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NEWER ANTIBIOTICS TO COMBAT ANTIBIOTIC RESISTANCE. NARRATIVE REVIEW AND FUTURE PROSPECTS.

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Abstract
Antibiotic resistance poses a significant threat to contemporary medicine, particularly to the efficacy of timely and decisive global health interventions targeting infectious diseases. This is primarily due to the systematic misuse and overutilization of antibiotics in human medicine and also agricultural production. Undoubtedly, the extensive or improper application of these medications in agriculture, animals, or humans leads to the development of drug-resistant microorganisms that have adapted to this intense selective pressure. The objective of this study is to investigate the alarming issue of antibiotic resistance and the proliferation of multidrug-resistant bacterial strains, which have become increasingly prevalent in healthcare facilities worldwide and threaten to impede efforts to control infectious diseases on a global scale. Possible strategies to halt antibiotic resistance are analyzed following a thorough examination of these phenomena and the multiple mechanisms that render certain bacteria resistant to antibiotics that were once effective against infections caused by the same pathogens. Hence, this article centers on the most auspicious novel chemical compounds presently under development that exhibit efficacy against multidrug-resistant organisms and are distinct from conventional antibiotics: To begin with, a comprehensive enumeration of the principal antibacterial agents undergoing clinical development (Phase III) between 2017 and 2022 is provided, with particular emphasis on those that are effective against infections caused by Neisseria gonorrhoeae, including multidrug-resistant isolates, and Clostridium difficile. The agents in development to treat drug-resistant tuberculosis (TB) comprise tetracycline derivatives (e.g., eravacycline), fourth generation fluoroquinolones (delafloxacin), novel combinations of one β-lactam and one β-lactamase inhibitor (e.g., meropenem and vaborbactam), siderophore cephalosporins (cefiderocol and plazomicin), and new aminoglycosides (plazomicin). The text concludes by discussing the potential benefits that may arise from the application of these compounds. Additionally, it acknowledges the existence of additional, albeit underdeveloped methods, such as antibiotic delivery systems utilizing nanoparticles.

Keywords : bacterial isolates; antibiotic resistance; novel antibiotics

Introduction

Alexander Fleming, the inventor of penicillin, foresaw in 1945 that improper use, and occasionally actual abuse, of antibiotics would hasten the emergence and dissemination of antibiotic-resistant bacteria. To illustrate, bacteria have the ability to utilize "non-lethal levels" of the antibiotic penicillin as a signaling agent with regulatory functions. β-lactamase enzymes, which are secreted by bacteria, are capable of hydrolyzing the amide bond present in the four-membered β-lactam ring. This enzymatic action renders the β-lactam antibiotic ineffective. Antibiotics have undeniably constituted a turning point in modern medicine and human history;

they are life-saving and indispensable against a wide variety of infectious diseases, including those associated with intensive therapies, cancer chemotherapies, organ transplants, and amputations. Numerous novel antibiotics were developed through research in the previous century.However, there has been a significant decrease in the discovery of antimicrobial agents since the 1990s, concomitant with a concerning surge in the issue of antibiotic resistance. Multidrug-resistant (MDR) bacteria, which are those that exhibit resistance to at least three distinct classes of antimicrobials, have become prevalent, particularly in hospital settings; within a few years, there is a danger of entering a "post-antibiotic era" in which infections that were once under control can rapidly transform into fatal threats. It is indisputable that antibiotic resistance has emerged as a significant contemporary health concern, exerting substantial clinical and economic repercussions. The eradication of pathogens such as vancomycin-resistant enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) has become exceedingly challenging. An estimated 2.8 million individuals contract an infection resistant to conventional antibiotics annually in a developed country like the United States alone, resulting in over 35,000 fatalities [1]. Antibiotic resistance causes approximately 33,000 fatalities annually in Europe [2]. Pneumonia and sepsis-causing blood infections significantly impact infant mortality during the initial five years of life on a global scale. Barely 30% of neonates afflicted with sepsis succumb to bacterial infections that are resistant to conventional antibiotics [3]. The World Health Organization (WHO) released a list of the most prevalent antibiotic-resistant bacteria worldwide in 2016, highlighting the critical need for novel therapeutic interventions against these pathogens [4]. Certainly, the objective is to assist nations in accelerating their domestic research, surveillance, and control efforts regarding new active ingredients. Each of the three categories on the list delineates the degree of danger posed by bacterial species resistant to antibiotics: critical, high, and medium. Mycobacterium, which comprises M. tuberculosis and is accountable for 1.8 million annual fatalities across the globe, has been omitted from this compilation due to its well-established status as a hazard. Notably, Gram-negative microbes present an imminent threat. Pseudomonas, Acinetobacter, and Enterobacteriaceae genera (including Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., Serratia spp., Proteus spp., Providencia spp., and Morganella spp.) are the most feared pathogens in healthcare facilities such as hospitals, nursing homes, and aged care facilities due to the potentially fatal nature of associated infections. Already, these pathogens have acquired resistance to carbapenems, life-saving antibiotics that are frequently administered to hospitalized patients due to their exceptionally potent nature. The escalating incidence of infections induced by carbapenem-resistant Enterobacteriaceae (CRE) is a cause for concern. These bacteria produce carbapenemases, most notably K. pneumoniae carbapenemase, which are capable of hydrolyzing and deactivating carbapenems and β-lactams. Campylobacter spp., Helicobacter pylori (the primary risk factor for gastric cancer), and MRSA are of the utmost importance. Salmonella spp. are accountable for the greatest number of food contaminations in Europe. (infectious food poisoning) and Neisseria gonorrhoeae (provoked sexually transmitted disease gonorrhea). In conclusion, Shigella spp., Haemophilus influenzae, and Streptococcus pneumoniae are accountable for the preponderance of community-acquired pneumonia and

respiratory infections, respectively. (caused by gastroenteritis and transmitted through contaminated foods or water) are classified as having a medium priority. Furthermore, it is worth noting that the potential dissemination of antibiotic-resistant organisms adversely affects the health of individuals who were not directly exposed to specific antibiotics. In light of this situation, which has transitioned from being a science fiction concept to a tangible reality, there is an immediate demand for novel antibacterial active ingredients to guarantee efficacious treatments against antibiotic-resistant infections.

