International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

The Antibiotic apocalypse - the rise of resistance and breaking the cycle of antibiotic resistance - a call to action

Author- Gupta Sakshi
Co-Author- Nagi Daksh*

Submitted: 25-06-2023 Accepted: 05-07-2023

ABSTRACT:
There are different pathways which were followed by bacterias to develop resistance against antibiotics resulting in failure of medications used against bacterial cells. This event concising therapeutic management of infections caused by bacterial cells. As per future prospective, that is a major problem in the healthcare system.To overcome antibiotic resistance several steps are taken at different levels, till an extent they can combat antibiotic resistance. Nowadays there are some other techniques developed that can be used to kill the bacterial cell, such as phage therapy or Photodynamic-antimicrobial Chemotherapy(PCAT).these techniques can be used as alternatives to antibiotics at some points.

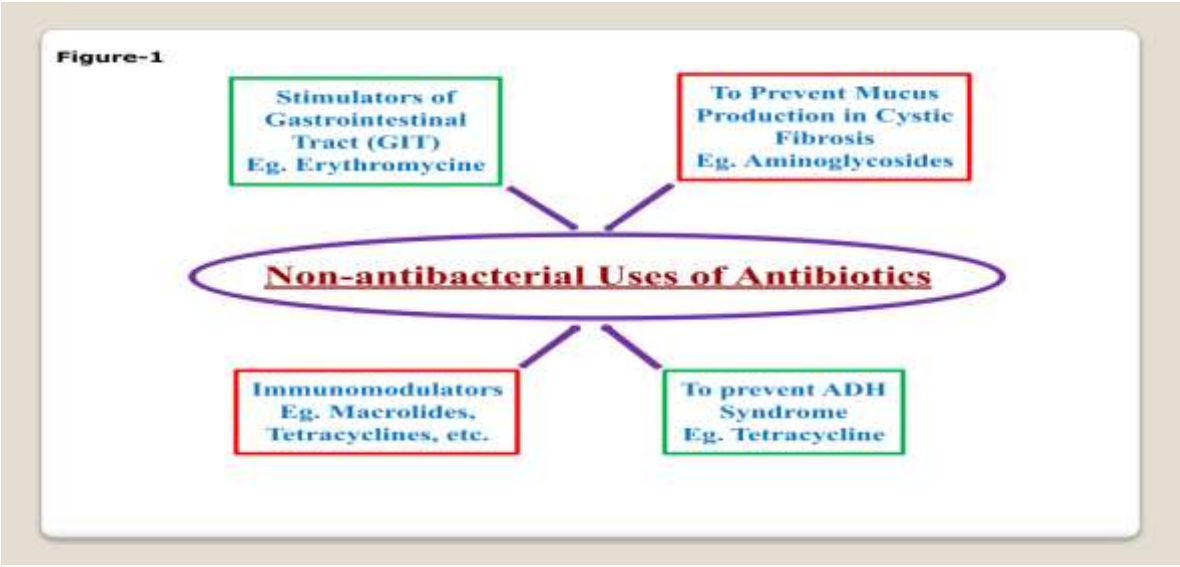
Keywords:

ADH: Antidiuretic Hormone
CDC: Centers for Disease Control and Prevention
CDSCO: Central Drugs Standard Control Organization
IDSA: Infectious Diseases Society of America
WHO: World Health Organization

I. INTRODUCTION

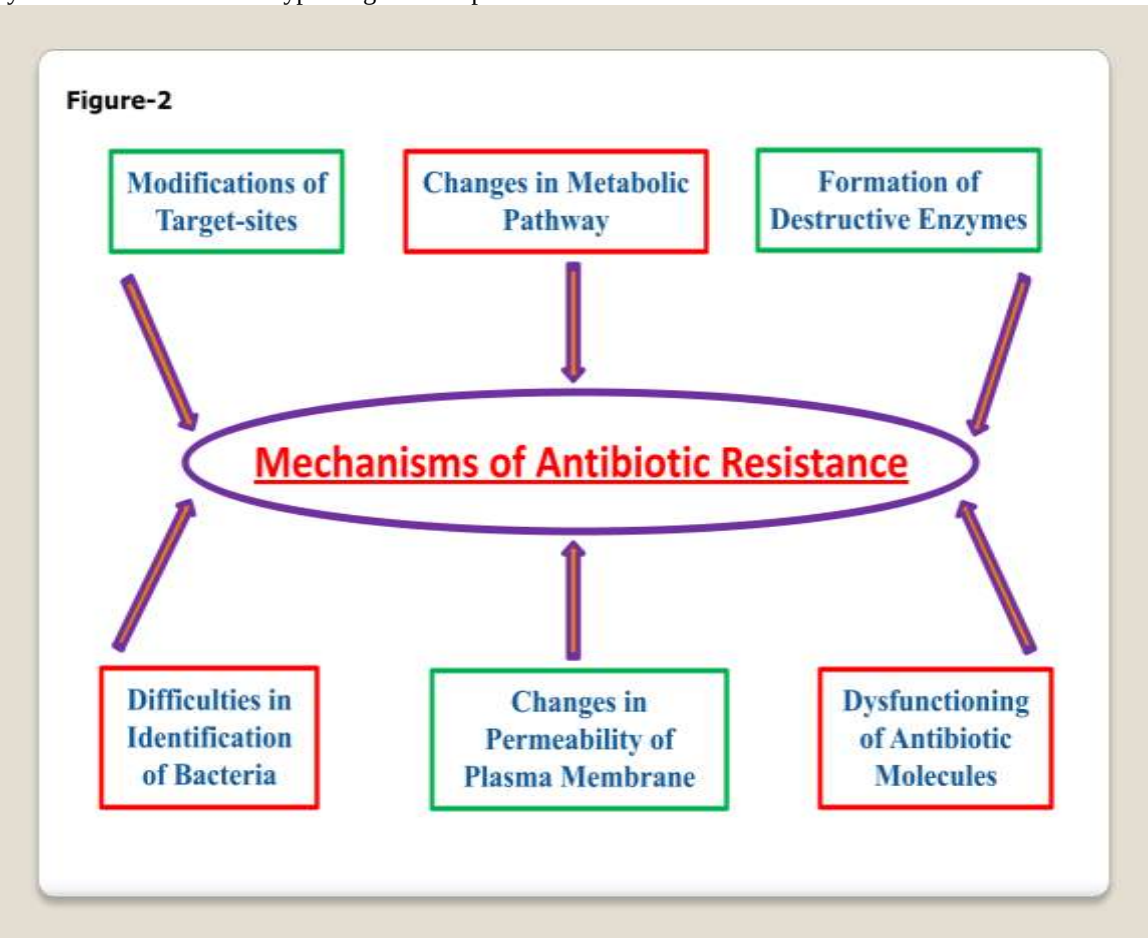
Antibiotics, also known as antibacterial agents, are a class of antimicrobials produced by micro-organisms or synthesized chemically to treat and prevent infectious diseases caused by bacteria, usually at very low concentrations [1]. Today, antibiotics are used not only for infection but also for some non-infectious conditions [Figure 1.], e.g. erythromycin is a gastrointestinal tract motility stimulator; macrolides, lincosamides, and tetracyclines have immunomodulatory effects and tetracycline has also been used to prevent antidiuretic hormone (ADH) syndrome; aminoglycosides may prevent the production of mucus in cystic fibrosis patients, etc [2]. Multiple uses and widespread use of antibiotics even where there is no need for antibiotic treatment, overuse and misuse of antibiotics, treatment with low doses for a long period, poor control and prevention of infections, etc., may lead to antibiotic resistance. And therefore, the director of the Centers for Disease Control and Prevention (CDC) Tom Frieden warned, "If we are not careful about antibiotic use, we will soon be in a post-antibiotic era [3].

