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RESEARCH ARTICLE

TACKLING ANTIMICROBIAL RESISTANCE: COMPREHENSIVEREVIEW OF MECHANISMS, TRENDS, AND STRATEGIES

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Abstract

Background:Antimicrobial resistance (AMR) is a major global issue that leads to more deaths, illnesses, and higher healthcare expenses. This review aims to synthesize the current understanding of AMR, including its mechanisms, prevalence, impact, and strategies to combat it.

Objectives: This review gives a complete summary of what we know about AMR, how it develops resistance, and its social and economic effects.. Additionally, it explores current and emerging approaches to combat AMR and antibiotic stewardship programme.

Methods: A thorough search of many research papers was done using databases like PubMed, Scopus, and Web of Science. Articles were selected based on relevance, scientific rigor, and recent publication date. Key themes were identified and synthesized to provide an integrated perspective on AMR.

Results: The review identifies several key mechanisms of resistance, including enzymatic degradation of antibiotics, alterations in drug targets, efflux pumps, and biofilm formation. The socio-economic impact of AMR is profound, affecting healthcare costs, economic productivity, and global health security. Current methods to fight AMR include better tracking, careful use of antibiotics, infection prevention, and creating new antibiotics and other treatments.

Conclusions: The review underscores the multifaceted nature of AMR and the need for a coordinated global response.Public health rules and working together globally are vital to reducing the impact of AMR and ensuring antibiotics remain effective for future generations.

Introduction:-

Antibiotics have been the most successful treatments in medicine. They are used for many health problems, so it would be terrible if they stopped working. Antimicrobial resistance (AMR) is a big global health problem where germs like bacteria, viruses, fungi, and parasites become resistant to medicines that used to kill them. This makes standard treatments useless, causing infections to last longer and increasing the risk of disease spread, severe illness, and death. The World Health Organization (WHO) says that about 700,000 people die from AMR every year, and this number is expected to grow quickly. Since many drug companies have stopped making new antibiotics, it's hard to find new treatments for AMR[1].

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Is AMR Caused By Nature Or Humans?[1]
The origins of Antimicrobial Resistance (AMR) can be both natural and man-made.

Natural Origins:
Microbial Evolution:
Bacteria and other microorganisms have evolved natural resistance mechanisms over millions of years. This includes the production of antibiotic-like substances by soil bacteria to outcompete other microorganisms.

Horizontal Gene Transfer:
Bacteria can share genetic material, including resistance genes, through processes like conjugation, transformation, and transduction. This happens naturally in the environment.

Environmental Microbiomes:
Natural places like soil, water, and animal guts have many different microbes. These environments can hold resistance genes that can be passed to harmful bacteria.

Man-Made Contributions:
1. Overuse of Antibiotics: Using antibiotics too much and in the wrong ways speeds up resistance. This includes giving antibiotics for viral infections (where they don't work) and using them to help animals grow faster.
2. Environmental Pollution: Pharmaceutical manufacturing, improper disposal of antibiotics and agricultural runoff contribute to the presence of antibiotics in the environment. This creates selective pressure on bacteria to develop and maintain resistance.
3. Global Travel and Trade: More travel and trade between countries helps resistant bacteria and genes spread from one place to another**.**[1].
Because of the widespread use of antibiotics and the rise of AMR, scientists are looking into bacteriophage therapy again. This review summarizes how bacteriophage therapy can help with AMR. First, it explains how bacteriophages work and their benefits. Finally, it highlights the challenges and important issues for future development of bacteriophage therapy[1].

