Recommended steps to reduce antibiotic resistance and new emerging treatment approaches to treat infections




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Abstract

Antibiotic resistance is a growing public health concern, and it poses a significant threat to human health. The overuse and misuse of antibiotics have contributed to the emergence of antibiotic-resistant bacteria, making it difficult to treat bacterial infections. This has led to the need for new approaches to treating infections, and researchers are exploring various options. The recommended steps to reducing antibiotic resistance include the appropriate use of antibiotics, preventing infections, and developing alternative treatments. Additionally, people can prevent infections by practicing good hygiene, getting vaccinated, and avoiding close contact with sick individuals. Emerging treatments for bacterial infections include bacteriophages, which are viruses that target specific bacteria, and antimicrobial peptides, which are naturally occurring molecules that can kill bacteria. These treatments show promise in treating antibiotic-resistant infections, and researchers are continuing to explore their effectiveness. In conclusion, reducing antibiotic resistance requires a multifaceted approach. Researchers are making progress in identifying new treatments, but it is essential to use antibiotics responsibly to preserve their effectiveness in the long term.

Keywords: Antibiotic Resistance, Appropriate Antibiotic Use, Bacteriophages, Antimicrobial Peptides, Bacterial Infections, Overuse, Misuse.

1. Introduction

Medicines known as antibiotics are used to both prevent and treat bacterial infections. In addition to saving patients' lives, antimicrobial therapies have been vital in achieving significant improvements in surgery and medicine (1). They have effectively avoided or managed infections that can develop in patients undergoing chemotherapy, dealing with long-term conditions like diabetes, end-stage renal disease, or rheumatoid arthritis, or recovering from difficult operations like organ transplants, joint replacements, or cardiac surgery (2). Antibiotics have also helped extend expected life spans by changing the outcome of bacterial infections (3).

When microorganisms like bacteria, viruses, fungi, and parasites evolve in ways that make antimicrobials ineffective, it is termed as antimicrobial resistance, also known as drug

resistance. "Superbugs" are germs that have developed resistance to most antimicrobials. One of the major dangers to food security, and global health today is antibiotic resistance (AMR). Anyone, of any age, in any nation, can become vulnerable to AMR. The abuse of antibiotics in both humans and animals is hastening the natural occurrence of AMR. As the effectiveness of the antibiotics used to treat them declines, a rising range of illnesses, including pneumonia, TB, gonorrhea, and salmonellosis, are becoming more challenging to treat. This is a major concern because a resistant infection may kill, spread to others, and impose huge costs to individuals and the society (4).

The way antibiotics are prescribed and used in the world needs to change immediately. Without a behavioural change, AMR will continue to pose a serious hazard even if new medications are formulated. Behavioural modifications must focus on improving food cleanliness, hand washing, practicing safer sex, and being vaccinated so as to stop the spread of diseases.

2. Scope of the problem

AMR is rising to dangerously high levels in all parts of the world. New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases. A growing list of infections – such as pneumonia, tuberculosis, blood poisoning, gonorrhoea, and foodborne diseases – are becoming harder, and sometimes impossible, to treat as antibiotics become less effective (5).

With a high prevalence of diseases that are resistant to treatment, AMR poses a serious public health threat in India. According to the Indian Council of Medical Research (ICMR), there are considerable variations by region in the prevalence of AMR. AMR is more common overall in hospitals than in the general population. According to a 2019 ICMR study, more than 70% of the bacteria causing bloodstream infections in hospitals were at least partially resistant to one of the regularly prescribed antibiotics (6). Another study published in the Lancet in 2020, reported that India has the highest burden of drug-resistant tuberculosis (TB) globally, with an estimated 27% of TB cases in India being resistant to at least one major anti-TB drug. Another study also estimated that by 2050, the annual number of deaths due to AMR in India could reach 10 million (7).

This emphasizes the urgent requirement for efficient AMR prevention methods in India; including encouraging sensible antibiotic usage, enhancing infection prevention and control procedures, and stepping up surveillance and monitoring of AMR. Without urgent action, we are heading for a post-antibiotic era, in which common infections and minor injuries can once again lead to mortality.

