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REVIEW ARTICLE

An increasingly dangerous threat to global public health: Anti- microbial resistance

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Abstract: Infectious diseases have claimed millions of lives, making antibiotics one of the greatest discoveries ofthe 20th century. Antibiotics, antivirals, antifungals, and antiparasitics are examples of antimicrobials, which are drugs that are used to treat and prevent infections in humans, animals, and plants. Antimicrobial Resistance (AMR) is the result of an organism's gradual change over time that causes bacteria, viruses, fungi, and parasites to become resistant to antibiotics. This makes infections more difficult to treat and raises the risk of disease transmission, serious illness, and death. Drug resistance makes antimicrobial drugs like antibiotics and others ineffective, making itharder or impossible to treat infections. Our ability to treat common infections is still in danger due to the emergence and spread of drug-resistant pathogens that have developed new resistance mechanisms, or antimicrobial resistance. The rapid global spread of "superbugs," or multi- and pan-resistant bacteria, which causeinfections that are resistant to current antimicrobial treatments like antibiotics, is particularly concerning. If coordinated cooperative action is not taken immediately both within and across various national and internationalorganizations, a post antibiotic era may become a reality rather than a dystopian nightmare for the twenty-first century. The mechanisms and contributing factors to microbial resistance as well as important tactics to counteract antimicrobial resistance are highlighted in this narrative review.

Keywords: Antibiotic Resistance; Health care associated infections; Drug development; Global health crisis; Stewardship; Emerging resistance.

1. Introduction

Drugs known as antibiotics either eradicate or inhibit the growth of germs. They are widely employed in the treatment of bacterial infections in humans and animals. It is necessary to use antibiotics precisely as prescribed in order to prevent antibiotic resistance. The development of resistant bacteria can result from misuse or overindulgence, which makes illness treatment more challenging. Always take the recommended course of antibiotics to the end, even if you start feeling better. Every medication used to treat viral, bacterial, fungal, or parasitic infections as well as long-term conditions like cancer and diabetes will eventually cause tolerance or resistance. This also applies to illnesses brought on or experienced by any living creature, such as humans, fish, plants, insects, animals, and so forth. Many physiological and biochemical processes are the basis of resistance.

Microorganisms that develop resistance to antibiotics are sometimes referred to as "superbugs". This leads to ongoing infections in the body, which reduces the effectiveness of the medications and increases the risk of infection spreading to other people. To address the growing threat that antibiotic resistance poses to public health globally, action must be taken by all facets of government and society. Since the discovery of antibiotics, there has been antimicrobial resistance, or AMR[1,2].

Over time, a number of factors have contributed to the worsening of the issue, including the use of antibiotics in agriculture, inappropriate prescription practices, and patients not completing prescribed courses. The main cause of antimicrobial resistance (AMR) is overuse and misuse of antimicrobial agents, such as the use of antibiotics, antivirals, antifungals, and antiparasitics. Globalization, misuse in agriculture, overprescription and incorrect use, and a lack of new antibiotics are among the issues that need to be addressed. Because of their importance in treating and preventing infectious diseases, antimicrobials must be kept as effective as possible. This is especially important in light of the recent death of noteworthy discoveries of novel molecules. Along with significant antimicrobial agents, the narrative review focuses on the mechanisms, causes, and contributing factors of microbial resistance strategies[3].

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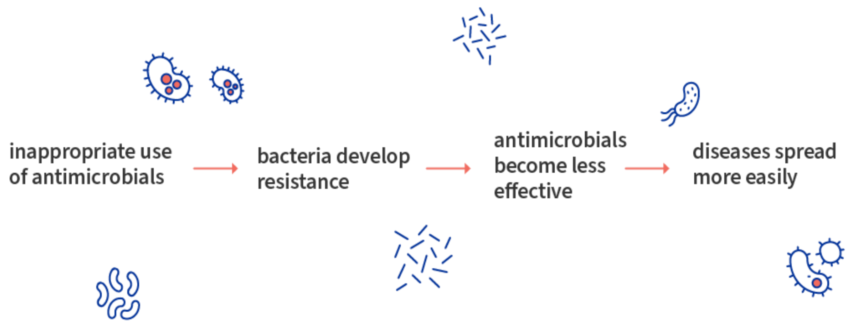

