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Review Of "Chasing Resistance: New Antibiotics For A Changing Landscape

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Abstract.*Antimicrobial resistance (AMR) is an age-old biological phenomenon, as evidenced by its evolutionary history and abundance of environmental immunity Antibiotics used by humans contributes to resistance to acquired disease, a public health issue that drives the selection of resistance genes. A.M.R. One of the most important strategies to combat AMR is the search for new antibiotics. During the 1980s, existing products were either enhanced or modified in antibiotics currently on the market. The World Health Organization (WHO) warns of limited new candidates and highly characterizes the current pipeline. After careful analysis of preclinical and therapeutic pipelines, it seems expected that very few new antibiotics will enter the market in the coming years . Most of these candidates do not meet the new standards required to adequately address the growing threat of antimicrobial resistance (AMR).The key principles to cope with the rapidly emerging AMR are diversity and innovation which are done. R&D efforts should address new antibiotic resistance. Although there is promising potential to change the dynamics between the spread of AMR, antibiotic reserves, and meeting new lead standards, we examine the historical context and challenges associated with drug a kills bacteria detection, and various other processes. Let us describe the proposed methods of revitalizing the pipeline.*

Keywords: *Chasing Resistance , Antibiotics, Antimicrobial resistance, Changing Landscape*

Abstrak.Resistensi antimikroba (AMR) adalah fenomena biologis yang sudah ada sejak dahulu kala, sebagaimana dibuktikan oleh sejarah evolusinya dan banyaknya kekebalan lingkungan. Antibiotik yang digunakan oleh manusia berkontribusi terhadap resistensi terhadap penyakit yang didapat, sebuah masalah kesehatan masyarakat yang mendorong pemilihan gen resistensi. A.M.R. Salah satu strategi terpenting untuk memerangi AMR adalah pencarian antibiotik baru. Selama tahun 1980-an, produk-produk antibiotik yang sudah ada ditingkatkan atau dimodifikasi menjadi antibiotik yang saat ini ada di pasaran. Organisasi Kesehatan Dunia (WHO) memperingatkan jumlah kandidat baru yang terbatas dan sangat memperhatikan jalur yang ada saat ini. Setelah melakukan analisis yang cermat terhadap jalur praklinis dan terapeutik, diperkirakan hanya sedikit antibiotik baru yang akan memasuki pasar pada tahun-tahun mendatang. Sebagian besar kandidat ini tidak memenuhi standar baru yang diperlukan untuk mengatasi ancaman resistensi antimikroba (AMR) yang semakin meningkat. Prinsip utama untuk mengatasi AMR yang berkembang pesat adalah keberagaman dan inovasi yang dilakukan. Upaya penelitian dan pengembangan harus mengatasi resistensi antibiotik baru. Meskipun ada potensi yang menjanjikan untuk mengubah dinamika antara penyebaran AMR, cadangan antibiotik, dan pemenuhan standar timbal baru, kami mengkaji konteks historis dan tantangan yang terkait dengan deteksi obat yang membunuh bakteri, dan berbagai proses lainnya. Mari kita uraikan metode yang diusulkan untuk merevitalisasi saluran pipa.

Kata Kunci: Mengejar Resistensi, Antibiotik, Resistensi Antimikroba, Perubahan Bentang Alam

1. INTRODUCTION

Antibiotics have long been considered a watershed moment in medicine, completely changing how we approach infectious diseases, saving many lives in the process and yet we have reached a pivotal moment in them in the application of the. The rise of antimicrobial resistance and the environmental consequences of antibiotic use are urgent challenges that need immediate attention and a reassessment of our consumption of critical care this solution is

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completely. [1] . In addition to reassessing antibiotic use as antibiotic resistance develops, new strategies must be developed to combat its relentless spread This topic will point to the need for a paradigm shift in how we discover and use antibiotics [2,3], recognizing that they are such limited and valuable resources to be protected for future generations [4]. Mechanisms of antibiotic resistance Apparently not caused by increased gene transfer and exist in addition to human-administered antibiotics [5, 6, 7] . Determinants of resistance in producers, nonproducers, soil, and environment bacteria exhibit different genetic molecules than pathogenic viruses This is reflected in different determinants resistance observed in antibiotic-free organisms and presumed in vivo resistance [8, . The accumulation and dissemination of these resources throughout human populations has created a tremendous opportunity to modify and expand resistance [10 The development of metagenomic sequencing techniques has enabled scientists to identify resistance genes in different environments, such as human and environmental commensal microbes, also as human diseases -Determinants and mechanisms of acquisition [11] . The first warning sign of possible development of resistance in clinical isolates can be obtained by taking resistant samples (12) Major achievements of mankind in th century so one of these twenty is synthetic antibiotics. Advances in antimicrobial strategies have transformed modern biomedical practice, aiming to define, shape and improve its possibilities as well as its limitations. Unfortunately, the efficacy of any therapeutic agent is limited due to the potential for resistance [13] . Because resistance threatens treatment efficacy, the development of next-generation antibiotics is essential. Once a bacterium develops resistance to a commonly effective treatment, it becomes resistant to antibiotics (in this case, antibiotics) [14] .

