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Novel Antibiotic Molecules in Clinical Settings, a Systematic Review

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Abstract: Background/Objectives: The European Medicines Agency (EMA) approved new antimicrobial agents against Gram-negative bacteria, such as cefiderocol, eravacycline, and aztreonam-avibactam, for the treatment of infection with carbapenem-resistant (CR)/carbapenemase-producing microorganisms. However, real-life data regarding their efficacy in clinical settings is still scarce. This systematic review refers to relevant studies aiming to establish whether these novel therapeutic options remain viable alternatives in treating infections caused by highly resistant Gram-negative microorganisms. Methods: To conduct our study, Pubmed, Web of Science, Science Direct, and ClinicalTrials.gov were screened. Studies published between the validation report provided by EMA for each molecule and 15 September 2024 were selected and then assessed based on their reference to patient clinical outcomes. The main inclusion criteria were first-hand results of their clinical experience with the molecules, treatment regimens, and clinical and microbiological outcomes (mortality, cure rates, and recurrence). Exclusion criteria included the absence of clinical data, studies not belonging to the specified time frame, and others. Results: Most studies using eravacycline and cefiderocol demonstrated at least non-inferiority regarding their clinical efficacy compared to the best-available therapy. Studies have yet to emerge on the aztreonam-avibactam combination. Conclusions: Eravacycline and cefiderocol present promising results, offering similar or superior results to the already available antibiotic options. They create new possibilities for treating patients with highly resistant Gram-negative microorganisms. More studies are required to draw definite conclusions. Nonetheless, the new molecules offer hope for an otherwise grim future.

Keywords: cefiderocol; eravacycline; antibiotic resistance; EUCAST; CLSI; FDA

1. Introduction

Antimicrobial resistance (AMR) is a global, ongoing crisis caused by the emergence of illness-producing pathogens that can withstand the effects of antimicrobials. In 2019, approximately 1.27 million deaths were directly attributed to AMR, with another 4.95 million deaths having this threat as an indirect contributor. Research into developing new antimicrobials, employing surveillance programs for AMR pathogens, and raising awareness concerning antimicrobial misuse are paramount to combating this threat and reducing the burden it produces on public health systems globally [1].

One of the more clinically relevant examples of acquired resistance is the recent surge in bacterial resistance to last-resort antimicrobials such as carbapenems; this resistance is often represented by the appearance of

carbapenemase-producing carbapenem-resistant (CP-CR) and non-carbapenemase-producing carbapenem-resistant (NCP-CR) bacteria [2–4]. CP-CR and NCP-CR resistance mechanisms are most commonly found in Gram-negative bacteria, with members of the Enterobacterales order, such as *Klebsiella pneumoniae,* and non-fermenter Gram-negative bacilli such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* representing species found in clinical settings which exhibit these resistance mechanisms [1–5].

The phenomenon follows a concerning trend, with associations between multiple types of resistance mechanisms narrowing the list of potential treatment options. Strains producing more than one type of carbapenemase, such as Ambler class B and D enzymes, are typically resistant to most conventional agents, thus being extended-drug resistant (XDR) or, at points, even pan-drug resistant (PDR) [6,7].

Several novel antibiotics have been made available to combat the emerging threat of MDR pathogens. Of these, cefiderocol (Fetcroja), eravacycline (Xerava), and the association of aztreonam and avibactam (Emblaveo) are some of the most recent therapeutic options, which have been approved for use by the European Medicines Agency (EMA) [8–10].

Eravacycline (ERV) is a fully synthetic tetracycline manufactured to maintain its antimicrobial activity even past resistance mechanisms that would inhibit other tetracyclines (i.e., efflux pumps) [11]. It was approved for use by the EMA in September 2018, mainly for treating complicated intra-abdominal infections with drug-resistant Gram-negatives; however, its activity beyond that against multidrug-resistant (MDR) *Escherichia coli* and streptococci strains is not well documented [8,11].

Cefiderocol (FDC, formerly known as S-649266) is a siderophore cephalosporin with promising in vitro activity against carbapenem-resistant Gram-negative bacteria (CR-GNB) [12,13]. It shares some similarities with ceftazidime and cefepime, with the added ability of iron chelation. This binding to ferric iron allows it to enter the bacterial cell through its active iron transport system and its ability, like other cephalosporins, to enter through porin channels [12]. It is reported as being generally well-tolerated; however, this data was based on limited clinical trials before the EMA's approval for use in April 2020 [9,13].

