistant determinants urges the adoption of a diverse methodological configuration to elucidate the evolutionary process of broad-spectrum antibiotic resistance. Because of the extremities and complexity of the flow of resistance determinants into pathogenic bacteria, the profile of 14,871 isolates tested for resistance capabilities against 21 different antibiotics in conjunction with the demonstration of biological materials was generated through a broad exploration of antibiotic resistance mechanisms and anticipated evolutionary paths [1]. In consideration of scientific research and actual prevention strategies, the reviewed profile is structured perfectly that allows a multilateral approach for further understanding the emergences of broad-spectrum antibiotic resistance in pathogenic bacteria and planning effective prophylactic steps.

Keywords: bacteria, antibiotic-resistant, Antibiotics, genetic mutation, phenomenon.

1. Introduction to Antibiotic Resistance

Antibiotics are agents that either kill or inhibit the growth of microorganisms, particularly pathogenic germs like bacteria, parasites, fungi, and viruses. In recent years, the unpredicted and invincible comeback of various pathogenic microbes has caused a growing concern against the efficacy of commercially available antibiotics. Antibiotic resistance is recently turning into a subject of growing concern throughout the world. Increasingly, microorganisms are evolving resistance to all ranges of antimicrobials. As a result, prescription drugs that once were able to cure such infections are no longer effective; hence, these are creating a threat to various aspects of global health. The ability of pathogenic germs to resist antibiotic treatment is referred to as antibiotic resistance. Consequently, an infection caused by antibiotic-resistant bacteria or germs can be treated by a limited number of pharmaceutical compounds. Hence, fast effective antibiotics or antiviral medication administration becomes impossible, resulting in spreading morbidity and fatalities. [2][3][4]

Globally, antibiotic resistance is currently a major health hazard. For many pathogenic bacteria, virulence is compounded by the development of resistance against widely prescribed antibiotics. Pathogenic bacteria replicate asexually, but due to rapid multiplication, there may be a spontaneous genetic mutation during DNA replication that imparts them resistance against antibiotics. It is predicted that by 2050, this number could reach 10 million deaths per annum worldwide if no corrective measures are taken. Moreover, globally, it is estimated that by 2050, the cost of post-antibiotic resistance will be around USD 100 trillion and it leads to the worldwide slowdown of GDP growth by 2-3.5%. In the human body, there are millions of various types of microorganisms that are helpful and necessary for a healthy immune system. But with food, these essential bacteria are destroying and resulting in health hazards. Due to consuming low concentrations of antibiotics for food preservation, pathogenic bacteria are gradually becoming resistant to different antibiotics. In developing nations, antibiotics are being over-prescribed, misused, and used without a doctor's prescription. Generally, low-income populations are consuming old antibiotics that do not cure their illnesses but instead promote resistance among the microbes. [5][6][3]

Literature Review

1.1. Definition and Significance of Antibiotic Resistance

One of the most remarkable success stories in the annals of modern medicine has unquestionably been the groundbreaking discovery of penicillin in the year 1928, along with its subsequent and transformative development as a vital antibiotic. Since that pivotal moment in history, numerous antibiotics have been formulated and have successfully combated previously deadly infectious diseases that once posed significant threats to human health. However, it has become increasingly clear, almost in tandem with the enhanced understanding of how antibiotics function and are distributed throughout the body, that pathogenic bacteria have the capacity to develop resistance against these life-saving treatments. Antibiotic resistance is defined as the acquired ability of various bacteria to withstand the effects of antibiotics, and this growing phenomenon has emerged as a substantial challenge for healthcare professionals and researchers in the effective treatment of bacterial infectious diseases. [1] [7][8][9]

Antibiotic resistance is not an isolated problem within our modern health care system. It is intrinsically rooted in the biological principle that resistance to a chemical compound can develop as soon as there is a compound acting on a biological system. In this respect, antibiotic resistance is a totally natural phenomenon, but its acceleration in bacteria is closely related with the overuse and geographically and chronologically uneven distribution of antibiotics. The healthcare implications are obvious, as infectious diseases that were almost dead have had their lethality rejuvenated. Patient care and availability of suitable drugs are becoming very limited for people infected with resistant bacteria, and the routine procedures in intensive care units rely on the effective control of bacterial infections with broad-spectrum antibiotics - since a highly weakened patient is a good target for an opportunistic bacterial infection, in the presence of bacteria that are usually considered harmless or of minor interest [10]. Many common infectious diseases could now become very difficult to control, as for example pneumonia, caused by Haemophilus influenzae or Klebsiella pneumoniae that have developed resistance to the first line of drugs or tuberculosis, due to the emergence of multidrug-resistant Mycobacterium tuberculosis. More than that, for some bacteria the last line of treatment is about to collapse, as is the case of

Staphylococcus aureus and vancomycin. This is particularly alarming in hospital settings, where resistance problems are usually detected earlier, and concerns various pathogens and not only resistant strains. Economic and social consequences are much wider than health care only, and are progressively gaining the attention they deserve. Neither the table of preference erga omnes of antibiotics nor the armament for the detection and control of resistance in hospitals are evenly distributed, though the problem is (and will even more be) universal, as are the pathogens that show resistance. The need to address the problem under the One-Health concept is being recognized, and although, the body is not mortal, society might incur in lots of trouble in the short and medium term. For this reason, and just stretching a bit the old Millennium oration, serious work has "to eliminate the threat [of antibiotic resistance] in the 3As, by using as the road ahead, vigilance, prevention and concerted action [of the global community]". [11][12][13]