3. Causes of the crisis in antibiotic resistance (AMR)

3.1 Excessive antibiotic use: Sir Alexander Fleming emphasized the issue of antibiotic misuse in 1945 when he foresaw that "public demand for the drug will then bring in an era of abuses." (8). Resistance can evolve on its own through mutation. Drug-sensitive competitors are eliminated by antibiotics overuse, leaving resistant microorganisms viable to proliferate due to natural selection (9). Despite warnings regarding overuse, antibiotics are overprescribed

worldwide. In many other countries, antibiotics are unregulated and available over the counter without a prescription. This lack of regulation results in antibiotics that are easily accessible, plentiful, and cheap; promoting their overuse (10).

3.2 Inappropriate Prescribing: Incorrectly prescribed antibiotics also contribute to the proliferation of resistant bacteria. Studies have shown that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30 - 50% of cases. The Centers for Disease Control and Prevention (CDC) estimates that at least 2 million people are infected with antibiotic-resistant bacteria each year in the United States, resulting in 23,000 deaths (11).
Studies have shown that inappropriate prescribing of antibiotics is common in India. For example, a study published in the Journal of Antimicrobial Chemotherapy in 2017 found that 52% of outpatient antibiotic prescriptions in India were inappropriate. Another study published in PLOS ONE in 2019 found that 66% of antibiotics prescribed for respiratory tract infections in a hospital in India were inappropriate(12). Low levels of antibiotics have been shown to contribute to strain diversification in organisms such as Pseudomonas aeruginosa. Subinhibitory concentrations of piperacillin and/or tazobactam have also been shown to induce broad proteomic alterations in Bacteroides fragilis (13).

3.3 Extensive Agricultural Use: Studies have demonstrated that direct interaction with livestock can result in the spread of germs that are resistant to antibiotics, which is a direct infection with resistant bacteria from an animal's source. Staphylococcus aureus germs, which are resistant to antibiotics and can infect humans, may also be present in manure.
The most typical foodborne bacteria are Campylobacter, Salmonella, E. coli, and Listeria species that alone account for over 400,000 Americans becoming sick from antibiotic-resistant infections every year. Also, dairy products and different types of meat can harbour pathogens both resistant and susceptible to antibiotics like Enterobacteriaceae (14).

3.4 Availability of Few New Antibiotics: There have been lesser attempts to produce new antibiotics recently, which can be attributed to several things.

Regulatory obstacles: Due to the high expenditures of clinical studies and the unpredictability of consumer demand, the regulatory environment for the development of antibiotics can become difficult. The extensive use of new medicines raises the possibility of AMR, which could affect market access and regulatory approval.

Economic challenges: Due to short treatment cycles and low cost, antibiotics are less profitable than other medications that are taken for a longer duration or prescribed for chronic diseases.
Public health issues: The effects of AMR on public health is a major source of concern. However, there is a lack of globally coordinated action to address this problem. Due to this, it may be challenging for businesses to give research and development of antibiotics priority (15).

3.5 The clinical and economic burden of antibiotic resistance: AMR poses a significant clinical and economic burden, both globally and within individual countries, such as India. Because infections are harder to cure when there is AMR, there may be an increase in both - morbidity and death; especially, by bacteria that are multidrug resistant, as these diseases

Table 1. CDC Assessment of Antibacterial Resistance Threats (5).

Urgent Threats
Clostridium difficile
Carbapenem-resistant Enterobacteriaceae (CRE)
Drug-resistant Neisseria gonorrhoeae
Serious Threats
Multidrug-resistant Acinetobacter
Drug-resistant Campylobacter
Fluconazole-resistant Candida (a fungus)
Extended spectrum beta-lactamase-producing Enterobacteriaceae (ESBLs)
Vancomycin-resistant Enterococci (VRE)
Multidrug-resistant Pseudomonas aeruginosa
Drug-resistant nontyphoidal Salmonella
Drug-resistant Salmonella Typhimurium
Drug-resistant Shigella
Methicillin-resistant Staphylococcus aureus (MRSA)
Drug-resistant Streptococcus pneumoniae
Drug-resistant tuberculosis
Concerning Threats
Vancomycin-resistant Staphylococcus aureus (VRSA)
Erythromycin-resistant Group A Streptococcus
Clindamycin-resistant Group B Streptococcus

may necessitate more vigorous therapy, longer hospital stays, and possibly greater mortality rates. Patients with antibiotic-resistant infections may require longer hospital stays and more intensive care, which can increase healthcare costs and pose a significant burden on patients and their families (5, 16). The assessment of antibacterial resistance AMR shown in Table 1.

