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New antibiotics targeting Gram-negative bacilli

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SUMMARY

Antimicrobial resistance (AMR) is an emerging global threat. It increases mortality and morbidity rates and places a heavy burden on healthcare systems. Healthcare professionals can address the increasing issue of AMR by advocating responsible antibiotic use and supporting the development of new medications. Despite the economic, logistic, and scientific challenges, it is reassuring that new agents continue to be developed. This review addresses new antibiotics in the pipeline. A review of the literature was conducted including Medline, and Clinicaltrials.org, for approved and in pipeline antibiotics in phase 3 or new drug applications (NDA). We found several new antibiotics and reviewed their current development status, mode of action, spectra of activity, and indications for which they have been approved. The included studies from phase 3 clinical trials were mainly utilized for the treatment of acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, and pneumonia acquired in healthcare settings. The availability of these agents is limited for high-priority organisms. The identified antibiotics were primarily based on previously known molecules or pre-existing antimicrobial agents. There is a limited number of antibiotics against high priority organisms. New antimicrobial agents targeting the top-priority organisms identified by the World Health Organization are urgently needed. However, some antibiotics target ESBL-producing Enterobacterales, carbapenem-resistant Enterobacterales, *Acinetobacter baumannii, and Pseudomonas aeruginosa.*

Keywords: Antibiotics, pipeline, novel antibiotics, new antibiotics, antibiotic resistance; multi-drug-resistance.

INTRODUCTION

Gram-negative bacteria exhibit intrinsic resistance mechanisms that contribute to the difficult to treat severe infections in humans. Their distinct cell wall structure, notably the outer membrane comprising polysaccharides, serves as a barrier against both the immune system and antimicrobial agents. Thus, Gram-negative bacteria represent a significant challenge in healthcare-associated infections such as pneumonia, bacteremia and urinary tract infections. These pathogens add further strain on healthcare systems, resulting in a high morbidity and mortality rates, exacerbated

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Table 1 - Gram-negative bacteria of critical/high priorities based on the World Health Organization.

Pathogen	*Priority Level*
Acinetobacter baumannii (Carbapenem-resistant)	Critical
Pseudomonas aeruginosa (Carbapenem-resistant)	Critical
Enterobacteriaceae (Carbapenem-resistant, ESBL-producing)	Critical
Helicobacter pylori (Clarithromycin-resistant)	High
Campylobacter spp (Fluoroquinolone-resistant)	High
Salmonellae (Fluoroquinolone-resistant)	High
Neisseria gonorrhoeae (Cephalosporin-resistant, Fluoroquinolone-resistant)	High

Notes:
Critical Priority: These pathogens represent a major threat due to their high levels of resistance, mortality, and limited treatment options. Their ability to evade current therapies and cause severe infections highlights the urgent action for new and effective anti-microbial solutions.
High Priority: These pathogens are of high concern due to their complex resistance profiles which complicate treatment and contribute to their high mortality rates. They pose substantial public health challenges by causing severe infections, highlighting the need for innovative solutions to overcome their increasing threat.

by the limited treatment options. This urgency is underscored by the World Health Organization (WHO) "WHO Bacterial Priority Pathogens List, 2024" (Table 1), highlighting the critical need for novel strategies and antimicrobial agents to combat these pathogens [1]. These pathogens are significant due to their public health importance, particularly in the context of increasing antimicrobial resistance (AMR). *Acinetobacter baumannii* (Carbapenem-resistant), *Pseudomonas aeruginosa* (Carbapenem-resistant), and Enterobacteriaceae (Carbapenem-resistant, ESBL-producing) have critical priority, while *Helicobacter pylori* (Clarithromycin-resistant), *Campylobacter spp* (Fluoroquinolone-resistant), Salmonellae (Fluoroquinolone-resistant), and *Neisseria gonorrhoeae* (Cephalosporin-resistant, Fluoroquinolone-resistant) have high priority.