Figure 1 Antimicrobial Resistance

2. Antimicrobial resistance

2.1 History of antimicrobial resistance

Antibiotic usage is widely used, and this has led to a number of decades' worth of antimicrobial resistance (AMR). Below is an in-depth synopsis: In the 1920s and 1940s, antibiotics were discovered. Penicillin was discovered in 1928 by Alexander Fleming, marking the beginning of the antibiotic era. Other antibiotics, including tetracycline and streptomycin, were developed in response to this breakthrough. By effectively treating bacterial infections, these medications transformed medicine. The 1940s–1960s were the "Golden Age" of antibiotics. The heyday of antibiotics was the years following World War II. The efficacy of these medications seemed miraculous, and they were widely used to treat a variety of bacterial infections. But this is also the period when antibiotic overuse and misuse began. From the 1950s to the 1970s, there was a rapid expansion in the range of antibiotics that could be obtained through the pharmaceutical industry[4]. Antibiotic overuse and misuse have increased since the 1960s as a result of their increased accessibility. For viral infections, for which antibiotics are useless, patients frequently demanded antibiotics. Antibiotics were used both as a preventative measure and to stimulate livestock growth in agriculture. From the 1970s to the present, the evolution of resistant strains has been facilitated by the widespread use of antibiotics, which has imposed selective pressure on bacteria that multiply quickly[5,6]. Drugs that were once effective became less effective as a result of the evolution and spread of these resistant bacteria. Travel and Globalization (Late 20th Century): The global spread of resistant bacteria was aided by an increase in foreign travel.

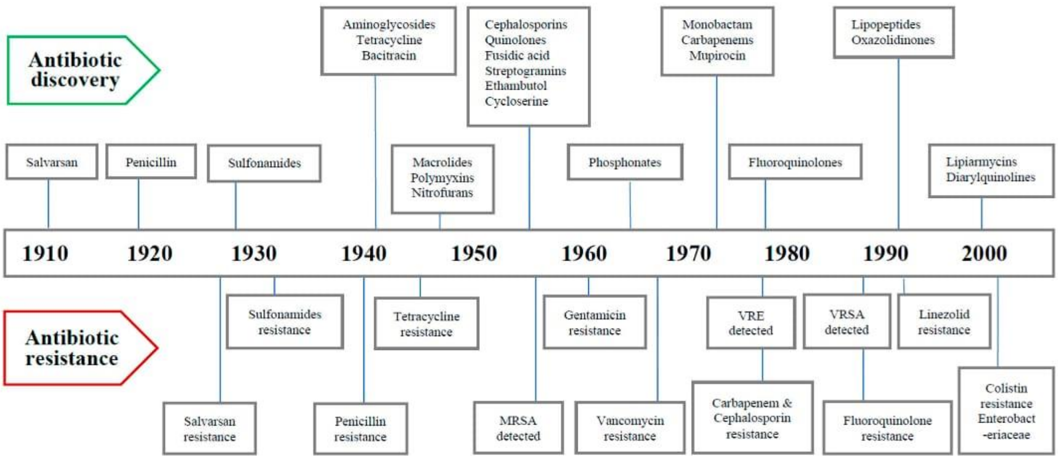

Figure 2 History of Antimicrobial Resistance

The world could soon be affected by resistant strains that spread from one area. The twenty-first century saw a slowdown in the discovery of new antibiotics, despite the rise in resistance. An antibiotic pipeline gap resulted from pharmaceutical companies' difficulties in discovering antibiotics that were economically feasible. The World Health Organization (WHO) and other organizations have identified antimicrobial resistance as a major global health threat of the twenty-first century. Ineffective standard treatments are caused by resistant infections, which raises mortality and healthcare expenses[7,8].