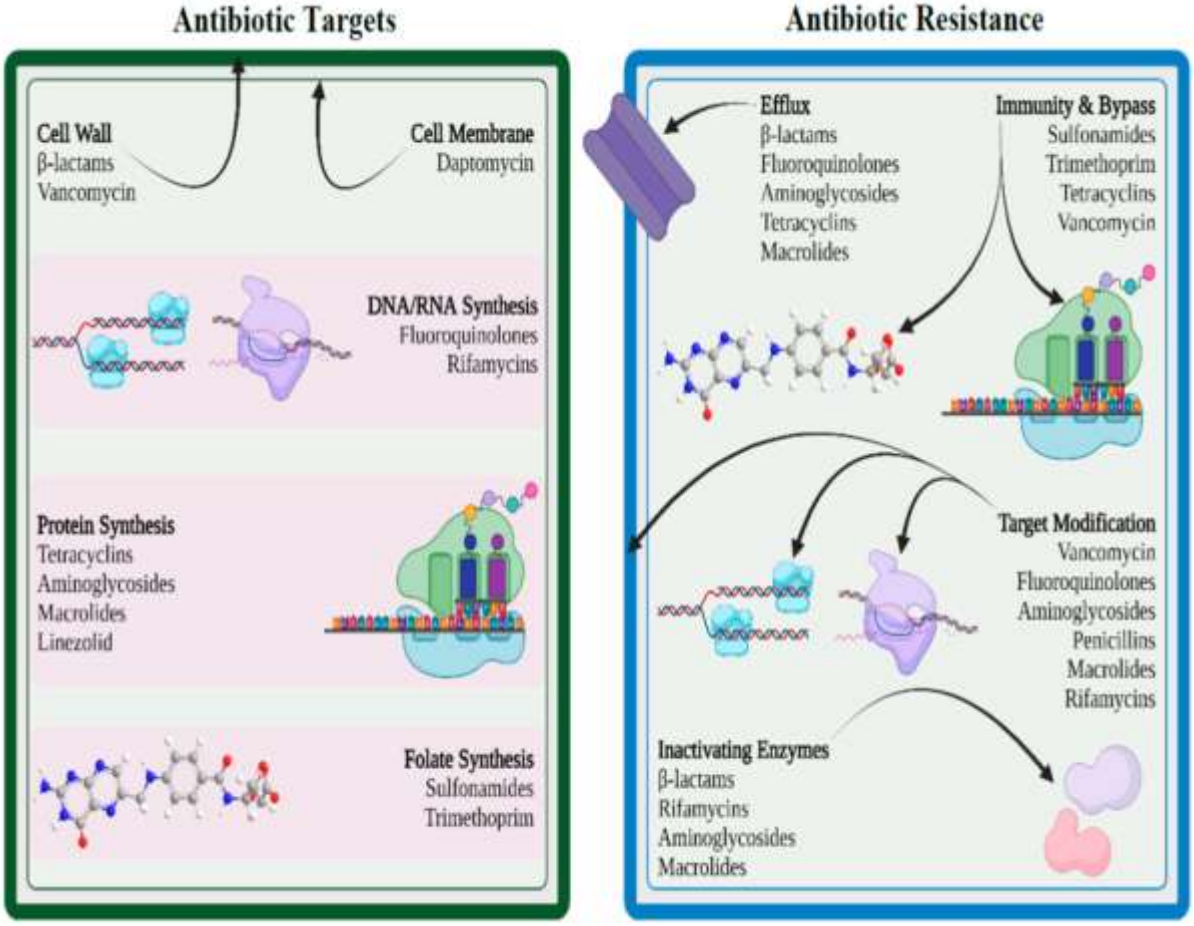
Superbugs[2]
Superbugs are germs that are very tough to treat because they have become resistant to the antibiotics. These include bacteria like MRSA, E. coli, and others that are very hard to kill with regular medicine. Because of this resistance, infections from these germs can be very serious and sometimes even deadly, especially in hospitals. They are called "ESKAPE" pathogens because they can "escape" the effects of drugs designed to kill them. Superbugs have become a big problem mainly because antibiotics have been overused and misused for many years. This makes treating infections much harder and leads to health issues[2].

Mechanisms of Drug Resistance[2]
The primary mechanisms through which drug resistance develops:
1) **Genetic Mutations**
Point Mutations: Changes in a single nucleotide can alter the target site of the drug, reducing its binding affinity.
Gene Amplification: Increased copies of a gene can lead to overproduction of a drug target, necessitating higher drug concentrations for effectiveness.
Chromosomal Rearrangements: Structural changes in chromosomes can lead to drug resistance.