METHODS

This review focuses on identifying and evaluating new antibiotics being in clinical trials or in the development pipeline as of 2024. A literature search was performed using multiple databases and resources. The search encompassed Medline, ClinicalTrials.gov, and relevant pharmaceutical company reports to gather information on antibiotics that were either in phase 3 clinical trials or had submitted New Drug Applications (NDA) for approval. The inclusion criteria were: antibiotics that were in phase 3 clinical trials or had recently received NDA approval for clinical use, studies published between 2020 and 2024 (to include recent studies).

Search Strategy
Medline: A detailed query was constructed using key terms like "antibiotics," "phase 3 clinical trials," "new drug application," and "2024 pipeline." Studies focusing on novel mechanisms of action or those addressing high-priority pathogens were given special attention.
ClinicalTrials.gov: We reviewed ongoing phase 3 trials for promising antibiotic candidates, particularly those targeting multi-drug-resistant organisms or infections with significant unmet medical needs.

RESULTS AND DISCUSSION

This review identified several new antibiotics that are currently in phase 3 clinical trials or awaiting approval via New Drug Applications (NDAs). In the following section we will discuss each of these antibiotics and summarize key concepts from the appropriate clinical trials.

β-lactam-β-lactamase inhibitor combinations

New strategies for the treatment of multidrug-resistant (MDR) bacteria include innovative combinations of β-lactam-β-lactamase inhibitors. These therapies combine β-lactam antibiotics with β-lactamase inhibitors to override resistance mechanisms. By inhibiting β-lactamases enzymes responsible for breaking down β-lactam antibiotics, these synergistic combinations enhance the efficacy of β-lactams. The latest treatment options, outlined in Table 2 in alphabetical order, encompass a range of promising β-lactam-β-lactamase inhibitor combinations.

Table 2 - New antibiotics in the pipeline for Gram-negative bacterial infections (alphabetical order).

Antibiotic	*Mechanism of Action*	*Spectrum of Activity*	*Clinical Uses*
Aztreonam-Avibactam	Aztreonam: monobactam; Avibactam: non-β-lactam β-lactamase inhibitor	Metallo-β-lactamases (MBL)-producing Gram-negatives	cUTIs, cIAIs, severe infections
Cefepime-Enmetazobactam	Cefepime: 4th-generatioon cephalosporin; Enmetazobactam: β-lactamase inhibitor	Extended-spectrum β-lactamases (ESBL)-producing *Enterobacteriaceae*, resistant Gram-negatives	cUTIs, severe Gram-negative infections
Cefepime-Taniborbactam	Cefepime: 4th-generatioon cephalosporin; Taniborbactam: β-lactamase inhibitor	Pseudomonas, Extended-spectrum β-lactamases (ESBL)- and Metallo-β-lactamases (MBL)-producing Enterobacteriaceae	cUTIs
Cefiderocol	Siderophore cephalosporin, uses bacterial iron transport to enter cells	Broad Gram-negative, including Pseudomonas, Acinetobacter, CRE	cUTIs, HABP, VABP
Eravacycline	Tetracycline derivative, inhibits protein synthesis by binding to 30S ribosomal subunit	Broad-spectrum, including CRE	cIAIs, other severe infections
Imipenem-Cilastatin-Relebactam (IMI-REL)	Imipenem: carbapenem; Cilastatin: prevents renal degradation; Relebactam: β-lactamase inhibitor	Broad Gram-negative, including Pseudomonas, CRE	cUTIs, cIAIs, HABP/VABP
Meropenem-Vaborbactam (MEV)	Meropenem: carbapenem; Vaborbactam: β-lactamase inhibitor	CRE, carbapenem-resistant pathogens	cUTIs, cIAIs, HABP
Plazomicin	Aminoglycoside, binds to 30S ribosomal subunit	CRE, multidrug-resistant Gram-negatives	cUTIs, bloodstream infections

Note: cUTI: Complicated urinary tract infections; HABP: hospital-acquired bacterial pneumonia; cIAI: complicated intra-abdominal infection; VABP: ventilator-associated bacterial pneumonia.

