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Review Article

Antibiotic Resistance: Global Threat To Public Health

Rushikesh S. Wable*, Vasant K. Jamble, Akanksha V. More

Department of Pharmacology, Delonix Society's Baramati College of Pharmacy, Barhanpur, Baramati Pune Maharashtra, India.

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ABSTRACT

Antibiotics are drugs used to prevent and treat infectious diseases in humans, animals, and plants. The problem of antibiotic resistance is linked to the overuse and abuse of these drugs and the inability of the pharmaceutical industry to create new drugs due to difficult regulatory requirements and diminished financial incentives. Many of these bacteria currently impose a significant clinical and financial burden on patients, families, and the U.S. healthcare system. The rapid emergence of resistant bacteria throughout the world jeopardizes the effectiveness of antibiotics that have transformed medicine and saved millions of lives. The molecular mechanisms of resistance to the evolution of bacteria genetics and biochemistry prove that it is difficult to maintain effective antibiotic activity, particularly due to the resistance shown to such problems.

INTRODUCTION

A phenomenon known as "antimicrobial resistance" occurs when bacteria, fungi, or viruses acquire the capacity to withstand or even completely destroy medications meant to eradicate them. Years before penicillin was ever put into the body, two members of the penicillin discovery team discovered bacterial penicillin enzymes. Alexander Fleming made the discovery of penicillin in 1928. Medication known as an antibiotic is used to treat and prevent infectious infections in plants, animals, and people. Antibiotics, antivirals, antifungals, and antiparasitic medications are among them. Antimicrobial resistance (AMR) is the state in which bacteria, viruses, fungi, and parasites cease to react to antimicrobial medications. Antimicrobial medications, such as antibiotics, become ineffective and make treating illnesses more challenging or impossible due to drug resistance. The risk of infection spread, serious disease, disability, and death rises as a result. First of all, Selman Waksman, the creator of streptomycin and a trailblazer in soil biological discoveries, initially defined "antibiotics" in a way that was significantly overinterpreted. Though it

***Corresponding Author:** Rushikesh S. Wable
Address: *Department of Pharmacology, Delonix Society's Baramati College of Pharmacy, Barhanpur, Baramati Pune Maharashtra, India.*
Email : rushiwable9321@gmail.com

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defines its application, it does not define the compound's class or natural function. The term “antibiotic” is used to refer to any class of organic molecules that, without considering the source of specific compounds or classes, suppresses or kills microorganisms through specific interactions with bacterial targets, at the risk of coming under fire from purist colleagues. Since synthetic medications interact with receptors, trigger particular cell processes, and induce biochemical mechanisms of interaction in infections, they are therefore classified as antibiotics. Trimethoprim, sulfonamide, and fluoroquinolone (FQ) are a few good examples.