2. **Efflux Pumps**
Cells can develop or overexpress efflux pumps, which are proteins that actively transport drugs out of the cell, reducing their intracellular concentrations and effectiveness.
3. **Drug Inactivation**
Enzymatic Degradation: Some bacteria make enzymes that break down antibiotics, making them useless. For example, β-lactamases destroy β-lactam antibiotics.
4. **Target Modification**
Alterations in the drug target(e.g., mutations in ribosomal RNA in bacteria) can reduce drug binding, rendering the drug ineffective.
5. **Altered Drug Uptake**
Changes in cell membrane permeability or transport mechanisms can reduce the uptake of the drug into the cell.

6. **Biofilm Formation**
Some microorganisms form biofilms, which are protective layers that encase the cells and limit drug penetration, leading to drug resistance.
7. **Alternative Pathways**
Cells can activate alternative biochemical pathways to bypass the metabolic step targeted by the drug.
8. **Dormancy and Quiescence**
Some cells can go into a resting state where they're less affected by drugs that target cells that are actively growing.
9. **Immune Evasion**
In cancer, cells can evade the immune system's response, which can be triggered or enhanced by some drugs, leading to resistance[2].

Examples of Drug Resistance
Antibiotics: Resistance mechanisms include β-lactamase production, efflux pumps, and target modification (e.g., MRSA with altered penicillin-binding proteins).
Antivirals: HIV can develop resistance through mutations in reverse transcriptase or protease enzymes.
Antifungals: Fungal resistance can involve efflux pumps, target modification, and biofilm formation.
Cancer Chemotherapy: Cancer cells may use efflux pumps (e.g., P-glycoprotein), DNA repair mechanisms, and altered drug targets to develop resistance[2].



Antibiotic Targets and How Bacteria Resist Drugs[2]

To Fight Amr, We Should[2]:
1. Use antibiotics wisely and only when needed.
2. Limit the use of antibiotics to prevent infections.
3. Educate patients about antibiotics and make sure they follow treatment plans.
4. Maintain good hospital hygiene and practice careful use of antibiotics.

The World Health Assembly has outlined five main actions to tackle AMR:

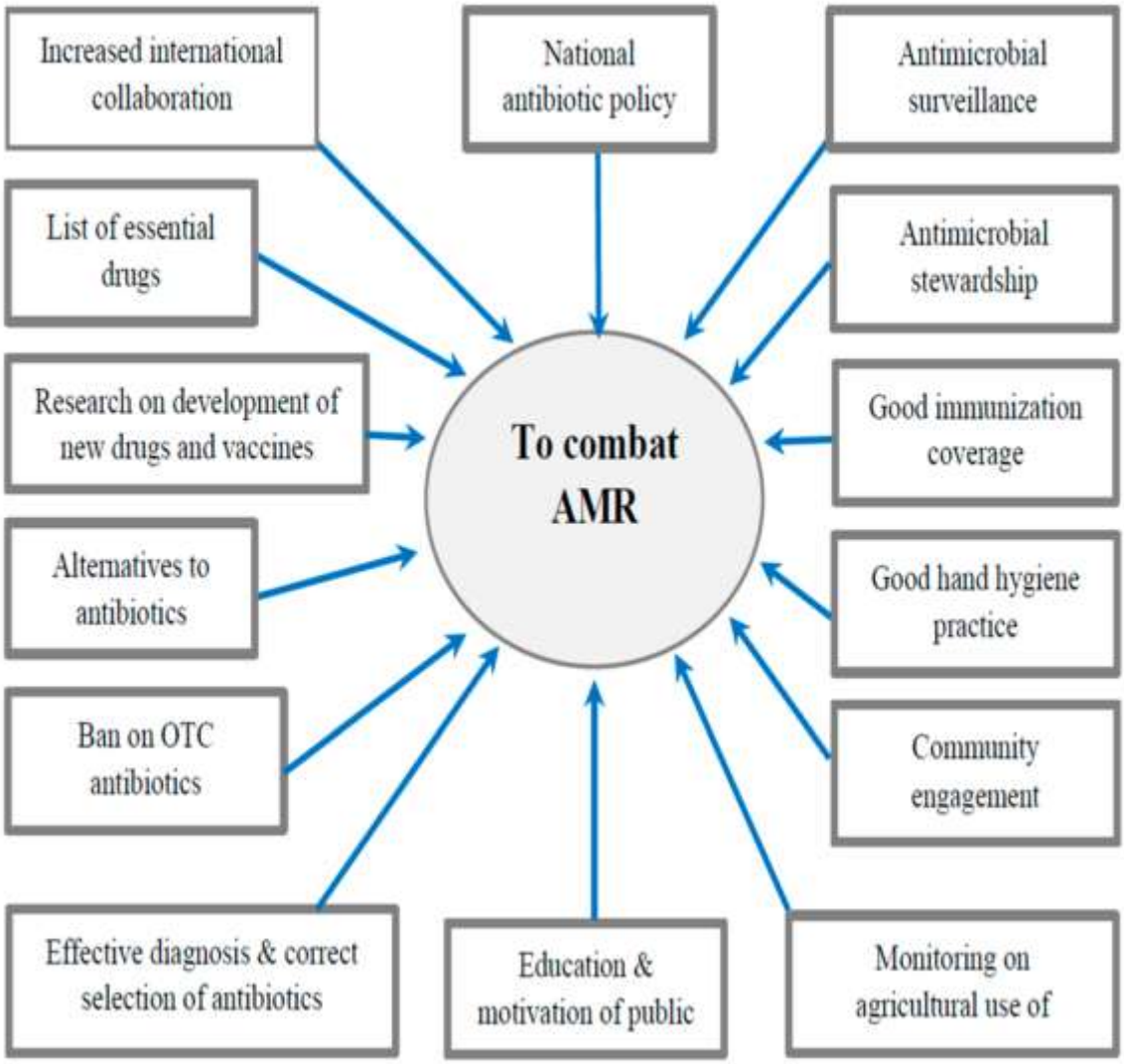
1. Raise awareness and understanding of AMR.
2. Improve knowledge through monitoring and research.
3. Ensure good sanitation, hygiene, and infection prevention.
4. Use antibiotics properly in both people and animals.
5. Invest in new medicines, diagnostic tools, and vaccines.