Meropenem-vaborbactam

Meropenem-vaborbactam (MEV) is a fixed combination antibiotic used for severe infections caused by MDR Gram-negative pathogens. It contains a combination of meropenem, a broad-spectrum β-lactam antibiotic and, vaborbactam, a β-lactamase inhibitor. MEV has an activity against *Klebsiella pneumoniae* carbapenemase (KPC) but has no efficacy against carbapenem-resistant *P. aeruginosa*, metallo-β-lactamases (MBL) carbapenemases, or OXA-48 [2]. This antibiotic had been approved for the treatment of complicated intra-abdominal infections (cIAI), hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and complicated urinary tract infections (cUTI) [2] [3]. TANGO I, TANGO II, and TANGO III trials were conducted to evaluate the efficacy and safety of MEV in treating infections caused by MDR Gram-negative bacteria. TANGO I focuses on the treatment for cUTIs, TANGO II examines cIAIs, and TANGO III investigates infections caused by carbapenem-resistant Enterobacteriaceae (CRE). Overall, these three trials support the use of MEV in treating serious infections caused by Gram-negative bacteria, filling a crucial gap in the treatment of MDR infections.

TANGO I trial: This randomized placebo-controlled phase III clinical trial was conducted to determine the efficacy and safety of MEV in treating patients with cUTIs caused by Gram-negative bacteria. 550 adult patients with cUTI were included in this study, and compared the 10-day efficacy of piperacillin-tazobactam and MEV [4]. MEV arm had a high overall success rate (98.4% versus 94%). In the modified Intention To Treat (ITT) analysis, 66.7% of the MEV arm and 57.7% of the piperacillin-tazobactam group experienced microbial eradication [4]. MEV was non-inferior for overall suc-

cess and microbial eradication in comparison to piperacillin-tazobactam for cUTIs [4]. The MEV effectively treated infections caused by several β-lactamases, including KPC and extended-spectrum β-lactamases (ESBL) [5]. MEV demonstrated a safety profile similar to that of meropenem alone, with the most frequent adverse event recorded during the trial was headache [4].

TANGO II trial: This randomized, double-blind, placebo controlled, phase III clinical trial evaluated the safety and efficacy of MEV in patients with cIAI caused by Gram-negative bacteria. In patients with carbapenem-resistant *Enterobacterales (CRE)* infections, MEV was evaluated against best-available therapy[6]. The study compared the best available therapy to MEV in 77 adults with confirmed or suspected infections caused by *CRE* [6]. MEV showed non-inferiority to best-available therapy in terms of clinical cure at the end of treatment and test of cure. MEV produced a greater clinical cure in microbiologic carbapenem-resistant *Enterobacteriaceae* modified ITT, with no change in microbiologic cure at therapy's conclusion [6]. At day-28, there was no discernible variation in mortality (15.6% versus 33.3%; P= 0.20). Adverse events were lower with MEV (84% versus 92%) and lower with renal adverse events (4% versus 24%) [6]. The most frequent adverse events were diarrhea (12%), anemia (10%), and hypokalemia (10%).

TANGO III trial: This trial was designed to determine the effectiveness of MEV in treating patients with infections caused by CRE. In a phase IIIb TANGO III open-label randomized clinical trial, the safety and effectiveness assessments of MEV in adults with HAP/VAP [7]. The study showed that MEV was effective against CRE infections, offering a promising option for the treatment of these pathogens.

Imipenem-cilastatin-relebactam

Imipenem-cilastatin-relebactam (IMI-REL) consists of a combination of antibiotics used for the treatment of serious infections such as cIAIs and cUTIs including CRE infections, caused by MDR Gram-negative bacteria. IMI-REL combines three agents, imipenem, a broad-spectrum β-lactam antibiotic with activity against both Gram-negative and Gram-positive bacteria, cilastatin, an inhibitor of imipenem renal metabolism, ensuring that imipenem remains active for its intended duration, and relebactam, a β-lactamase inhibitor, that prevents imipenem from being inactivated by β-lactamase. Relebactam has activity against (ESBL)-producing *Enterobacterales*, KPC, CRE, and carbapenem-resistant *P. aeruginosa*. However, it is inactive against *Acinetobacter baumannii, Stenotrophomonas maltophillia,* and producers of MBL and OXA-48 [8]. RESTORE-IMI-1 and RESTORE-IMI-2 trials were conducted to determine the effectiveness and safety profiles of IMI-REL in patients with complicated infections.

