A Review: Antimicrobial Resistance

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Abstract: Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi and parasites change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness and death. As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective and infections become increasingly difficult or impossible to treat. To appreciate the mechanisms of antimicrobial resistance, it is important to understand how antimicrobial agents act. Prevention and control of these infections will require new antimicrobial agents, prudent use of existing agents, new vaccines, and enhanced public health efforts to reduce transmission. Misusing and overusing different antibacterial agents in the health care setting as well as in the agricultural industry, are considered the major reasons behind the emergence of antimicrobial resistance. Many studies have demonstrated the disadvantages financial consequences of AMR including extremely high healthcare costs due to an increase in hospital admissions and drug usage. Although gaps in knowledge about AMR and areas for improvement are obvious, there is not any clearly understood progress to put an end to the persistent trends of antimicrobial resistance.

Keywords: Antimicrobial resistance, AMR, cost, Health; Mechanism; Resistance; Antibiotic, Challenges, Prevention and control, Strategies.

1. INTRODUCTION

Antimicrobial resistance is one of the major public health problems, especially in developing countries where relatively easy availability and higher consumption of medicines have led to disproportionately higher incidence of inappropriate use of antibiotics and greater levels of resistance compared to developed countries. In India, the infectious disease burden is among the highest in the world and a recent report showed the inappropriate and irrational use of antimicrobial agents against these diseases, which led to an increase in development of antimicrobial resistance. Besides, it has been shown that the health sector in India suffers from gross inadequacy of public finance which will result in the conditions favourable for development of drug resistance. A recent study highlighted the importance of rationalizing antibiotic use to limit antibiotic resistance in India. Antimicrobial resistance will result in difficulty in controlling the diseases in the community and ineffective delivery of health care services.

Microorganisms have existed on the earth for more than 3.8 billion years old and exhibit the greatest genetic and metabolic diversity. They are an essential component of the biosphere and serve an important role in the maintenance and sustainability of ecosystems. It is believed that they compose about 50% of the living biomass. In order to survive, they have evolved mechanisms that enable them to respond to selective pressure exerted by various environments and competitive challenges. The disease-causing microorganisms have particularly been vulnerable to man’s selfishness for survival who has sought to deprive them of their habitat using antimicrobial agents. These microorganisms have responded by developing antimicrobial drug resistance to fight off this offensive. The discovery of antimicrobial agents resulted in successful treatment and elimination of infections. Previously, fatal diseases were treatable in a significant number of patients. Development of antimicrobial agents for clinical use has been most successful in targeting essential components of 5 general areas of microbial metabolism: cell wall synthesis, protein synthesis, RNA synthesis, DNA synthesis and intermediary metabolism. However, the discovery of antimicrobial agents has been tempered by the emergence of microbial pathogens that are resistant to antimicrobial agents where microbial pathogens have developed numerous resistance mechanisms that enable them to evade the effects of antimicrobial agents. As a result, many have become resistant to almost every available antimicrobial agent.

Little is known regarding the epidemiological aspects of antimicrobial resistance in most South East Asian countries. Although many international agencies, like the World Health Organization, European Centre for Disease Control and World Health Assembly resolutions have highlighted antimicrobial resistance as a major public health issue, it will be a big challenge to tackle the problem for the policy makers and health care providers. The World Health Organization has proposed a regional strategy on antimicrobial resistance with the goal of minimizing the morbidity and mortality due to antimicrobial resistant infection to preserve the effectiveness of antimicrobial agents in the treatment and prevention of microbial infections. From the public health point of view, it is important to look for the existing situational analysis in the Indian context, so that appropriate interventions can be initiated at community level to tackle the problem. With this background, the study analysed the situation of problem burden and various factors with recent developments, challenges and strategies required to tackle the Antimicrobial Resistance.
2. Causes of Antimicrobial (Drug) Resistance

Microbes, such as bacteria, viruses, fungi, and parasites, are living organisms that evolve over time. Their primary function is to reproduce, thrive, and spread quickly and efficiently. Therefore, microbes adapt to their environments and change in ways that ensure their survival. If something stops their ability to grow, such as an antimicrobial, genetic changes can occur that enable the microbe to survive. There are several ways this happens.