4. Recommended Steps to Reduce Antibiotic Resistance

Several actions can be taken by health care providers (HCPs) and facilities to reduce AMR, according to the CDC, other groups, and experts. What follows is an explanation of each of these actions.

4.1 Adopt Antibiotic Stewardship Programs: Antibiotic stewardship involves making a commitment to use antibiotics only when needed, choosing the proper drug, and administering the medication at the appropriate dose and duration in every case (17). Successful implementation of an antibiotic stewardship program requires an interdisciplinary team, system innovation, educational intervention, and feedback provided to health care workers (18). A review of 24 studies published from 1996 to 2010 demonstrated that antibiotic stewardship programs achieved an 11% to 38% reduction in defined daily dose per 1,000 patient-days. This result included significant reductions in total antibiotic consumption, duration, and inappropriate use (19).

4.2 Optimize Therapeutic Regimens: Antibiotics are generally prescribed according to a fixed regimen that involves a specific dose, dosage frequency, and length of treatment. Recent evidence indicates that extended regimens may be unnecessary, since many clinical trials have shown that shorter courses of therapy are often just as effective as longer ones. One study showed that patients with hospital-acquired infections (HAI), including ventilator-associated pneumonia (VAP), who had received appropriate antimicrobial therapy had good clinical responses within the first six days. Results from a multicenter, randomized controlled trial of

01 patients also indicated that clinical outcomes for patients receiving appropriate empiric therapy for microscopically proven VAP for eight days were similar to those for patients who had received treatment for 15 days (18).

4.3 Improve Diagnosis and Diagnostic Tools: Perhaps the most effective way to reduce inappropriate antibiotic use is to eliminate diagnostic uncertainty. Identifying antibiotic-resistant infections can be challenging, so selection of antibiotic treatments is often empiric. In the United States (US), a recent report showed that a microbiological diagnosis was made in only 7.6% of 17,435 patients who were hospitalized with community-acquired pneumonia (CAP) (20). Multiple antimicrobials are often administered simultaneously in the hope that one will be useful in controlling an unidentified pathogen. More commonly, general practitioners may prescribe successive courses of antibiotics until an effective treatment is found. This approach can be harmful because it subjects the patient's microbiota to intense and repeated selective pressure, which encourages the development of AMR (21).

4.4 Improve Tracking Methodologies: The CDC has recently implemented the National Healthcare Safety Network (NHSN) for use by health care facilities to electronically report infections, antibiotic use, and resistance. These data allow regions, states, and facilities to identify and track antibiotic-resistant bacteria that are responsible for many HAIs. As more hospitals submit data to the NHSN database, they will be able to track antibiotic usage and bacterial resistance, enabling areas of concern to be addressed, needed improvements to be made, and successes to be shared (22).

4.5 Prevention and control: AMR is accelerated by the misuse and overuse of antibiotics, as well as poor infection prevention and control. Prevention of infection can significantly decrease resistance by eliminating the need for antibiotics in the first place. Patients are placed at risk for antibiotic-resistant infections when pathogens are transferred from one patient to other. To accomplish this goal, compliance with infection-control guidelines established by the health care facility is essential. Diligent hand hygiene before and after all patient is critical to reduce the risk of transmitting both antibiotic-susceptible and antibiotic-resistant bacterial pathogens. Disinfection of the health care environment and patient-care equipment should also be required (8). Growing concern spurs public and private initiatives, policies, and investments. In addition to adopting the recommended steps, a clearly defined, comprehensive, national action plan needs to be established to manage the AMR crisis (23).