1.2. Historical Context and Evolution of Antibiotic Resistance

Since their advent, antibiotics have caused a revolutionary change in medical practice and the successful management of bacterial diseases. Wounded soldiers have been successfully treated due to antibiotics, which has significantly reshaped mainstream healthcare. However, within a couple of decades of their first use, bacteria resistant to antibiotics had already been isolated. The ability for certain bacteria to resist the effects of drugs or other biocidal agents is not a new biological phenomenon, and, indeed, the ontogeny of resistance predates the first ever use of antibiotics. A mutation leading to streptomycin resistance had already existed in Mycobacterium tuberculosis strains before streptomycin emerged as the treatment of choice [1]. Resistance of the enteric bacteria that cause dysentery appeared due to the en masse oral treatment of this disease with dose una, an ancient Chinese therapy based on the premiere antibiotic of the early 20th century, sulfanilamide. The origins of resistance mechanisms against antibiotics, therefore, long predate the years between the late 1940s and 1970s when the antibiotic resistance crisis took off in full force. While the specter of the wide dissemination of multidrug resistance in common pathogens is a relatively new and increasingly worrying development, the picture is not altogether bleak. Several episodes in the past have shown that it is possible to successfully stem or avert the escalation of the situation to a "post-antibiotic" era [14]. This history is rife with all too often forgotten lessons that remain relevant today, and an understanding of the past is thus crucial for the development of an effective strategy to tackle the morass of contemporary pathogens resistant to antibiotics. The interplay between the indiscriminate use of antibiotics and the emergence of resistant strains will be addressed, with a closer focus on the societal and clinical practices that have allowed this age-old back-and-forth battle to escalate into a problematic crisis in the late 20th and early 21st centuries. [15][16][7][17]

2. Mechanisms of Antibiotic Resistance

Antibiotics are substances that suppress the growth or destroy pathogenic or disease-causing bacteria. The discovery and development of antibiotics has been one of the greatest achievements in medical history. Since then, pathogenic bacterial infections have been controlled effectively and human beings' life span and expectations of life have significantly increased and brought down the morbidity and mortality caused by bacterial infections [18]. Although antibiotics have conquered some infectious diseases, current pathogenic bacteria have developed the mechanisms of antibiotic resistance [19]. Despite a continual flow of new antibiotics, both naturally derived and synthetic, bacteria readily evolve mechanisms of resistance—and long-term solutions to the problem remain elusive. This article reviews some of the underlying mechanisms of antibiotic resistance and discusses current research and development of alternative, bacteriostatic strategies. [7]

There are two types of antibiotic resistance in pathogenic bacteria: intrinsic resistance and acquired resistance. The former refers to a natural and existing property of a species of bacteria. It has evolved alongside the presence of the antibiotic or a similar substance in the natural habitats of the organisms. For example, the outer membrane of Gram-negative bacteria reduces their susceptibility to harm by hydrophobic antibiotics, the presence of which in fact triggers the induction of efflux pumps and endogenous endonucleases that degrade the DNA of the attacking organisms. Furthermore, colonization resistance prevents potentially pathogenic microbes to colonize the exposed surfaces of the human body. Acquired resistance on the other hand is specific for antibiotics, which only comes into being after an organism has been exposed to these substances. It is driven by the acquisition of genetic information. Two crucial mechanisms of acquired resistance are spontaneous mutations in the genetic material of an organism, or horizontally acquired resistance genes. In the latter case, genetic information for antibiotic resistance may be transferred between bacteria of different species by so-called mobile elements, such as plasmids or transposons. [7][20][21]

2.1. Intrinsic vs. Acquired Resistance

Antibiotic resistance is one of the most serious threats to global public health. Whilst considerable research has been devoted to understanding the mechanisms underlying this adaptability, treatment strategies have not shown commensurate progress. In order to develop more effective strategies, a clearer elucidation of both the mechanisms of resistance and the ways in which bacteria adapt is required. This section provides a brief primer on bacterial adaptability in the face of antibiotic challenge as a foundation for more comprehensive studies to follow. [22][23]

2.1. Intrinsic vs. Acquired Resistance

When exploring bacterial adaptability to antibiotics, it is useful to outline the fundamental differences between intrinsic and acquired resistance. Intrinsic resistance is defined as the inherent ability of some bacteria to resist certain antibiotics due to structural or functional properties built into them as part of their genetic composition. For example, the outer membrane of Gram-negative bacteria acts as a barrier, preventing the entry of large molecules including many antibiotics [24]. Conversely, acquired resistance results from genetic mutations in susceptible bacteria or the acquisition of new genes through horizontal gene transfer, which either prevent the antibiotic from acting as intended within the bacterium or enable the bacterium to actively degrade the antibiotic. This provides a trait that allows the bacteria to adapt to the presence of an antibiotic and subsequently proliferate in its presence [25]. Intrinsic resistance can be thought of as the normal, constitutive characteristics of a species, akin to the natural browsing height of a giraffe being taller than the feeding range of other herbivores. Subtle variations in this height would resemble low-level genetic alterations in a bacterial species that have little broader consequence. Breadth of diet, on the other hand, can be thought of as akin to acquired resistance, making it possible for a population to adjust to a new circumstance over the course of multiple generations. Thus, acquired antibiotic resistance entails a significant, often quite specific development in the genetic make-up of a given bacterial population, providing a trait that aids in the expansion and transmission of that population. The development of two distinct, yet complimentary, ‘routes’ by which bacteria may adapt to antibiotic challenge provides the potential for the development and existence of both extremely broad and highly nuanced adaptive pathways. Environmental material (antibiotics) then shifts from an uninfluential niche variable to a selective agent. Amplification of the hypothetical dietary adaptation would enable these giraffes to flourish and eventually outcompete other herbivores, leading to a possessor dependant evolutionary escalation to taller plant forms. The implications of this adaptability are vast, and their comprehension is vital for the intelligent development of strategies to counter the exponential increase in the clinical prevalence of multi-drug resistant ‘superbugs’. [16][26][20][27]