Aim

Purpose of this research is to understand the resistance to regular antibiotic regimen and identify recently introduced antibiotics employed to counter the development of resistance to conventional antibiotics.

Materials and method

The following electronic databases were searched from their inception until January 2023: Cochrane Database of Systematic Reviews, EMBASE, MEDLINE (Ovid), CINAHL, International Pharmaceutical Abstracts, Global Health, Web of Science and Google Scholar. Key search terms included antibiotic, antimicrobial, antibacterial, drug resistance, overuse, misuse, consumption, inappropriate prescription, self-medication, knowledge, stewardship, survey, dentistry, dentists, pharmacists, physicians, and health services.

Dissertation data were searched for on-going and unpublished studies. The reference lists of all eligible studies were checked for additional studies. Hand-searching of selected journals was performed in order to identify any missed studies. Only english language literature was included, and there was no restriction on the date of publication.

Results

A total of 634 publications were initially retrieved. The writers used a screening process to determine the relevance of article titles to the issue of interest, and only those deemed pertinent were selected for inclusion. After removing 312 duplicate articles and excluding those that were not relevant to the topic of interest, a total of 107 papers were included based on an assessment of their summaries. Subsequently, an additional screening procedure was implemented, resulting in the exclusion of 64 out of the initial 107 articles on the basis of keyword analysis. As a result, 43 articles were deemed suitable for inclusion in the review.Divergences among the evaluators about the correlation between an article and a particular keyword were resolved by supplementary deliberations with a third reviewer.The study exclusively incorporated original publications while excluding case reports, reviews, and editorials.

Discussion

Awareness of the issue of antibiotic resistance has increased in recent years, including in the

political sphere: The G20 countries decided in 2017 to intensify global collaboration on this matter in order to stimulate the research and development of antimicrobial molecules, beginning with existing antibiotics. The FDA has granted approval to eight novel antibiotics since 2017, one of which is intended for the treatment of multidrug-resistant tuberculosis. The majority of these medications were derived from conventional molecules and specifically target Enterobacteriaceae that are resistant to carbapenems and other pathogens deemed hazardous by the World Health Organization [4].

In order to enhance comprehension and awareness regarding antimicrobial resistance, augment investment in novel pharmaceuticals, diagnostic instruments, vaccines, and additional interventions; mitigate the occurrence of infections via efficacious hygiene practices; optimize the utilization of antimicrobial drugs in the realm of human and animal health; and bolster knowledge and data collection pertaining to this matter [5]. As a result, the development of novel molecules is crucial for addressing the emergence of resistance mechanisms, optimizing the efficacy of current antibiotics, and advancing research into diagnostic tests that are progressively more reliable for identifying resistant bacteria and determining antibiotic sensitivity.

The presenting article analyzes the most promising new compounds still undergoing preclinical and clinical investigation, including the active ingredients that entered Phase III last year and the agents of pharmacological interest that obtained market authorization between 2017 and 2022, from a chemical and clinical perspective. The most recent research findings are presented alongside the necessary strategies to combat the issue of antibiotic resistance, with a discussion of future prospects.

Principal Agents Authorized to Sell Between 2017 and 2022

The FDA has granted approval to eight novel antibiotics as of 2017. The majority of approved compounds are designed to combat carbapenem-resistant Enterobacteriaceae and other WHO-listed pathogens (of high and medium priority). Eravacycline and omadacycline are both tetracycline derivatives. Semisynthetic in nature, omadacycline exhibits efficacy against Gram-positive bacteria, including the challenging-to-eradicate MRSA, as well as certain Gram-negative bacteria. For the treatment of community-acquired pneumonia (CAP), it has received approval. In contrast, eravacycline is an approved treatment for complicated intra-abdominal infections despite being entirely synthetic. Additional research must be conducted before the clinical profile of these antibiotics can be more precisely defined. In addition, a novel amalgamation of β-lactam antibiotics and β-lactamase inhibitors has emerged as a promising prospect, exhibiting efficacy against K. The carbapenemase for pneumonia (KPC) has received approval. This is the vaborbactam-meropenem (a β-lactamase inhibitor) and meropenem combination. Nonetheless, novel therapeutic alternatives for carbapenem-resistant A. CRPA) and CRAB (Carbapenem-resistant Pseudomonas aeruginosa) remain deficient. Recent years have seen the approval of pretomanid, a nitroimidazo-oxazine developed by the TB Alliance, as the only antibiotic approved to treat tuberculosis.