Natural (Biological) Causes

Selective Pressure: In the presence of an antimicrobial, microbes are either killed or, if they carry resistance genes, survive. These survivors will replicate, and their progeny will quickly become the dominant type throughout the microbial population.

Mutation: Most microbes reproduce by dividing every few hours, allowing them to evolve rapidly and adapt quickly to new environmental conditions. During replication, mutations arise and some of these mutations may help an individual microbe survive exposure to an antimicrobial.

Gene Transfer: Microbes also may get genes from each other, including genes that make the microbe drug resistant. Bacteria multiply by the billions. Bacteria that have drug-resistant DNA may transfer a copy of these genes to other bacteria. Non-resistant bacteria receive the new DNA and become resistant to drugs. In the presence of drugs, only drug-resistant bacteria survive. The drug-resistant bacteria multiply and thrive. of adding antibiotics to agricultural feed promotes drug resistance. More than half of the antibiotics produced in the United States are used for agricultural purposes.1, 2 However, there is still much debate about whether drug-resistant microbes in animals pose a significant public health burden.

3. The classification of Antimicrobial Resistance Resistance is developed in the following two ways:

- Horizontal Gene Transfer
- Mutation

Horizontal Gene Transfer

Bacteria can share genes with each other in a process called horizontal gene transfer. This can occur both between bacteria of the same species and between different species and by several different mechanisms, given the right conditions. Gene transfer results in genetic variation in bacteria and is a large problem when it comes to the spread of antimicrobial resistance genes. Ways for Bacteria to share their genes:

- Conjugation: Two bacteria can pair up and connect through structures in the cell membranes and then transfer DNA from one bacterial cell to another.
- Transduction: There are viruses called bacteriophages that can infect bacteria. These viruses sometimes bring along genes that they picked up during infection of another bacterium. These genes may then be incorporated into the DNA of the new bacterial host.
- Transformation: Some bacteria can take up pieces of DNA directly from the environment around the cell.
Bacteria grow and multiply fast and can reach large numbers. When bacteria multiply, one cell divides into two cells. Before the bacterium can divide, it needs to make two identical copies of the DNA on its chromosome; one for each cell. Every time the bacterium goes through this process, there is a chance (or risk, depending on the end result) that errors occur; so-called mutations. These mutations are random and can be located anywhere in the DNA. Mutations can also form due to external factors like radiation or harmful chemicals. Mutations can result in antibiotic resistance in bacteria. Resistant bacteria survive antibiotic treatment and can increase in numbers by natural selection.

4. Mechanism of Action of Antimicrobial Resistance

In order to appreciate the mechanisms of resistance, it is important to understand how antimicrobial agents act. Antimicrobial agents act selectively on vital microbial functions with minimal effects or without affecting host functions. Different antimicrobial agents act in different ways. The understanding of these mechanisms as well as the chemical nature of the antimicrobial agents is crucial in the understanding of the ways how resistance against them develops. Broadly, antimicrobial agents may be described as either bacteriostatic or bactericidal. Bacteriostatic antimicrobial agents only inhibit the growth or multiplication of the bacteria, giving the immune system of the host time to clear them from the system. Complete elimination of the bacteria in this case, therefore, is dependent on the competence of the immune system. Bactericidal agents kill the bacteria and therefore, with or without a competent immune system of the host, the bacteria will die. However, the mechanism of action of antimicrobial agents can be categorized further based on the structure of the bacteria or the function that is affected by the agents. These include the following:
- Inhibition of the cell wall synthesis
- Inhibition of ribosome function
- Inhibition of nucleic acid synthesis
- Inhibition of folate metabolism
- Inhibition of cell membrane function

5. Mechanism of Antimicrobial Resistance

- Decrease Permeability
- Antibiotic Modification
- Efflux Pump
- Target Modification
Decrease Permeability
It involves the ability of microbes to prevent drug entry into the cytoplasm by decreasing permeability of membrane. For example, changes in membrane permeability in penicillin-resistant Pseudomonas prevent the antibiotic from entering the cytoplasm.

Antibiotic Modification
Resistance can arise from the micro-organisms ability to enzymatically split apart (destroy) the antibiotic. Bacteria produces enzymes that degrade or inactivate specific antibiotic. For example, β-lactamase that destroy the active component of penicillin, extremely important antibiotic for treating human infection.