International Measures:

1. Work together with global organizations, governments, and other groups to tackle AMR.
2. Set up global networks to track antibiotic use and AMR.
3. Improve lab abilities to detect and report harmful pathogens that affect global health.
4. Create international systems to quickly identify and respond to new pathogens.

National Strategies:

1. Create and enforce rules for careful use of antibiotics in healthcare and farming.
2. Strengthen national efforts to monitor and track AMR by connecting public health and veterinary sectors.
3. Develop new tests for identifying pathogens and checking resistance.
4. Invest in research for new antibiotics and vaccines.
5. Build skills and enhance global cooperation to fight AMR.



Major Interventions to Fight AMR[2]

Alternatives To Antibiotics[2]

As antibiotic resistance continues to rise, exploring alternatives to traditional antibiotic therapy becomes increasingly important. Here are some promising alternatives to antibiotic therapy:

1. Phage Therapy

Phage therapy targets specific harmful bacteria without affecting helpful ones. Recently, there have been successful treatments using bacteriophages in the U.S. and Europe. In the U.S., the FDA approved a clinical trial where bacteriophages were used to treat patients with drug-resistant S. aureus infections. Many patients were successfully treated and had few side effects. The FDA also approved phage therapy for various acute infections like joint, bone, and wound infections. Right now, the easiest-to-get bacteriophages come from Poland, Russia, and Georgia.

2. Antimicrobial Peptides (AMPs): These are short proteins that break down bacterial cell membranes, killing the bacteria. They are a natural part of the immune system in many organisms.

3. Probiotics and Prebiotics:

Probiotics: These are live good bacteria that help fight harmful bacteria in the gut, lowering the risk of infections.

Prebiotics: These are special types of food that feed and help grow good bacteria in the gut.

4. Bacteriocins: These are proteins made by bacteria that can kill or stop the growth of similar bacteria.

5. Immune Modulation

Immunotherapy:

This can involve using monoclonal antibodies or immune-stimulating agents to boost body's immune response to fight bacterial infections.

Vaccination:

Development of vaccines can prevent bacterial infections, reducing the need for antibiotics.

6. Plant-Based Compounds

Phytochemicals: These compounds are found in plants and have antimicrobial properties, such as essential oils, tannins, and alkaloids.

7. CRISPR-Cas Systems

Mechanism: This can be used to target and destroy specific bacterial DNA, rendering the bacteria non-viable.

