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AN OVERVIEW OF THE WORLDWIDE PROBLEM OF ANTIBIOTIC RESISTANCE: A REVIEW

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ABSTRACT

Antibiotics, which have previously revolutionized medical research, are now under jeopardy due to the emergence of multidrug resistance among dangerous microorganisms. The abuse of antimicrobial medicines, as well as the unavailability of newer treatments owing to stringent regulatory restrictions and decreased commercial incentives, has been blamed for the antimicrobial resistance problem. Emergent bacteria, resistance mechanisms, and antimicrobial drugs must all be studied in order to slow the rate of resistance. Health-care environments, as well as the environment and agricultural sectors, need multidisciplinary approaches. Probiotics, antibodies, and vaccinations are examples of progressive alternative treatments that have showed encouraging outcomes in studies, suggesting that they may be used as preventative or supplementary therapy in the future.

KEYWORDS: *Antibiotics, Antimicrobial Resistance, Alternative Therapies, Evolution, Multidrug Resistance.*

1. INTRODUCTION

Antibiotic resistance is a long-standing concern, and the "resistome" is a dynamic and growing issue. Overpopulation, increasing worldwide movement, increased use of antibiotics in clinics and livestock production, selection pressure, inadequate sanitation, wildlife dispersal, and a poor sewage disposal system are all factors that contribute to the global resistome. Antibiotic therapy is one of the most used methods of infection control in contemporary medicine. Many antibiotics were developed during the "golden era" of antibiotics, which lasted from the 1930s through the 1960s. Unfortunately, due to researchers' inability to keep up with the speed of antibiotic discovery in the face of developing resistance bacteria, this period came to an end. Predisposing factors for the development of antibiotic resistance include a persistent inability to create or find new antibiotics, as well as indiscriminate antibiotic usage.

Antimicrobial resistance (AMR) is a significant worldwide hazard to human, animal, and environmental health that is gaining traction. The development, spread, and persistence of multidrug-resistant (MDR) bacteria, often known as "superbugs," is to blame. MDR bacteria may be found in the animal, human, and environment triangles or niches, and these diseases are all interconnected. Excessive use of antibiotics in animals (food, pets, aquatic), antibiotics sold over-the-counter, increased international travel, poor sanitation/hygiene, and release of nonmetabolized antibiotics or their residues into the environment through manure/feces are all possible causes of "the global resistome" or AMR. These variables lead to the development of MDR bacterial illnesses in the population due to genetic selection pressure.

The worldwide use of antimicrobials in cattle has recently shown hotspots of antibiotic usage across continents, which will have economic and public health implications in the coming years. Antibiotics are widely used in food animals such as cattle, poultry, and pigs, and it is predicted that by 2030, their usage would have increased by 67 percent in the world's most populous nations. The effectiveness of an antimicrobial agent is harmed by the potential for tolerance or resistance to develop from the first time it is used. Antimicrobial agents used to treat bacterial, viral, fungal, and parasitic illnesses fall under this category. Several physiological and pharmacological processes may be at play as this resistance develops. It's important not to exaggerate the complexity of all the processes involved in the development and spread of resistance. Furthermore, a critical issue is the absence of basic data on these particular topics, which has resulted in a lack of major accomplishments in managing resistance development. Various institutions and organizations across the world have acknowledged this significant worldwide public health issue. Numerous suggestions and resolutions have been presented, as well as several reports, but little progress has been achieved so far. Antibiotic resistance is, unfortunately, a never-ending problem[1].

Antibiotics were discovered at a pivotal point in human history, revolutionizing medicine and saving many lives. Unfortunately, these "magic bullets" have been accompanied by diseases that have developed resistance to them. Medical professionals are now expressing grave worry about a return to the pre-antibiotic era. Fortunately, over 20,000 putative resistance genes (r genes) have been discovered after analyzing the available bacterial genomes; nevertheless, functional resistance determinants in different microorganisms are much fewer in number. Antibiotic resistance to various antimicrobial drugs was initially identified in intestinal bacteria, such as Salmonella, Shigella, and Escherichia coli, in the late 1950s and early 1960s. These resistant

strains caused massive clinical, economic, and human-life losses, mostly in poor countries. In the industrialized world, however, it was seen as a minor health issue limited to intestinal bacteria. This myth was dispelled in the 1970s when it was discovered that Neisseria gonorrhoeae and Haemophilusinfluenzae are both ampicillin resistant, with Haemophilus also resistant to tetracycline and chloramphenicol. Antimicrobial resistance has increased as a result of increased usage, especially in poorer countries where these medicines were readily available without a prescription.