RESTORE-IMI-1: A randomized multicenter, phase III clinical trial of IMI-REL vs meropenem examined the primary endpoint of clinical responses and the secondary endpoint of microbiological success. The study included adults with cIAI secondary to Gram-negative imipenem-resistant organisms [9-11]. The study showed that IMI-REL was as effective and had comparable safety profile as meropenem. Another trial compared IMI-REL vs colistin base activity and imipenem-cilastatin (colistin/imipenem). The IMI-REL group showed an overall response of 71.4% in the supplemental microbiological modified ITT, while the colistin/imipenem group showed an overall response of 70% (adjusted difference -7.5; 95% CI -27.5 to 21.4). In comparison to colistin/imipenem, the all-cause 28-day mortality rate for IMI-REL was 9.5% versus 30%, respectively [9].

RESTORE-IMI 2: The RESTORE-IMI 2 is a phase III, double-blind randomized, multi-center clinical trial of patients with cUTIs and compared IMI-REL with piperacillin-tazobactam. However, all patients received linezolid. The study primary endpoint was clinical responses and secondary endpoints were tolerability, safety and microbiological responses. This study involved 536 adults with HAP/VAP, and was completed on April 3, 2019. In relation to the 28-day all-cause mortality, IMI-REL performed equally well compared to piperacillin/tazobactam (15.9% vs. 21.3%) and had a favorable clinical response (61.0% and 55.8%) at early follow-up [12].

Cefepime-Enmetazobactam (CEF-ENM)

Cefepime-Enmetazobactam (CEF-ENM), a β-lactam and β-lactamase inhibitor, inhibits ESBL and classes A and D carbapenemases [13, 14]. CEF-ENM was recently approved for therapy of cUTIs/pyelonephritis, HAP/VAP, and the associated bacteremia [15]. *In vitro*, CEF-ENM had an excellent

activity against ESBL-producing *Enterobacterales* [16]. In the ALLIUM trial, a randomized controlled trial, the overall cure rate was 79.1% (273/345) vs. 58.9% (196/333), in the CEF-ENM and piperacillin-tazobactam, respectively (between-group difference, 21.2% [95% CI, 14.3% to 27.9%]) [17]. However, it is important to note that most of the organisms were susceptible to CEF-ENM [18]. A post-hoc analysis was performed excluding those with piperacillin-tazobactam MIC of > 8 µg/mL and showed better outcomes in CEF-ENM (79.1% [250/316]) vs. piperacillin/tazobactam group (60.3% [182/302]) (treatment difference, 18.8% [95% CI, 11.6%-25.7%]; $P < .001$) [19].