Aztreonam-avibactam (AZA) is a novel combination of aztreonam, a beta-lactam that is not hydrolyzed by metallo-beta-lactamases (MBLs), and avibactam, a diazabicyclooctane beta-lactamase inhibitor [14–16]. Even though aztreonam on its own is a viable treatment option for isolates with MBLs, most difficult-to-treat bacteria are capable of producing several beta-lactamases with varied spectra of activity; the addition of avibactam can provide the required protection against non-MBL beta-lactamases to ensure that aztreonam achieves its antimicrobial effect. Other beta-lactamase inhibitors can also be associated with aztreonam; however, the aztreonam-avibactam association seems to be the most promising [15,16]. Aztreonam-avibactam is one of the most recent therapeutic options made available against difficult to treat Gram-negative isolates, and it was approved for use by the EMA in April 2024 [10].

This systematic review aims to evaluate data from clinical trials and real-world evidence on cefiderocol, eravacycline, and aztreonam-avibactam from their EMA approval until 15 September 2024 and establish whether these novel therapeutic options remain viable alternatives in the treatment of infections caused by highly resistant Gram-negative microorganisms.

2. Materials and Methods

2.1. Search Strategy and Sources

To conduct our study, Pubmed, ScienceDirect, Web of Science, and Clinicaltrials.gov were screened using a series of keywords and boolean operators adapted for each molecule. For Clinicaltrials.gov, the time frame associated with the name of each molecule was the only criterion applied to our study.

The recommendation of use for each molecule and their intended use in the context of Gram-negative microorganisms, specifically Enterobacterales and non-fermenters Gram-negative bacilli, determined our methodology to include the following keywords "Carbapenem-Resistant", "Drug Resistance, Bacterial", "Multidrug-Resistant Organisms", "Carbapenemase-producer", "Extended-drug resistance", "Panresistance". Besides the name of each molecule, specific keywords were employed to find all studies, including first-hand clinical experiences with the molecule. Following this approach, keywords specific to in vivo results were selected, including: "Clinical", "Treatment outcome", "Mortality", "Morbidity", "Recurrence", and "Patient". Considering the scope of our paper, reviews and meta-analyses were not included in our results. The keywords were used in association with boolean operators and following different approaches specific to each particular database.

Studies and trials published between the validation report provided by EMA for each molecule (e.g., eravacycline—20 September 2018; cefiderocol—23 April 2020; aztreonam-avibactam—22 April 2024) and 15

September 2024 were selected based on their title and abstract. Papers and trials were then assessed to establish their eligibility through full-text analysis.

A thorough overview of the strategy employed for each database can be found in Supplementary Table S1.

2.2. Eligibility Criteria

For a study to be considered eligible to be included in the review, it had to include (1) first-hand clinical experience with the novel molecules, (2) a description of the cohort (i.e., median age, clinical diagnosis, comorbidities, severity of infection; isolated microorganism to be either Enterobacterales or non-fermenter Gram-negative bacilli; and treatment-regimens), (3) an overview of the evolution under treatment (i.e., clinical cure and microbiological cure; mortality; if available, recurrence and readmission; and side-effects).

Reasons for exclusion included: (1) the study did not include first-hand clinical experience (i.e., reviews, meta-analyses, in vitro studies), (2) the novel antibiotic was not explicitly used in the study or data regarding the results of treatment with the molecules were not available in the text, (3) the strains treated were not *Enterobacteriaceae* or Gram-negative non-fermenters, (4) the study was not pertaining the human treatment, (5) the study was not published in the specified time-frame, and (6) study was not published in English.