Figure-1



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

The term "Antibiotic Resistance" indicates the self-modification of a bacterial cell in such a way that leads to ineffectiveness or degradation of an antibiotic. Antibiotic resistance may be a form of different leading mechanisms [Figure 2.] such as 1) modification of an antibiotic component in terms of chemical changes by bacterial enzyme, completely enzymatic destruction of an antibiotic; 2) a decrease in antibiotic molecule efflux and penetration or a decrease in permeability; 3) alterations in target sites by bacteria such as modifying target site in the mutation form, enzymatic alterations and bypassing or complete replacement of the site of a target; 4) a change in metabolic pathways in bacterial cell to prevent antibiotic molecule effect; 5) sometimes bacterial cell adopts such an environment which leads to difficulties in its identification by antibiotic molecule. These are some adherently found mechanisms that could lead to the worldwide increasing burden of bacterial mutants, which is inevitable and has led to decreasing the antibiotic efficacy, withdrawal of antibiotics and even deaths due to such bacterial infections that are resistant therapeutically to antibiotics [4].



The emergence of antibiotic resistance development and its spread in bacterial cells is now a common universal threat to humans as well as animals that are usually not stoppable nevertheless can be tackled and controlled in the most effective and possible ways. In 2013, the Centers for Disease Control and Prevention (CDC) reported eighteen drugs resistant bacterial strains that are the biggest threats to the United States of America. These drugs-resistant bacterial strains were classified based on concern level as: urgent, serious, and concerning The world health organization (WHO) and other regulatory bodies such as the Infectious Diseases Society of America (IDSA), the CDC, etc., have been certified antibiotic resistance, a crisis because the death rates have increased compared to last decades due to an increased antibiotic-resistant bacterial strains. According to the CDC, approximately 23,000 people in the USA die every year from infections caused by antibiotic-

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

resistant bacteria [3]. Moreover, it is also estimated that antibiotic resistance may lead to a loss of up to £64 trillion ($100 trillion) to the global economy and around 300 million deaths by 2050 [5]. In this way, the pharmaceutical companies have stopped developing new antibiotics and the quinolones were the last new class of antibiotics that were discovered and came into the market four decades ago. Professional healthcare providers have also reduced antibiotic prescribing and suggest alternatives to antibiotics. This emergence of antibiotic resistance urges us to identify the molecular mechanisms leading to antibiotic resistance and impels us to act urgently for making strategies and taking steps at all society levels to reduce or combat the impact and spread of resistance. the World health organization (WHO) passes the pathogens list, according to their severity related to antibiotic-resistance of microbial species as shown in Table-1.[5]