Cefepime-Taniborbactam

Taniborbactam (VNRX-5133) has a broad-spectrum inhibitory activity against Ambler class A (ESBLs), B (NDM and VIM), C (AmpC from *P. aeruginosa*), and to a lesser extent on D (OXA) β-lactamases. It can also inhibit metallo-beta- and serine-beta-lactamases [20]. Taniborbactam has a specific interaction at key amino acid like K224 in NDM-1, which results in restoring susceptibility to cefepime in certain resistant strains [21]. The combination of CEF-TANI showed an overall susceptibility of 98.9% against tested Gram-negative pathogens, which was significantly higher than other tested comparator agents with susceptibility rates ranging from 39.6% for cefepime to 86.3% for ceftazidime/avibactam [22]. Adults with cUTI are presently participating in a phase III clinical trial (ClinicalTrials.gov - NCT03840148; CERTAIN-1 trial) that compares cefepime-taniborbactam (CEF-TANI) to meropenem [23]. In this trial, 436 of 661 hospitalized adults with cUTIs were part of the microbiologic intention-to-treat (microITT) population and CEF-TANI group demonstrated 70.6% composite success rate (microbiologic and clinical success) vs. 58% in the meropenem group (difference, 12.6%; P = 0.009) [24]. At follow-up of 28 to 35 days, CEF-TANI demonstrated higher composite and clinical success rates than meropenem [24]. The frequencies of serious adverse events were similar in the CEF-TANI group (35.5%) and the meropenem group (29.5%) [24]. The most frequent adverse events were headache, gastrointestinal events, and hypertension. In an analysis of the impact of genotypes on the clinical response, the composite success rate for cefepime-resistant *E. coli* was 47.4% (9 out of 19 patients), and for ESBL *E. coli*, it was 52.0% (13 out of 25 patients) for the meropenem group [25]. In contrast, CEF-TANI achieved high composite success rates in patients with resistant *Enterobacterales* [25]. The composite success rate for *CRE* was 87.5% (7/8 patients), while for Enterobacterales carrying a carbapenemase gene, it reached 88.9% (8 out of 9 patients). The distribution of carbapenemase genes consisted of 5 OXA-48-group, 2 KPC-3, and 2 NDM-1 variants, as outlined in the same source [25]. For patients with *Pseudomonas aeruginosa*, CEF-TANI showed a composite success rate of 50.0% (8 out of 16 patients) and a clinical success rate of 81.3% (13 out of 16 patients). In comparison, the rates for meropenem-treated patients with *P. aeruginosa* were 57.1% (4 out of 7 patients) for composite score and 85.7% (6 out of 7 patients) for clinical success rate [25].

Unfortunately, recent studies have shown that escape variants are emerging with resistance to CEF-TANI [26]. Variants such as NDM-9 and NDM-30, exhibit resistance to taniborbactam due to single amino acid substitutions (Glu152Lys). These changes disrupt the electrostatic interactions within the active site loops of MBLs', resulting in ineffective binding of taniborbactam [26]. The emergence of these escape variations highlights the continued difficulty in developing potent inhibitors against MBLs and highlights the necessity of ongoing studies and developments required to successfully combat antimicrobial resistance [27]. The investigation into heteroresistance to CEF-TAN focused on MBL-encoding Enterobacterales isolates sourced from the CDC and FDA Antibiotic Resistance Isolate Bank. Through population analysis profiling, the study revealed a notable prevalence of heteroresistance (85%), surpassing the rates of resistance (12%) and susceptibility (3%) within the examined samples [28].

Sulbactam-Durlobactam

Sulbactam-Durlobactam (SUL-DUR) is a combination antibiotic therapy designed for the treatment of MDR Gram-negative bacteria especially those secreting β-lactamases. SUL-DUR contains a combination of sulbactam, a β-lactamase inhibitor, and durlobactam, a novel broad range β-lactamase inhibitor of class A and some class C enzymes. Durlobactam is a diazabicyclooctane inhibitor and was previously known as ETX2514 and its addition increased the susceptibility of clinical *A. bau-*

mannii isolates to sulbactam in a murine model of infection [29]. *A. baumannii-calcoaceticus* (ABC) is known for its resistance to multiple classes of antibiotics, making treatment of such infections difficult. A phase 3 randomized clinical trial aimed to determine the efficacy and safety of intravenous SUL-DUR (versus a comparator regimen, in treating patients with *A. baumannii-calcoaceticus* complex infection.

The ATTACK study was done at 59 clinical sites in 16 countries and included 181 adults with confirmed carbapenem-resistant *A. baumannii-calcoaceticus* complex. Patients received either SUL-DUR or colistin for 7-14 days and all patients received imipenem-cilastatin [30]. In the overall assessment, SUL-DUR demonstrated non-inferiority to colistin concerning 28-day all-cause mortality (19% vs. 32%, respectively; 95% CI -30·0 to 3·5). Additionally, SUL-DUR exhibited significantly reduced nephrotoxicity (13% vs. 38%; p<0·001) and maintained comparable rates of serious adverse events and treatment-related discontinuations of 11% in the sulbactam-durlobactam group and 16% in the colistin group [30]. In a review article, SUL-DUR has been shown to revert sulbactam-resistant isolates back to susceptibility, enhancing treatment options for infections previously deemed untreatable [31].