2.3. Data Items

Data extracted from eligible articles: (1) the identified pathogens, (2) control therapy or best available therapy, if available, (3) the country the study took place, (4) clinical diagnosis of the patients included in the study, (5) in vitro susceptibility to the novel molecule used, (6) details regarding resistance mechanisms related to each strain, if available, (7) the number of patients included in the study, (8) the mean age of the cohort, (9) severity of infection as defined using specific scales of assessment (i.e., SOFA score, APACHE score, CCI score, and others, if available), (10) comorbid conditions in the cohort, (11) previous treatment and if the treatment failed, (12) treatment regimens and dosage, (13) duration of treatment, (14) clinical outcomes and microbiological outcomes (i.e., cure, mortality, recurrence, and readmission), (15) follow-up period, and (16) possible adverse events.

3. Results

3.1. General Considerations

Figures 1–3, showing each molecule's PRISMA flowcharts [17]. Supplementary Table S1 provides additional information regarding our methodology, including the search strategy used.

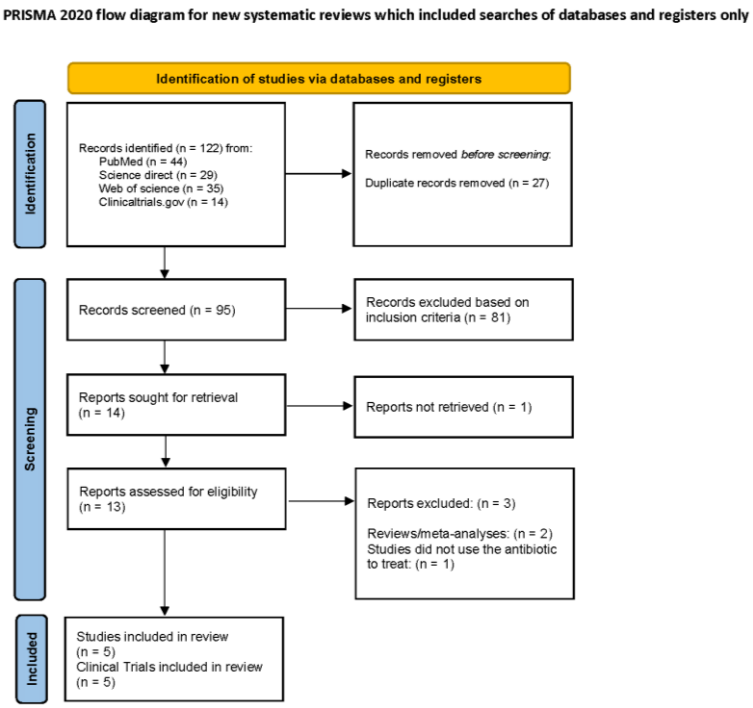

Figure 1. PRISMA 2020 flow diagram for Eravacycline.

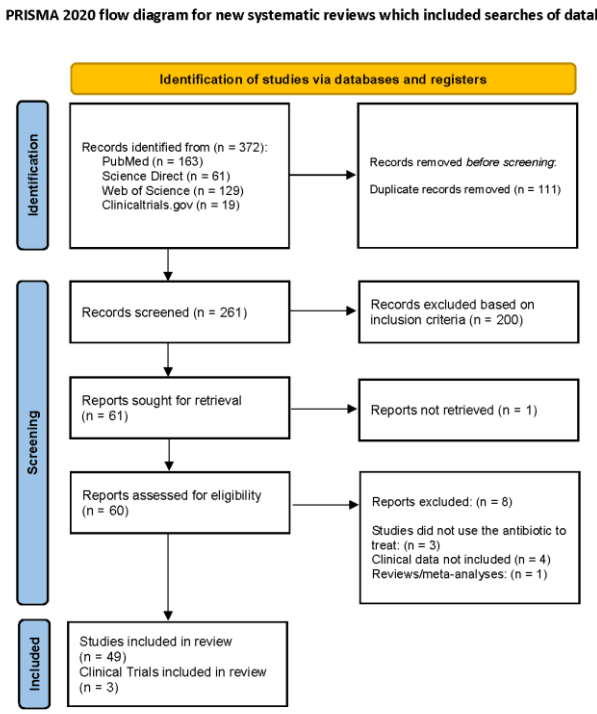

Figure 2. PRISMA 2020 flow diagram for Cefiderocol.