2.2. Genetic Basis of Resistance Mechanisms

The genetic basis of resistance mechanisms in bacteria is addressed. The first section deals with chromosomal mutations and the emergency of bacteria with low permeability to antibiotics to their targets. Plasmids and transposons are often associated with various resistance traits subjected to selection by antibiotics. In all cases the molecular basis of the resistance mechanism is examined and particular genes associated with resistance are noted. In the final part the role of gene transfer mechanisms in the spread of resistance is considered. The developmental harvest of plasmid and chromosomal genes conferring resistance to antibiotics in bacteria of clinical, veterinary, and agricultural importance is a worrying feature of contemporary world, because of the extremely efficient ways of transporting these genes between unrelated bacteria. By analyzing the genetic basis of the resistance mechanisms, a capacity of bacteria of different species is acquired to counteract the lethal action of structurally unrelated compounds. Common pathogens of humans developed various means of overcoming nearly all major families of antibiotics presently in more liberal clinical usage, such as ß-lactams, aminoglycosides, tetracyclines, chloramphenicol, quinolones, and others [25]. [7][28]

Antibiotics do not cause resistance but frequent and high exposure of antibiotics to bacteria creates a selection pressure which triggers resistance strategies of bacteria. Genes responsible for resistance are often found on plasmids or other mobile genetic elements of bacterial chromosome. Their presence on mobile genetic elements facilitate transfer to un-related bacteria in a process referred as horizontal gene transfer (HGT) via conjugation, transduction, or transformation. Movement of cellular DNA among closely linked bacteria is referred as transformation. Conjugation requires autonomously replicating genetic elements known as conjugative plasmids that cause the movement of plasmid from donor cell to a recipient cell. The movement of genes confers new metabolic capabilities to the recipient, thereby at the same time increasing their adaptive potential and competitive advantage in both natural and man-made ecosystems. [2][29][30]

2.3. Mechanisms of Resistance in Different Classes of Antibiotics

2.3. Efflux drug transporters at the forefront of antimicrobial resistance

Antibiotics represent the best approach to cure pathogenic bacterial infections. Consequently, antibiotic resistance is a major problem, compromising the treatment of bacterial infections. It has been twenty years since the first case of bacterial strain resistant to antibiotics within a clinical environment was reported. It has been confirmed that most pathogenic bacteria employ multiple resistance mechanisms in response to antibiotics, while the formation of biofilm adds further complexity to the development of resistance. Bacteria, archaea, and the eukaryotic unicellular organisms (yeast and fungi) employed a similar molecular mechanism of efflux to protect them against noxious chemicals, including antibiotics. In prokaryotes this defense mechanism was demonstrated with the operation of five superfamilies of energy dependent efflux pumps. Apart from mentioned organisms, some parasites, including helminths and insects also use this protective system. This review will focus on an evolutionary and mechanistic aspect of drug efflux and its role in antibiotic resistance in clinically-relevant pathogenic bacteria [31]. To date, the rapid emergence of bacterial antibiotics resistance has become a great threat to public health. The main studied resistance to antibiotics strategies are formed by changing the target sites through genetic changes, drug enzymes synthesis to inactivate antibiotics, penetrating bacterial membranes limitation, with efflux pumps reduction the intracellular antibiotics accumulation. Exactly, efflux systems are inclined to remove various kinds of antibiotics like fluoroquinolones, dyes, detergents, CCPs and biocides similarly, so efflux pumps were decided to known ability the wide range of antibiotics exporting this review will present the classification of the main escapes mechanism trying to reduction antibiotics effectiveness and making resistance on that bases disease more complex and serious [32]. [7][33][34][9]

There are a number of strategies employed in the bacterial kingdom to evade the antibiotic action. These strategies can be categorized according to the kind of antibiotics the bacterium is confronted with. It is intended in this section to first classify resistance strategies according to different antibiotics, followed by an analysis of each resistance strategy of each antibiotic class in the bacterial landscape. This review attempts to organize examples of resistance mechanisms to penicillins, tetracyclines, macrolides, streptogramins, aminoglycosides, quinolones, rifamycins, sulfanomides, and polymyxins according to the aforementioned approaches the bacteria make to evade antibiotics. Broad and clinically relevant examples are chosen. There are surely other antibiotics that are commonly used in clinics, but this review does not attempt to exhaust all examples. Generally, bacteria evade the actions of antibiotics by: changing the antibiotics (e.g. modification or degradation of antibiotics) thus they are not harmful; modifying themselves so the antibiotics are ineffective; reducing the amount of antibiotics internalization, or actively expelling antibiotics by employing efflux pumps. On the other hand, antibiotics exert their action by: impeding the inhibition of essential biosynthetic pathways (e.g. specific protein synthesis, DNA replication, or repair of cellular structures); cause leakage of cellular content, or membrane disorganization. The first group of antibiotics is mainly the older classes such as penicillin and streptomycin whereas the second group belongs to the most recent discovery such as polymyxin. [35][36][37][38]