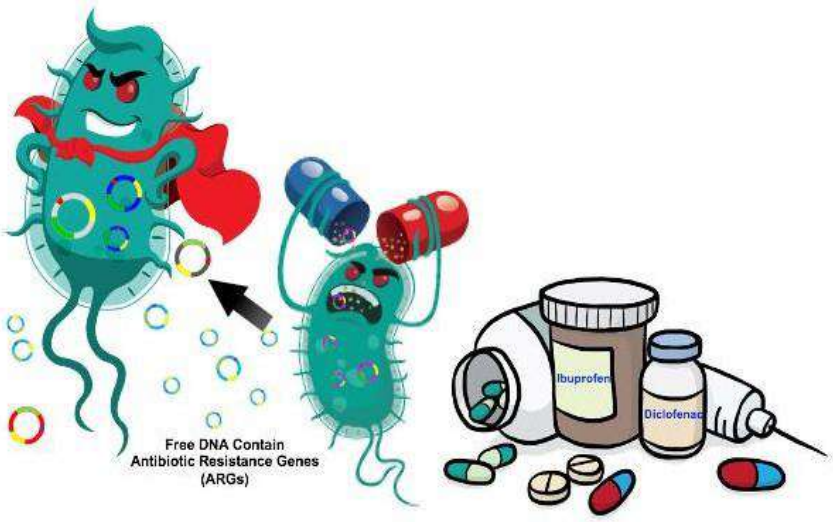

Figure 1: Antibiotic Resistance

AMR is a natural process brought on by pathogen genetic alterations over time. Its emergence and spread have been exacerbated by human activities, particularly the misuse and overuse of antibiotics in the treatment, prevention, or control of disease in people, animals, and plants. Figure 1 illustrates how the misuse and abuse of antibiotics, as well as the pharmaceutical industry's incapacity to develop new medications because of onerous regulatory requirements and reduced financial incentives, are all contributing factors to the issue of antibiotic resistance. Numerous microorganisms have been classified as urgent, significant, and concerning concerns by the Centers for Disease Control and Prevention (CDC). Currently, a large number of these bacteria place a huge financial and clinical burden on patients, families, and the American healthcare system. The world over, resistant bacteria are spreading quickly, endangering the efficacy of antibiotics that have revolutionized medicine and save millions of deaths.

HISTORY

There is ample evidence of how microbiological diseases were treated in ancient Egypt, Greece, and China. When Sir Alexander Fleming discovered penicillin in 1928, modern antibiotics were born. Since then, penicillin has transformed contemporary medicine and saved millions of lives. Penicillin was successful in controlling bacterial infections among World War II soldiers. Antibiotics were initially used in the 1940s to treat serious infections. But soon after, penicillin resistance emerged as a significant clinical issue, endangering many of the advancements made in the decade before in the 1950s. Nonetheless, the first cases of methicillin-resistant Staphylococcus aureus were discovered in the United States in 1968 and the United Kingdom in 1962 within that same decade. Regretfully, resistance was soon

found in practically all antibiotics that had been produced. In order to address methicillin resistance in both S. aureus and coagulation-negative staphylococcus, vancomycin was first used in clinical settings in 1972. Vancomycin resistance is extremely difficult to treat, hence you are unlikely to find it in a clinical setting. Nonetheless, reports of vancomycin-resistant staphylococci date back to 1979 and 1983. To address issues with antibiotic resistance, the pharmaceutical industry produced a huge number of new antibiotics between the late 1960s and the early 1980s. However, after that, the pipeline for new medication introductions started to dry up. Thus, a few decades after the first patients received antibiotic treatment in 2015, bacterial illnesses resurfaced as a hazard.

EPIDEMIOLOGY

The World Health Organization (WHO) stated in its global report on the surveillance of MRs that MRs in a wide range of infectious agents have become a serious public health problem and that the post-antibiotic era is a real possibility for the 21st century. Although there is a clear gap in the surveillance and lack of methods standards in many countries around the world, the World Health Organization (WHO) reported a very high rate of resistance for MRs associated with health care (HCA) and Community-acquired (CA). Antibiotic resistance accounted for about 700,000 deaths in 2014, and the world population is estimated to be between 11 and 444 million by 2050, lower than in the absence of the World Health Problem (O'Neill, 2014). The number of deaths due to antibiotic resistance in different parts of the world will increase by 2050, if this phenomenon is not addressed. Some countries may have resistant to antimicrobials, including India, Nigeria, Indonesia and Russia, which have already reported high rates of malaria, HIV, or tuberculosis, so that resistance to current therapies may increase (O'neill 2014). The data indicated that fluoroquinolone resistance in E. coli was reported in 92 of the 194 member states and 5 of the 6 global regions of the World Health Organization. Similarly, in 86 Member States and 5 regions, the third generation of cephalosporin resistance (probably due to extended spectrum cephalosporinase) was recorded. Comparable numbers were found for third-generation resistance to cephalosporin or carbapenem in K. pneumoniae and for methicillin resistance in S. aureus.

- **Gram-negative organisms**

Although resistance to Gram-positive clinical isolates has increased, the development of new antibiotics has partially compensated [15]. The same cannot be said for multiresistant Gram-negatives, where even the resistance of aminopenicillin is increasing and already at a high level. Plasmid-mediated quinolone resistance (PMQR) has been the subject of intense and growing concern in the last two years, despite growing concerns.