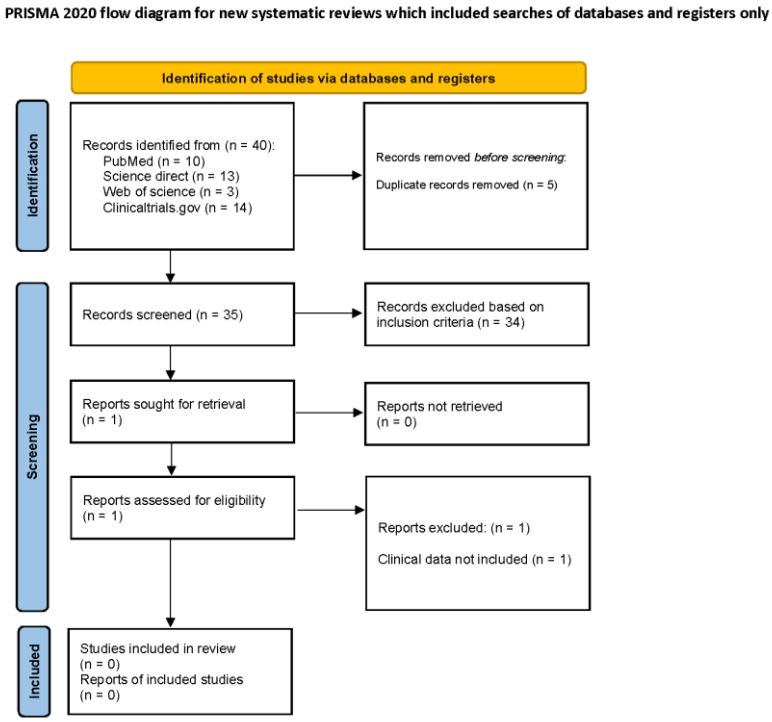

Figure 3. PRISMA 2020 flow diagram for Aztreonam-avibactam.

3.1.1. Eravacycline

A total number of 122 papers were identified from Pubmed (n = 44), ScienceDirect (n = 29), Web of Science (n = 35), and Clinicaltrials.gov (n = 14). After removing duplicates (n = 27), 95 were screened following our inclusion criteria. Eighty-one manuscripts (n = 81) did not meet the inclusion criteria. One could not be retrieved from the remaining manuscripts (n = 14). Following full-text analysis (n = 13), three reports were excluded, two reviews, and one study did not use the antibiotic for treatment. Ten manuscripts (n = 10) were included in our analysis, five research papers [18–22], and five clinical trials [23–27].

A flow diagram following the PRISMA guidelines for systematic reviews following the process is available in Figure 1 [17].

3.1.2. Cefiderocol

A total number of 372 papers were identified from Pubmed (n = 163), ScienceDirect (n = 61), Web of Science (n = 129), and Clinicaltrials.gov (n = 19). After removing duplicates (n = 111), 261 were screened following our inclusion criteria. Two hundred manuscripts (n = 200) did not meet the inclusion criteria. One could not be retrieved from the remaining manuscripts (n = 61). Following full-text analysis (n = 60), eight reports were excluded, three studies that did not use the antibiotic for treatment, four that did not include clinical data in their paper, and one review. Fifty-two manuscripts (n = 52) were included in our analysis, forty-nine research papers [28–76], and three clinical trials [77–79].

A flow diagram following the PRISMA guidelines for systematic reviews following the process is available in Figure 2 [17].

3.1.3. Aztreonam-Avibactam

A total number of 40 papers were identified from Pubmed (n = 10), ScienceDirect (n = 13), Web of Science (n = 3), and Clinicaltrials.gov (n = 14). After removing duplicates (n = 5), 35 were screened following our inclusion criteria. Thirty-four manuscripts (n = 34) did not meet the inclusion criteria. Following full-text analysis, the last study (n = 1) did not offer clinical data and was excluded from our research. No manuscripts were included in our analysis.

A flow diagram following the PRISMA guidelines for systematic reviews following the process is available in Figure 3 [17].

3.2. Clinical Efficacy

3.2.1. Eravacycline

Out of the ten studies included in this review, two offered information strictly regarding the use of Eravacycline [19,22], while eight studies detailed its performance in comparison or association with other treatment measures, most notably therapy with carbapenems (ertapenem [24–26], meropenem [18,23], or both [21]), levofloxacin [26,27] and colistin [20]. One study [21] is also a pooled analysis of two clinical trials [23,24], while another study [18] is a detailed interpretation of the results of one of the trials mentioned above. Nonetheless, the conclusions of the two studies were considered when writing this review. Thus, the patients described therein were not added to the total number of patients, as they refer to the same patients as those described in the clinical trials.