Materials and Methods

3. Epidemiology of Antibiotic Resistance

Resistance to antibiotics has been observed almost immediately after the drugs have been implemented in healthcare settings. Because the spread of resistance across bacterial populations and the development of resistance genes typically happens much more quickly, informed policy is needed to detect and curtail resistance before it becomes widespread. During the last decade of the 20th century, resistance to traditional antibiotics adopting and spreading among bacterial populations in virtually every corner of the globe. Bacterial strains that are resistant to antibiotics have now been found from the remote regions of the Antarctic to the most populous African and Asian countries. Trends in the emergence and spread of resistance to individual drugs can vary vastly across different local populations or geographic regions, overuse and misuse of antibiotics by both narrow and broad-spectrum agents and over the counter distribution of these drugs to treat infections. Healthcare and agricultural settings have been in the recent past and continue to occupy a significant chunk of the footprint that has been catalyzing and facilitating the spread of resistance [39]. Within healthcare settings, a particularly alarming development is manifested by hospital-acquired infection; the incidence rates and distribution of infection caused by drug-resistant organisms should drive the lesson home about the clinical backdrop for what continues to pose a serious public health crisis, which governments and healthcare providers everywhere have yet to get their heads around, and act accordingly. To compound all this, the rate of resistance development is frequently higher in the low and middle-income countries, a subgroup of global society that generally pairs higher rates of infectious disease burden with, on the whole, poorer health infrastructures and lower access to medical services [40]. Socioeconomic and geopolitical factors also tend to maintain and exacerbate the spread of resistance to drugs by forcing people, for instance, to rely on substandard or counterfeit drugs, which, if they do contain some active agent, are found to rapidly cause the emergence of resistance. [41][16][42]

3.1. Global Trends in Antibiotic Resistance

Serious infectious diseases caused by bacteria that have become resistant to commonly used antibiotics have become a major global healthcare problem over recent years [43]. Although antibiotic resistance is a natural phenomenon, it has reached dangerously high rates worldwide. Variations in resistance rates across countries are striking, often without any discernible pattern in relation to their national income, healthcare, or other well-known factor. In part, these disparities reflect differences in institutional and financial capacity for monitoring and controlling resistance, and in some less developed countries basic resistance monitoring systems do not exist. International monitoring programs have, however, documented the increase of multi-drug resistant organisms both in hospital and community-acquired infections and in more and more locations. Travel is speeding the spread of resistant strains; resistant bacteria spread not only through travel-associated diseases, but also through carriage in healthy travelers and through travel-related enterprise. Globalization of agriculture and food trade also help resistance to spread. Despite the large differences among the developing and developed world, the same general phenomena are observed worldwide. Antibiotic resistance commonly starts in the late 70s followed by a certain lag to the introduction of new molecule classes. The increase is in first instance linear, then accelerating; a crash in the healthcare system is usually happening when high resistance rates are finally widely recognized, often with the collapse of the communitarian healthcare or with the recognition of a local hotspot. Misuse or overuse of antibiotics is the typical abundant soil where resistance grows. Industrialized countries currently in a high resistance phase follow developing countries in a few decades, when resistance rates start to increase developing countries are observed at the beginning of the same linear acceleration process. These observations signal out a series of hotspots deserving full attention from a global risk perspective. As already stressed, organized responses are less powerful, when IMO is at work biosphere amplifies the potential effect. Furthermore, a combined approach involving intensifying schemes in a given location with a sudden deflecting strategies in bordering areas is still beyond practical feasibility. In light of the above, antibiotic resistance appears fully as a globally connected risk; the urgency for coordinated global action is unequivocally posed to mitigate its impact. [23][6][22][9][17][44]

Given the complexity of the issues at stake and the specificity of local conditions, it is virtually impossible for individual countries to adequately respond to this risk. The general ineffectiveness of all the therapeutic interventions carried out after resistance has grown has been extensively documented. Roughly drafted, these interventions late take in life and therefore untreated diseases grow until health systems collapse, thus pushing the resistance, during the same process increasingly ignoring the class of antibiotics that should rise successively connected to resistance patterns. Statistically, the overall trends of such array of responses, though particular timing and modalities vary consistently, are the same in almost all countries. On the other hand, the pace of the acceleration of antibiotic resistance may differ in the various locations; resisting class of bacteria and kind of diseases that more strongly push resistance are not always the same; quarantining and control on exchanges may exert a differential, though hardly predictable, effect on the speeding of resistance transmission. However, the plethora of the interacting factors involved and local specificities of the variables in combination with the general inadequacy of responses make the task of the standard global risk analysis and management relatively limited. It focuses on the few topics having a more widespread and straightforward resonance, or connected with single and well-defined points. It follows an analysis carried out in a broader and less sectorial perspective. Regarding the global risks of antibiotic resistance, adding to the awareness of policymakers, the media and the civil society at large. The object is to warn about the complex and interconnected risk facets of antibiotic resistance, the possible outcome of the acceleration of this process to typical locations, and to stress the urgency and complexity of the corrective actions required to effectively contrast its progress. [45][46][47][48][49][50]

3.2. Factors Contributing to the Spread of Antibiotic Resistance

There are a multitude of different elements that contribute significantly to the rapid and alarmingly easy spread of antibiotic resistance within bacterial populations, and these elements are often exacerbated by a societal disregard for crucial public health duties. To delve deeper into this urgent matter, the various roles played by the different contributors to resistance that fall within human control are dissected; notably, these factors extend beyond just the strict overuse of antibiotics in medical settings. The individual members of society, who remain somewhat complacent and may consider themselves mere spectators to the escalating prevalence of drug-resistant pathogens, might understandably feel helpless when confronted with such a potent and adaptive evolutionary foe. However, it is essential to recognize that not only are there more contributing factors that account for the alarming spread of antibiotic resistance than one might intuitively have scheduled an awareness of, but also that the few factors among them, which are elusive and difficult to modify, actually lend themselves to critical public health focus. A more extensive consideration of the underlying factors that lead to antibiotic resistance presents cautionary insights, suggesting the necessity for a heightened multidisciplinary approach that extends far beyond the limited current practice of merely directing resistance-prevalence efforts toward health care providers alone. Only through a comprehensive and collaborative strategy that encompasses various sectors can we hope to effectively combat the looming threat of antibiotic resistance. [39] [51][52][53][54]