Inadequate hygienic conditions aided resistance propagation, and insufficient health-care funding restricted access to new and effective antibiotics. Antibiotic resistance has been designated a "global public health issue" by a number of influential organizations, including the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America, the World Economic Forum, and the World Health Organization (WHO). The World Health Assembly has asked WHO to develop a worldwide action plan to address the issue of antibiotic resistance. The recent release of a book titled "The growing danger of antimicrobial resistance alternatives for action" has added to the issue's value. People in the United Kingdom voted for a £10 million government-sponsored award (the Longitude Prize challenge) to develop new antibiotic resistance-fighting methods. By 2015, President Barack Obama has instructed the National Security Council to develop a comprehensive national action plan to combat antibiotic resistance, based on the recommendations of the US President's Council of Advisors on Science and Technology.

Antibiotic resistance does not seem to be decreasing globally, but it may be shifting in the wrong direction. Antibiotic resistance has a complex etiology, and its effects are seen all across the world. Several efforts have been made to define the various elements of antibiotic resistance, as well as potential remedies to address this worldwide problem. However, a well-coordinated effort is missing, especially at the governmental level across the globe. 16 Antibiotics have played a pivotal part in social and medical evolution, and they are now required in all health-care systems. Without efficient antibiotic treatment to prevent bacterial infections, contemporary medicine's successes, such as organ transplantation, cancer treatments, preterm baby care, and a multitude of sophisticated major operations, would not have been feasible. If comprehensive global action plans are not implemented soon, we may face grave consequences in terms of social, medical, and economic possibilities. We attempt to depict the global scale, main etiologies, and effects, as well as highlight important regions that need immediate attention[2].

1.1 The Emergence of Antibiotic Resistance:

Microorganisms have evolved rigorous methods to evade the deadly effects of antimicrobial compounds as a result of Darwinian selection. The majority of antibiotics are generated naturally by microorganisms such as saprophytic bacteria or environmental fungus, but some are modified synthetic antibiotics and a few are entirely synthetic, such as fluoroquinolones and sulphonamides. Various species have developed defensive mechanisms against them, including changes in the target location, drug entrance or distribution blockage, and enzyme synthesis that may destroy antimicrobials. As a result, antibiotic resistance may simply represent Darwinian competition from natural antimicrobial components generated from microbes. 29,30 The results of a functional meta-genomic study of soil microorganisms showed a wide range of genetic factors linked to antibiotic resistance. Although little is known about this feature in human

infections, enzyme synthesis (-lactamases) is an unusual example of a naturally occurring resistance mechanism that has an effect on human health.Although few results suggested a more complex relationship, it is thought that different antimicrobial compounds generated by saprophytic bacteria inhibit the development of other species present in that environment, providing a reciprocal advantage in such environments. The concentration of antimicrobial compounds in the soil seems to be considerably lower, and may not be able to prevent the development of adjacent bacteria, according to the researchers. Second, evidence suggests that antimicrobials at sublethal concentrations have a substantial influence on microbial physiology and evolution, and that they may function as efficient signaling molecules that drive host or microbial gene expression. Another significant question is why just a few saprophytic bacteria generate carbapenems, a kind of broad-spectrum antibiotic. Several genes involved in carbapenem production may be involved in biofilm development and quorum sensing. These results raise additional questions about the drugs' unintended consequences. Resistance does not just develop against natural antimicrobials; it also develops against synthetic antimicrobials[3].