Table-1 : According to the World health organization (WHO) pathogens

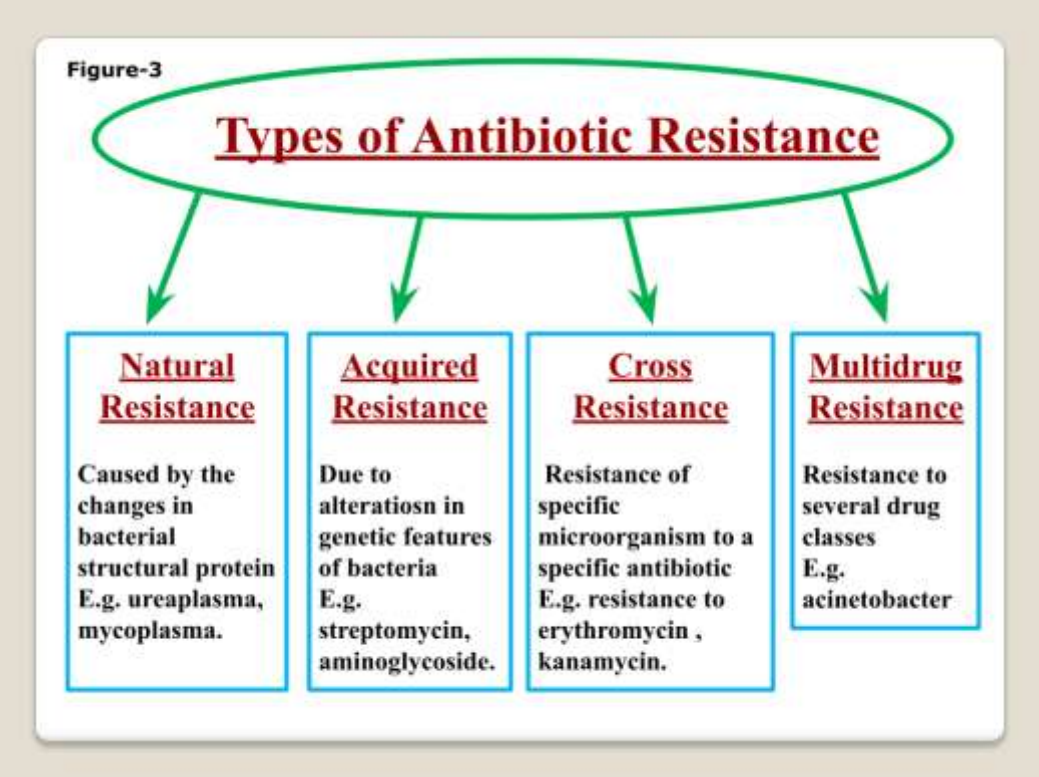
# Critical Position :	
Species Name	**Resistance To**
Acinetobacter baumannii	**carbapenem-resistant**
Pseudomonas aeruginosa	**carbapenem-resistant**
Enterobacteriaceae	**carbapenem-resistant, 3rd generation cephalosporin-resistant**
# HIGH POSITION :	
Species Name	**Resistance To**
Enterococcus faecium	**vancomycin-resistant**
Staphylococcus aureus	**methicillin-resistant, vancomycin intermediate and resistant**
Helicobacter pylori	**clarithromycin-resistant**
Campylobacter	**fluoroquinolone-resistant**
Salmonella spp.	**fluoroquinolone-resistant**
Neisseria gonorrhoeae	**3rd generation cephalosporin-resistant fluoroquinolone-resistant**
# MEDIUM POSITION:	

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

Species Name	Resistance To
Streptococcus pneumoniae	**penicillin-non-susceptible**
Haemophilus influenzae	**ampicillin-resistant**

1. Classes of Antibiotic Resistance

The generation of antimicrobial resistance can be classified on the basis of its nature of occurrence as following [Figure 3.].



1.1. Natural Resistance

This type of resistance is generated by the changes that occur in the structural proteins of a bacterium. The bacteria lacking cell walls namely ureaplasma and mycoplasma are the key examples of Natural Resistance. The mechanism of resistance-generating L-forms of bacteria is known as the alterations in permeability of the bacterial plasma membrane, e.g. the bacterial species pseudomonas and acinetobacter [6,7].

1.1.1. Acquired Resistance

The changes occurring in main chromosomes or extrachromosomal structure of plasmid, transposons, etc., may result in the alterations in genetic features of a bacterial cell causing resistance. These mutations are the results of physical or chemical factors that are ultimately decreasing drug permeability or leading to changes in drug-target sites. The antibacterials like streptomycin, aminoglycosides, and erythromycin develop resistance to these forms through the target shielding mechanism [8].

1.1.2. Cross Resistance

A specific type of microbe induces resistance against a specific class of antibiotics or a particular antibiotic. This is known as an 'Identical-resistance Mechanism'. The bacteria Escherichia coli (E. coli) is the best example of this type of resistance against the antibiotics erythromycin and kanamycin [9,10].

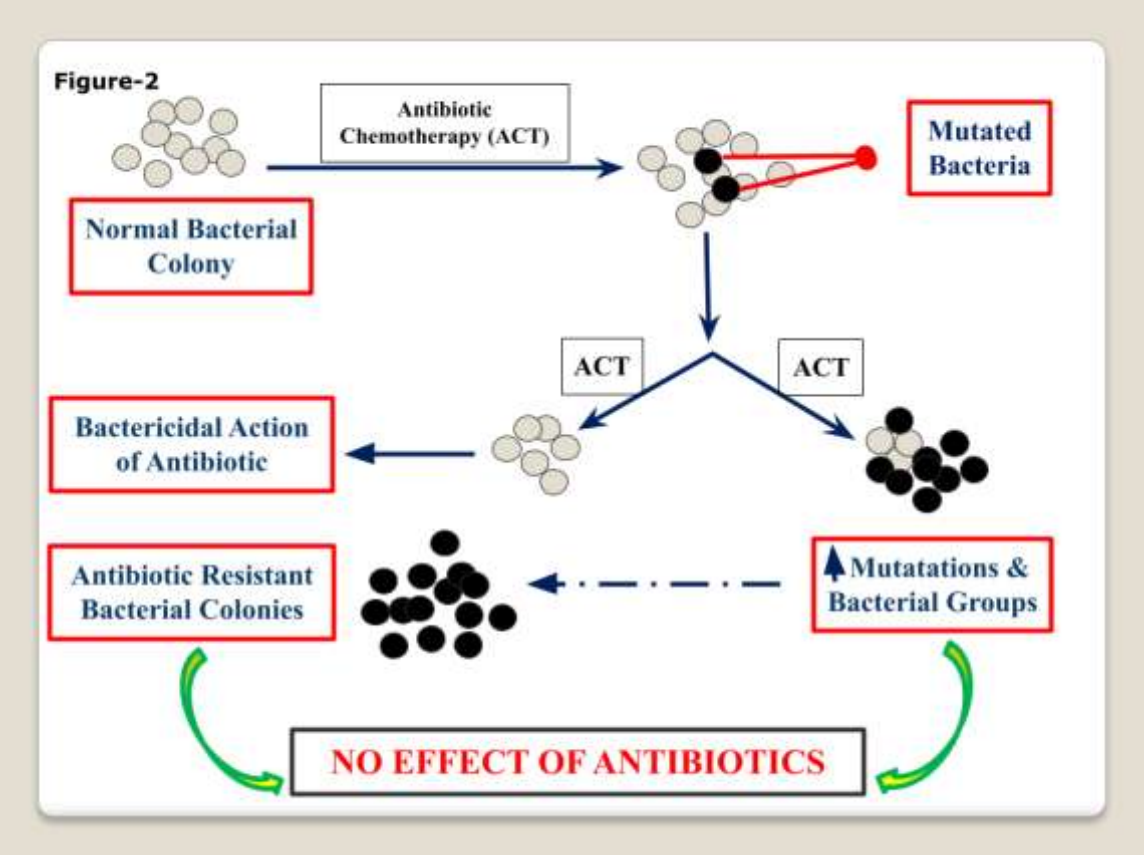
International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