Inappropriate antibiotic prescriptions in human medicine are a major, and arguably dominant, factor in the emergence of treatment-resistant bacteria within the context of hospital and community-acquired infections [55]. Consonant with common evolution thereof, the unbroken supply of antibiotic treatments exerts a selective force for the proliferation of genetic lineages within a bacterial population that independently renders them tolerant to the drug, whilst the rest, susceptible strains, are killed as the residues of the antibiotic clear commodities. Though natural barriers to the acquisition of antibiotic resistance limit human control thereupon, frequent, superfluous, and/or uncompleted drug prescriptions speed the rate of resistance spread. The inappropriate use of antibiotics for agriculture purposes is another main cause for the rise of pathological bacterial strains that defy any treatment. Administration of antibiotics to livestock is chosen from a bottom-line-oriented experimental basis, in lieu of a public health scrutiny. Sucrose doses of the drug are used to accelerate animal growth and prevent potential, disease-related economic losses. Footballs of the justification for this misuse of antibiotics revolve around the notion that there is no health detriment to those who consume such this meat after undergoing, of debatable effectiveness, mandatory withdrawal periods of antibiotics doses. [56][57][58][59]

Results and DIscussion

4. Clinical Implications of Antibiotic Resistance

There are a growing number of diseases that are becoming more difficult to treat. Many types of bacteria that cause infection are evolving to become resistant to the antibiotics we use to treat the infections they cause. As bacteria become increasingly resistant to various antibiotics, the normal routes to treat those infections are limited. As a result, there is a lack of existing antibiotics that could effectively treat pathogens involving Gram-negative bacteria. With the spread and development of multidrug-resistant (MDR) and pan-resistant strains, infections by such bacteria are increasingly becoming untreatable [43].

Antibiotic resistance is an important aspect with life-threatening consequences. For doctors, treating patients who have infections caused by resistant bacteria is just like taking up a challenge. The burden in such cases is terrifically high as most conditions are not treatable with the standard antibiotics. The emergence of infectious diseases caused by pathogens showing resistance to multiple drugs is a major clinical problem. Cases involving resistant bacteria are treated with significantly fewer antibiotics. This can only be worrying since this limitation can seriously affect the treatment options. The morbidity and mortality of patients can be increased due to infectious diseases caused by MDR and pan-resistant bacteria. This can also negatively affect the unsuccessful treatment of immunocompromised or those who need an operation of any kind as they become more susceptible to infections. Material damages can be observed during the treatment process and after treatment when the resistance spreads throughout the center. With all of these, it becomes clear that it may not be possible to apply quality care to patients affected by resistant microorganisms. In short, the effects of antibiotic resistance on human health are a worrying and frightening picture. [7][4][15][6]

4.1. Impact on Treatment Efficacy

Of most pressing concern, however, is the impact of antibiotic resistance on the efficacy of infections treatment, particularly in the context of clinical practice. Evidence of emerging resistance may lead physicians to combine traditional therapeutic regimens with a variety of alternatives but frequently less effective modes of treatment [43]. It is in the clinic where resistance patterns have the most direct consequences. Cases of the failure of front-line antibiotic treatments, followed by more holistic approaches, are becoming increasingly commonplace, with the clinical struggle against resistant strains being an arduous one. The treatment of Carbapenem-resistant Enterobacteriaceae and Methicillin-resistant Staphylococcus aureus is a significant burden in an already stretched healthcare service, among clinical consequences such as longer periods of recovery and an elevated likelihood of complications. The responsibility placed upon healthcare professionals by increasingly complex and resource-intensive treatment plans is likely to be unparalleled to date. Furthermore, there is a growing concern that attempts to arrest the development of resistance in bacteria may be lagging behind the ability of bacteria to evolve resistant mechanisms, resulting in an involutionary arms race in which the selective advantage is with those bacteria most inclined to virulence. It is important that – beyond the respondent to this threat – individual treatment practices take into account the exigency of the situation to best make use of currently available treatments. The generation of customized care-plans developed for individual patients will likely offer a better treatment outcome by improving the targeting of bacteria. Some of the more illustrative virus-side strains and a consideration of their possible implications for therapeutic approaches offer a stark reminder of the immediacy of this crisis and the high premium that can be placed upon experimental re-evaluation of the situation. [60][61][62][63]

4.2. Increased Healthcare Costs

Antibiotic resistance (ABR) is considered a challenge for healthcare systems, as it has direct tangible effects on income or resource use. There have been few economic evaluations of interventions that attempt directly to reduce or stabilize bacterial resistance or ABR; most work has modeled the effects of particular interventions. The longevity and depletion of an arsenal of first-line antibiotics, coupled with the relative paucity of new antibiotics, has sparked urgency about the reemergence of widespread bacterial resistance to therapeutics. Trade-offs between minimizing public health costs from containing resistance and the direct monetary costs of containing resistance to treatment are illuminated using an epidemiological simulation model. These costs do indeed depend on many parameters, including the efficiency, efficacy and scale of the intervention, as well as the epidemiological context, which together determine the aggregate cost of evolving resistance. [17][6][64]