Antibiotic Resistance's Cause

Antibiotic resistance is the ability of a bacterium to withstand antibiotics, which are designed to kill or inhibit its growth.. The process by which a bacterium exhibits resistance, and the ability to withstand various strategies so resist the edge are two important variables affecting evolution. [15,16] . Strains can be intrinsically resistant or respond negatively to transgenes expressed in transgenes from one virus to another through various mechanisms such as plasmids, transgenes, genes, phages, and etc. Furthermore, changes in cellular genetic material, especially chromatin instability, can cause cross seed -collisions. [17] . When resistance markers are found on plasmids, resistant viruses reproduce rapidly. Multiple metabolites act silently to protect the bacterial cell wall from various chemical stimuli, resulting in target mutations, enzymatic cleavage, and changes in efflux pump protein secretion in For

biological reasons, first-generation antibiotics have encountered antibiotic resistance in a wide range of clinical conditions. [18] . Antibiotic resistance has become a serious global health problem, associated with increased mortality and morbidity rates.. Increased resistance to many antibiotics has affected diseases of Gram-positive and Gram-negative bacteria cause no treatment, making conventional antibiotics useless This resistance has affected antibiotics bad effectiveness in clinical settings , their [19] antibiotic resistance was first documented in the 1930s, . with the advent of sulfonamides, a process that anticipated the establishment of antibiotic resistance in the natural habitat before the antibiotic era. Human activity has led to increased use of potent antibiotics, changed their importance, and increased resistance to bacteria Since their first clinical use, and expansion and fragility due to chemical degradation cell walls Antibiotics may require chemical modification to prevent degradation. [20] . However, studies suggest that identification of bacterial penicillinase, as well as microbial genes or other cofactors, can improve antibiotic effectiveness before human intervention to provide drugs used in natural resistance mechanisms have evolved, . genetic changes in bacterial strains, and presence of antibiotic resistance genes.. These genes arose in natural gene pools and spread rapidly to various pathogens in many taxonomic groups Consequences and lack of effective control strategies, associated challenges in treating vectors and related diseases f Requires the development of new therapies and a broader range of antibiotics Also rapid methods of identifying pathogens and their chemical sensitivity in emergency situations such as viral diseases Researchers suggest that reason good understanding of the biomedical pathways of infectious diseases Can provide new opportunities for communication, for all of these

Antibiotic Resistance

pment and use of antibiotics, from the discovery of penicillin to modern practice. Discuss the initial interest in these medical advances and the conflicting views that gradually emerged. [21] . Mechanisms of resistance: Count established mechanisms of antibiotic resistance, such as the role of plasmids, gene upregulation, and genetic modification Clinical research: Search research results and case studies illustrating the widespread consequences of antibiotic resistance in clinical settings, particularly clinical and health care disorders. [22] . Epidemiology: Explore studies on the prevalence and distribution of antibiotic-resistant microbes around the world. Highlight any high-risk areas or diseases. [23] .