In conjunction with bedaquiline and linezolid, it constitutes an entirely novel therapeutic approach

for adult patients afflicted with pulmonary multidrug resistant (MDR) tuberculosis and extremely resistant tuberculosis (XDR). The majority of trade-approved antibiotics are efficacious in the treatment of complex urinary tract infections and infections originating within the abdomen. Certain challenges have been brought to light by companies engaged in the investigation of novel antibiotics. Achaogen, a biotechnology firm that produced the aminoglycosydic plazomicin, which was approved in 2018, declared bankruptcy a few months later despite having received $2.4 million from Boston University's CARB-X project for the development of the new drug [6]. Post-marketing data are not yet accessible for the eight antibiotics that were recently authorized by the FDA. Therefore, additional research is required to establish the therapeutic profile and determination of their suitability for specific patient populations.

Eravacycline is a (Derivative of tetracycline)
Eravacycline, a member of the tetracycline class of entirely synthetic fluorocyclines, was developed by Tetraphase Pharmaceuticals and received approval from both the EMA and FDA in 2018. Its indication for use is the treatment of complicated intra-abdominal infections (cIAI). The product is branded and marketed as Xerava®. Constriction of cIAI into the abdominal region (peritoneal cavity, mesentery) typically produces diffuse or localized peritonytes [7]. Such infections are associated with substantial mortality rates, particularly when left untreated; therefore, initiating antibiotic therapy promptly is critical and, in certain instances, life-preserving. Typically, a considerable variety of enteric microorganisms, including Enterobacteriaceae (K. pneumoniae, E. coli), Enterococcus spp., and Bacteroides spp., are implicated in the manifestation of symptoms. An increase in multidrug-resistant pathogens of the aforementioned species poses a significant hazard to the treatment of intra-abdominal infections and is a critical global health issue. The list of eight antibiotics authorized from 2017 to 2020 includes eravacycline and relebactam with imipenem/cilastatin combination (Recarbrio®, approved in 2019). These antibiotics represent the most recent and innovative therapeutic alternatives available to patients diagnosed with cIAI. Eravacycline was purposefully formulated to address the issue of acquired resistance that was observed in the case of conventional tetracyclines. Resistance to tetracyclines is primarily conferred by pathogens through two mechanisms: the acquisition of genes encoding efflux pumps and the presence of ribosomal protection proteins (RPPs). A wide range of efflux pump varieties can be found in both Gram-positive and Gram-negative bacteria. In the case of Gram-negative bacteria, the most prevalent efflux pumps are encoded by the tet(A) and tet(B) genes, whereas in Gram-positive bacteria, they are tet(K) and tet(L).
Tetracyclines of the first generation are more susceptible to inactivation by efflux pumps than those of the second or third generation (doxycycline, minocycline, tigecycline), which are not susceptible to the actions of the pumps. Active reduction of the antibiotic concentration within the bacterial cell via inducible synthesis of membrane proteins encoded by genes (tetA and tetB) located on plasmids or transposons constitutes efflux [8].
The interactions between the tetracyclines and the binding site on the 30S ribosomal subunit are weakened by these proteins. In fact, tetracyclines function by impeding the transfer of acyl-tRNA to that subunit through the inhibition of protein synthesis. Additionally, resistance to first and

second generation tetracyclines is induced by RPP, albeit to a lesser extent than the antibacterial activity of the most recent generation tetracyclines. Other mechanisms of acquired resistance to tetracyclines include mutations in the 16S RNA subunit; nevertheless, their prevalence is considerably lower in comparison to efflux pumps and ribosomal proteins. Tetracyclines of the third generation, also known as glycylcyclines (tigecycline and the novel eravacycline), overcome the primary obstacles to tetracycline activity: Efflux pumps are unable to identify these molecules due to the substitution at position 9 of the tetracycle. This distinguishes them significantly from prior iterations of tetracyclines. Furthermore, their sensitivity to the activity of ribosomal protection proteins is absent [8].
Eravacycline maintains the pharmacophore that is characteristic of tetracyclines; nevertheless, it undergoes two distinct modifications in ring D: an adduct of a fluorine atom at position C7 and a pyrrolidine acetamide group at position C9. The tigecycline structure is devoid of fluorine and instead contains a tertiary amino group.
Eravacycline exhibits activity against Gram-positive and Gram-negative bacterial strains due to substitutions at positions 7 and 9. These activities have been observed in vitro to generate resistance in various mechanisms to first- and second-generation tetracyclines. Eravacycline, similar to other tetracyclines, exerted its antibacterial effect through a reversible binding mechanism to the 30S subunit of the ribosome, thereby impeding the entrance of molecules comprising the aminoacyl-tRNA complex. In contrast to conventional tetracyclines, eravacycline exhibits a significantly stronger interaction with the ribosome due to its capability of identifying multiple assault sites and thereby stabilizing the resulting complex. While the compounds of the initial and subsequent generations exhibit bacteriostatic properties, eravacycline demonstrates bactericidal activity against specific strains of A in vitro. E. baumannii. E. coli, in addition to K. Pneumonia pneumoniae.
Eravacycline exhibited significant in vitro efficacy, as quantified by MIC90, against a wide range of Gram-positive pathogens, including E. faecalis in addition to E. faecium, which are both vancomycin-resistant, and S. Staphylococcus aureus (MRSA), in addition to Gram-negative pathogens such as Enterobacteriaceae resistant to carbapenems. These pathogens are among those accountable for cIAI; therefore, clinical trials have demonstrated the efficacy of the drug. The observed efficacy of eravacycline against isolated isolates of A is highly encouraging. baumannii is carbapenem-resistant and MDR.
Eravacycline exhibits MIC90 values for a wide range of Gram-positive and Gram-negative pathogens that are conspicuously diminished in comparison to antibiotic MIC90 values, including imipenem and vancomycin, and continue to be lower even when compared to tigecycline. Furthermore, it should be noted that eravacycline does not exhibit any cross-resistance mechanism with other antibacterial classes, including carbapenems, fluoroquinolones, penicillins, cephalosporins, or cephalosporins. The primary metabolite of the antibiotic is CYP3A4. Consequently, concurrent use of eravacycline with potent inducers of this cytochrome (phenytoin, rifampicin, carbamazepine, phenytoin, among others) expedites the metabolism of the antibacterial drug, resulting in a reduction of its plasma concentration.