Increased healthcare costs have been found to be linked to treatment of antibiotic-resistant infections. The medical cost per patient afflicted with an antibiotic-resistant infection varies from $18,588 to $29,069 according to estimates. Estimated healthcare costs due to antibiotic-resistant infections reach as high as $20 billion, with an additional $35 billion per year attributed to lost productivity. This burden extends to families and communities that face financial challenges due to lost wages or increased healthcare expenses. Ultimately, the crisis of ABR is also a humanitarian challenge, beyond just clinical or public health concern. Public and health sector policy makers face difficult choices in how to contain the spread of resistance, while caring for the sick in effective and efficient ways. Deciding what resources to allocate to R&D, improving surveillance, containment and public education programs is hard at the best of times, more so when wider historical, endemic and infrastructural issues systematically condition the effectiveness of interventions. At the same time, it is possible that ongoing or emergent resistance may relegate current treatment methods to near obsolescence, raising the specter of a substantial cost of care that will threaten the longer term financial sustainability of the health sector. [65][66][67][68]

4.3. Emergence of Multi-Drug Resistant Pathogens

Infection by a bacterial pathogen generally results in the activation of an immune response in the host cell. In order to combat an infection by a pathogenic bacterium, macrophages and dendritic cells will engulf invading bacteria in a process known as phagocytosis, which will result in the fusion of the endosome in which the bacterium is to the lysosome. This exposure will result in the degradation of the bacterial proteins and the presentation of the bacterial antigens to the immune system, generating an adaptive immune response. It is now well known that antibiotic compounds will target essential processes in the bacteria cells such as the synthesis of the peptidoglycan of the bacterial cell wall, the functions of the ribosome, etc. Because of these targets, it is to be expected that the antibiotics will also play a role in immune response. For example, it has been shown that the number of bacteria present in a macrophage will be a factor that determines the CD4/CD8 T-cell response and in turn the outcome of the infection. There is a burst of interest in this research area since a few years ago, and is likely that the coming years will see increased information on the effects of antibiotics in the host immune response against bacteria [43]. The emergence of multi-drug resistant bacteria represents a significant challenge in the time to combat infections. Pathogens have evolved multiple mechanisms by which they can acquire multiple resistance traits, and there are many reports documenting bacteria that are resistant to almost all currently available antimicrobial compounds. The implication of these multi-drug resistant pathogens in terms of public health is therefore a major concern, particularly for the risks that they pose for vulnerable populations, such as hospitalised individuals or people with pathologies that weaken the immune system. Interestingly, many studies show a link between antibiotic resistance and metabolism, and it is becoming increasingly clear that resistance may come at a metabolic cost for the bacteria. Since the availability of nutrients is a limiting factor in infected tissues, such studies highlight that weakening of the bacteria by antibiotic treatment may result in symbiotic benefits for the infection control by the host organism. In light of these observations, it is becoming clear that a better control of the training regimen may result in a more efficient way to control the infection. Beyond a deeper understanding and analysis, a multitude of investigations that are still needed in order to better understand the patterns of resistance acquisition and how best to inhibit them. A joint national and international effort in this respect, aimed at development of innovative therapeutic strategies and novel public health policies, is an urgent priority [69]. [70][4][71][72]

5. Strategies for Combating Antibiotic Resistance

Antibiotic resistance in pathogenic bacteria is an urgent, worldwide public health threat. It arises by numerous complex mechanisms, facilitating numerous bacterial pathogens in their ability to circumvent the effects of antimicrobial drugs. The consequences of rising antibiotic resistance rates are profound, as common infections and minor injuries that have been treatable for decades are again becoming life-threatening. The core aims of this text are (1) to outline the basic biological principles underlying the development of antibiotic resistance; (2) to provide a comprehensive review of the more important mechanisms of antibiotic resistance in bacteria; and (3) to review some of the most promising current and future strategies for tackling antibiotic resistance. Central to the discussion in the final part is an examination of the roles of antibiotics and of antibiotic stewardship programs, together with the development of novel antibiotic drugs and of alternative therapies. Also considered are the key roles of infection prevention and control measures and of the need to re-educate large sectors of both the general public and the medical practitioner community. [22][7][6]

5.1. Antibiotic Stewardship Programs

Antibiotic stewardship programs are crucial in the fight against increasing antibiotic resistant pathogenic bacteria. Having an antibiotic stewardship program in place as a healthcare facility, long term care facility, or any clinical setting, will help prevent the overuse and misuse of antibiotics in patient populations [73]. The Centers for Disease Control partners with other federal agencies and the public health community to implement a national strategy to combat antibiotic resistance. With this, specific goals were set to implement more effective stewardship interventions in order to optimize antibiotic use while working to maintain and advance patient outcomes. Having an antibiotic stewardship program will focus on improving patient safety measures especially as it relates to antibiotic drug exposure and reducing rates of CDI. Increasing stewardship efforts will work to improve the rapid identification and notification of resistance patterns to emerge. Published data show that effective stewardship programs correlate with improved patient outcomes and reduced antibiotic resistance rates. It’s expected that within these programs more interdisciplinary teams, especially including pharmacists and infection control personnel, will expand and garner new knowledge. This will include best practices relating to the prescription, delivery, and use of antibiotic drugs. Healthcare facilitators are highly encouraged to educate and train other healthcare providers within a facility in the principles and commitment to the stewardship of antibiotics. With prescription/discharge data analytics, antibiotic stewardship teams will be provided with greater statistical insight to inform prescribing behaviors and policy activations. Economic evaluations on costs of acute care of stewardship and outcomes relevant to the clinical nature of the current setting are useful in expanding these programs. Successful cases will add to these broadened understandings and will be used in the synthesis and dissemination of best practices relating to antibiotic stewardship programs in the clinical settings. [74][22][42]