Efflux pump
Bacteria can produce pump that sit in their membrane or cell wall. These so-called Efflux pumps are very common in bacteria and can transport a variety of compounds such as single molecules and nutrients. Some of these pumps can also transport antibiotic out from the bacteria, in this way lowering the antibiotic concentration inside the bacterial cell. Cytoplasmic and membrane proteins in these bacterial cells acts as pumps to remove the antibiotic before it can affect the ribosomes in the cytoplasm. In some cases, mutations in the bacterial DNA can make the bacteria produce more of a certain pump, which in turns increases resistance. For example, Bacterial species such as E. coli and Sauers (staphylococcus aureus), which are resistant to tetracycline, actively export the drug.

Target Modification
A fourth route leading to microbial resistance involve altering the drug target. Some streptomycin resistant bacterial species can modify the structure of their ribosomes so that the antibiotic cannot bind to the ribosome and protein synthesis is not inhibited. Other target includes RNA polymerase and enzyme involve in DNA replication.

6. Present situation
Drug Resistance in Bacteria
Some bacteria have developed resistance to antibiotics that were once commonly used to treat them. For example, Staphylococcus aureus (‘golden staph’ or MRSA) and Neisseria gonorrhoea (the cause of gonorrhoea) are now almost always resistant to benzyl penicillin. In the past, these infections were usually controlled by penicillin.

The most serious concern with antibiotic resistance is that some bacteria have become resistant to almost all of the easily available antibiotics. These bacteria are able to cause serious disease and this is a major public health problem. Important examples are:
- ethicillin-resistant staphylococcus aureus (MRSA)
- vancomycin-resistant Enterococcus (VRE)
- multi-drug-resistant Mycobacterium tuberculosis (MDR-TB)
- carbapenem-resistant Enterobacteriaceae (CRE) gut bacteria

Colistin is the only last resort treatment for life-threatening infection caused by carbapenem resistant Enterobacteriaceae (i.e., E. coli, Klebsiella, etc). Bacteria resistant to colistin have also been detected in several countries and regions, causing infection for which there is no effective antibiotic treatment at present. The bacteria, Staphylococcus aureus, is part of our skin flora and is also a common cause of infections both in the community and in health-care facilities. People with Methicillin-resistant Staphylococcus aureus (MRSA) infections are 64% more likely to die than people with drug-sensitive infections.

Drug Resistance in Mycobacterium tuberculosis
Antibiotic-resistant Mycobacterium tuberculosis strains are threatening progress in containing the global tuberculosis epidemic. Mycobacterium tuberculosis is intrinsically resistant to many antibiotics, limiting the number of compounds available for treatment. This intrinsic resistance is due to a number of mechanisms, including a thick, waxy, hydrophobic cell envelope and the presence of drug degrading and modifying enzymes. Resistance to the drugs which are active against M. tuberculosis is, in the absence of horizontally transferred resistance determinants, conferred by chromosomal mutations. These chromosomal mutations may confer drug resistance via modification or overexpression of the drug target, as well as by prevention of pro drug activation. Antibiotic resistant Mycobacterium tuberculosis strains are threatening progress in containing the global tuberculosis epidemic.

WHO estimates that, in 2018, there were about half a million new cases of rifampicin-resistant TB (RR-TB) identified globally, of which the vast majority have multi-drug resistant TB (MDR-TB), a form of tuberculosis that is resistant to the two most powerful anti-TB drugs. Only one-third of the approximately half a million people who developed MDR/RR-TB in 2018 were detected and reported. MDR-TB requires treatment courses that are longer, less effective and far more expensive than those for non-resistant TB. Less than 60% of those treated for MDR/RR-TB are successfully cured.
Drug Resistance in Viruses
Viruses can become resistant through spontaneous or intermittent mechanisms throughout the course of an antiviral treatment. Immunocompromised patients, more often than immunocompetent patients, hospitalized with pneumonia are at the highest risk of developing oseltamivir resistance during treatment. The three FDA-approved neuraminidase antiviral flu drugs available in the United States, recommended by the CDC, include: oseltamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab).