Generally, only two dosages were used: 1 mg/kg eravacycline administered intravenously every 12 h [18–25] or 1.5 mg/kg eravacycline administered intravenously every 24 h [22,25–27]. In some cases, doses were also rounded up or down to produce an exact overall quantity [19]. Treatment duration varied between studies and within studies, though most had a mean at around or below 10 days [19,20,22,26,27], and all studies had a mean treatment duration of at most 14 days.

Although eravacycline use is explicitly defined as being intended only for complicated intraabdominal infections (cIAI), two clinical trials also investigated the molecule's effectiveness in the treatment of complicated urinary tract infections (cUTI) [26,27]. One study [19] focused on the efficacy of eravacycline in regards to *A. baumannii* strains rather than based on infection site, which meant that their patients were from a more diverse range of pathologies, including pneumonia, skin, and soft tissue infections, as well as bone and joint infections. Another study [20] compared the use of eravacycline in burn injuries with the use of colistin in historical cohorts.

In studies investigating patients with cIAI treated with eravacycline, out of a total of 923 patients, clinical success was achieved for 768 patients (83.20%), clinical failure was considered for 129 patients (13.98%), and the remaining 26 (2.82%) had an indeterminate response. The end-of-study mortality was 29 patients.

In studies investigating patients with cUTI treated with eravacycline, out of a total of 901 patients, clinical success was achieved for 727 patients (80.69%), clinical failure was considered for 131 patients (14.54%), and the remaining 43 (4.77%) had an indeterminate response. The end-of-study mortality was four patients.

In the study investigating the use of eravacycline in patients with burn injuries, seven patients (63.63%) out of 11 had favorable outcomes.

In the case of the study investigating the effect of eravacycline on carbapenem-resistant and carbapenem susceptible *A. baumannii* strains, out of 46 patients, microbiological eradication was achieved for ten patients

(21.74%). In comparison, clinical failure was considered for 13 patients (28.30%). End-of-study mortality was 14, 10 infected with carbapenem-resistant *A. baumannii*.

One study [18] noted that, regarding cIAI infections, the likely cause for clinical failure was a combination of several factors, such as unplanned surgical or drainage procedures, initiation of rescue antibacterial therapy, or persistence of clinical symptoms, potentially associated with an underlying condition. It could also be the case that the cause for clinical failure in other studies may be similar.

Regarding resistance mechanisms, the most common pathogens found across all studies were *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *E. coli*, and *Enterobacter cloacae/asburiae*. Of these pathogens, *A. baumannii* and *K. pneumoniae* isolates were also found with carbapenem resistance, though the mechanisms were not described.

3.2.2. Cefiderocol

Among the 52 studies included, 34 were conducted without a comparator variable [28,32,34–37,39,40,43,45,47,54,56–76,79], while the other 18 used different antibiotics, alone and in association, to evaluate the clinical efficacy of cefiderocol. Colistin [29–31,38,41,42,44,48–53,55], other beta-lactam antibiotics, including meropenem [31,44,48–50,53,77], ampicillin-sulbactam [38,42,48,50–53], ceftazidime-avibactam ± aztreonam [31,44,46], piperacillin-tazobactam [31,42,44], fosfomycin [31,48–50,52,53], tigecycline [31,41,48–50,53] were the most commonly best available options used to perform the evaluation.

To evaluate the susceptibility of the antibiotic, 29 studies utilized the recommendations issued by EUCAST [30–32,34–36,38,41,43,45,46,48–52,54–56,58,59,61–63,67,71–73,76], 14 studies those issued by Clinical & Laboratory Standards Institute (CLSI) [28–30,33,36,37,45,57,60,65,66,68,70,75], and 5 FDA [30,36,37,40,68]. Some studies followed the recommendations of more than one institution to confirm the susceptibility of cefiderocol [30,36,37,45,68], while others did not include in their manuscript the method used for interpretation [39,42,44,47,53,64,69,74,77–79].