1.1.3. Multi Drug Resistance

Multidrug resistance (MDR) is a result of improper use of antibiotics which leads the several kinds of modifications in the structure of pathogen's species. Acinetobacter species were noticed to create resistance against a number of antibacterial classes. This activity of acinetobacter bacteria against antibiotic aminoglycosides, penicillins, quinines, and cephalosporins, is mediated on account of inappropriate antibiotic use [8].

2. Generation of Antibiotic Resistance in Bacterial Species

At the beginning of antibiotics' chemotherapies, no bacteria are generally resistant to antibiotics [11]. However, the presence of any bacterial strains (which is resist to an antibiotic's pharmacological action) is reported after mutations in bacterial genetic material due to several factors including changes in the bacterial environment, long-term antibiotics' exposure with inappropriate use, etc. These genetic mutations lead bacteria to adapt to their resistance-creating environment. This survival mechanism of bacteria, with respect to antibiotics, is impelling slowly formation in antibiotic-resistant bacteria species [Figure4], and hence, these modifications in a bacterium structure make antibiotics unable to perform their therapeutic actions.



The following listed mechanisms [Figure 2.] can be considered the pathways leading to the production of antimicrobial-resistant microorganisms.

2.1. Mechanisms of Antibiotic Resistance Against Bacteria

2.1.1. Changes in Bacterial Target Sites

The most common technique through which bacteria develop resistance against antibiotics is the changes in their target sites. The types of changes are following:

2.1.1.1. Target Shielding: A bacterial cell initiates shielding of its target sites by some variations in genes that encode specific proteins

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

responsible for the bacterial-induced resistance. This resistance-producing technique of bacteria provides sufficient protection to the bacteria during an exposure of antibiotic therapy. For example, streptococcus spp. develops resistance against tetracycline by tooling the target shielding [12].

2.1.1.2. Modification of Target Sites: The configuration changes that occur in bacterial target sites during the antibiotic exposure is called 'Potential Modifications' and account for the most common process responsible for creating resistance against an unknown number of antibiotics in various bacterial pathogens. These modifications in target sites can be achieved specifically by the following three pathways:

I) A point mutation in genes, e.g., E. coli-induced resistance against rifampicin [13].
II) Enzymatic alteration in binding sites, e.g., Pneumococci- and enterococci-induced resistance against macrolides and lincosamides [14,15].
III) Bypass of the original target, e.g., Staphylococcus aureus (S. aureus)-produced resistance against penicillins particularly methicillin [16,17].

2.1.2. Enzymatic Actions

A number of microbial species are synthesizing various enzymatic components in response to antibacterial therapy and making the treatment ineffective by degrading antibiotics partially or completely. For example, streptococci release enzymes that particularly catalyze the antibacterial activity of erythromycin, aminoglycosides, etc [18].

2.1.3. Changes in Permeability of Plasma Membrane

There are several antibiotics that produce their actions in the cytoplasm of a bacterial cell to resist its growth. The altered permeability of the bacterial plasma membrane prevents the drug uptake into the cells and thus, less or no therapeutic effect of a drug is produced. Antibiotics like fluoroquinolones, tetracyclines, etc., are ineffective against microbes like pseudomonas and acinetobacter baumannii. And such antibiotics are generally inhibited for their antibacterial activity by the same mechanism of modified plasma membrane porosity. This type of mechanism is commonly seen in the case of gram-negative bacteria [18,19].

2.1.4. Alteration in Drug Metabolic Pathways

The pathways, that are part of drug metabolism, get affected due to altered metabolic signaling in bacteria and lead to the ineffectiveness of antibiotic usage, e.g. sulfonamides work as bactericidal drugs by preventing the synthesis of folate in cells and thereby inhibiting the growth of bacteria. There are a number of mechanisms disrupting the activity of antibiotic sulfonamides and finally resulting in the bacterial-induced resistance to these agents [18]. The mechanisms processing inhibitory antibacterial activity of antibiotics are following:

2.1.4.1. Destruction of Antibiotics

It is the breakdown of antibiotic molecules from the potential cleavage actions of lethal enzymes produced by bacteria. For example, bacteria like staphylococcus spp. produce beta-lactamase which makes monobactam antibiotics unable to act as antibacterial agents by breaking down their beta-lactam rings in their structures which finally resulted in the generation of antibiotic resistance [18].

2.1.4.2. Dysfunctioning of Antibiotics

It is a structural modification of antibiotic molecules defined by the addition or subtraction of different chemical groups and rings, instability of bonds, or other structural changes. These structural changes in an antibiotic compound are accompanied by the action of various catalytic enzymes produced by bacterial species which ultimately reveals the dysfunction of antibiotic molecules. For example, the aminoglycoside modifying enzymes (AME) produced by Enterococcus faecium, Serratia marcescens, etc., [20] act by modifying hydroxyl or amine groups of aminoglycoside antibiotics and provoke antibiotic resistance specifically against aminoglycosides.