All antiretroviral (ARV) drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant HIV (HIVDR). People receiving antiretroviral therapy can acquire HIVDR, and people can also be infected with HIV that is already drug resistant. Levels of pre-treatment HIVDR (PDR) to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) among adults initiating first-line therapy exceeded 10% in the majority of the monitored countries. Increasing levels of resistance have important economic implications since second- and third-line regimens are much more expensive than first-line drugs.

Drug Resistance in Malaria Parasites
Malaria, the most prevalent and most pernicious parasitic disease of humans, is estimated to kill between one and two million people, mainly children, each year. Resistance has emerged to all classes of antimalarial drugs except the artesminisin’s and is responsible for a recent increase in malaria-related mortality, particularly in Africa. The emergence of resistance can be prevented by the use of antimalarial drug combinations. Artemisinin-derivative combinations are particularly effective, since they act rapidly and are well tolerated and highly effective. Widespread use of these drugs could roll back malaria.

Artemisinin-based combination therapies (ACTs) are the recommended first-line treatment for uncomplicated P. falciparum malaria and are used by most malaria endemic countries. ACTs are a combination of an artemisinin component and a partner drug. In the WHO Western Pacific Region and in the WHO South-East Asia Region.

In the WHO Eastern Mediterranean Region, P. falciparum resistance to sulf oxide-pyrimethamine led to artesunate-sulf oxide-pyrimethamine failures in some countries, necessitating a change to another ACT.

Drug Resistance in Fungi
Systemic fungal infections pose a serious clinical problem. Treatment options are limited, and anti fungal drug resistance is increasing. In addition, a substantial proportion of patients do not respond to therapy despite being infected with fungi that are susceptible to the drug. The discordance between overall treatment outcome and low levels of clinical resistance may be attributable to anti fungal drug tolerance.

Many fungal infections have existing treatable issues such as toxicity, especially for patients with other underlying infections (e.g., HIV).

Drug-resistant Candida auris, one of the most common invasive fungal infections, is already widespread with increasing resistance reported to fluconazole, amphotericin B and voriconazole as well as emerging compounding resistance. This is leading to more difficult to treat fungal infections, treatment failures, longer hospital stays and much more expensive treatment options.

7. Challenges
- Strengthening of Surveillance Data
- Standard Operating Guidelines
- Improvement in antibiotic prescription practices
- Over the counter sale of antibiotics
- Poor sanitation, endemic infections, malnutrition
- Limited public awareness and government commitment
- Lack of coordination and fragmentation of effort.

8. Call to Action

National Strategies
AMR is a complex problem that requires a united multisectoral approach. The One Health approach brings together multiple sectors and stakeholders engaged in human, terrestrial and aquatic animal and plant health, food and feed production and the environment to communicate and work together in the design and implementation of programmes, policies, legislation and research to attain better public health outcomes.

Gleator innovation and investment are required in operational research, and in research and development of new antimicrobial medicines, vaccines, and diagnostic tools especially those targeting the critical gram-negative bacteria such as carbapenem-resistant Enterobacteriaceae and Acinetobacter Bahmani. The launch of the Antimicrobial Resistance Multi Partner Trust Fund (AMR MPTF), the Global Antibiotic Research & Development Partnership (GARDP), AMR Action Fund and other funds and initiatives could fill a major funding gap. Various governments are piloting reimbursement models, including Sweden, Germany, the USA and the United Kingdom. More initiatives are needed to find lasting solutions.

To improve awareness and understanding of AMR through effective communication, education, and training, India has taken the initiative and some plans are as follows:
- Jaipur Declaration on antimicrobial resistance in September 2011.
- The National Action Plan on AMR was adopted in April 2017.
• Food Safety and Standards Authority of India (FSSAI) released “Antibiotic Residues limits” in food from animals’ origin.
• Strengthening the AMR surveillance network for key pathogens and enrolment in WHO Global Antimicrobial Resistance Surveillance system (GLASS).