2. REVIEW OF LITERATURE

J. Daviesin his study talks about many of the routes that are responsible for the release of resistance-driving substances into the environment are monitored and controlled by environmental authorities (e.g., antimicrobials, metals, and biocides). As a result, environmental regulators should play a key role in the creation of global and national antimicrobial resistance (AMR) action plans. The absence of environmental-focused mitigation measures in current AMR action plans is considered to be a result of our lack of basic knowledge of many of the major problems. Here, we'll look at the issue of AMR in the environment through the eyes of an environmental regulator, using the Environment Agency (England's regulator) as an example to draw worldwide similarities. The issues that are important to environmental regulators are outlined in order to answer the following questions: What are the AMR's drivers and pathways? What are the implications for environmental regulators' regular job, powers, and responsibilities? What are the information gaps that prevent environmental protection from AMR from being delivered? We provide a series of thought experiments that demonstrate how various mitigation methods may work. We conclude that: (1) AMR Action Plans do not cover all potentially relevant AMR routes and drivers in the environment; and (2) AMR Action Plans are inadequate in part due to a lack of research to guide policy, which must be addressed[4].

T. P. Van Boeckel et al.in his study discloses that antimicrobials are important medicines whose effectiveness is jeopardized by antimicrobial resistance's development and dissemination. Antibiotics are given to food animals for a broad range of nontherapeutic reasons, including growth enhancement. Concerns about the development of resistance and its dissemination to humans as a result of nontherapeutic antimicrobial usage have resulted in a slew of contradictory behaviors and viewpoints. Based on the "precautionary principle," substantial evidence supports the elimination of nontherapeutic antimicrobials (NTAs) in Europe. Even yet, solid scientific proof of the benefits and drawbacks of NTAs is not apparent to all stakeholders. Antibiotic resistance in microorganisms linked with animals fed NTAs and their food products has been found in significant amounts. This resistance spreads to other animals and people both directly and indirectly via touch, the food chain, water, air, and manured and sludge-fertilized soils, among other things. Modern genetic methods are helping to unravel the ecological effect of

NTAs, but modeling efforts are hampered by a lack of crucial information on microbial and antibiotic doses at each step of the transmission chain. Nonetheless, the increasing body of data documenting the transmission of resistant bacteria from animals to humans, including that resulting from the use of NTAs, recommends discontinuing NTA usage in order to decrease the growing environmental burden of resistance genes[5].

N. Zisko et al.in his study discloses about the antibiotic therapy of serious illnesses and the execution of medical and surgical operations under the protection of antibiotics are two main ways that contemporary medicine saves lives. However, we have not kept up with microorganisms' capacity to evolve resistance to antibiotics developed during the golden period of antibiotic discovery, from the 1930s through the 1960s. That period is referred to as "golden" because achievement appeared regular at the time; it is referred to as a "era" since it came to an end. When corporate scientists tried to develop fundamentally novel medicines with action against resistant infections instead of creating variations of existing treatments, they mostly failed. Industry shifted its attention to medicines that prevent or ameliorate noninfectious illnesses after a series of expensive failures to find new antibiotics that would be destined for short-term usage even if they gained regulatory clearance. As individuals in richer areas run out of effective antibiotics, they are forced to share them with those in poorer areas who couldn't buy them in the first place[6].

3. DISCUSSION

3.1 The Global Economic Scenario of Antibiotic Resistance:

Estimating the precise economic effect of antibiotic-resistant bacterial diseases remains a major worldwide problem. In this case, determining the illness distribution linked to antibiotic resistance is critical. Antibiotic resistance is a significant financial burden for the whole globe. Antibiotic-resistant pathogen-associated hospital-acquired infections (HAIs) kill 99,000 people per year in the United States alone. About 50,000 Americans died in 2006 as a result of two prevalent HAIs, pneumonia and sepsis, costing the US economy $8 billion. Antibiotic-resistant bacterial infections need at least 13 days in the hospital, resulting in an extra 8 million hospital days per year. There have been reports of costs of up to $29,000 per patient treated for an antibiotic-resistant bacteria illness. In all, economic losses of approximately $20 billion have been reported in the United States, with yearly productivity losses of roughly $35 billion owing to antibiotic resistance in health-care systems.