The Environmental Resistome and Its Relation to Antimicrobial Resistance

AMR is a common, chronic natural phenomenon that predates humans [24,25] . Acute antimicrobial resistance (AMR) may be due to a variety of metabolic genes involving aspects of bacterial cell function AMR origin [26] . The entire set of genes that directly or indirectly contribute to antibiotic resistance is called environmental resistance. Current evidence suggests that the environment is an important source and reservoir of immunity. Organisms with antimicrobial resistance (AMR) elements and genetic mechanisms for their spread are found in a variety of environments including land, sea, air, animals, and built environments Research suggests a long natural history of resistance relationships pathogens, Antibiotic resistance genes associated with β- have been identified lactams, tetracyclines, and glycopeptides in Beringian permafrost samples of about 30,000 years, Implementing focused metagenomic analysis. [27] . Ancient modern bacterial resistance has not changed much, as indicated by genomic comparisons between modern bacterial isolates and permafrost species that are about 2.7 million years old [28] . Phylogenetic analysis of 300,000-year-old permafrost samples from Mammoth Mountain in Siberia indicates that OXA genes for the production of β-lactamases have been present on plasmids for approximately one million years [29] . AMR indicators were detected in untouched contaminated soil within Mackay Glacier, an area where antibiotics are not used by humans. Soft tissue from Copper Age mummified individuals revealed the presence of resistance genes to β-lactams and glycopeptides, suggesting that these genes colonized in ancient populations [30] . Antibiotic resistance results from the intake of antibiotics other than human sources, as reflected in the diversity of resistance determinants found in antibiotic-free environments and the strength of a it is anti-inflammatory against many pathogens [31] . and gene upregulation does not occur [32] . The range of resistance genes and machinery identified in producers, nonproducers, soils, and bacterial environments is larger than that found in pathogens [33] . Once collected and transmitted to humans and animals, it offers great potential for prolonged and disseminated resistance [34] . Metagenomic and sequencing technologies enable researchers to examine resistance genes in a variety of organisms, including the environment and human and social bacteria, as well as the mechanisms by which human diseases acquire determinants if resisted [29] . The sampling resistor can provide one

Antibiotic Resistance Revealed

Antibiotic resistance represents a complex evolutionary adaptation by which bacteria respond to the persistent challenges posed by chemotherapy. Clinically, when a new antibiotic is first introduced, it effectively targets all relevant pathogens. however, over time, continued use of these antibiotics promotes bacterial growth, making treatments less effective. [36] . These changes are analyzed from an evolutionary perspective, with bacteria altering their interactions with both antibiotics. [37] . 1. acquire intracellular gene mutations or (2) acquisition of exogenous genes by high-risk gene transfer (HGT). [38] The text includes important clues to resistance. These mutations primarily affect three classes of genes: those encoding antibiotic targets, genes involved in antibiotic transport, and genes which controls the transparency of cargo. Compelling and intriguing data suggest that commensal or ambient bacteria are reservoirs for antibiotic resistance genes. These genes can then be transferred to harmful bacteria in humans by horizontal gene transfer (HGT). It is widely accepted that the natural environment is rich in bacteria capable of producing antibiotics. [40] . To survive in the midst of antibiotic production, these microorganisms must acquire a collection of antibiotic resistance genes. Without such genes, drug development itself would be a blur.

Resistance, tolerance, and perseverance

The term "resistance" refers to the ability of a pathogen to naturally develop when high concentrations of antibiotics are used. [41] . A laboratory method called antibiotic susceptibility testing (AST) is used to assess bacterial resistance. These tests fall into two categories: phenotypic testing, which uses methods such as broth microdilution (BMD) or disk diffusion testing, and genotypic testing, which screens for resistance by detecting specific resistance genes so [35,36] . Phenotypic testing is the medical standard, but genotypic testing is expensive and limited to specific genes. [42] . The BMD method provides a semi-quantitative analysis of the minimum inhibitory concentration (MIC) of antibodies. [43] . The minimum dose needed to inhibit bacterial growth, over approximately 16 to 20 hours, is facilitated by the Minimum Inhibition Concentration (MIC) [36 but it should be noted that the MIC is independent of treatment efficacy an accurate explanation does not always exist for an antibiotic in a pathogen [44].

Tolerance refers to the ability of a bacterium to withstand high concentrations of antibiotics without changing the minimum inhibitory concentration (MIC), resulting from a decrease in essential bacterial activities This tolerance is due to in genetic variation or may result from various environmental stresses. [45] . In contrast to resistance, tolerance affects antibiotics

rather than antibiotics and develops through two distinct mechanisms. It is marked by a succession of onsets, inherited or acquired, that manifests in a steady state.

Chronic tolerance is a temporary condition resulting from scarcity or stress.

1. tolerance is defined by slow development, which can be inherited or acquired, and manifests in a steady state .
2. Gap-induced tolerance is a temporary state resulting from scarcity or environmental stress.

Instead of increasing the antibiotic dosage, the antibiotic should be left on hold for a longer period of time to kill resistant bacteria. [39] . One way to measure tolerance is the minimum duration of killing (MDK99), which defines how long it takes to eradicate 99% of bacterial cultures. 'Robustness' refers to a specific proportion of the clonal bacterial population that is resistant to antibiotic therapy but physiologically dormant, while'resistance' and 'tolerance' refer to the overall bacterial population [46] .