8. Synthetic Biology

Engineered Bacteria: In this process, bacteria can be designed which can produce antimicrobial substances.

9. Quorum Sensing Inhibitors

Mechanism: They can disrupt the communication systemsthat bacteria use to coordinate activities like biofilm formation and virulence factor production.

10. Nanotechnology

Nanoparticles: Utilizing nanoparticles with antimicrobial properties (e.g., silver nanoparticles) to kill bacteria.

11. Photodynamic Therapy (PDT)

Mechanism: By using light-activated compounds (photosensitizers) to produce reactive oxygen species that kill bacteria.

12. Enzyme Therapy

Lysins: Enzymes derived from bacteriophages that can degrade bacterial cell walls, leading to cell lysis.

These alternatives to antibiotic therapy offer promising avenues for combating bacterial infections and reducing reliance on traditional antibiotics, thereby helping to mitigate the spread of antibiotic resistance[2].

Combining Bacteriophages and Antibiotics: A Better Approach[1]

Using both bacteriophages and antibiotics together to treat AMR infections looks very promising. Here are some examples:

Wound Infections:

Combining bacteriophages with antibiotics has been effective in treating chronic wounds, including those with antibiotic-resistant bacteria like MRSA.

Respiratory Infections:

Research shows that using both phages and antibiotics can help treat respiratory infections from resistant bacteria like Pseudomonas aeruginosa.

Gastrointestinal Infections:
This combination is showing good results in treating infections from harmful bacteria like E. coli and Salmonella.

Sepsis:
In animal studies, using both phages and antibiotics together has led to better results in treating sepsis from multi-drug resistant bacteria[1].

Bacteriophage Cocktail[1]
A bacteriophage cocktail is a mixture of multiple bacteriophages designed to target a broader range of bacterial strains or to enhance the efficacy against a specific bacterial pathogen.
Examples of Bacteriophage Cocktails are:

Phage Therapy for MRSA:
A cocktail targeting multiple strains of MRSA has shown success in treating skin infections and wounds.

PhageGuard:
A commercial phage cocktail used in the food industry to target Listeria monocytogenes, reducing contamination in food products.

Pyophage:
A therapeutic phage cocktail developed in Georgia, used to treat various bacterial infections, including those caused by Pseudomonas, Staphylococcus, and Streptococcus species[1].

Antibiotic Stewardship Program[3]
Using antibiotics wisely is important to treat infections effectively, protect patients from harm, and fight antibiotic resistance. Antibiotic stewardship programs help doctors use antibiotics better and avoid unnecessary use.

Key Parts of Hospital Antibiotic Stewardship Programs:
1. **Leadership Commitment:** Hospital leaders need to provide the necessary resources, like staff and technology.
2. **Accountability**: Appoint a physician and a pharmacist to manage the program and ensure its success.
3. **Pharmacy**: Expertise: Have a pharmacist, ideally as a co-leader, to guide the program and improve antibiotic use.
4. **Action:** Use methods like regular reviews of antibiotic use and requiring approval for certain prescriptions to improve how antibiotics are used.
5. **Tracking:** Keep track of how antibiotics are prescribed, the effects of interventions, and issues like C. difficile infections and resistance patterns.
6. **Reporting:** Share information on antibiotic use and resistance regularly with doctors, pharmacists, nurses, and hospital leaders.
7. **Education:**Teach doctors, pharmacists, nurses, and patients about the risks of antibiotics, resistance, and how to use them properly.

By following these steps, an ASP helps to ensure that antibiotics remain effective for treating infections, reduces the chances of side effects, and limits the development of antibiotic resistance.

Conclusion:-

Antimicrobial resistance (AMR) is a major global health threat, making it hard to treat common infections and leading to higher medical costs, longer hospital stays, and more deaths. The overuse and misuse of antibiotics in people, animals, and farming have sped up the spread of resistant germs. To fight AMR, we need to use several strategies: promoting careful use of antibiotics, improving infection prevention, investing in new treatments and research, and educating people about using antibiotics responsibly. Tackling AMR needs everyone—governments, healthcare providers, businesses, and the public to work together to keep current treatments effective and find new solutions for the future.

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