2.2. Mechanism of drug resistance

The summary of common mechanisms for drug resistance is as follows: drug modification through enzymatic means, alteration of the antimicrobial target, and inhibition of drug penetration or accumulation.

2.2.1. Drug modification or inactivation

Antibiotics that are hydrolyzed or chemically changed by resistance genes to become inactive can be rendered inactive. Resistance to several antimicrobial classes is caused by this mechanism. By impeding the drug's ability to bind to its bacterial target, for example, the enzymatic transfer of chemical groups to the drug molecule can lead to aminoglycoside resistance. The β-lactam bond in the drug molecule's β-lactam ring may be hydrolyzed by an enzyme, leading to bacterial resistance in the case of β-lactams. Should the β-lactam bond be broken, the drug loses its antibacterial properties. β-lactamases are the most common mechanism through which β-lactam resistance occurs. Adenosine diphosphate (ADP) ribosylation, glycosylation, phosphorylation, and resistance to lincosamides and macrolides are the common ways that rifampin becomes inactive[9].

2.2.2. Prevention of cellular uptake or efflux

Because antimicrobial medications prevent the drug from entering the target cell, they can build up in microorganisms and cause resistance to them. This strategy is commonly used by gram-negative pathogens and may involve changes to the lipid composition, concentrations, or selectivity of porin channels in the outer membrane. For example, OprD porin, the primary aperture through which carbapenems enter the pathogen's outer membrane, is commonly reduced in Pseudomonas aeruginosa in order to confer resistance to the antibiotic. Additionally, many gram-positive and gram-negative pathogenic bacteria produce efflux pumps, which actively transport an antimicrobial drug out of the cell and prevent it from increasing to an antibacterial level. Resistance to β-lactams, tetracyclines, and fluoroquinolones, for example[10].