3. Factors Promoting Antibiotic Resistance

3.1. Environmental Factors

Environmental factors play various roles in creating antibiotic resistance generally in terms of the improper management of the following: aquatic facilities, municipal wastewater, medical waste, manufacturing effluents, and several husbandry factors [21].

3.2. Unusual Usage of Antibiotics

The factors such as the use of antibiotics at a large scale, multiple prescriptions, or usage in inappropriate ways, could be the reason for (i) the

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

generation of resistance in a number of bacterial species and (ii) the loss of effectiveness of antibiotics [22].

3.3. Multiple Uses of Antibiotics

Antibiotics were used as non-curative options for conditions like metaphylaxis in the early 2000s, accounting for 25-50 percent of global antibacterial usage [22].

3.4. Effects of Food Industries

These may include: attendance of antibiotics in animal feedstock reported to spread antibiotic-resistance [21,22].

4. Urgent Actions are Needed to Tackle Spreaders of Antibiotics Resistance

Antibiotic resistance has now become life threatening and a worldwide growing major problem with antibiotic chemotherapy. It is leading antibiotic treatment less effective against a number of growing lethal infections such as gonorrhea, pneumonia, salmonellosis, and tuberculosis that ultimately are responsible for the death [23,24]. To combat and prevent the spread of resistance, there is a need of making good sound strategies with the impactful considerations. Following measures and actions may be taken into account to resolve the crisis of antibiotic resistance.

4.1. General Precautions

This may include various important steps and considerations to adhere and follow for minimizing chances of antibiotic resistance such as; 1) take antibiotics on prescriptions only, 2) use in complete doses, 3) adherence to the prescription is mandatory for the complete recovery from any infection, 4) stop taking antibiotics unnecessary if a health care professional or doctor has been refused, 5) do not take antibiotics in the 'Self-Medication' practice, 6) do not practice antibiotics as an OTC drugs' application, 7) the chances of getting infections can be minimized by hand washing regularly before taking food, avoiding other when feel uneasy or unwell, keeping up to date with vaccinations, etc [25].

4.2. Appropriate Use of Antibiotics

Antibiotics should not be used for non-therapeutic purposes, if it is the case, must be discontinued. Several epidemiological surveys have found the practice of inappropriate use of antibiotics, such as sometimes antibiotics are prescribed for non-bacterial illness (viral conditions) like cold, flu, etc., which should be regulated, prevented and avoided, attentively. Antibiotics should be taken on the advice of a professional healthcare provider with a full course-term. Because renouncing the treatment in the early stages may urge the growth of bacteria and finally it leads to generating antibiotic-resistant bacteria [25]. In this regard, the appropriate use of antibiotics may be a major key to evading complications associated with the resistance.

4.3. Alternatives to Antibiotic Chemotherapy

The new and novel non-antibiotic ways for the treatment and prevention of infections should be investigated and encouraged to find out. For example, after observing the health conditions and type of infections in patients, some approaches such as probiotics, immunomodulators, vaccines, antivirulence, adjuvant therapies etc., can be practiced in lieu of antibiotic chemotherapy. However, antibacterial vaccines have been extensively studied and found to have limited success in humans as compared to animals. On the other hand, probiotics and their combinations are the most deserving alternatives due to their significantly beneficial results in infections treatment. Toxin antidotes are another approach used where antibiotics should not be but this therapy has fewer applications in infections on account of their adverse effects [26]. The use of these alternatives could be crucial to evade the problem of antibiotic resistance. In addition to above alternatives, the following therapies can also be helpful and have found with fascinating outcomes in treating infectious patients:

4.3.1. Phage therapy

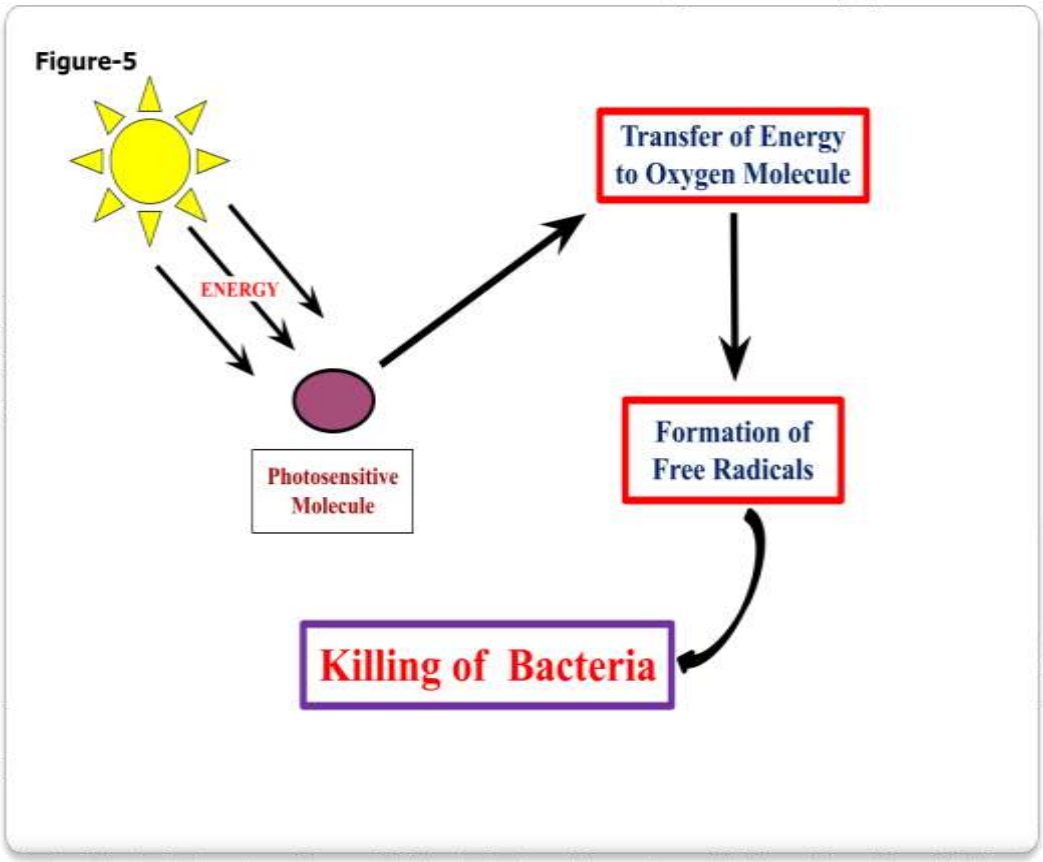
This alternate works with the bacteriophage application and therefore, can be defined as a 'Phage Therapy'. The bacteriophages do not affect the cell lines of other microorganisms rather killing potentially a number of bacteria. This characteristic action of bacteriophages comes from an enzymatic-bacterial lysis as they secrete an enzyme called C1 phage lysine which dissolves the cell wall of bacterial species such as streptococcus pneumonia [27].