Action at community level
Globally, infectious diseases still continue to be significant cause of morbidity and mortality, affecting more the countries where health services are not sufficiently accessible. In a review of antibiotic misuse in the community reported that at community level, more than one third of patients were non-compliant to the antibiotic regimen and one quarter kept the unused antibiotics for use in future. This indicates a poor antibiotic-taking behaviour. Review on population perspective of AMR, suggests that prevention of AMR in an individual suffering from infection is one of the basic methods to prevent further spread of resistance to the wider community. The increasing rate of resistance among community acquired infections like upper and lower respiratory tract infections, bacterial diarrhoea, typhoid fever is not matched by development of newer antibiotics. Thus, there is urgent need for reforms at community level for curtailing AMR. Different measures directed to control and prevent AMR at community levels are the need of an hour.

Rational use of antibiotics
Irrational use of medicines is a serious global problem. In developing countries, at primary level, less than 40% of patients in the public sector and less than 30% of patients in the private sector are treated in accordance with standard treatment guidelines. This mandates public and professional education towards rational use of antibiotics.

Over-the-counter (OTC) antibiotics
Measures that preserve the efficacy of antimicrobials are mainly directed towards the hospitals and drug providers and missing antibiotic use without a prescription. In systematic review of non-prescription antimicrobial use, Morgan et al., reported that non-prescription use of antimicrobials varied from as low as 3% in northern Europe studies to 100% in African studies. This implies an urgent need for regulatory control on OTC use of antibiotics.

Guidelines for use of antibiotics at local levels
About use of antibiotics in common situations, Bhagwati A. discussed that an empirical antibiotic therapy should be started considering the clinical condition of the patient and prevalent pathogen and resistance pattern in a locality. An Appropriate change in antibiotics is required as per the sensitivity of the microbe. Antibiotic guidelines are therefore must to optimize antibiotic selection with their dosing, route of administration and duration of therapy.

Standards of hygiene
Use of alcohol-based hand rubs or washing hands has proven efficacy in prevention of infection. This factor can restrict the spread of infection and thereby the AMR. Willingness to put up with high standards of hygiene is the need of an hour.

Other approaches
These include identifying residents with MDR infections and use of standard treatment regime for their management, vaccination, infection prevention strategies and ban on OTC sale of antimicrobials.

At hospital or health care setting
A person or a patient in a health care facility is at higher risk of infection with common pathogens. For control and containment of AMR, experts recommend some of the measures as discussed herein.

Infection prevention and control within health-care facilities
Infection prevention and control measures are designed to reduce the spread of pathogens, including resistant ones within healthcare facilities and to the wider community. This can prevent further infections and AMR spread. Recommended measures to prevent and control infection in a health-care facility.
• Establishing an infection prevention and control committee (IPC).
• Good hand hygiene practices.
• Effective diagnosis and treatment of infection.
• Rational antimicrobial use.
• Surveillance of antibiotic resistance and antibiotic use.
• Improving the antimicrobial quality and supply chain.
• Good Microbiology Practices.

Surveillance of Antibiotic resistance and antibiotic use
All over the world, surveillance is considered as strength of the programmes directed towards AMR. The objective of surveillance is to facilitate the containment of antibiotic resistance. It is a useful tool that generates data on antimicrobial use and AMR which is essential in updating national EDLs and formulating infection control policies. It may also help in improving antimicrobial prescribing and development of empirical therapy or standard treatment guidelines. National policy on AMR in India recommends three types of surveillances which include comprehensive surveillance, sentinel surveillance, and point prevalence.

Good Microbiology Practices
From accurate collection, handling of specimens to the speedy reporting with standard microbiology practices may help in prevention of AMR spread. Testing with international standards, reporting of resistance pattern to IPC and monitoring the sterilization and disinfection activities underlie the good microbiology practices.

At personal / patient level
Role of Physician
Along with providing direct patient care, complying with local infection control and antibiotic use policies and timely notifying resistant cases to IPC, the physician can play a major role in combating AMR. Identifying and preventing situations that may act as nodes for infection may help curtail unnecessary infections and thereby AMR.

Role of Nurses/health care providers
Since nurses/health care providers are in direct contact with the patients, they are amongst those related to either spread or control of infection and AMR. Educating nurses and health care providers about the AMR and aseptic practices may help to control the spread of infections. Monti et al., have reviewed the role of nurses in preventing AMR and reported the initiatives by Thailand like having Master’s programme in infection control nursing with other short training courses and involvement of nurses in AMR prevention and control programme.