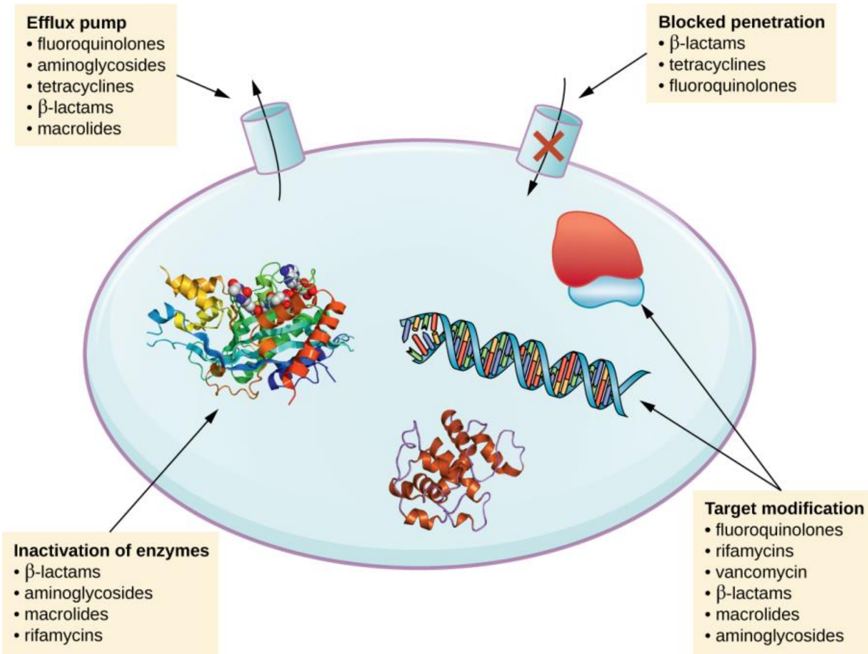

Figure 3 Mechanism of Drug Resistance

2.2.3. Target modification

Drug binding to antimicrobial medications can be hampered and the medication rendered ineffective by structural changes to their highly specific targets. Because of a natural selection advantage, bacteria can spontaneously mutate the genes encoding antibacterial drug targets, leading to the development of drug resistance. Many people have seen this process of resistance development. Mutations in the penicillin-binding proteins (PBPs) that affect their active site have the ability to inhibit the binding of β-lactam antibiotics and give resistance to multiple medications in this class. Genetic mechanisms are a common means by which Streptococcus pneumoniae strains modify their own PBPs. Staphylococcus aureus strains achieve methicillin resistance (MRSA) by acquiring a new low-affinity PBP, rather than structurally altering their existing PBPs[11].

2.2.4. Extended spectrum beta lactamase- producing gram-negative pathogens

Extended-spectrum β-lactamases (ESBLs) are produced by gram-negative pathogens that exhibit resistance to antibiotics that go far beyond penicillins. All penicillins, cephalosporins, monobactams, and β-lactamase-inhibitor combinations are resistant to the spectrum of β-lactams inactivated by ESBLs, but not carbapenems. The fact that the genes encoding ESBLs are typically found on mobile plasmids that also carry genes for resistance to other drug classes (such as tetracyclines, aminoglycosides, and fluoroquinolones) and may be easily transferred to other bacteria through horizontal gene transfer raises even more concerns. Some people's intestinal microbiota contain these multidrug-resistant bacteria, but they are also significant contributors to opportunistic infections in hospitalized patients, which can subsequently spread to other individuals[12].

2.3. Sources and routes of transmission of antimicrobial resistance

In order to promote responsible use of antimicrobials and enhance surveillance, addressing AMR requires a multidisciplinary approach involving healthcare, agriculture, environmental management, and international cooperation.

2.3.1 Sources

- Overuse and Misuse of Antibiotics in Humans and Animals: AMR is greatly increased when antibiotics are overused or misused in humans and animals.
- Healthcare Facilities: Poor hygiene, contaminated equipment, and ineffective infection control procedures can all lead to transmission in healthcare facilities.
- Farming: The application of antibiotics in agriculture, including cattle husbandry, may cause resistant strains to emerge.
- Environment: Antibiotic resistance (AMR) may be exacerbated by the release of pharmaceutical waste, including antibiotics[13,14].

2.3.2 Routes

- Person-to-person: Directly from person-to-person contact, particularly when good hygiene precautions are not taken.
- Food chain: Eating food tainted with bacteria, usually from antimicrobial-treated animals or through contaminated crops.
- Water and Environment: Antibiotic residues, among other pharmaceutical residues, have the potential to infiltrate water sources and transmit resistance.
- Surgery, medical procedures, and the use of medical devices are all instances in which transmission may happen[15,16].

3. How to combat antimicrobial resistance?

The foundation of contemporary medicine consists of antimicrobial medications. Drug-resistant pathogens are posing a threat to our ability to treat common infections and carry out life-saving operations such as organ transplants, hip replacements, chemotherapy for cancer, and cesarean sections. Drug-resistant infections also harm plants and animals, lower farm productivity, and jeopardize food security[17,18].