- **Streptococcus Pneumoniae**

The current levels of penicillin and macrolide resistance in Europe from some major countries. Most countries in northern Europe have lower penicillin resistance than the countries in southern Europe. Penicillin resistance and reduced sensitivity only increase significantly in Sweden and Slovenia, and the level of reduced sensitivity only increases in Finland. The reduction in sensitivity strains has greatly reduced in the United Kingdom.

- **Meticillin-resistant Staphylococcus aureus (MRSA)**

The UK appears to have the largest anomaly in almost all resistance, similar to the geographical neighbours of northwest Europe, but the MRSA has joined the club Med, the highest in the country and indeed among all the major industrialized countries in Europe. To date, this problem has

resisted major investment in infection control, perhaps because little has been done in this regard.

- **Enterococci**

Most clinical infections are caused by Enterococcus faecalis, but in recent years, Enterococcus faecium has become a major multi-resistant osocomial pathogen. On the other hand, E. faecium and E. faecalis both have high-level aminoglycoside resistance (HLAR). In Europe, most countries have a HLAR rate of 2%.

BENEFITS OF ANTIBIOTICS

In addition to saving lives, antibiotics have been instrumental in the development of significant medical and surgical advancements. They have been successful in preventing or treating infections that arise in patients undergoing chemotherapy, chronic illnesses like diabetes, end-stage renal disease, or rheumatoid arthritis, as well as complex surgeries like organ transplants, joint replacements, or heart surgery. Because they alter the course of bacterial infections, antibiotics also contribute to extending predicted lifespans. The average life expectancy of Americans today is around 80 years, compared to approximately 56,4 years in 1920. Worldwide, antibiotics are beneficial in much the same ways. Antibiotics lessen the burden of sickness and fatalities from food-borne infections and other diseases connected to poverty, even in developing nations where sanitation standards are still low.

RISK FACTOR

Antibiotic-resistant bacteria can spread to others, like any other bacteria. As a result, antibiotic resistance is widespread in the medical world.

Older people are more vulnerable.

Other risk factors for antibiotic resistance are as follows.

- Having AIDS.
- Immune suppressing therapy (such as for lupus or another autoimmune disease).
- Having cancer or going through chemo.
- Having an organ transplant.

If the antibiotics commonly prescribed no longer work, the doctor can examine the bacteria and see if the antibiotics are still working against it.

Complications from antibiotic resistance include:

- Longer hospital stays.
- Side effects from harsher medicine.
- More health care costs.
- Added follow-up doctor's visits and treatments.
- Greater risk of extended illness or death.
- Lack of treatment options.

MECHANISMS AND ORIGINS OF ANTIBIOTIC RESISTANCE

The molecular mechanisms of antibiotic resistance have been studied in depth and include research into the genetic and biochemistry of many different aspects of bacterial cell function. In fact, research into the effect and resistance of antibiotics has significantly contributed to understanding cell structure and function. The resistance process is widely distributed in the microbial kingdom and is well described in various microbial and pathogen diseases; most of them are transmitted through a different gene transfer mechanism as shown in figure 2. Several types of resistance to the evolution of bacteria genetics and biochemistry prove that it is difficult to maintain effective antibiotic activity, particularly due to the resistance shown to such problems.