5.2. Development of Novel Antibiotics and Alternatives

Pathogenic antibiotic resistant bacteria pose one of the most important health challenges of the 21st century. The discovery of the first antibiotic, penicillin, in the 1920s represented a revolution in public health—mortality rates from bacterial infections plummeted [75]. However, the overuse and abuse of antibiotics by the general public and in agriculture coupled with the natural evolutionary processes of bacteria has led to the present crisis. Bacteria such as Escherichia coli (E. coli), Staphylococcus aureus, and Mycobacterium tuberculosis have developed antibiotic resistance and new strains continue to emerge that can circumvent the latest drug. It is liable that deaths occurring from antibiotic resistant strains will continue to rise in the future as resistance becomes more common. There have been only incremental advances in antibiotic development in the past 30 years; novel classes of molecules and technologies are now providing new possibilities and avenues for the development of antimicrobial therapies. [6]

The WHO has predicted that by 2050 10 million people will die annually if no new treatment is found. The emergence of extensively drug-resistant (XDR) tuberculosis in South Africa has raised great concern. Bacteria have been found that are resistant to the last line of defense antibiotics. The rise in resistance has occurred as a function of two main factors. Firstly, exposure of the infectious bacteria to biocides due to their extensive use in households and hospitals. This has meant the unscreened spread and creation of quaternary ammonium compounds, triclosan, and other biocides that are similar in action to antibiotics has exacerbated the problem. Secondly, the abuse and overuse of drugs, some of which are given prophylactically, can kill both harmful and beneficial bacteria in the gut. Only a fraction of bacteria within a human body can be treated with the antibiotic, and some may become resistant and further exchange resistance genes with other bacteria. However, the new technologies and strategies that are currently being developed tackle a broad spectrum of resistant bacteria or disease-causing bacteria. [76][77]

5.3. Enhancing Infection Prevention and Control Measures

5.2. Decolonization and Pathogen Reduction Approaches to Prevent Antimicrobial Resistance

Interrupting transmission and infection caused by multidrug-resistant organisms (MDROs) in healthcare settings can help mitigate the global antimicrobial resistance (AMR) crisis, reduce illness and death, increase patient safety, and extend the usefulness of currently available antimicrobial medications [78]. A major strategy in these endeavors is improving infection prevention and control (IPC). Effective prevention of new MDRO infections or colonization from occurring would drastically transform the threat MDROs pose. Current methods, however, are insufficient, and the recent increase of AMR necessitates new approaches. 10-year UK-AMR plan: one of the strategies within a strong IPC program. Despite the global success of such efforts in reducing illness, AMR development, and death, recent downward trends in healthcare-associated MRSA infections have reversed as of the COVID-19 pandemic [79]. In the United States, infections caused by resistant organisms increased by 15% during the pandemic. Other successes such as effective IPC strategies, along with antibiotic stewardship, have similarly saved lives and reduced unnecessary antibiotic use, showing the potential success of intervention. Improvements in IPC also tend to be highly cost-effective. Many HAIs are preceded by colonization with the infecting pathogen, and subsequent colonization can occur with other MDROs causing illness (e.g., VRE, ESBL). Reducing colonization with MDROs can help break the chain of MDRO infection. Patients entering healthcare facilities frequently do so already colonized, often asymptomatically, which increases risk. Once colonized, patients' subsequent risk of infection rises through the use of invasive devices, receipt of antibiotics, and surgery. Pathogens most likely to cause HAIs can be transmitted through known patient contacts (e.g., visitors, healthcare workers), or indirect contact (e.g., contaminated instruments, medical equipment). [80][81]

6. Future Directions in Addressing Antibiotic Resistance

The world is currently engaged in a substantial and ongoing global battle against the alarming rise of antibiotic resistance among pathogenic bacteria. This issue, which has been a concern since the introduction of antibiotics, is gaining increasing recognition due to its profound implications for public health and medical treatments. Awareness regarding the severity of the challenge posed by antibiotic-resistant bacteria began to increase over two decades ago. However, despite widespread acknowledgment that action must be taken urgently, the implementation of a well-coordinated global response to tackle this pressing issue is unfortunately lagging significantly behind expectations. Meanwhile, many bacterial pathogens are rapidly gaining the capability to resist the effects of most, if not all, currently available antibacterial medications and treatments. There are certain promising areas where the progressively deepening understanding of the mechanisms driving bacterial resistance is paving the way for novel chemistry that holds great potential for developing innovative pharmaceutical compounds. These promising areas encompass enhanced screening techniques that are specifically designed to discover novel antibacterial compounds, new and improved chemical methodologies that facilitate better penetration of the drug molecules into bacterial cells, and methods for altering the pharmacokinetic properties of previously identified, but poorly performing early-stage candidates that still hold potential for success. Additionally, the use of bioinformatics, coupled with access to meticulously analyzed bacterial genome sequences, allows for a much faster and more effective evaluation of changes in microbial targets that are critical in combating resistance. In response to the growing threat of antibiotic resistance, it is clear that new chemical entities are still desperately needed in our fight against these hardy bacteria. However, equally important is the need for the application of diverse scientific disciplines to promote innovative methods in drug discovery and development processes. A vital component of this comprehensive strategy is the emphasis on exploring novel, non-antibacterial approaches that can help maintain the effectiveness and utility of existing and future antibiotics against resistant strains. Additionally, understanding the ecological aspects—specifically, studying domestic behaviors as well as systemic changes concerning the use of antibiotics in households, healthcare facilities, and agricultural practices—is essential. Such understanding not only further illuminates this issue but also helps us trace the journey of the drug through these interconnected systems, ultimately aiding in our efforts to address antibiotic resistance more effectively. [82] [7][15]

6.1. Technological Innovations in Antibiotic Research

Technological innovations are shaping antibiotic research. Developed in the 20th century, many antibiotics are becoming rapidly ineffective against their bacterial targets. As a response of bacteria to these antibiotic compounds or their natural analogs, many strategies have been developed for survival, proliferation, and spread. These bacteria are considered antibiotic resistant. There is, therefore, a growing demand for new antibiotic therapies. Researchers and engineers have developed novel microbiological, engineering, computer science and other ways to increase the effectiveness of antibiotics and expand the scope of their work. [83][41]