Eravacycline administered intravenously has been approved as Xerava® for the treatment of cIAI in adult patients in several European countries and the United States since 2018. Depending on the prescribed therapy, the recommended dosage is 1 mg/kg administered every 12 hours for 4 to 14 days. The clinical response and acceptability of eravacycline were comparable to those of ertapenem and meropenem in two double-blind clinical trials. Microvescicular liver steatosis accompanied by lactic acidosis and severe liver dysfunction (LASH syndrome) can be induced by high dosages of intravenous tetracyclines. However, the occurrence of this complication has not been documented in cases involving third-generation intravenous tetracyclines (eravacycline, tigecycline, omadacycline).

Eravacycline is a novel alternative for the management of cIAI, particularly against bacterial species resistant to conventional antibiotics, due to its broad spectrum of activity against clinically significant common pathogens (including those that express mechanisms of acquired resistance to tetracyclines), increased in vitro potency, and improved tolerability profile in comparison to tigecycline.

Delafloxacin (fourth-generation fluoroquinolone)

Fluoroquinolones have been utilized therapeutically for over half a century and are effective antibiotics. The rise in cases of resistance and the occurrence of adverse effects have, nevertheless, significantly restricted their application. Delafloxacin, the final fluoroquinolonic antibiotic to be approved, is the only anionic (non-zwitterionic) antibiotic in its class. The drug's enhanced in vitro activity against numerous Gram-positive pathogens, including quinolone-resistant strains, can be attributed to its unique molecular structure [9].

Delafloxacin, marketed under the brand name Baxdela®, was initially developed by Melinta Therapeutics and subsequently received FDA approval in 2017 for the management of acute bacterial skin and skin structure infections (ABSSSI). These infections are correlated with considerable rates of illness and death. As causative agents, a multitude of Gram-positive and Gram-negative bacteria have been identified. However, globally, S. is the most hazardous pathogen associated with ABSSSI. Surgical site infections are frequently associated with Gram-positive (Enterococcus spp., Streptococcus pyogenes) and Gram-negative (P. aeruginosa and E. coli) bacteria, after Staphylococcus aureus. The existence of pathogens resistant to conventional antibiotics, particularly MRSA Staphylococci, is a significant concern. This not only contributes to the rise in mortality rates but also escalates the financial burden on hospitals treating these infections. Various antibiotics and therapeutic approaches are recommended in accordance with current treatment guidelines, contingent upon the nature of the infection (abscesses, purulent or non-purulent erysipelas, necrotizing infections) and its severity.

In the context of managing infections induced by methycillin-sensitive S. When confronted with MSSA, it is advisable to employ oxacillin or other penicillins resistant to β-lactamases; individuals with a specific allergy to penicillins should consider cephalozoline. In the event that MRSA is identified as the causative agent, additional potent antibiotics including vancomycin, linezolid, daptomycin, or ceftarolines are administered. In certain situations involving both MRSA and MSSA, antimicrobial agents considered "outdated" include clindamycin, minocycline, or the

trimetoprim-sulfametoxazole combination. Nevertheless, each of these antibiotics is accompanied by certain drawbacks: elevated hospital expenses and potential toxicity (linezolid), diminished sensitivity necessitating the administration of larger doses (vancomycin), and an elevated risk of contracting C. difficile. Clindamycin (D. difficile) infections. In order to combat resistant pathogens that induce ABSSSI, new active antibiotics have been investigated, with a particular focus on infections caused by MRSA. Drugs that have been approved most recently consist of delafloxacin, tedizolid, oritavancin, and dalbavancin.

The activity of Delafloxacin is enhanced in acidic environments . Furthermore, it exhibits encouraging effectiveness against a broad range of Gram-positive and Gram-negative bacteria that are implicated in severe acute cutaneous infections. Delafloxacin is distinguished from other fluoroquinolones by the lack of a basic group at position C7; consequently, this molecule is a weak acid and, unlike the majority of antibiotics in its class, functions as an anion at neutral pH. Additionally, a chlorine atom is introduced at position C8, functioning as an electron-attractor group on the aromatic ring. This modification enhances the polarity, activity, and stability of the compound.

In contrast to the cyclopropyl group found in ciprofloxacin and moxifloxacin, delafloxacin showcases a substantial heteroaromatic substitution in position N1, resulting in a molecular structure that is considerably larger than that of alternative fluoroquinolones. The carboxyl group in C3 is the only ionizing group because C7 lacks a basic group. The anionic form of delafloxacin (COO^-) is the predominant form (98.5% concentration) at a neutral pH of 7.4. However, at a slightly acidic pH of 5.2, the neutral form predominates (62.7% concentration). The aforementioned alterations significantly affect the antibiotic's efficacy and potentially account for its heightened potency when exposed to an acidic pH level, in contrast to other fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, second and third generation, respectively), whose activity drastically diminishes in an acidic environment. Additionally, compared to conventional fluoroquinolones, Delafloxacin exhibits lower MIC values against a broad spectrum of Gram-positive pathogens. Before delafloxacin, the most recent fluoroquinolonic antibiotic was finafloxacin. Approved in 2014 for the treatment of acute otitis, it differs significantly from delafloxacin in the following ways: the group at position C7 is altered to be more basic; C8 lacks a chlorine atom; and N1, like other fluoroquinolones, retains the cyclopropyl group.