Aztreonam-Avibactam

The REJUVENATE study assessed the safety and pharmacokinetics of avibactam-aztreonam (AVI-AZM) in hospitalized adults with cIAI [32]. This combination had an overall clinical cure rates of 58.8% and a microbiological success rate of 60.9% [32]. The most common adverse events were diarrhea (14.7%) and elevated hepatic enzyme (26.5%). The REVISIT Study evaluated the efficacy of this combination in the treatment of cIAI. A total of 282 patients received AVI-AZM with or without metronidazole (MTZ), and 140 patients received meropenem (MER) with or without colistin (COL) [33].

Upon completion of the test-of-cure, AVI-AZM ± MTZ and MER ± COL exhibited favorable microbiological response rates of 75.7% and 73.9%, respectively, indicating comparable efficacy in managing the infections [33]. Among cIAI, the 28-day all-cause mortality rates were 2.9% for MER ± COL and 1.9% for AVI-AZM ± MTZ. Furthermore, for hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP), the mortality rates were reported at 10.8% for AVI-AZM ± MTZ and 19.4% for MER ± COL [33].

Ceftazidime- Avibactam

In a preprint study, ceftazidime-avibactam (CAZ-AVI) had been used in febrile neutropenia in patients with hematopoietic stem cell transplant (HSCT) recipients and patients with acute leukemia as compared to the best available therapy (BAT). A total of 300 patients were included and 143 patients had hematopoietic stem cell transplantation (HSCT) or hematologic neoplasms. Patients treated with CAZ-AVI were more likely to have a microbiologically documented infection in 59% vs. those in the best available therapy arm with a rate of 28.3% [34]. Sepsis emerged as the primary complication in the CAZ-AVI cohort, affecting 59.0% of patients vs. 15% in the best available therapy arm. In a multivariable logistic regression analysis, CAZ-AVI was a significant independent risk factor for mortality (aOR 7.82) and sepsis (aOR 6.33) [34].

For COVID-19 patients with ventilator-associated pneumonia (VAP) and hard-to-treat non-fermenter Gram-negative bacteria, CAZ-AVI had shown promise as a treatment. In a case series of 23 patients, the microbiological eradication rate was 52.3%, and the 30-day mortality rate was 60.8% [35]. In treating nosocomial pneumonia, including VAP, CAZ-AVI showed non-inferiority to meropenem, with clinical cure rates of 68.8% vs. 73% for meropenem [36]. An in vitro study demonstrated that CAZ-AVI displayed high activity rates against resistant strains, with 94.9% susceptibility among Enterobacteriaceae and 60% in *P. aeruginosa* [37]. The use of CAZ-AVI for pediatrics in critical condition showed a 30-day mortality rate of 37.8% and 80% of patients with confirmed carbapenem-resistant infections had microbiological clearance [38].

Cefiderocol

Cefiderocol, a siderophore cephalosporin, binds to extracellular ferric iron to help it enter bacteria more easily and inhibits cell wall synthesis [39]. Cefiderocol was first approved by FDA on November 14, 2019, for treating cUTIs and on September 28, 2020, for HAP and VAP. In clinical trials, such as APEKS-cUTI, APEKS-NP, and CREDIBLE-CR, cefiderocol was non-inferior to imipen-

em/cilastatin and meropenem [40]. However, cefiderocol had a greater all-cause death rate in cases of severe infections, especially those involving Acinetobacter spp. in CREDIBLE-CR trial [40, 41]. In the APEKS-cUTI study, the composite outcome of clinical and microbiological eradication of Gram-negative bacteria was achieved in183 (73%) of 252 patients in the cefiderocol group and 65 (55%) of 119 patients in the imipenem-cilastatin group (treatment difference of 18.58%; 95% CI 8.23-28.92, p = 0.0004) in cUTIs [40, 42].