Most studies utilized the standard dosage of administration, 2 g every 8 h infused over 3 h. Dosage adjustments depended on kidney function [28,30,31,37,39,41,43,44,46–51,58–63,65,66,69–71,73–76,79]. Considering the molecule's novelty, data on antibiotic use in pediatric populations is scarce. Nonetheless, a loading dose of 60 mg/kg, then 40 mg/kg every 8 h infused over 3–4 h, has been proven effective in a preterm neonate infected with a VIM-producing *P. aeruginosa* strain [63]. Similar results were obtained in the case of a 10-year-old child with cystic fibrosis, infected with *Achromobacter* spp. However, the loading dose was maintained for the whole course of treatment, and the regime included cefiderocol, meropenem/vaborbactam, and an IV bacteriophage (Ax2CJ45ϕ2) [69].

The mean duration of treatment was typically between 7 and 14 days. However, some studies reported longer courses of treatment [37,41,43,59,64,68,75], some reaching over 50 days to achieve a clinical cure [59,64].

Unlike eravacycline, the heterogeneity of available data made the evaluation of patients' outcomes difficult to separate among studies based on the localization of the infection. However, the most common types of infection treated with cefiderocol were pneumonia (most notably ventilator-associated, hospital-acquired, or healthcare-associated) and bloodstream infections.

Out of a total of 1990 patients from all of the studies on cefiderocol use included in this review, 1118 achieved clinical success, 362 were considered clinical failures (or equivalent thereof), and 510 had an indeterminate result. The total end-of-study mortality was 643. It is important to note that this evaluation did not consider the intricacies and conditions associated with each study. Clinical success or failure should be read as a pooled prevalence of outcomes rather than an assessment that accounts for confounding factors and other statistically relevant factors.

Among the facets contributing to cefiderocol resistance, several clinical and microbiological factors have been identified. The rate of microbiological failure seems to be higher in monotherapeutic courses of treatment through the selection of highly resistant mutants. In one instance, when comparing the patients' outcomes after infections with CR-*A. baumannii*, 42.9% of patients receiving monotherapy experienced microbiological failure, while those receiving combination therapy experienced the same phenomenon in 6.3% of cases [30]. However, other studies could not come to the same conclusion, with no significant difference being identified between the cohorts of CR-*A. baumannii* or CR-*P. aeruginosa* treated with cefiderocol alone or in combination [33]. Similar conclusions were also observed in other studies, not strictly referring to Gram-negative non-fermenters [54,73].

Disruptions of the *piuA* (a *TonB*-dependent siderophore receptor gene) and *pirA* (a ferric enterobactin gene) were in cefiderocol-resistant strains [47,50,57]. For Enterobacterales, mutations of the *cirA* gene, which encodes a catecholate siderophore receptor, could also contribute towards resistance. Other alterations, such as efflux pump activity, porin mutations, and permeability, could also be associated with a rise in MIC [48–50].

Structural alteration on PBP3, the primary target for cefiderocol, could also alter susceptibility. The A515 substitution was identified as one possible mutation contributing to a rise in cefiderocol MIC [70].

The presence of NDM-class enzymes was associated with a higher cefiderocol resistance rate, reaching levels as high as 66.8% out of 343 Enterobacterales strains [31]. A similar trend could be observed in another study where 40% of 52 NDM-producing *K. pneumoniae* were resistant to cefiderocol [31].

For CR-*A. baumannii*, a novel substitution (R148Q) in ADC-73, an AmpC class enzyme, was associated with cefiderocol resistance after two courses of treatment [47]. For *P. aeruginosa*, one study identified PDC-392 and PDC-394, two AmpC class enzymes, that could contribute towards a rise in MIC, with two strains acquiring resistance throughout treatment [46]. The same study reported that continuous cefiderocol infusion could hinder the emergence of resistance, using this strategy for two patients and achieving clinical cure in the studied cohort. The implications are even more relevant, considering that this approach yielded success for cases of meningitis and bone and joint infections.

Adverse effects seem rare and tend to be mild when present. However, instances of acute interstitial nephritis, thrombocytopenia, alteration of liver function, allergic reactions, and infections with *C. difficille* could be identified [31,34,37]. Acute kidney injury was associated with the use of cefiderocol in some cases, although at lower rates compared to colistin [34,55].

