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Current Promising Antibiotics and Future Approaches in Combating Carbapenemase-Producing *Enterobacteriaceae* †

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Abstract: Carbapenem-resistant (CR) Gram-negative bacilli, including *Enterobacteriaceae* and the non-fermenters, represent the most notorious pathogens due to the high incidence of morbidity and mortality, especially in immunocompromised patients in intensive care units. Carbapenem resistance is mainly associated with the production of carbapenemases, which are β-lactamases belonging to different Ambler classes (A, B, D) that can be encoded by both chromosomal and plasmid-mediated genes. These enzymes represent the most potent β-lactamases, hydrolyzing a wide variety of β-lactams, including carbapenems, cephalosporins, penicillin, and aztreonam. The major issues associated with carbapenemase production are both clinical, posing significant challenges in the treatment of healthcare-associated infections by compromising the activity of the last-resort antibiotics, and epidemiological, due to their dissemination across almost all geographic regions. An important advancement is a handful of newly launched antibiotics targeting some of the current most problematic Gram-negative pathogens, namely carbapenem-resistant *Enterobacteriaceae* (CRE). The most appropriate antimicrobial therapy to treat CRE infections is still controversial. Combination therapy is preferred over monotherapy due to its broad-spectrum coverage, synergic activity, and low probability of selecting resistance. In this mini-review, current and future promising antibiotics that are currently under investigation for winning the war against the emerging CRE are discussed.

Keywords: carbapenem-resistant *Enterobacteriaceae* (CRE); carbapenemases; multi-drug resistance; novel antibiotics

1. Introduction

In 2017, World Health Organization (WHO) published a list of resistant bacteria against which there is an urgent need to develop new antibiotics [1]. Critical priority bacteria included carbapenem-resistant *Enterobacteriaceae* (CRE). These bacteria are among the most common pathogens associated with severe infections, such as sepsis, pneumonia, urinary tract, and intra-abdominal infections.

Consequently, CREs have a major impact, both clinically and economically [2]. Initially, *Enterobacteriaceae* posed a threat to public health because of their ability to resist the action of beta-lactam antibiotics by producing broad-spectrum beta-lactamases. This situation has led to the use of carbapenems as first-line drugs [3]. The use of carbapenems as a treatment for resistant bacteria has led to CRE's emergence over time. In response to the CRE threat, efforts have been made to reduce the spread and prevent the development of resistance from reducing nosocomial infections associated with CRE by up to 60% by the end of 2020 [4]. The American Society of Infectious Diseases has launched the "10 × 20" campaign to develop 10 new antibiotics by the end of 2020, with two such antibiotics already receiving FDA approval [5].

For challenging the Gram-negative resistant bacteria, polymyxins and tigecycline were considered an option, but resistance to these antibiotics is increasing alarmingly [6]. Additionally, phosphomycin and aminoglycosides are used occasionally [7]. Carbapenems still play an important role in treating CRE, either in high doses in combination with other active agents, or dual therapy. Old antibiotics such as minocycline, doxycycline, sulfamethoxazole (SXT), and chloramphenicol may be effective against certain CRE isolates [8,9]. In response to increasing resistance, several new antibiotics have been developed that target KPC (*Klebsiella pneumoniae* carbapenemase) - producing *Enterobacteriaceae* and multiple-drug resistant (MDR) *P. aeruginosa*. Other antibiotics in the final stages of development target pathogens that produce metallo-beta-lactamases (MBL) and MDR *A. baumannii* [10]. Currently, ceftazidime/avibactam, ceftolozane/tazobactam, meropenem/vaborbactam, and eravacycline have been included in clinical therapy in America and Europe, while plazomicin has received FDA approval [10].