Antibiotic adjuvants.

The question of whether an antibiotic has antimicrobial activity alone is only one part of a wider debate. When combined with antibiotics, the antibacterial activity of this drug increases. Non-antibiotic compounds that improve antibiotic activity in vitro are called "antibiotic adjuvants" or "antibiotic potentiators." Some researchers even categorize these compounds as "antibiotic cofactors," "resistance modifiers," or "immunosuppressive factors." [47] . Adjuvants not only enhance the efficacy of antibiotics but can also facilitate or prevent antibiotic resistance. The use of combination therapy is a common strategy to prevent or reverse antibiotic resistance. However, this generally requires the use of a single antibiotic, rather than a single antibiotic combination. The rationale for concomitant use of two antibiotics is to achieve synergistic effects, which only occur when the combined in vitro effect of the two agents exceeds the individual effect of each agent when used [1]. 48] Ideally, the dose of both agents is reduced to reduce the risk of toxicity. However, this is not always the case, due to the continued emergence of many drug-resistant bacteria.

Antibiotics found in aquatic habitats

The aquatic environment has attracted considerable attention in the search for new drugs. These habitats contain a wide range of antibiotic-producing species, including halophiles, barophiles, and thermophiles, which are among the largest in the world. In a recent study between 1984 and 2022, half of the 182 natural products identified contained new

antibiotics. Most of these compounds have been found in silk fungus and Streptomyces species that thrive in these harsh environments. [49] Several antibiotic-producing microorganisms were also found in hydrothermal vent cold oysters. Oceanic rifts driven by tectonic activity often produce cold air. [50] . Methane and other hydrocarbons, sometimes accompanied by hydrogen sulfide, are common in these areas. Cold-water summer habitats mostly maintained by specialist chemical producers are supported by such chemically diverse conditions. [51] These ecosystems, despite their name, are not always colder than the nearby ocean. Instead, unlike nearby humidifiers, it is much cooler. When dissolved metals such as iron, copper, zinc and others are thrown from superheated water in a hot spring, they rapidly migrate into nearby cold water [52] due to abundant rainfall that is trapped for the construction of a cage capable of harboring pharmaceutical bacteria. Hydrothermal gases have also been detected in seafloor fractures. Scientists have successfully synthesized a new antibiotic with a unique structure, created by a bacterium called Streptomyces. [53] . As an example of bioprospecting in this context, WU20 used a method that combines metabolomics profiling techniques with dormant metal-induced biosynthetic genes This particular Streptomyces was discovered in the metallic waters of Guishan Island beach off Taiwan. Found in the vent . [54,55].

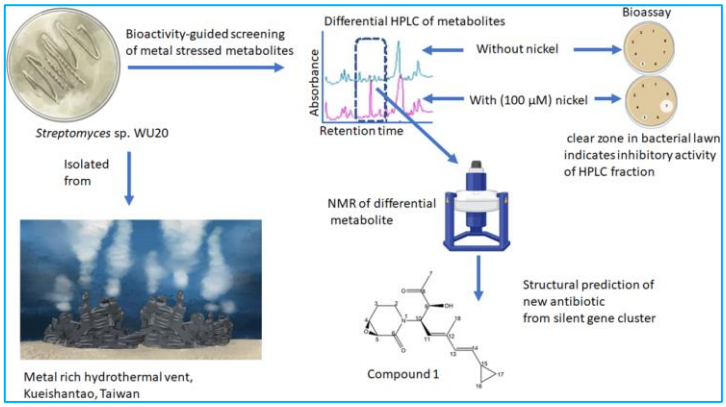

Figure 1: In reaction to nickel, Streptomyces sp. shows the induction of silent biosynthetic gene clusters.

2. CONCLUSIONS

Antibiotics are very important and offer many benefits. Our reliance on these drugs to treat infectious diseases is not surprising, they should never be treated as just things Antibiotics are also necessary to complete complex surgeries such as organ transplants life-saving replacement and prosthetic transplantation successfully It is a relatively recent development contextualised against extensive history and consequently indicate anti-inflammatory drugs the

understanding of bacterial resistance as an adaptive, continuous process of creation and the evolutionary theories of Charles Darwin. Increasing understanding of environmental reservoirs of resistance has made it possible to predict potential mechanisms of resistance to new drugs, allowing us to prepare early for clinical interruptions Important that we find a common approach that takes full advantage of our newly acquired skills and sophisticated technology. If we have failed in this responsibility, the next generation may face a reality reminiscent of the pre-antibiotic era.

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