4.3.2. Photodynamic-antimicrobial Chemotherapy (PCAT)

This technique is also used to avoid the multiple usages of antibiotics. The photosensitive molecules involved in the PCAT usually work on the principles, (i) absorption and transferring

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

energy into biological acceptors and (ii) generating an excess of free radical species. These increased levels of free radicals then combat the bacterial growth and lead to the death of bacterial cells [Figure 5.]. For example, photosensitizer rose bengal, the best example of PCAT, is used with methicillin to prevent bacterial growth against several species like S. aureus [28]



4.3.3. Nanotechnology

The pharmaceutical new generation formulations such as 'Nano-Structured formulations (NSFs)' have emerged as a promising approach to encapsulate antibiotics in order to limit the bacterial progress during an infection and thus, combat the complications associated with antibacterial resistance [29].

4.4. Development of New Antibiotics

The process of battling bacterial-resistant strains through healthcare systems and pharmaceutical companies is going on since last more than 30 years. Antibiotics should be developed and synthesized in such ways that reveal no effects of the existing mechanisms of resistance. The trend of making derivatives of existing drugs is a well-known approach to overcome any type of difficulty of drugs such as to improve bioavailability, to increase solubility, to avoid toxicity, to change pharmacological activity, to combat the resistance of microbes, etc. Antibiotics show bacterial resistance, can be derived into new components by replacing or removing the group, the ring, the bridge, or the chain from an antibiotic structure which is responsible for its bacterial resistance [30]. The development of new antibacterial drugs can also be initiated by re-evaluating the existing pharmacological agents either of antibacterial interest or non-antibacterial that target differently the pathogens responsible for antibiotic resistance. When a particular drug molecule is modularized to another form that is more effective in nature is generally called molecular modeling, like ampicillin antibiotic complexes (HAI: hept -ane-2-carboxylic acid) are more potent than alone ampicillin and such complexes have been reported as target specific

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

larger bioactive molecules which synthesized following a complexation reaction of metal ions viz. Gd(III), Co(II), Cu(II), and Ni(II) [29]. This is only and the great recommendation just through a small chemical modification to produce antibiotic derivatives free of resistance to treat the same condition, but to get derivatives of choice, more efforts should be made.

4.5. Investigation of Rejected, Discarded or Withdrawn Antibiotics for New Therapeutic Indications

The repurposed strategy is now-a-days widening throughout the world and most scientists are looking to investigate side uses of present drugs even for antibiotics. In this respect, start-up industries or companies can pick this opportune time to generate new, effective and bacterial resistance evading antibiotics. For instance, daptomycin, an aminoglycoside antibiotic forsaken due to its higher toxicity by one company, and now it has become primarily medicine (in a different regimen) for those serious infections caused by gram-positive bacteria by another company [31]. The repurposing of drugs, in the case of antibiotics, could be an important strategy to overcome the spreading bacterial resistance.

4.6. Public Education, Public Awareness and Public Health

Public education and awareness about antibiotics and antibiotic resistance can improve quality of life and puts a good healthy impression among the people. The knowledge about antibiotics and antibiotic resistance should be initiated at school levels or such programs should be run by colleges, institutes, universities, govt. or NGOs, in both rural and urban areas, that aware to the people regarding the appropriate use and resistance of antibiotics and how can we fight and further evade from an infection?; for example 1) an e-Bug program is regulated by PAN-European regulatory bodies to educate children and their parents about the consideration of antibiotic uses and their resistance development; 2) Antibiotic Awareness Day is run in Canada and Europe, annually; 3) Get Smart: When Antibiotics Work, a program about awareness of antibiotics uses, developed by the CDC in the United States. In India and other developing countries, more advanced programs should be planned and presented among the people and also strictly regulated. The continuously increasing population is making India to be the first country in a few years in the world, which will have the highest antibiotic resistance cases, and at that time, India will be having no more such preventive measures that can overcome such serious situations.

5. Steps to Control Antibiotics Resistance at Several Levels

5.1. Control at Societal Level: by public awareness camps or eLearning programs at the academic level and making finally the population knowledgeable against the menaces of antibiotic resistance [32,33].

5.2. Control at Environmental Level: by complete management of husbandry waste products, industrial waste, waste water, medical waste, etc [33].

5.3. Control at Clinical Level: by appropriate use of antibiotics, decreased self-medication, and use of alternatives to antibiotics such as vaccines, probiotics, phage therapy, PCAT, immunity modulators, etc [33].

5.4. Control at Research & Development Level: by developing new antibiotic entities for resistance producing specific or multi-microorganisms or by finding new antibiotic uses of other approved drug molecules for the same [33].

6. Important Initiatives Started Throughout the Globe for Tackling Antibiotic Resistance

6.1. Global Action Plan on Antimicrobial Resistance (GAP-AMR)

The GAP-AMR was launched on the 22nd of October 2015 by 68 world health Assemblies in collaboration with the WHO [34].