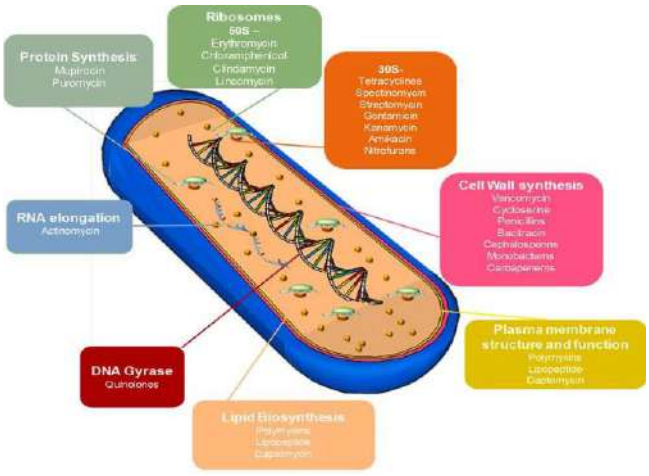

Figure 2: Mechanism of antibiotic resistance in bacteria

GENETIC JUGGLERY

The -lactamase enzyme gene is probably the most widely distributed gene in the world; random mutations of enzyme encoder genes lead to modified catalysts with an increasingly extensive resistance spectrum. The archetypical plasmid encoded -lactamase, TEM, has created a vast tribe of related enzyme families, providing sufficient evidence of its adaptability. The -lactamase gene is old and found in remote, desert environments, indicating that a new -lactamase has evolved substrate ranges. Another example is the new Extended Spectrum-lactamase (CTX-M), which was obtained from the Kluyvera strain in the environmental environment and was discovered in the clinic in the 1990s, the first enzyme to hydrolyze the Extended Spectrum Cephalosporin at a clinically significant level. The CTX-M genes and subsequent variants (so far more than 100 different amino acid substitutions have been identified) are highly effective in transmission and are a global phenomenon and threat. Such r-gene epidemics with effective HGT and rapid mutational radiation are almost impossible to control. Macrolide antibiotics such as erythromycin and its successors are widely used to treat gram- positive infections in order to deal with the problem of methicillin resistance. It is not surprising that resistance strains are now widespread because of a variety of different mechanisms. Macroscopic drugs and related antibiotics are bound to different sites in the 50S ribosomal subunit peptide exit tunnel. Resistance can be caused by changes in the RNA and protein components of the tunnel. Recently, a specific rRNA change caused by resistance to all antibiotics in this site of the ribosome was described, and this change is spreading. Another example of bacterial genetic juggling is the recent emergence of a new FQ resistance mechanism. When high-performance FQs were introduced in 1987, some foolish experts predicted that the resistance of this new class of gyrase inhibitors was unlikely, because at least two mutations were required to produce significant resistance phenotypes. It was also suggested that resistance to horizontal transmission of FQ would not occur. However, mutants of target bacterial glycogen genes and FQ leakage from cells are increasingly common. More unexpectedly, a transmittable mechanism of FQ deactivation appears. This mechanism occurs because many aminoglycosides N-acetyltransferase have the ability to change secondary amines on FQs and reduce activity. The latter does not result in a high level of FQ resistance but can produce a low level of tolerance that Favours the selection of resistance mutations. Another unpredictable FQ resistance mechanism is known as the widely distributed family of DNA binding proteins, Qnr, which is responsible for low resistance to quinolone. We have not heard the end of the quinolone resistance saga. The morality of the story... you shouldn't try to second-guess the microbes! Resistance can occur biochemically.

- **Intrinsic resistance:**

Bacteria can survive antibiotics through mutations in structure and components, and through evolution they can survive by internal resistance. For example, antibiotics that affect the walls of bacteria, such as penicillin, cannot affect bacteria that have no cell walls. Resistance: Bacteria may have the ability to resist the activity of certain antimicrobial agents previously sensitive. Bacteria can obtain resistance through new genetic mutations that help bacteriophages survive or by getting DNA from already resistant bacteria. For example, Mycobacterium tuberculosis resistance to rifamycin.

- **Genetic change:**

Bacterium DNA changes and changes the production of proteins, which leads to different bacterial components and receptors that do not recognize bacteria by antibiotics. Bacteria that share the environment may contain intrinsic

genetic determinants of resistance, which could change the genome of the bacteria. For example, Escherichia coli (E. coli) and Haemophilus influenza resistance to trimethoprim are examples.

- **DNA transmission**:

Bacteria can share genetic components with other bacteria and transmit resistant DNA through horizontal gene transmission. Normally, bacteria acquire external genetic material in three main stages: transformation (through the incorporation of naked DNA) conversion (through the phagocytosis process) conjugation (through direct contact). For example, Staphylococcus aureus is resistant to methicillin (MRSA). Some organisms are resistant to multiple antibiotics. For example, e. coli and Enterococcus are usually resistant to at least one antibiotic, sometimes a combination of antibiotics, such as macrolides, tetracyclines, beta-actams, quinolones, sulfonic acids, tetracyclines, and rifamycin, because they are inhibited by ceshfoxitin, ciprofloxacin, and erythromycin.