5. New agents for the treatment of bacterial infections

There have been a few new antibiotics that have been approved and are now available for use, as well as some in development. Cefiderocol and Fosfomycin were approved for the treatment of urinary tract infections (24,25). Lefamulin and Omadacycline were approved for the treatment of CAP caused by certain gram-positive bacteria. (26,27). Teixobactin has shown activity against a range of gram-positive bacteria, including drug-resistant strains. Clinical trials are currently ongoing (28). It is important to note that while these new antibiotics offer hope in the fight against AMR, they should be used judiciously to prevent the emergence and spread of further resistance. The prevention and control of antibiotic resistance is tabulated in Table 2

Table 2. WHO: Prevention and control of AMR

Individuals
To prevent and control the spread of antibiotic resistance, individuals can:
Only use antibiotics when prescribed by a certified health professional.
Never demand antibiotics if your health worker says you don't need them.
Always follow your health worker's advice when using antibiotics.
Never share or use leftover antibiotics.
Prevent infections by regularly washing hands, preparing food hygienically, avoiding close contact with sick people, practicing safer sex, and keeping vaccinations up to date.
Prepare food hygienically, following the WHO Five Keys to Safer Food (keep clean, separate raw and cooked, cook thoroughly, keep food at safe temperatures, use safe water and raw materials) and choose foods that have been produced without the use of antibiotics for growth promotion or disease prevention in healthy animals.
Health professionals
To prevent and control the spread of antibiotic resistance, health professionals can:
Prevent infections by ensuring that your hands, instruments, and environment are clean.
Only prescribe and dispense antibiotics when they are needed, according to current guidelines.
Report antibiotic-resistant infections to surveillance teams.
Talk to the patients about how to take antibiotics correctly, AMR and the dangers of misuse.
Talk to your patients about preventing infections (for example, vaccination, hand washing, safer sex, and covering nose and mouth when sneezing).

6. New Approaches to Treating Bacterial Infections

In addition to the development of new antibiotics, there are also several new approaches to the treatment of bacterial infections that are being explored now. Here are some examples:

6.1 Bacteriophage therapy: Bacteriophages are viruses that infect and kill bacteria. Bacteriophage therapy involves using a specific phage to target and kill bacterial pathogens. This approach has shown promise in treating multidrug-resistant bacterial infections, particularly in cases where traditional antibiotics are ineffective (29).

6.2 CRISPR-Cas systems: CRISPR-Cas systems are genetic tools that can be used to selectively target and modify DNA. They are being explored as a potential treatment for bacterial infections by targeting and disabling virulence factors or antibiotic resistance AMR genes (30, 31).

6.3 Immune-based therapies: Immune-based therapies involve harnessing the immune system to target and kill bacterial pathogens. Examples include monoclonal antibodies, which can be designed to specifically target bacterial antigens, and phagocytic cells, which can be activated to engulf and kill bacteria (32, 33).

6.4 Antimicrobial peptides: Antimicrobial peptides are naturally occurring molecules that can kill bacteria by disrupting their cell membranes. They are being explored as a potential alternative to traditional antibiotics, particularly for the treatment of multidrug-resistant bacterial infections (34).

6.5 Repurposing existing drugs: There is growing interest in repurposing existing drugs for the treatment of bacterial infections. For example, some drugs that are used to treat other

diseases, such as cancer or autoimmune disorders, have been shown to have antibacterial properties (35). It is important to note that while these new approaches offer promise in the fight against AMR, they are still in the early stages of development and further research is needed to determine their safety and efficacy.

7. Conclusion

Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics. Despite the alarming and increasing threat posed by emerging antibiotic-resistant bacteria worldwide, the implementation of recommended steps, new policies to manage the crisis, renewed research efforts to find novel agents and approaches to treating bacterial infections could dramatically reduce these risks. HCPs, researchers, policymakers, and representatives of the pharmaceutical industries have begun to come together in these ways to fight the AMR crisis. Although success will require a considerable investment of human and financial resources, the cost of not acting would likely be much greater.

When infections can no longer be treated by first-line antibiotics, more expensive medicines must be used. A longer duration of illness and treatment, often in hospitals, increases health care costs as well as the economic burden on families and societies. AMR is putting the achievements of modern medicine at risk. Organ transplantations, chemotherapy, and surgeries such as caesarean sections become much more dangerous without effective antibiotics for the prevention and treatment of infections.

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Solution on page 96

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