One important area of innovation is the development of new drug discovery techniques and approaches for antibiotics. Such methods as high-throughput screening and computational modeling are being adapted to antibiotic discovery. The role of synthetic biology in the creation of both new antibiotics and the improvement of existing therapeutics based on antibiotics is blooming. New engineering techniques greatly facilitate the creation of synthetic bacterial defense mechanisms, bacteriophages, and other tools. These techniques can also be used in the production of antibiotics. For example, genetically modified bacteria are used to produce analogs of traditional antibiotics, ativation of the synthesis of which is oppressed in bacteria. There is a growing market for similar analogs, because the pathogens almost ceased to develop resistance to them. [84][85]

Another important area of innovation is the development of new methods for tracking antibiotic resistance and understanding its patterns. The increased availability and constant decrease in price of sequencing have spawned countless projects to analyze the resistance of pathogens at the genomic level; mathematical modeling and the development of new statistical tools have advanced the understanding of the spread of antibiotic resistance in microorganism populations; the reverse engineering methods of the study of biological systems have shed light on both the classical and novel defense mechanisms of bacteria. It should be pointed out that very few innovations in the field of antibiotics research will be isolated from the academic environment or the close collaboration between academic and industrial teams. This because the basic scientific problems arising in this area usually lie at the junction of several scientific fields and are difficult to solve within the framework of a single group. On the other hand, such solutions usually depend on a large number of factors and require an integrated approach. Finally, there is a tendency to use the most advanced scientific methods. One of the fastest growing areas of research in medical chemistry is the use of artificial intelligence to identify new antimicrobial compounds ([86]). [67]

6.2. Global Collaborative Efforts and Policies

It is acknowledged by communities of inquiry that antimicrobial resistance may reasonably be classifiable as a problem of global proportions [87]. "It is a problem that spans countries and continents, and it is a problem too big for nations on their own to handle; indeed, most low and middle-income countries will struggle, if not be unable to tackle antimicrobial resistance alone. However, strong, cooperative, civil society coalitions and supportive provincial and national governments are laying the foundation for this model of advocacy that breaks down the distinction between the local and global" [88].

It is recognized that primary responsibility for public health rests with national authorities and that collaboration among nations "to promote and protect the health of the world's people may have the greatest chances of success". It is further acknowledged that local government "has a duty to understand and take responsibility for ensuring that antibiotics are used appropriately and effectively, and that adequate pharmaceutical and clinical services are in place to guarantee this". This partly involves ensuring that, at an institutional level, health workers have the proper expertise to understand and treat illnesses; awareness of the nature, causes, and effects of antimicrobial resistance among health care providers; participation in disease surveillance, and allowing regular strains of bacteria the chance to prevail and to defer the use of antibiotics to cases of clear need. Other suggested measures include the establishment of international frameworks for the sharing of all the above, running campaigns to inform the public of this, the development of a common research agenda and funding proposals to assist research in these areas, and the fostering (at a global level) of public-private partnerships to facilitate research and access to drugs and medical technologies. Because antimicrobial resistance takes on a different character in different places and because what is required may differ between infections, it is suggested that those tasked with writing funding policy papers become self-conscious of these considerations. Alliance at all levels and among all admissible parties—patients, doctors, pharmaceutical companies, their partners in the bio-pharmaceutical industry, governments, academic researchers—are held to be imperatively required if this threat is to be managed. [89][90]

Conclusion

Antibiotic resistance has surpassed an alarming level worldwide. Pathogenic bacteria have developed several mechanisms to neutralize the effects of antimicrobial agents, and the rate of emergence of resistant strains is proceeding rapidly. The best example of the widespread events of antibiotic resistance in pathogenic and opportunistic bacteria is methicillin-resistant

Staphylococcus aureus, vancomycin-resistant enterococci, extended-spectrum β-lactamases–producing E. coli and Klebsiella spp., and carbapenemase-producing Pseudomonas spp. and Acinetobacter baumannii. The consequences of antibacterial resistance is further complicated by the pathological problems of being non-antibacterial sensitive strains. Research is being carried out to overcome antibacterial resistance. However, the complete removal of these resistant strains and the simplicity of treatment is a multidimensional challenge, It is necessary and urgent for the control of antibiotic resistance by state organs and health organizations. In the last decade, antibiotic resistance has not been prevented despite the significant increase in knowledge on the subject and the decrease in the use of inappropriate antibiotics. Moreover, efforts have to be made to remove resistant strains and non-antibacterial pathogenic strains together. The ability to adapt to environmental conditions is making this a multidimensional subject. Because of the rapid spread of the mechanisms that cause the bacteria to resist antibiotics, it is clear that this issue can only be overcome with a collective mind and in the global dimension. In addition to the development and determination of new antibiotic agents, the opportunities for the treatment of the pathogenic agent should be well evaluated. There should be a variety of antibiotic agents that work on different points on the pathogen. However, most of the studies are carried out on the target point of pathogen cell walls, DNAs, or protein synthesis. This is the most striking point and offers alternatives. To help prevent resistance to these points, agents that disrupt other cellular structures or molecular functions should be investigated. The requirements of global collaboration and effective policies are urgently needed. It is vital to develop effective measures to limit the use of antibiotics in community and clinical settings and restrict the availability of antibiotics. Education and awareness are fundamentally important for infection prevention and control. Effective strategies such as drug regulation and bio security measures are needed to restrict antibiotic use together with immunization campaigns. Despite these measures, antibiotic resistance is continuously emerging and evolving, making it among the most notable challenges of the global healthcare system.

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