HOW TO PREVENT ANTIBIOTIC RESISTANCE

To help prevent antibiotic resistance, follow

- The doctors instructions when taking antibiotics.
- End all antibiotic courses, even if you feel better.
- Do not share your medications with others.
- Never take other people's medicine.
- Don't put pressure on the doctor to give you antibiotics.
- To prevent bacterial infection in the first place:
- Maintain a healthy lifestyle (diet, exercise, sleep), to reduce your chances of developing illness.
- Practice good handwashing techniques.
- Do not share food or beverages with anyone.
- Wash fruits and vegetables before eating.
- Do not eat raw meat, fish or eggs.
- Practice safe sex.
- Keep wounds clean and covered.
- Do not share any personal property (cloth, razor, brush).
- Cough or sneeze into the elbow.

STRATEGIES TO OVERCOME ANTIBIOTIC RESISTANCE

Globally, endeavours are underway to boost antibiotic efficacy and discover novel drugs to halt the rise of antibiotic resistance. Good efficacy, higher activity than current antibiotics, and an optimal safety profile are the main prerequisites for the introduction of novel antibiotics. Medical professionals feel that the creation of new medications is long overdue because they have witnessed the proliferation of bacteria resistant to antibiotics, even on the last line of treatment. Consequently, the efforts taken to combat antibiotic resistance are covered in this part, along with the latest advancements in the research and production of antibiotics. The development of antimicrobial chemotherapy is believed to benefit from technological breakthroughs as well as advances in chemical and biological approaches. Even though a number of these methods have been studied for more than a decade, the development and production of potent antibiotics proceeds very slowly.

Antimicrobial combination treatment

Restoring bacteria’s susceptibility to antibiotics has also been demonstrated to be possible with combination treatment. Combining the sensitivity of two or more medications to pathogenic germs suggests a synergistic impact that might boost the effectiveness of treatment. According to Fischbach (2011), there are essentially three possible mechanisms of action for antibiotic combination therapy: (i) targeting targets in different ways (such as combined antibiotics for antituberculosis therapy), (ii) targeting distinct targets in the same way (such as trimethoprim and sulfamethoxazole), and (iii) targeting the same targets through

different mechanisms (such as streptomycin). Combination antibiotics are always the best option when treating infectious illnesses including HIV/AIDS, malaria, and TB since they increase the treatment's efficacy. In contemporary clinical settings, combination antibiotic treatment is the first line of defence against MDR infection in the absence of a quick discovery of potent antibiotics. Polymyxin and colistin, for instance, are used in combination to treat MDR Gram-negative infections.

Adjuvant-drug combinations

Additional chemicals known as adjuvants aid in boosting the action of antibiotics. Usually, these compounds do not kill bacteria on their own. Augmentin®, a combination of clavulanic acid (-lactam inhibitors) and -lactam antibiotics, is a prime example. By blocking the -lactamase enzyme, which often results in the inactivation of antibiotics, clavulanic acid helps to increase the efficacy of amoxicillin. Although not all -lactamases generated by microbes are responsive to -lactamase inhibitors, this approach is helpful in avoiding resistance. Because of this, researchers are creating novel -lactamase inhibitors, such BLI-489 and LK-157, which have demonstrated promising in vitro outcomes in the suppression of broad-spectrum -lactamase (ESBL) pathogens. Furthermore, as Levasseur et al. found, P. aeruginosa was susceptible to ceftazidime, a member of the cyclosporin antibiotic class, and its percentage rose from 65% (when taken alone) to 94% when coupled with Avibactam. The primary cause of P. aeruginosas resistance to cefalosporin medicines is the overexpression of AmpC B-lactamase, which is encoded by chromosomes. It has been shown that avibactam can alleviate ceftazidime resistance. Avibactam activity, a potent inhibitor of AmpC hydrolytic activity, may be the primary factor in its effectiveness when used in conjunction with Ceftazidime to treat P. aeruginosa.