3.1. Rational use of medicine and irrational prescribing of antimicrobials

3.1.1 Situation in developed countries

The concept of the rational use of medicines is a few thousand years old, as evidenced by the statement made by the Greek physician and earliest anatomist Herophilus, "medicines are nothing in themselves but are the very hands of God if employed with reason and prudence." In 1985, the World Health Organization (WHO) defined the term "judicious or rational use of medicine" (RUM) as "Patients receive medications appropriate to their clinical needs, in doses that meet their requirements, for an adequate period of time, and at the lowest cost to them and their community." Also, the World Bank has defined RUM in terms of two levels: (i) the use of medications based on scientific data about drug safety, efficacy, and compliance; and (ii) the requirement to optimize medication benefits in the health system with limited resources in order to guarantee cost effectiveness. In order to deliver efficient and high-quality healthcare, RUM has been regarded as a strategic issue. Antimicrobials are almost universally classified by law as prescription-only medications in the industrialized world. Antibiotics can be purchased over-the-counter by tourists frequently, even in EU nations, according to a recent Norwegian study. Numerous efforts have been made to increase the caution and selectivity of antimicrobial prescribing as a result of growing awareness of the negative effects of irrational and reckless prescriptions on antimicrobial utilization and the resulting elevated rate of antimicrobial resistance. Reasonable and cautious prescription practices can be considered a sign of high-quality medical care. However, until recently, developed nations all over the world continued to experience depressingly high rates of irrational prescribing. Examples of non-concordant prescribing include rates as high as 30% in the USA, despite strict regulation by the FDA, and reports of non-concordant prescribing as high as 60% in China, where the respected National Medical Products Administration is in charge of strict drug strategies. Strong regulations, like those in Europe, don't seem to be able to stop medical professionals from prescribing antibiotics carelessly. For this reason, many developed nations have recently launched campaigns to increase public awareness of the problems and improve prescriber education regarding antimicrobial resistance (AMR)[19,20].

3.1.2. Situation in developing countries

In reality, antibiotics are sold over-the-counter in many EU countries, despite the fact that selling them without a prescription is prohibited in every EU member state. Laws mandating that antimicrobials be prescribed by registered medical professionals only also apply in a number of low- and middle-income countries (LMICs). According to reports, the private healthcare sectors in most LMICs have lax regulations and inadequate implementation, resulting in at least 19–100% of all antimicrobials being retailed without a prescription outside of northern Europe and North America. Approximately 80% of all pharmaceutical products prescribed in low- and middle-income countries (LMICs) are distributed by individuals with minimal training or education in medicine dispensing, according to data recorded by the World Health Organization. The required laws pertaining to prescription-only medication were not implemented nationwide by the regulatory agencies in numerous LMICs. So, by offering antibiotics for sale over the counter and online, pharmacies seize the chance to increase their profit margin.

Brazil and other Latin American countries are concerned about the excessive use of antibiotics, particularly when taking antibiotics for self-medication. About one-fifth of all antibiotic use in Brazil was done so for self-medication, despite laws pertaining to medicine prohibiting it. A different recent study reveals a significantly greater percentage of patients 66.2% self-medicating with antibiotics, and approximately 33% of those patients do so in the absence of any microbial illnesses. The Brazilian Health Surveillance Agency created new guidelines for the non-prescription over-the-counter sale of antibiotics in 2010. In order to prove their legitimate prescriptions for antibiotics to the public audit team during regular and ad hoc inspections, pharmacists must keep a record of their sales of antibiotics. According to this new law, pharmacists who fail to provide such proof could face serious civil and criminal penalties. According to one study, Brazil's antimicrobial over-prescription rate has decreased since these laws went into effect. Research findings indicate that the regulatory authority's strict policies and planning could potentially alter the general drug consumption scenario by encouraging the wise and responsible use of antibiotics and other medications[21,22].

3.2. Strategies to combat antimicrobial resistance

For four billion years, microbes have successfully coexisted on our planet. The microbial community has exhibited remarkable resilience in the face of various global disasters. Over time, these microscopic organisms have effectively demonstrated that the survival of the fittest The inappropriate use of antibiotics is one of many causative factors contributing to antimicrobial resistance (AMR), which is a complex natural phenomenon. The above-discussed promotion of the prudent use of antibiotics is just one component of the global, national, and local line of attack strategy that must be combined in the fight against AMR. Antibiotic demand decreases when infection rates decline. Effective strategies to prevent and control infections involve simple actions like cultivating and maintaining hand hygiene routines. The fight against antimicrobial resistance (AMR) necessitates teamwork, interdisciplinary strategies, and continuous supervision and monitoring protocols. Seven strategies were recommended by the Global Alliance for Infections in Surgery to prevent infections acquired in hospitals and communities. Increased cooperation between governments, non-governmental organizations, professional associations, and international agencies is one of the strategies suggested by the WHO. Other suggestions include the creation of new networks to monitor antimicrobial use and antimicrobial resistance (AMR), a worldwide strategy to combat the production of fake antimicrobials, financial incentives for the development of novel medications and vaccines, and the creation of new or strengthened AMR containment initiatives[23,24].