Quinolones inhibit topoisomerase IV and bacterial DNA. Delafloxacin exhibits structural characteristics that enable it to bind to DNA gyrase and topoisomerase IV of both Gram-positive (S. aureus) and Gram-negative (E. coli) bacteria with equivalent affinity. This decreases the probability of resistance development, which necessitates the accumulation of numerous mutations at the dual enzyme level.

The 2016 study conducted in collaboration with the European Committee on Antimicrobial Susceptibility Testing (ECOCAST) and Clinical and Laboratory Standards Institute (CLSI) revealed that delafloxacin exhibited the lowest minimum inhibitory concentrations (MIC values) against MSSA, MRSA, and S. In comparison to clindamycin, linezolid, levofloxacin, ceftaroline,

ciprofloxacin, and oxacillin, aureus is more susceptible to this antibiotic [10]. The MIC values for Delafloxacin against Enterobacteriaceae (E. coli) isolated from the urine of patients with urinary tract infections were equivalent to the fifth part of those of ciprofloxacin. The efficacy of delafloxacin in combination with caspofungin against numerous Gram-positive infections was demonstrated in another in vitro study. Caspofungin is an antifungal medication that functions by impeding the synthesis of the polysaccharide constituents found in S. bacterial biofilm. S. aureus [11]. As previously stated, delafloxacin exhibits activity at an acidic pH. This has been substantiated through a comparative analysis of this antibiotic with other fluoroquinolones across disparate pH levels. Furthermore, the efficacy of delafloxacin against fluoroquinolonic-resistant bacterial strains has been validated through in vitro investigations: It exhibits bactericidal activity against E. 6 hours of coli and S. aureus within ten hours. Additionally, it has demonstrated greater efficacy in combating Gram-negative pathogens, including H. N. influenzae. Legionella spp., P. aeruginosa, gonorrhoeae, and H. pylori.

A protracted record of adverse events has been associated with fluoroquinolones, encompassing tendinitis, tendon injuries and swelling, memory impairments, muscle discomfort or weakness, peripheral neuropathy, and exacerbations of myasthenia gravis. Consequently, numerous fluoroquinolones available in the United States, such as delafloxacin, are accompanied by a marked warning regarding these effects, which is prominently displayed on the outer packaging and in the package leaflet. Additional limitations have been imposed by the EMA regarding the utilization of these antibiotics; they may only be administered to specific infections that are severe infections for which no other antibiotics can be used.

Peripheral neuropathies and effects on the nervous system were identified by the FDA throughout the clinical development of delafloxacin, alongside diarrhea linked to C. D. difficile; nevertheless, there was no higher incidence of these effects observed in the cohort that received the antibiotic compared to the comparator cohort. A multitude of investigations have been conducted to scrutinize the distinct adverse effects associated with the classification of fluoroquinolones. In clinical models, delafloxacin has not been associated with myocardial infarction (e.g., QT stretching) at concentrations exceeding therapeutic levels, in contrast to moxifloxacin. Furthermore, an additional investigation was undertaken concerning photosensitivity, which is frequently linked to the existence of a halogen substituent at position C8 (as is the case with lomefloxacin, which contains a fluorine in C8) [12]. In this regard, delafloxacin, which contains a chlorine atom at position C8, was determined to be non-phototoxic. Nevertheless, the safety profile of delafloxacin will be solidified through its implementation on a larger scale.

Delafloxacin (Baxdela®) exhibits favorable properties, as indicated by its pharmacological data: it maintains 60% bioavailability following oral administration, it mildly inhibits cytochrome P450 3A, it interacts with a limited number of other drugs, and it does not cross-resistand with fluoroquinolones presently available in the market. For the management of acute cutaneous infections, this medication is offered in tablet and intravenous forms. Additionally, it exhibits potential efficacy in treating respiratory infections [13]. This must undoubtedly be confirmed through additional research in the future years.