Modifications to the chemical structure

One potential solution to the issue of antibiotic resistance is the structural alteration of commercially marketed medications. For instance, vancomycin is a potent antibiotic that works well against Gram-positive bacteria. After over 60 years since the discovery of this antibiotic, resistant strains of bacteria have now emerged; one such example is the Vancomycin-Resistant Enterococcus (VRE). This glycopeptide-based antibiotic's peripheral components have been modified through research, and this has allowed researchers to circumvent the developed mechanism of resistance by introducing two new bacterial-killing mechanisms: (1) binding pocket modifications; and (2) induced permeability of the bacterial cell membrane. This results in a decreased sensitivity to resistance and a 6000-fold increase in its efficacy against Van-A (resistant to teicoplanin and vancomycin) VRE.

- Derivatives of aminoglycosides

Both gram negative and gram-positive bacteria are susceptible to the action of streptomycin, the first aminoglycoside antibiotic, which was discovered in 1943. Because of their varied molecular structures, aminoglycoside antibiotics have varying activity profiles. Typically, these antibiotics are employed as a second or third line of treatment for infectious illnesses including MRSA and MDR-TB. As a result, it is seen quite concerning when resistance to aminoglycoside develops. The activity of aminoglycoside-modifying enzymes (AMEs) is linked to the primary variables that contribute to the development of resistance to aminoglycosides. Five key pathways have been discovered that may be effective: Drug pairings and reprocessing, AME expression control, finding novel aminoglycosides to counteract AMEs, using AME inhibitors, and high-throughput techniques to obtain novel aminoglycoside activity are all discussed.

Substitutes for antibiotics

Some researchers are now turning to biopharmaceuticals as alternatives to antibiotics as a new way to combat antimicrobial resistance. Zaplewski and colleagues identified 19 methods that are already being developed in academia and industry, 10 of which could have a good clinical impact, feasibility and safety. Among these substances, seven (antibodies, lysines, vaccines, designed phages, wild-type phages, probiotics and immune stimulation) are already in clinical trials, while the other three (antimicrobial peptides, host defense peptides and antibiofilm peptides) are in the preclinical phase. Since there is already no drug on the market, the success of seven drugs in clinical trials has a positive influence on the application of antibiotic alternatives as antimicrobials. As an innovative strategy to counteract antimicrobial resistance, some researchers are now looking at biopharmaceuticals as an alternative to antibiotics. Ten of the 19 approaches that Zaplewski and colleagues identified as being in development in academia and industry have the potential to have good clinical effect, practicality, and safety. Of these compounds, three antimicrobial peptides, host defense peptides, and antibiofilm peptides are in the preclinical stage, while seven antibodies, lysines, vaccinations, customized phages, wild-type phages, probiotics, and immune stimulation are now undergoing clinical trials. The seven medications that have successfully completed clinical studies have a favorable impact on the use of antibiotic substitutes as antimicrobials, as there is currently no medication available on the market. One technique that might be useful for antimicrobial chemotherapy is the identification of quorum detection (QS) as a target for antibiotics. using substitutes like antibodies. Targeting QS of pathogenic bacteria is possible. Bacteria utilize QS, a sophisticated regulatory communication mechanism, to release tiny molecular weight compounds. It is hypothesised that P. aeruginosa and other MDR bacterial infections can be suppressed by QS inhibitors. By focusing on these non- essential processes, QS may be a viable target for medication development in the future and slow the emergence of resistance. Bacteriophages are thought to be an antibacterial agent that may be used to fight bacteria that are resistant to antibiotics and a potential first step in the fight against antibiotic resistance. For instance, Phico Therapeutics is creating a technique known as SASPjectTM that is meant to preserve native flora while quickly targeting and eliminating 99.9% of bacteria in only two minutes. A bacteriophage a modified and incapacitated bacterial virus with antimicrobial protein genes makes up SASPjectTM. The target bacteria receive an injection of the gene, and when it expresses itself, the bacterial DNA becomes inactive. As of right now, using this technology does not offer pathways for developing resistance. The use of phage and antibiotic combination is especially intriguing since, in contrast to using either antibiotic alone, it gives strong antibacterial action while lowering the likelihood of resistance developing.

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