According to the experts at the Research and Development Corporation, a non-profit worldwide organization based in the United States, a worst-case scenario may emerge in the near future in which the globe is left without any effective antimicrobial agents to treat bacterial illnesses. In this scenario, the worldwide economic burden would be about $120 trillion ($3 trillion annually), which is almost equivalent to the current annual US health-care expenditure. In general, the global population would be severely impacted: by 2050, about 444 million people will have died from diseases, and birthrates would be quickly declining. These losses are catastrophic, but owing to data limitations, such as the inclusion of general conditions and illnesses vulnerable to antibiotic resistance, these numbers only provide a partial picture of the economic consequences of antibiotic resistance. The use of antibiotics in animals and the food sector is another important aspect of AMR that was overlooked in the study. It is a key player in the rising AMR, and it may result in its own anticipated economic losses. In many poor nations, the use of antimicrobials as

growth promoters is also a common occurrence. This technique has been prohibited in the European Union since 2006.

Current cost estimates for antibiotic resistance are restricted in scope and do not take into account the wider societal benefit of antibiotics. These are predisposing variables that lead to error in estimating the true economic cost that the globe is bearing as a result of this problem. Prospective research should use macroeconomic techniques that include all of the consequences of growing antibiotic resistance, including the decrease in efficacy of different medicines in contemporary medicine, to obtain an accurate estimate of the economic implications produced. The precise assessment of the global economic cost of antibiotic resistance may not be completely determined until these problems are addressed[7].

3.2 Causes of Antibiotic Resistance:

Many variables are now at play in the complex genesis of antibiotic resistance. These include insufficient regulations and usage imprecision's, a lack of awareness in best practices that leads to unnecessary or inept antibiotic use, the use of antibiotics as a growth promoter rather than to control infection in poultry and livestock, and online marketing that made the unrestricted availability of low-grade antibiotics very accessible. Overuse of antibiotics is the primary driver of resistance development, as Sir Alexander Fleming predicted when he said that "the public would want the medicine and then will begin an age... of abuses." Antibiotics kill susceptible germs, but they leave resistant pathogens alone, which multiply and flourish as a result of natural selection. Despite the fact that misuse of antibiotics is highly prohibited, over prescription persists throughout the world. In 30 percent to 50 percent of instances, treatment reasons, agent selection, and antibiotic medication duration are all incorrect, according to many studies. Antibiotics are utilized as a growth enhancer in cattle all over the world. Approximately 80% of antibiotics are marketed in the United States only for use as growth supplements and illness control in animals, according to estimates. In another research, a worldwide map of 228 nations was created to show antibiotic use in cattle; the overall antibiotic consumption was estimated to be 63,151 tons in 2010. Van Boeckel et al. also predicted a 67 percent increase in antibiotic use by 2030, almost doubling in the fast growing and densely populated nations of Brazil, Russia, India, China, and South Africa[8].

3.3 Drivers of antibiotic Resistance:

Understanding the different causes of antibiotic resistance is now the most important step in dealing with this worldwide problem. Antibiotic resistance selection in health care systems, the environment, and agriculture/livestock is a natural process (Figure 1). Sanitation settings, infection control standards, water hygiene systems, medication quality, diagnostics and treatments, and travel or movement restrictions are all significant variables that may contribute to antibiotic resistance. In addition to mutations in different genes on the microorganism's chromosome, the interchange of genetic material across organisms plays an important part in antibiotic resistance dissemination. Plasmid transmission is the most common way for antimicrobial resistance genes to be transferred to a host cell. Antibiotics may affect this process by promoting the transfer of resistance components, as well as exerting a selective strain on resistance development. The demonstration of resistance transmission dynamics has raised awareness and knowledge of how resistant infections spread from one person to the next. The feco–oral route is the most significant mode of transmission at the community level, particularly

for resistant Enterobacteriaceae infections, which are typically transmitted owing to sanitation failure. CA-MRSA, which is typically spread owing to extended hospital stays or unsanitary hospital environments, is also an excellent example of understanding the transmission dynamics of resistance at the human–human level. For resistant N. gonorrhoeae, sexual intercourse is also a means of transmission[9].