4. Discussion

4.1. Susceptibility and Resistance Breakpoints

Before use in clinical settings, studies following the in vitro susceptibility of the new molecules among the main CP-GNB (KPC, NDM, and OXA-48-like producing Enterobacterales, CR-*P. aeruginosa*, CR-*A. baumannii*, and *Stenotrophomonas maltophilia*) found FDC to be a potential option for treatment, having an anticipated susceptibility rate of more than 80% [80]. Regarding ERV and AZA, anticipated susceptibility was similar, except for the situations involving non-fermenters. ERV anticipated susceptibility was lower than 30% for CR-*Pseudomonas aeruginosa*, while for AZA, it was expected to be between 80-30% in the case of CR-*P. aeruginosa* and less than 30% for CR-*A.baumannii* [80].

In reality, clinical data regarding the efficacy of cefiderocol is still scarce, especially data that can be correlated with a comprehensive characterization of the strains that were treated with the aforementioned molecule [18,21,28,29,31,32,36,37,40,41,43–50,54–58,63,65–67,70–73,75–78,81–84]. The results seem variable, thus enforcing the need for further research.

One of the most concerning perspectives concerning FDC is the difference among recommendations in assessing susceptibility. EUCAST [85], CLSI [86], and CA-SFM [87] all have different intervals that evaluate the susceptibility for FDC; thus, results can significantly vary depending on the standard used for interpretation. This hypothesis has already been approached and confirmed in at least two studies in 2023 [37,88] and one in 2024 [45], establishing a basis for investigating if strains already tested are truly susceptible to cefiderocol. Even with updates regarding the recommendations, the issue can be considered unchanged as of the publication date of this paper. However, representatives of the institutions mentioned above have identified the problem and, alongside *Shionogi* et al., focus on determining the best susceptibility testing method concerning FDC [89]. In our opinion, this is the most troubling finding, as a lack of coherency between EUCAST, CLSI, and CA-SFM can cause confusion in interpretation and lead to incorrect results and improper patient care. This is especially the case for patients whose samples are interpreted in multiple laboratories using differing interpretation standards.

Also of note, susceptibility for eravacycline has repeatedly been noted as difficult to quantify, with thresholds having been defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and U.S. Food and Drug Administration (FDA) as 0.5 mg/L, but only for *E. coli* by EUCAST [90], and only for a restricted number of species by the FDA, respectively [91]. To overcome this, one study presumed that all the bacterial pathogens involved in their analysis were to be considered susceptible [18]. Other studies based their assumption on in vitro studies for MIC_{90} for carbapenem-susceptible and carbapenem-resistant *Acinetobacter baumannii* strains [19] and aerobe Gram-negative bacteria [21].

4.2. Resistance Mechanisms

A frugal landscape has been described addressing what resistance mechanisms could hinder these molecules' effectiveness given the short time period of exposure to clinical strains; the issue of how germs will adapt comes into question. Thus, in order to fully understand the way in which these novel molecules can be used, more studies need to be conducted.

Several β-lactamases have been identified to contribute towards resistance to cefiderocol:

- NDM-producing strains, i.e., NDM-1,-5, -7, and -9, have been shown to reduce susceptibility to FDC, both in vitro [92–95] and in vivo [28,31,32,36,37,40,43,45,46,48,50,54,56,58,65,67,71,73,76,96,97], with as much as 55% of cohorts being non-susceptible to the molecule.
- Variants of KPC, i.e., KPC-31, -41, and -50, affect the susceptibility of other molecules, such as ceftazidime/avibactam, and are also involved in FDC-reduced susceptibility [94,98–100].
- ESBLs that show activity against FDC include PER class (i.e., PER-1,-2, -6, -7) [95,98,101,102] and SHV class enzymes (i.e., SHV-2, -12) [95,101]. Other enzymes raised the MIC but did not alter the overall susceptibility of the molecule [92].
- OXA-427, a novel carbapenemase identified in *Enterobacteriaceae* [103,104], could also determine lower FDC susceptibility [105].
- Other class B carbapenemases contributed to a rise in MIC for FDC SPM-1, VIM-2, AIM-1, and GIM-1, but data was insufficient to conclude [92,98].