Plazomicin

Plazomicin, a semisynthetic parenteral aminoglycoside that inhibits bacterial protein synthesis, was utilized in the EPIC trial for cUTI and the CARE trail for serious carbapenem-resistant Enterobacteriaceae (CRE) infections [43].

In the EPIC phase three trial, upon test of cure, plazomicin outperformed meropenem in composite cure rates for cUTI and acute pyelonephritis (81.7% vs 70.1%; 95% Cl 2.7-20.3]) [44].

In the CARE study, 39 patients were randomly assigned, with 18 administered plazomicin and 21 colistin. The microbiologic modified intention-to-treat population included 37 patients with confirmed CRE, out of which 29 had bloodstream infections and 8 had HAP or VAP . The trial primary endpoint was a composite measure of death from any cause within 28 days or significant disease-related complications. The trial was prematurely halted due to slow enrollment, leading to a small sample size that prevented formal hypothesis testing. The primary endpoint event was observed in 4 of 17 patients (24%) treated with plazomicin and in 10 of 20 patients (50%) treated with colistin, with a difference of −26% points (95% CI: −55 to 6) [45].

Lefamulin

The effectiveness and safety of lefamulin, a novel pleuromutilin antibiotic, were assessed in the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and 2 trials for the treatment of community-acquired pneumonia (CAP) vs. moxifloxacin. Early clinical response (ECR) rates were 89.3% for lefamulin versus 93% for moxifloxacin, while investigator assessment of clinical response (IACR) was 83.2% for lefamulin and 86.7% for moxifloxacin [46]. In the evaluation of Lefamulin for therapy of patients with CAP due to atypical pathogens, ECR was 84.4-96.6% and 90.3-96.8% for Lefamulin and moxifloxacin, respectively. In addition, IACR at test of cure was 74.1-89.7% and 74.2-97.1% for lefamulin and moxifloxacin, respectively [47].

Eravacycline

Eravacycline, a novel fluorocycline antibiotic, has shown promising results in the IGNITE 1 and IGNITE 4 studies, which evaluated its effectiveness against MDR bacteria and cIAIs. In the phase 3 IGNITE 4 trial, a prospective randomized, double-blind, double-dummy, multicenter, conducted across multiple countries, eravacycline showed non-inferiority in clinical cure rates compared to meropenem (90.8% vs 91.2%; 95% CI, -6.3 to 5.3) when treating cIAIs, particularly caused by MDR Gram-negative and Gram-positive bacteria. Despite these encouraging outcomes, further studies are needed to assess the efficacy of eravacycline for infections beyond intra-abdominal sources. .In treating cIAIs, the IGNITE 1 trial assessed the safety and efficacy of eravacycline in comparison to ertapenem. Eravacycline showed no discernible inferiority to ertapenem with clinical cure rates of 86.8% and 87.6%, respectively [48]. In a meta-analysis, there were no significant differences in clinical response in the modified ITT (OR, 0.91, 95% CI 0.62-1.35), microbiological ITT (OR, 0.93, 95% CI 0.61-1.41) and clinically evaluable patients (OR, 0.98, 95% CI 0.55-1.75) or in all-cause mortality (OR, 1.18, 95% CI 0.16-8.94) [49]. The two antibiotics were well tolerated; however, eravacycline caused less nausea and diarrhea than conventional tetracyclines [49]. A study included 75 immunocompromised patients, 18% had lower respiratory tract infections and 26% had intra-abdominal infections. Notably, 24% of the patients had bacteremia, with *Enterococci* accounting for 37% and Enterobacterales for 58.7% of cases.

The primary outcome of the study indicated a 30-day survival rate of 81.3%. Furthermore, 90.7% of the patients did not experience infection recurrence within the same period, while 5.3% reported probable drug-related adverse events, primarily gastrointestinal issues (4%) and rash (1%).