2. Current Promising Antibiotics in Treating CRE Infections

Selecting an antimicrobial compound for carbapenem-resistant (CR) Gram-negative infections is almost always challenging, although the degree of difficulty varies depending on the specific clinical scenario. The major issues associated with carbapenemase production are clinical, due to compromising the last-resort antibiotics activity used for treating serious infections and epidemiological due to their dissemination into various bacteria across almost all geographic regions. An important advancement is the newly launched antibiotics targeting some of the current most problematic Gram-negative pathogens, namely carbapenem-resistant *Enterobacteriaceae* (CRE). Ceftazidime/avibactam and meropenem/vaborbactam for CRE and ceftolozane/tazobactam for carbapenem-resistant *P. aeruginosa* infections have become important contemporary treatment options in countries where these agents have become available for clinical use [11]. Other new agents such as plazomicin, approved by the FDA in 2018, eravacycline, potent against MDR-*Enterobacteriaceae*, and *A. baumannii* isolates [12], and omadacycline, active against MRSA, MDR-*Streptococcus pneumoniae*, and ESBL-producing *Escherichia coli* isolates [13] are briefly presented in Table 1.

Table 1. Current promising antibiotics in treating carbapenem-resistant *Enterobacteriaceae* (CRE) infections [1].

Drug	Mechanism of Action	Indications	Limitations
Ceftazidime/avibactam	Cell wall synthesis inhibitor	cUTI, cIAI, BSI, pneumonia	Occurrence of resistance
Ceftolozane/tazobactam	Inhibition of PBPs	cUTI, cIAI	Occurrence of resistance
Meropenem/varbobactam	Cell wall synthesis inhibitor	cUTI, cIAI, BSI, pneumonia	-
Ceftaroline/avibactam	Inhibition of PBPs	cUTI	Occurrence of resistance due to mutations in KPC-producing *Enterobacteriaceae*
Imipenem/cilastatin-relebactam	Renal dehydropeptidase inhibitor/beta-lactamase inhibitor	cUTI, cIAI, pneumonia	Severe hypersensitivity reactions

Aztreonam/avibactam	Cell wall synthesis inhibitor	cIAI	Likelihood of resistance among MBL- and AmpC-co-producing *K. pneumoniae*
Meropenem/nacubactam	Cell wall synthesis inhibitor	cIAI	Occurrence of resistance; alterations of renal function
Plazomicin	Protein synthesis inhibitor	cUTI, BSI, pneumonia	Ineffective against MBL-producers
Eravacycline	Protein synthesis inhibitor	cIAI, pneumonia	Not indicated for the treatment of cUTI
Cefiderocol	Cell wall synthesis inhibitor	cUTI	Under investigation in clinical trials
Omadacycline	Protein synthesis inhibitor	cUTI, pneumonia, acute SI	Limited action against ESBL-producing *K. pneumoniae*
Delafloxacin	Protein synthesis inhibitor (topoisomerase IV and DNA gyrase)	Acute SI, pneumonia	Peripheral neuropathy and central nervous system effects

[1] cUTI, complicated urinary tract infections; cIAI, complicated intra-abdominal infections; BSI, bloodstream infections; SI, skin infections; PBP, penicillin-binding protein; KPC, *Klebsiella pneumoniae* carbapenemase; NA, not available.

3. Future Perspectives in CRE Treatment

The scientific community has focused its efforts on identifying new strategies for combating drug resistance by repositioning non-antibiotic drugs in the antimicrobial arsenal or reconceptualizing old antibiotics.

One of the methodologies in the post-antibiotic era is the use of non-antibiotic drugs for the treatment of multidrug-resistant infections [14]. The benefits are considerable; the details of these drugs' pharmacokinetics and toxicity are already known, and therefore the drugs can be passed directly into phase 2 of clinical trials [15]. However, the costly disadvantage of clinical trials and patent rights remains [16]. Several drugs administered either alone or in conjunction with classical antibiotics have been shown to be effective in removing resistance in CRE, such as antiretroviral compounds (Zidovudine) [17,18], antifungals (Cyclopirox) [19], anticancer compounds (Gallium, Mitotane, Tamoxifen) [20–22], and antidepressants (Sertraline) [23]. Many of these even have different therapeutic targets from conventional antibiotics, which act on DNA, the cell wall, or protein translation. Ciclopirox effectively inhibits CRE growth despite its resistant status by interfering with galactose metabolism and LPS (lipopolysaccharides) biosynthesis [19]. Gallium can inhibit ferric redox reactions and associated pathways due to its similarity to iron and can stop the bacterial growth of microorganisms resistant to the last-resort antibiotics [20].