6.1.1. Structure

According to the 'Global Antimicrobial Resistance and Use Surveillance System (GLASS)', AMR surveillance actions are divided into a set of technological elements. These modules are a summary of their regularly based data, with the goal of creating information for specific applications depending on the country and regional needs. GLASS also helps governments improve the quality and representativeness of their data by designing and implementing surveys and research. list of initiatives has been shown in Table-2.

Table-2 : Lists of Initiatives programs against Antibiotic Resistance :

Start-ups or programmes stepped out worldwide to reduce the threats of antimicrobial resistance

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

S.NO.	INITIATIVE PROGRAMS	WHEN/ WHERE	Launched by	Objectives
1).	Global action plan to tackle AMR	2015/ switzerland	WHO	● strengthens the public awareness regarding AMRthrough research. ● Increase in the effectiveness of antibiotics.
2)	Antibiotic review kit (ARK)	2015/ UK	Department of health	● stop unnecessary antibiotic prescription ● To reduce self medication of antibiotic
3)	One health national action plan	2016/ China	China's health authority with 14 ministries	● To reduce the use of antibiotics among hospitals. ● To cover-up the antibiotics resistance .
4)	National antimicrobial resistance policy	2011/ India	Ministry of health and family welfare government of India	● To acknowledge threats of AMR ● To recognise about the factors influencing AMR ● To rationalise the use of antimicrobials
5)	AMR tool kit	2015/ England	Health education England	● To prevent and control infections ● To promote stepworld ship against resistance

6.1.2. Partnerships

GLASS is backed by the WHO AMR Surveillance and Quality Assessment Collaborating Centers Network and developed in conjunction with AMR regional networks such as the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR), the European Antimicrobial Resistance Surveillance Network (EARS-Net), and the Latin American Network for Antimicrobial Resistance (LANAMR).

6.1.3. Objectives

The following steps can be considered as the important objectives of GAP-AMR:

a) To raise antimicrobial resistance awareness and knowledge.
b) To make surveillance and research more effective.
c) To lessen the risk of infection.
d) To make the best practice of antimicrobial drugs.
e) To assure long-term investment in the fight against antimicrobial resistance.

6.2. One-Health National Action Plan (OHNAP)

The OHNAP, a China-based international program, concerns with various necessary steps about antibiotics' application. The China's Health

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 3514-3526 www.ijprajournal.com ISSN: 2249-7781

Authority (CHA) have worked with 14 Chinese ministries from 2016 to 2020 to limit the use of antibacterial in medical prescriptions, and they were efficacious in decreasing the use of antibiotics among hospitalized patients, with rates declining from 59.4% in 2011 to 36% in 2019 [34,35].

6.3. Antibiotic Review Kit (ARK)

Antibiotic Review Kit (ARK), an antimicrobial initiative by the department of health and social care, the United Kingdom (DHSC, UK), is aimed to reduce unnecessary antibiotic use in hospitals by stopping unusual antibiotic chemotherapy. The DHSC UK gives a tagline to this initiative as "Start Smart Then Focus" which covers the ARK and ARK-associated aspects. This eLearning step was developed in partnership with the British Society of Antimicrobial Chemotherapy [36,37].

6.4. Antimicrobial Resistance (AMR) Toolkit

In 2015, the Health Education England (HEE) launched an initiative towards tackling antimicrobial resistance in collaboration with the Public Health England (PHE), the National Health Service (NHS, England) and NHS Improvement, the Care Quality Commission, and the National Institute for Health and Care Excellence, and with the goal of teaching people how to manage infectious diseases and prevent them [37].

6.5. National Antimicrobial Resistance Policy-India

In 2011, an initiative was taken by the "Ministry of Health and Family Welfare, Government of India" towards the acknowledgement of threats related to antimicrobial resistance, to recognize the factors that directly or indirectly affect the resistance in the microorganism and to rationalize the use of antibiotics in treatments [38].

6.6. National Action Plan on Antimicrobial Resistance (NAP-AMR, 2017-21)

The NAP-AMR is largely concerned with bacterial resistance and regulated by the Central Drugs Standard Control Organization (CDSCO). The program was invented to successfully address AMR in India while also contributing to worldwide efforts to battle this public health problem. The NAP-AMR builds and enhances governance structures and the ability of all stakeholders to decrease the impact of AMR in Indian population at a large scale [32].

II. CONCLUSION

In a nutshell, antibiotic resistance is an urgently managing problem for maintaining public health issues because it is spreading everywhere and leading to the ineffectiveness of antibiotic treatment and more death than non-infectious diseases. Hence, before using antibiotics, we should have (at least) knowledge regarding general precautions and their appropriate uses. We should also consider the given recommendations from various health care regulatory bodies such as the WHO, the CDC, the CDSCO, the HEE, the NHS, the CHA, etc., about the definite and appropriate uses of antibiotics, how and when antibiotic should be taken, and the related parameters. Designing and synthesizing such antibiotics that are broad-spectrum and active against multidrug-resistant bacteria, for example β-lactam-resistant bacteria, Methicillin-resistant S. aureus (MRSA), etc., can impart an important step to control antibiotic resistance and also to treat infections. The main idea of the great significance is to tackle the AMR crisis by the presentation of awareness and specific education among the people regarding antibiotics' actual uses, their adverse effects, and the control of AMR-spreading components.

REFERENCES

1. Tripathi KD. Essential of Medical Pharmacology. 6th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2008.
2. Pasquale TR and Tan JS. Non-antimicrobial Effects of Antibacterial Agents. Clin Infect Dis 2005; 40: 127-135.
3. Antibiotic Resistance: Threats in the United States. Centers for Disease Control and Prevention. 2017. http://www.cdc.gov/drugresistance/threat-report-2017/index.html, [accessed 13 March 2021].
4. Schmieder R and Edwards R. Insights into antibiotic resistance through metagenomic approaches. Future Microbiol 2012; 7: 73-89.
5. Antimicrobial Resistance: Tackling a Crisis for the Future Health and Wealth of Nations. 2014. http://amr-review.org, [accessed 14 March 2021].
6. Waglechner N and Wright GD. Antibiotic resistant: It's bad, but why isn't it worse?. BMC biology 2017; 15: 1-8.