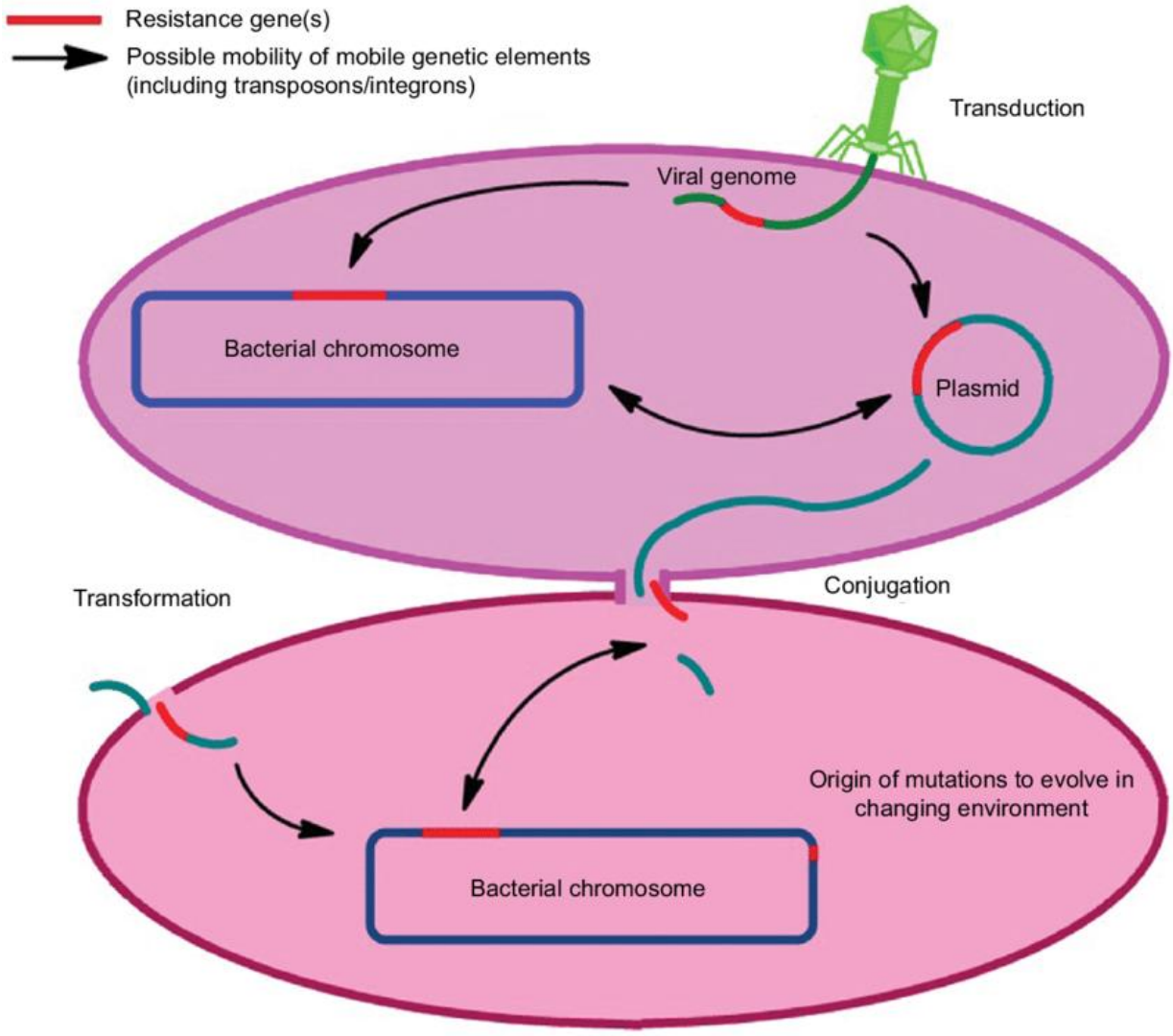

Figure 1: Drivers of antibiotic resistance transmission[10]**.**

3.4 Therapeutic Strategy:

Despite clinical evidence that methods based on small molecule monotherapy are ineffective in resistance situations, infection control has long been a major concern of the evolutionary race. The evaluation of different candidates for infection control throughout the development phase indicates that the emphasis of research would be on new antibiotic discovery and identification. Unfortunately, biotherapeutics such as antibiotics, new combination therapies, and drug delivery methods are still lagging behind the development of novel small molecules, which are often

extensions of existing medication classes. Globally, systemic monotherapy approaches are ineffective because resistance has surpassed medication development. Instead of fighting bacterial development, control efforts may be better served by exploring resistance mechanisms based on genetic inspiration, such as furanones used by red sea algae to disrupt resistant bacteria's quorum sensing.