Another promising strategy in the context of antibiotic resistance is the use of liquid ion-based antimicrobial agents (ILs). ILs are generally defined as salts composed solely of cations and anions, with melting points below 100 °C, mostly liquid at room temperature [24]. ILs are not new compounds, dating back more than a century, but have raised the awareness of the scientific community due to their tunable biological properties that allow them to be exploited to generate new and unlimited pharmacological combinations with antimicrobial effects [25]. For example, Ferraz et al. reported that the administration of ampicillin-based ILs inhibited the bacterial growth of several drug-resistant Gram-negative species (*E. coli*, *Klebsiella pneumoniae*), as well as Gram-positive strains of *Staphylococcus aureus* and *Enterococcus faecalis*, being superior to sodium ampicillin and bromide and chloride salts. Additionally, the administration of ILs led to the reduction in MIC (minimum inhibitory concentration) for two Gram-negative antibiotic-resistant *E. coli* strains harboring TEM and CTX M9 and CTX M2, respectively, demonstrating the potency of these ampicillin-based ILs for fighting Gram-negative resistant bugs [26]. Other studies have shown the effectiveness of combining organic cations such as choline, alkylammonium, alkylpyridiniums, and alkylimidazoliums with various inorganic anions or antibiotics (ampicillinate, carbenicillinate, oxacillinate and cephalothinate or penicillin hydrolyzate, and amoxicillin hydrolyzate) in combating the problem of antibiotic resistance in various *Enterobacteriaceae* strains [26–29]. ILs can also be combined with phage therapy or lysine therapy to strengthen the therapeutic arsenal in the context of antibiotic resistance

[30]. Important attention is also given to polyionic liquids (PILs), which can be designated to achieve amphiphilicity, thereby allowing the polymer's rapid and efficient transfer through the lipid bilayer of the bacterial membrane [31]. It has been documented that PILs with high cation density and long alkyl chains have superior antimicrobial efficacy to their small-molecule counterparts [32]. However, the use of PILs is currently limited by bioaccumulation in the environment, and studies are focused on identifying compounds with optimal biodegradability [31].

Testing drugs in clinical trials to investigate their ability to kill bacteria in ways other than conventional methods is extremely laborious and expensive, and most of the time, the results are modest. Thus, the development of new methodologies that reduce costs and increase the discovery of new antibiotics is essential to reinvigorate the antibiotic pipeline. Machine learning approaches can address many of these issues associated with the synthesis, identification, and clinical validation of new compounds with antibiotic properties. A pioneering deep-learning approach has identified new antibiotics from a pool of more than 107 million molecules, also known as the ZINC15 database. Remarkably, one of these compounds, halicin, is structurally divergent from conventional antibiotics and is potent over a wide range of microorganisms, including *Mycobacterium tuberculosis* and CRE. Halicin efficiency on pan-resistant *Acinetobacter baumannii* was also confirmed by in vivo studies. This study highlighted the pivotal role of artificial intelligence approaches in describing and predicting potential candidates' properties in reversing antibiotic resistance [33]. Additionally, some studies have highlighted the role of machine learning approaches in optimizing antibiotic combinations to reverse carbapenem resistance in Gram-negative organisms such as *A. baumannii* [34].

Another strategy exploited to reverse antibiotic resistance comes from synthetic biology, and involves redesigning existing antibiotics to overcome natural resistance mechanisms. The concept is based on developing a "LEGO" set of molecular pieces that can be altered and joined together to generate larger molecules with improved antibiotic capabilities. This has been demonstrated with a new class of drugs called streptogramins, which block bacterial growth by interfering with protein synthesis. In this regard, Li et al. built new streptogramins from scratch, creating a series of modules that can be modified as needed to generate a series of variations in the structure of streptogramin molecules. After modifying and assembling these molecular LEGO pieces, it was observed that these variations had antimicrobial activity on a wide range of pathogens, including streptogramin-resistant *S. aureus*. Therefore, the synthesis and assembly of slightly modified modules can revitalize several antibiotics classes that have been abandoned due to the natural mechanisms of bacterial resistance, offering new hopes in the war against CRE [35]. Another LEGO-like approach is expected to revitalize endolysins, enzymes employed by bacteriophages to produce cell lysis and virion release, and currently used in the therapeutic management of Gram-negative bacteria [36].

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