7. Claessen D and Errington J. Cell Wall Deficiency as a Coping Strategy for Stress. Trends in microbiology 2019
8. Hasan HT and Harmoosh R. Mechanisms of Antibiotics Resistance in Bacteria. Sys Rev Pharm 2020; 11: 817-823
9. Jahne MA, Rogers SW, Ramler IP, et al. Hierarchal clustering yields insight into multidrug-resistant bacteria isolated from a cattle feedlot wastewater treatment system. Environmental monitoring and assessment 2015; 187: 4168
10. Ng, HF. Selection And Characterization Of A Tigecycline-Resistant Mutant Of Mycobacterium Abscessus To Identify Possible Resistance Determinants (Doctoral dissertation, UTAR), 2019.
11. Kadhum HA and Hasan TH. The Study of Bacillus Subtils Antimicrobial Activity on Some of the Pathological Isolates. International Journal of Drug Delivery Technology 2019; 9: 193-196.
12. Li W, Atkinson GC, Thakor NS, et al. Mechanism of tetracycline resistance by ribosomal protection protein Tet(O). Nat Commun 2013; 4: 1477.
13. Campbell EA, Korzheva N, Mustaev A, et al. Structural mechanism for rifampicin inhibition of bacterial RNA polymerase. Cell 2001; 104: 901-912.
14. Leclercq R. Mechanisms of resistance to macrolides and lincosamides: nature of the resistance elements and their clinical implications. Clin Infect Dis 2002; 34: 482-492.
15. Roberts MC. Update on macrolide-lincosamide-streptogramin, ketolide, and oxazolidinone resistance genes. FEMS Microbiol Lett 2008; 282: 147-159.
16. Chambers HF and Deleo FR. Waves of resistance: Staphylococcus aureus in the antibiotic era. Nat Rev Microbiol 2009; 7: 629-641.
17. Chambers HF. Methicillin resistance in staphylococci: molecular and biochemical basis and clinical implications. Clin Microbiol Rev 1997; 10: 781-791.
18. Munita JM and Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectrum 2016; 4: 1-24.
19. Santajit S and Indrawattana N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. BioMed research international, 2016.
20. Ramirez MS and Tolmasky ME. Aminoglycoside modifying enzymes. Drug Resist Updat 2010; 13: 151-171.
21. Berendonk T, Manaia C, Merlin C, et al. Tackling antibiotic resistance: the environmental framework. Nat Rev Microbiol 2015; 13: 310-317.
22. Fair RJ and Tor Y. Antibiotics and Bacterial Resistance in the 21st Century. Perspect Med Chem 2014; 6: 25-64.
23. Antibiotic resistance. http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en, [accessed 6 August 2020].
24. Santos L and Ramos F. Antimicrobial resistance in aquaculture: current knowledge and alternatives to tackle the problem. Int J Antimicrob Agents 2018; S0924-8579: 30081-30085.
25. Antibiotic/Antimicrobial resistance. http://www.cdc.gov/drugresistance/protecting-yourself-family, [accessed 3 May 2021].
26. Tillotson GS and Theriault N. New and alternative approaches to tackling antibiotic resistance. F1000 Prime Reports 2013; 5: 51.
27. Wittebole X, Roock SD, and Opal SM. A historical overview of bacteriophage therapy as an alternative to antibiotics for the treatment of bacterial pathogens. Virulence 2014; 5: 226-235.
28. Ilizirov Y, Formanovsky A, Mikhura I, et al. Effect of Photodynamic Antibacterial Chemotherapy Combined with Antibiotics on Gram-Positive and Gram-Negative Bacteria. Molecules 2018; 23: 3152.
29. Abbas M, Fisal R, and Orabi AS. Enhancement of the biochemical activity of some market antibiotics by chemical modification: Synthesis, characterization, and biochemical evaluation. J Chin Chem Soc-TIAP 2020; DOI: 10.1002/jccs.202000158.
30. Coates AR and Hu Y. Novel approaches to developing new antibiotics for bacterial infections. Brit J Pharmacol 2007; 152: 1147-1154.
31. Tally FP and DeBruin MF. Development of daptomycin for Gram-positive infections. J Antimicrob Chemother 2003; 46: 523-526.
32. National Action Plan on Antimicrobial Resistance.

https://ncdc.gov.in/WriteReadData/l892s/File645.pdf [Accessed 11 Jan, 2022].
33. Uchil RR, Kohli GS, Katekhaye VM, et al. Strategies to Combat Antimicrobial Resistance. J Clin Diagnos Res 2014; 8: ME01-ME04.
34. Global Antimicrobial Resistance and Use Surveillance System (GLASS). https://www.who.int/initiatives/glass [accessed 5 November 2021].
35. Antimicrobial resistance. https://www.who.int/china/health-topics/antimicrobial-resistance [accessed 5 November 2021].
36. Antibiotic Review Kit (ARK). http://www.arkstudy.ox.ac.uk/ [accessed 12 November 2021].
37. Walker AS, Budgell E, Laskawiec-Szkonter M, et al. Antibiotic Review Kit for Hospitals (ARK-Hospital): study protocol for a stepped-wedge cluster-randomised controlled trial. Trials 2019; 20: 421.
38. Ranjalkar J and Chandy JS. India's National Action Plan for antimicrobial resistance-An overview of the context, status, and way ahead. J Family Med Prim Care 2019; 8: 1828-1834.
39. Data courtesy of the Food and Drug Administration's Center for Drug Evaluation and Research. http://www.centerwatch.com/drug-information/fda-approved-drugs.html, [accessed 8 May 2021].