The primary outcome of the study indicated a 30-day survival rate of 81.3% [50]. Furthermore, 90.7% of the patients did have infection recurrence within 30 days, while 5.3% had probable drug-related adverse events, primarily gastrointestinal problems (4%) and rash (1%) [50]. The approved

eravacycline dose is 1 mg/kg every 12 hours. The antibiotic is an essential choice for patients with few treatment options because of its broad-spectrum activity, which includes efficacy against CRE [51, 52]. The development of a therapeutic drug monitoring assay has enhanced the ability to track serum levels, ensuring optimal dosing and safety [53]. However, eravacycline does not need renal or hepatic dose adjustment.

Challenges and potential of AI in antibiotic discovery

While innovative approaches, such as artificial intelligence (AI), have been integrated into early-stage antibiotic research, they have not yet resulted in the discovery of new antibiotics [54]. However, the time needed for drug development can be greatly decreased by using AI to quickly evaluate large chemical libraries in order to find possible antibacterial agents [55, 56]. It has been confirmed that machine learning algorithms are more effective than conventional techniques at finding novel antimicrobials, which improves the effectiveness of the drug design process [57]. According to research, machine learning can help detect improper prescription practices and forecast antimicrobial resistance (AMR), thereby enhancing antimicrobial stewardship initiatives [58]. Machine learning algorithms could help antimicrobial stewardship teams with a variety of tasks, including predicting AMR, selecting the best antibiotic therapy, and identifying inappropriate prescribing practices [58]. Although these methods could have potential to accelerate and enhance the research process, tangible breakthroughs in the form of novel antibiotic treatments have yet to emerge. This highlights the complexity of antibiotic discovery and suggests that, while AI and other modern techniques are promising tools, further advancements and refinements are needed before they can fully translate into practical, real-world medical solutions.

CONCLUSIONS

There is a sizable gap in effective therapies when it comes to antibiotic treatment options for high-priority organisms, especially MDR *Pseudomonas aeruginosa* and CRE. Because these pathogens can evade current treatment modalities, there is a significant risk to public health, as there is an increase in morbidity, mortality, and healthcare costs. The pipeline for novel antibiotics is still constrained, despite the urgent need. The fast evolution of resistance mechanisms among these organisms is rendering many traditional antibiotic classes ineffective. The situation is made worse by the sluggish rate at which novel drugs are developed and brought into clinical practice. Because of this, doctors frequently use older antibiotics, which may be less effective and have higher toxicity or side effects. These pathogens have been designated as high priorities for AMR action by the WHO, highlighting the critical need for novel antimicrobial agents. In addition to fighting current infections, effective novel treatments are necessary to stop the possible development of resistance. This involves creating drugs with brand-new modes of action that get around established resistance mechanisms.

The absence of diverse representation in clinical trials could be one drawback of this review and could skew the results in favor of particular settings or demographics. The possibility of the development of AMR quickly, particularly in Gram-negative bacilli is a major limitation. In addition, not all antibiotics have long-term safety and data on all possible side effects. The widespread use of new antibiotics may be restricted by their high cost as well as problems with affordability and accessibility for patients in various healthcare settings and this raises the issue of equity. There is encouraging evidence to support the use of novel antibiotics that target Gram-negative bacteria, providing useful substitutes for treating infections that are resistant to multiple drugs. To prevent the emergence of resistance, their effectiveness must be counterbalanced by suitable antibiotic stewardship programs.

There is an urgent need for improved surveillance, stewardship initiatives, and research into combination therapies that could maximize the use of currently available antibiotics in addition to new drug discovery. To address the AMR crisis and make sure that medical professionals have the resources they need to treat infections brought on by these dangerous pathogens, investment in these areas is essential. In order to stem the flow of antibiotic resistance, new antibiotics targeting high-priority organisms must be developed quickly. Effective treatments must be preserved for future generations, which means that pharmaceutical

companies, researchers, and healthcare policymakers must work together to promote innovation.

Conflict of interest
None to declare

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