Role of Pharmacist
Pharmacists can counsel patients with viral infections about the ineffectiveness of antibacterial and can recommend appropriate OTC medication for supportive care. Referral to physician is a must if a bacterial infection is suspected. Above all, most importantly, addressing patient and clinician concerns related to antimicrobial and understanding of the appropriate use of these agents, pharmacist can be an essential arm in preventing AMR. The pharmacist is the key person to educating patients about antimicrobial use and the importance of complying with the prescribed treatment regime. This may help to reduce the unnecessary use of antibiotics.

At patient level
(a) Aseptic protocol for any procedures.
Parameswaran et al., reported that MDR microbes caused 30.2% of the catheter-related blood-stream infections and empirical treatment had no role in prevention of such infections. This mandates use of aseptic protocol to minimize local or systemic infections associated with any procedures.
(b) Breaking the chain of inactivity.
By simple means, like covering your mouth while coughing or sneezing, infections spreads can be reduced.
(c) Compliance to the antimicrobial regime and antibiotics.
Improved compliance definitely improves the rate of infection control. Patient education on compliance with antibiotics is a must. Using established regimes for prophylactic use of antibiotics in high-risk cases and for the shortest duration possible can minimize the risk of AMR.

Other Measures
Pharmaceutical promotion
WHO recommends that pharmaceutical firms should strictly adhere to the standards of drug promotion, direct-to-consumer advertising and advertising on the internet. There is a need to identify and prohibit any incentives promoted by pharmaceutical companies that possibly encourage inappropriate antimicrobial use.

Antibiotic use in animals
Use of antibiotic avoparcin in food of the animals in Europe was the cause of development of vancomycin-Resistant Enterococci (VRE) and consequent colonization in human intestine, thus highlighting its importance [16]. WHO specifically called for stricter legislation to minimize antimicrobial usage in animals. Improved sanitation, provision of probiotics or nutritional supplements in feed and vaccination for common animal diseases can help reduce the antimicrobial use in animals.

Rapid understanding of the AMR mechanisms
In their review, Bergeron and Ouellette suggested that genotyping of bacteria and identification of resistant genes in bacteria can impact the treatment of infections and contribute to the control of AMR.

Innovation in new drugs and technology
Concerns of increased antibiotic resistance led to the urgent need to concentrate on the issue of new drugs and vaccines development to combat AMR. Collaborated efforts of national, international, government and academic networks are needed to identify new classes of antibiotics and diagnostic technologies. Providing research funding for development of new antimicrobials to pharmaceutical companies for diseases of public health importance can advance new drug development. In summary, it is necessary to enforce essential actions to be taken by government to inspire change by all stakeholders related to AMR as described in the WHO policy package for combating AMR. This policy package refers to:
• Dedicate to a comprehensive, financed national plan with accountability of each one involved and engagement of civil society
• Improve and strengthen surveillance and laboratory capacity and facilities
• Regulate and encourage rational use of medicines, even in animal husbandry, and ensure proper patient care
• Improvise on infection prevention and control
• Promote and pursue innovations and research and development for new tools.

Conclusion
From this review we found that prevention is still the best tool to reduce the infection spread and thereby AMR. Along with rational use of existing antimicrobial drugs, development of new effective compounds and new diagnostic technology is needed. Joint efforts from patients, prescribes and individuals to international regulators and policy makers are needed to fight against the globally spreading antimicrobial resistance. It is clear that antimicrobial drug resistance is becoming a lethal problem and posing a great threat to our health care system. Antimicrobial Resistance can lead to increased mortality, morbidity, length of hospital stays, costs of treatment and loss of production in animals. Prevention and control of these infections will require new antimicrobial agents, prudent use of existing agents, new vaccines, and enhanced public health efforts to reduce transmission. It is well known that any use of antimicrobials however appropriate and justified, contributes to the development of resistance, but widespread unnecessary and excessive use makes the situation worse.
As a rule, rational use of antimicrobials at every level is the key to limiting the spread of the resistance. Therefore, based on the above information, the following recommendations are:

- Health workers should give attention to antimicrobial resistance while treating infectious diseases with antimicrobial agents.
- To spread awareness about the current situation and run programmes beneficial for underprivileged people.

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