A Novel B-Lactam Combination: Meropenem–Vaborbactam, for the Treatment of Enterobacteriaceae Infections Resistant to Multiple Drugs.Infections caused by Gram-negative pathogens, particularly carbapenem-resistant Enterobacteriaceae, which the World Health Organization has classified as critical priority pathogens endangering global health, have increased steadily in recent times. The Enterobacteriaceae family comprises exclusively of Gram-negative bacteria, which are prevalent in the intestinal tract of animals and are accountable for a diverse array of intestinal and urinary tract infections [14]. The primary means by which these pathogens acquire resistance to numerous conventional antibiotics is through the synthesis of carbapenemases, which are enzymes consisting of a diverse range of beta-lactamases. These enzymes are capable of hydrolyzing carbapenems, penicillins, certain cephalosporins, aztreonam, and beta-lactamases. Standard β-lactamase inhibitors, including clavulanic acid, tazobactam, and sulbactam, do not inhibit the activity of these enzymes, except in exceptional circumstances. KPC is the enzyme that is most commonly synthesized by pathogens classified within the Enterobacteriaceae family. It is unsurprising that pathogens capable of producing CRE are frequently isolated from the urine of patients, given that Enterobacteria cause the majority of complicated urinary tract infections (cUTI), particularly those that are associated with a high mortality rate. Mortality resulting from invasive infections caused by CRE ranges from 26% to 44% [15]. In addition to the synthesis of carbapenemases, Enterobacteria employ various mechanisms to acquire resistance, including efflux pumps, enzymatic degradations, porine-level mutations, and modifications to the target site. Regrettably, the available therapeutic modalities for CRE infections are quite restricted. Certain pathogens may not respond to first-line antibiotics, leaving patients with rather outdated antibiotics, polymyxins, aminoglycosides, or the rediscovery of colistine, which has by no means negligible toxicity, as treatment options [16]. Clearly, new compounds are required to treat infections caused by Gram-negative bacteria. Historically employed therapeutically for many years, aminoglycosides are antibiotics. The three proteins comprising subunit 50S (the mechanism of action of streptomycin) and potentially additional proteins from subunit 30S (all other aminoglycosides) are inextricably linked to them within the ribosomal site [17]. Consequently, the ribosome is obstructed at the beginning codon (AUG), leading to the detachment of the ribosomal complex and an inadequate protein synthesis. Antibiotics that are bactericidal toward Gram-negative aerobes as well as certain Gram-positive and Mycobacteria species. Parenteral administration is restricted to critical infections involving Gram-negative bacteria and as an antitubercular agent; in fact, a considerable number of aminoglycosides exhibit nephrotoxicity and ototoxicity when delivered intravenously. There is a growing prevalence of antibiotic resistance phenomena of this category emerging. The prevailing resistance mechanism involves the synthesis of enzymes (e.g., acetyltransferase, phosphorylase, adenosyltransferase) that render the antibiotic inactive via conjugation reactions, sacrificing amine and oxidyl functions [18]. This renders the enzyme less similar to the binding sites found in the bacterial ribosome. The susceptibility of distinct aminoglycosides to these enzymes varies. Amikacin and netilmycin, both of semisynthetic origin, have a minimal susceptibility due to the

presence of substitutes that sterically obstruct the binding to the inactivation enzyme. Additionally, elevated resistance can be achieved through ribosomal modifications, such as methylations of particular bases (guanine) in subunit 16S of rRNA. Resistance to aminoglycosides by enzymes is extremely prevalent among Enterobacteriaceae species [19].
Siderophores: Cefiderocol is a cephalosporin.
Cephalosporins, which are classified as β-lactam antibiotics, were identified in 1945 by Giuseppe Brotzu, an Italian chemist and rector of the University of Cagliari in Sardinia. Their mode of action is precisely the same as that of penicillins: they inhibit the process of bacterial wall synthesis. Each of the five generations of cephalosporins has a distinct antimicrobial spectrum that gradually expands until it reaches the fifth generation, which is also effective against MRSA. Indeed, compounds of the most recent generation (ceftobiprole, ceftarolin, ceftolozane) have been formulated with the explicit purpose of countering multidrug-resistant bacterial strains. As a treatment for community-acquired pneumonia, ceftobiprole is efficacious against Staphylococcocchi that are resistant to methylcillin. Ceftolozane, when combined with tazobactam (Zerbaxa®), an inhibitor of β-lactamase, exhibits a strong affinity for carbapenem-resistant Enterobacteriaceae and Pseudomonas aeruginosa [20].
Cefiderocol, a member of the siderophore cephalosporins, is the first antibiotic of its kind to receive approval from both the FDA in 2019 and the EMA in April 2020. It was approved for the treatment of cUTIs caused by Gram-negative, ventilator-associated bacterial pneumonia (VABP) and community-acquired bacterial pneumonia (HABP) [21].
Siderophores, which possess the distinctive characteristics of chelate ions, particularly iron, are generated and secreted by a wide variety of bacterial species in order to facilitate the ion transport into the cell, which is essential for bacterial growth and the maintenance of biological functions. A functional unit that binds iron (transferrin or lactoferrin) and a peptide that interacts with a receptor located on the surface of the bacterial membrane comprise the structure of all siderophores.

Anticipated future developments

Since 2017, only two antibiotics out of a total of eight have been approved as new chemical scaffolds. In reality, the remaining antibiotics are derivatives of classes of compounds that already exist and offer advantages and benefits over conventional antibiotics.
The majority of the eight novel antibiotics exhibit activity against ESBL (extended spectrum β-lactamase) enzymes, specifically carbapenem-resistant Enterobacteria (KPC producers). Conversely, only a limited number of compounds demonstrate activity against carbapenem-resistant Pseudomonas aeruginosa and multidrug-resistant Acinetobacter. baumannii organism. Unfortunately, therapeutic alternatives for the latter remain exceedingly limited in number. The primary indications for these antibiotics are cUTI and cIAI. Additional scientific evidence is required in order to evaluate their efficacy in the management of alternative infections. Plazomycin, vaborbactam, and meropenem were all included in the World Health Organization Model List of Essential Medicines.