Though biologics are still in their infancy in terms of bacterial infection management, their potential to fight MDR cannot be ignored. Small compounds will always play an important part in infection control; nevertheless, the hunt for a viable therapeutic candidate based on biological inspiration may be pursued more logistically. Various drug development tools are necessary to address biologics' shortcomings, such as controlled delivery options, partial in vitro stability, insufficient high-throughput, advanced screening tools, inefficient pharmacokinetics, and comparatively unknown pharmacodynamics, but they are not as radical as those available for small molecule development. Between biologics combinations, compounds based on biological inspiration, and medication delivery technologies, a huge potential exists by accident. As a result, a paradigm shift similar to that seen in cancer and complicated viruses might be used to eliminate vulnerable bacteria, manage antibiotic resistance, and protect the host microbiota. A mix of traditional antibiotics, new adjuvants, and feasible restricted delivery methods may be used to create this kind of strategy. Advanced bioinformatics to identify optimal combination delivery and novel targets may offer significant advantages, as opposed to many costly development methods that often fail in trials[11].

Nanotechnology is becoming more widely used in medicine, therefore it is not surprising to find these technologies being used to combat the threat of antibiotic resistance. Nanoparticles may be used in a variety of ways to treat infections therapeutically. They may be combined with currently available antimicrobials to improve their physiochemical action against drug-resistant bacteria. Second, colloidal zinc, silver, copper, and titanium may be employed as antibacterial agents in and of themselves. Antibiotics' main targets are the inhibition or disruption of bacterial cell walls, proteins, and nucleic acids production, but nanoparticles have been found to impact the respiratory system, resulting in the formation of reactive oxygen species, which eventually leads to bacterial mortality. Nanoparticles also target the bacterial cell wall, thus silver nanoparticles, for example, may be used with medicines to increase their antibacterial activity via synergy.

Antimicrobial peptides (AMPs) are new antimicrobial agents that may be found in animals, microbes, and plants. They have a wide range of activity and are particularly effective against bacteria, fungus, and protozoans. The amphipathic structure of AMPs allows them to interact with bacteria' cell walls and cellular membranes. Although antimicrobial action is typically due to disruption to cellular membranes, AMPs may also target other proteins, DNA, RNA, and regulatory enzymes, and therefore seem to be a potential alternative to traditional antibiotics. However, as soon as AMPs are used in clinical practice, resistance to these compounds is expected; therefore, it is critical to investigate the molecular mechanisms of their action and gain a better understanding of resistance to these compounds in order to plan rationally for the use of AMPs as an alternative to antibiotics[3].

4. CONCLUSION

We should strive to get a better understanding of the scope of the AMR problem. In order to manage AMR, it is critical to gather comprehensive and reliable data. The current concern about this problem stems from a lack of knowledge. At this point, it is impossible to forecast the future situation with certainty, although the management of AMR seems to be extremely challenging due to the shortage of new antibiotics. To address this problem, multifaceted methods should be used. Medical students, doctors, and pharmacists must get ongoing and updated training.

Regulations should be put in place, with antibiotic usage being closely monitored as part of the policy. For the development of novel screening and diagnostic instruments, a worldwide and multidisciplinary approach must be considered. The issue's ecological and environmental components should not be overlooked; all aspects of "one health" should be included in the control strategy. Alternative methods, particularly in poor nations, may be beneficial. The current level of worldwide attention shows that AMR is no longer an unnoticed problem. Although this focus is insufficient in and of itself to fight AMR, a worldwide code of behavior including all available methods for combating AMR may eradicate the disease in the future. Antibiotic alternatives such as probiotics and lytic bacteriophages may assist to reduce the worldwide burden of AMR. Antibiotics, infection management, vaccination, encouraging healthy food supply practices, and control of person-to-person transmission via screening, treatment, awareness, and education may all help to keep AMR from spreading and spreading. Tracking, bio-surveillance, and response and preventive measures for AMR and MDR pathogens at the national, regional, and global levels may assist to manage the "global resistome."

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