Researchers need time to overcome the scientific challenges posed by the rapidly evolving resistance mechanisms of microbes, especially those that involve cytoplasmic membrane-linked efflux pumps with broader substrate specificity and reduced cell-wall permeability. An estimated 6–8 years of research are needed to find a new antibacterial active.

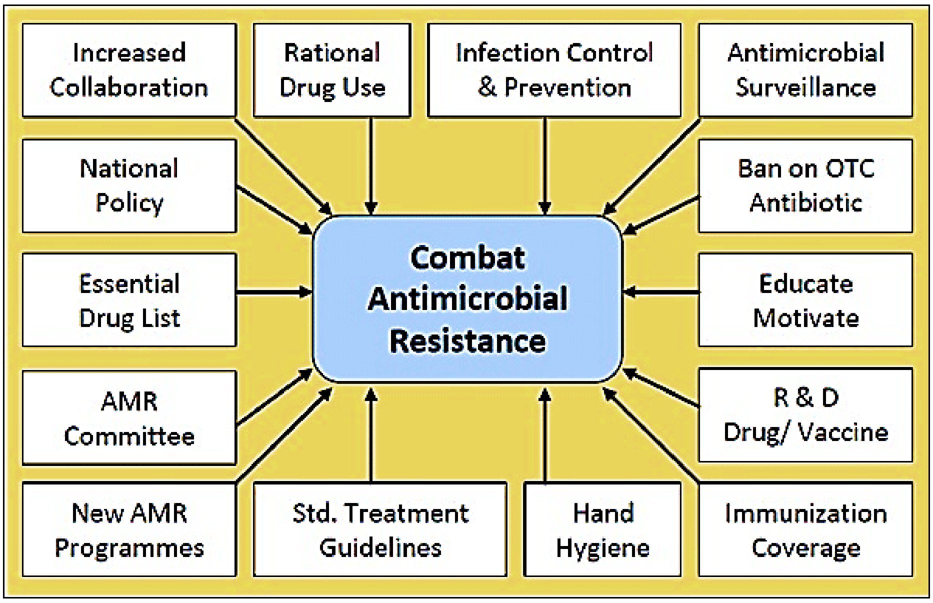

Figure 4 Several Approaches For Combating of Antimicrobial Resistance

3.3. Recommended U.S Government Action To Combat Antimicrobial Resistance

- Funding for AMR mitigation ought to be a part of any legislation passed by Congress to combat the coronavirus.
- More funds should be provided by the US to support AMR monitoring and reduction initiatives.
- The US needs to create a detailed action plan right away.
- The US should encourage R&D more.
- The US should take the lead globally in addressing AMR.
- Simplifying and improving Medicare reimbursement methods should be the top priority for the United States[25].

4. Conclusion

Amidst the current global threat of antimicrobial resistance and the urgent need to control it and find new antibacterial products, the various stakeholders have stepped up to maintain and promote the national and international antimicrobial resistance research community as well as to integrate research and public health. A cooperative research project named the Joint Programming Initiative on Antimicrobial Resistance has garnered support from 18 European nations as well as Canada in response to this threat. With the understanding that collaboration is the only way to achieve the critical mass and scientific expertise needed to tackle the most important and urgent research questions regarding antimicrobial resistance, it has set up a strategic research agenda. Nonprofit organizations such as Antibiotic Action, the World Alliance Against Antibiotic Resistance, and the Antibiotic Resistance Initiative, among others, are supporting other important initiatives in this process. Global coordination in the fight against antibiotic resistance will be necessary to persuade the public and decision-makers of the advantages of tackling the threat of antibiotic resistance from a medical and economic perspective.

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