Extensive advancements in research have resulted in a proliferation of novel antibiotics that effectively combat Gram-negative bacteria. Comprising combinations of β-lactams and β-lactamase inhibitors, the majority of compounds that have been approved and are currently in clinical development since 2017 target pathogens included in the WHO's 2016 critical priority, high priority, and medium priority lists [22]. CEFiderocol is the sole antibiotic that exhibits activity against the three pathogens deemed critical priority, in addition to the SPR-206 phase I compound, which is a polymyxin analogue renowned for its remarkable antibacterial spectrum. As of the conclusion of 2020, a total of 43 antibiotics were undergoing clinical development. Among these, 15 were in Phase I, 13 were in Phase II, and 13 were in Phase III. In vitro efficacy assessments demonstrated the utility of 19 antibiotics against infections caused by pathogens belonging to the ESKAPE group, which comprises Enterococcus faecium, S. K. aureus. pneumocolitis, A. aeruginosa, B. baumannii, Enterobacter species, which are accountable for the six most prevalent nosocomial infections associated with healthcare. Obviously, it is critical that newly developed antibiotics lack cross-resistance with pre-existing compounds. Cross-resistance mechanisms are, in fact, another factor that influences the search for novel antibacterial pharmaceuticals derived from the modification of conventional antibiotics. Finding novel chemical structures with unidentified targets and binding sites, on the other hand, is exceedingly challenging and produces fewer results than alternative methods. Moreover, apart from the small and large molecules examined in this review, there exist alternative non-traditional methods that have the potential to be efficacious in treating recurrent C. This includes fecal bacteriotherapy, which is also referred to as fecal microbiome transplantation. The occurrence of C. difficile infections. Due to significant barriers, additional non-traditional methods (including immunomodulators and phage products) have yet to progress into clinical development. Regrettably, unfavorable market trends persist: private investment has declined further in recent years, while public investments in the development of new antibiotics have increased marginally (primarily from Germany, the United Kingdom, and the United States, owing to organizations such as BARDA, CARB-X, and GARDP). Several pharmaceutical companies are discontinuing their research efforts in this field, primarily due to the exorbitant expenses associated with the clinical development phase of an antibiotic. Eleven new antibiotics are anticipated to be approved within the next five years, given the comparatively lengthy duration of clinical development; however, numerous compounds are likely to stagnate in Phases II and III owing to the substantial financial investments involved.

Development of antibiotic resistance related to proliferation of SARS-CoV-2. An investigation carried out by The Pew Charitable Trusts, an American non-profit organization, and published in March 2021, scrutinizes the data of approximately 6000 hospitalized patients who tested positive for SARS-CoV-2 in the United States [23]. The study analyzes the time span from February to July 2020. In the first half of the pandemic, antibiotic treatment was administered to 52% of patients, according to the collected data; that percentage increased to 90% between March and April. Conversely, a proportion of 36% of hospital admissions necessitated the concurrent

administration of multiple antibiotics. Antibiotics were frequently prescribed as a preventive measure against bacterial infections that followed viral infections, frequently prior to the confirmation of the bacterial infection. An additional element that exacerbated the situation was the challenge faced by medical personnel in differentiating between bacterial pneumonia and viral pneumonia caused by SARS-CoV-2. This difficulty was particularly pronounced during the initial months of the emergency, when understanding of SARS-CoV-2 was extremely limited. The results indicate that an excessive prescription of these medications is most likely the cause, as a significant number of patients did not require antibiotic treatment. It is possible for patients who have been diagnosed with viral infections to develop bacterial infections, which can exacerbate the patient's clinical condition and complicate treatment. A total of 20% of the patients who tested positive for SARS-CoV-2 had contracted bacterial pneumonia, specifically community-acquired pneumonia. Antibiotics were administered to 96% of COVID-19 patients within the initial 48 hours following their admission to the hospital. Few patients were prescribed additional antibiotics within the 48 hours following admission. Nevertheless, when only 33% of patients who received a minimum of one antibiotic had a confirmed diagnosis of community-acquired bacterial pneumonia were considered. This indicates that the antibiotic was prescribed unnecessarily in the remaining 67% of cases, thereby contributing to the growth of antibiotic resistance. Furthermore, the research findings revealed that the antibiotics utilized most commonly were macrolide azithromycin (which accounted for over 50% of hospital admissions), ceftriaxone (42%), vancomycin (25%), and the combination of piperacillin and tazobactam (23%). Antibiotics of this nature are frequently prescribed with the specific intention of treating bacterial pneumonia. Numerous patients with interstitial pneumonia caused by SARS-CoV-2 have received azithromycin, which is typically prescribed for the eradication of Legionella or Chlamydia, both of which are capable of inducing a comparable pneumonia. Additionally, it is noteworthy that antibiotic treatment for 29% of the patients has resulted in an elevated risk of contracting pathogen C. difficile in nature. The extensive utilization of antibiotics, particularly those with a broad spectrum of activity against bacteria, throughout the pandemic poses a potential hazard to the advancements and outcomes attained in scientific research in recent times. Certain circumstances and particular factors can facilitate or impede the transmission of multidrug-resistant organisms. The potential ramifications of the SARS-CoV-2 pandemic on hospital transmission of these pathogens are examined in a study published in the Journal of Hospital Infection in 2020. Given the current precarious state of affairs, it is even more apparent that the endeavors of recent years will inevitably culminate in the creation of an expanding array of antibiotics that are efficacious against multidrug-resistant organisms. However, references to more than just antibiotics have been made in recent times; an increasing number of research organizations are placing emphasis on novel therapeutic strategies as an additional tool in the battle against antibiotic resistance.

The Use of Nanomedicine to Combat Infectious Diseases

Destruction of the extracellular matrix comprising the bacterial biofilm (aggregations of microorganisms that form surface-adherent coatings) could be a viable strategy. Biofilm formation is linked to approximately 60% of microbial infections, as the bacteria that are structured within it

possess the ability to withstand the immune system of the host and numerous antibiotics. The biofilm degradation results in the liberation of bacteria, which subsequently reestablish their susceptibility to antibiotics. At this time, research organizations are investigating the conjugation of ramnolipids (biosurfactants secreted by the pathogen P. aeruginosa) with polymer nanoparticles as a means to develop polymeric lipid nanoparticles that can be used to counteract the resistance of H. bacterial biofilm to antibiotics that are commonly used.
The aforementioned system is composed of chitosan polymer core encapsulating clarithromycin; in addition to possessing antibacterial properties, it inhibits biofilm formation and bacterial adhesion. Rhamnolipid-coated silver and iron oxide nanoparticles, which have been demonstrated to be efficacious in eliminating S., have been synthesized using the same principle. biofilms of S. aureus and P. aeruginosa.
Additional structures that have been assessed for their capacity to function as antimicrobial drug release systems are crystalline liquid non-lamellar nanoparticles. These nanoparticles consist of numerous amphiphilic structures arranged in a broad surface area, and they possess the capability to encapsulate drugs that are both hydrophilic and hydrophobic. An instance of this is positively charged nanoparticles containing rifampicin, which inhibited the growth of S. with lower MIC values than non-encapsulated rifampicin. S. aureus. Additionally, nanoparticles and natural compounds can be combined in novel ways: Rodenak-Kladniew investigated the integration of chitosan and eugenol, a naturally occurring phenolic compound, into a lipid matrix that also contained the antibiotic ofloxacin. Enhanced bactericidal activity was observed against Pseudomonas aeruginosa and Salmonella. S. aureus.
Utilizing polymeric materials that react to pH and the presence of enzymes at the site of infection are among the innovative methods for releasing antibiotics. This enables the active ingredient to be delivered precisely where the infection is situated. Additionally, photodynamic therapy and antimicrobial oligonucleotides are being investigated. A novel approach has been devised wherein the antibiotic ciprofloxacin is loaded into photoactivable liposomes; the authors assert that the release of approximately 90% of the active substance occurred in under 30 seconds.
When treating multidrug-resistant strains, combined therapy is frequently preferred over monotherapy due to the fact that the concurrent use of multiple antibiotics with synergistic effects prevents antibiotic resistance, expands the antimicrobial spectrum, and reduces therapy-associated adverse effects. Significant advantages can be derived from co-encapsulating multiple antibiotics into nanosystems. For instance, liposomes containing ciprofloxacin and colistine have been synthesized by research groups in order to combat P. aeruginosa infections. Results obtained in vitro indicate that monotherapy is less efficacious than combined therapy.
Additionally, nanoantibiotics represent a promising area of study. By converting therapeutic agents into structures corresponding to the nanoscale, their chemical–physical properties can be altered, their bioavailability can be enhanced, and their interaction and penetration into the bacterial wall can be improved, thereby increasing their efficacy against resistant strains. Nanocrystal formulations of clarithromycin have demonstrated efficacy against multidrug-resistant H. pylori: Nanocrystals of clarithromycin enable targeted delivery to the intended site, exhibiting a superior

therapeutic profile in comparison to suspension and particle formulations. Several nanostructured systems containing antimicrobial peptides and antibiotics are undergoing clinical trials at present. As an illustration, several liposomal ciprofloxacin inhalation formulations are currently in Phases I, II, and III of clinical development. Similarly, a liposomal amikacin formulation intended to treat recurrent P. aeruginosa infections in patients with cystic fibrosis has already reached Phase III. Utilizing liposomes as antibiotic carriers in nanomedicine offers numerous benefits, including enhanced pharmacokinetic parameters and biodistribution in particular, and a reduction in toxicity. The process by which liposomal vesicles fuse with the bacterial cell's outer membrane enhances the antibiotic's penetration and release into the cell. While nanostructured systems are primarily applied in the fields of oncology and cancer immunotherapy, they have the potential to revolutionize antibiotic delivery, an area that still has significant unexplored potential [24]. Translating antibiotic-loaded nanostructured systems into clinical practice is evidently complicated and requires additional research and efforts to combat antibiotic resistance, a "silent" pandemic at present. By utilizing nanoparticles, resistance mechanisms can be circumvented: These structures facilitate a more efficient internalization of hydrophilic and hydrophobic antibiotics that are delivered selectively to the site of infection and are not enzymatically deactivated. Multiple studies have documented that the utilization of nanoparticles laden with antibiotics or antimicrobial peptides results in substantial decreases in minimum inhibitory concentrations (MIC values) when compared to the corresponding values anticipated when employing non-encapsulated active ingredients. It is feasible to impede the progression of antibiotic resistance mechanisms in this manner. Notwithstanding the encouraging outcomes observed in vitro, the inclusion of formulations in clinical trials remains limited, a factor that can be attributed to the exorbitant expenses associated with such preparations [25].
A catastrophic projection was included in a 2014 article titled "Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations" by Jim O'Neill, which was commissioned by the British government. According to the author's estimation, antibiotic resistance will be responsible for an estimated 10 million deaths annually by 2050, which is greater than the combined mortality toll from cancer and diabetes. This forecast has been referenced in a multitude of additional scholarly sources, such as health authorities and the media. The lamentable value was obtained by multiplying the number of bloodstream infections across the nation by the national resistance rates, as documented by the European Antimicrobial Resistance Surveillance Network, in the model utilized for the report. Naturally, these are projections concerning a highly delicate subject matter, which further complicates the task of articulating an exact viewpoint. To take tangible action, solid data on antibiotic resistance is required not only in Europe, as examined in the report, but also in less developed nations.

Conclusion

The advancement of scientific knowledge in the forthcoming years will be pivotal, and while the medications examined in this assessment merely signify starting points, they nonetheless constitute a substantial progression that, when coupled with personal accountability and conduct, can genuinely affect change and enable an overturning of present estimations.

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