Considering that FDC acts as a "Trojan horse", entering the periplasmic space rather than directly binding to the cell wall, similar to other beta-lactam antibiotics, and then binding to PBP-3, mutations affecting either permeability or efflux contribute to resistance [98].

On the topic of siderophore receptors, studies tend to agree that in Enterobacterales, mutations usually occur in the *cirA* gene, which codifies an iron transporter [84,92,100,106–111], some authors reported similar findings in *S. maltophilia* [112]. In the case of *Pseudomonas* spp. and *Acinetobacter* spp. reduced susceptibility was identified in strains presenting either deficiency or deletion of *piuA* (*P. aeruginosa* and *A. baumannii*), *piuD* (*P. aeruginosa*), or/and *pirA* (*P. aeruginosa* and *A. baumannii*) [113–120]. Other receptors identified that could potentially be confirmed as contributors towards resistance could be *fecI, fiu, fhuA, fepA, tonB* (in *S. maltophilia*), and others [92].

Porins involved in reducing the susceptibility of FDC through mutations, disruption truncation, and/or deletion consist of *ompK35*, *ompK36*, and *ompK37* for *K. pneumoniae* [94,114,121,122] and *oprD* for *P. aeruginosa* [114,123]. Data is still scarce in the case of other Enterobacterales, *A. baumannii*, and *S. maltophilia*. The rise in MIC values is not necessarily significant, even if, on occasion, it could amount to a 4-fold increase (ex. 0,031 to 0.125 mg/L) [114]. However, in some instances, a more significant increase could be identified (ex., 0.25 to 4 mg/L) [123].

Other irregularities associated with cefiderocol resistance include mutations on PBP-3 [84,92,109,124,125] and mutations of *baeS,* part of a 2-component regulation system [92,122,126].

In Enterobacterales, some studies attribute resistance to eravacycline to multiple mutations throughout the *lon* gene [127,128]. The gene is responsible for producing an ATP-dependent protease, which is involved in biofilm formation, motility, and stress responses. The paper published by Xu et al. [127] assessed that a rise in MIC for ERV in *Klebsiella pneumoniae* strains correlated with mutations in different gene regions. However, another critical aspect observed was collateral sensitivity to several other molecules (i.e., aztreonam/avibactam and ceftazidime/avibactam). These results were reproducible in vitro and in vivo in a mouse cutaneous abscess model.

Zhang et al. identified mutations within the *vgrG* gene [129]. The direct correlation with ERV resistance is not fully elucidated.

Studies show that the upregulation of the AcrA-AcrB-TolC multidrug efflux system, known for its ability to eliminate antibiotics, including tetracycline and its derivatives, can reduce susceptibility [127,130–132]. However, other studies tend not to agree with this line of thought. The strains analyzed by Zhang et al. observed similar expression levels of efflux components among the studied strains [129].

On the contrary, upregulation of the outer membrane proteins OmpA and OmpU increases the membrane's permeability, thus partially explaining a higher influx of AZA and CZA and higher sensitivity towards these molecules [127].

The acquisition of heteroresistance [46,57,71,129,133,134] represents one of the critical aspects regarding all studied molecules. Bacterial subpopulations developed from a parental strain can develop different levels of resistance towards eravacycline, thus enforcing the hypothesis that inefficient testing can lead to treatment failure by selecting highly resistant individuals [135,136]. Therefore, monotherapy could sometimes prove inefficient, while combination therapy could lead to better bactericidal activity (ex. ERV and polymyxin B) [129,137]. Like other instances, heteroresistance is not always stable and can be lost without selective antibiotic pressure [129,136,138]. For FDC, heteroresistance follows a similar trend; thus, combination therapy with molecules such as meropenem, fosfomycin, colistin, and others could improve the therapeutic outcome [46,57,71].

Albeit *Proteus* spp. are commonly known to be inherently less susceptible to the action of tetracyclines and their derivates [139], a study conducted by Chen et al. [140] identified a susceptibility rate of over 60% when ERV was tested. Similar results were observed for *Morganella* spp., the percentage of susceptibility being 58% [140].

Previous studies confirmed the inefficacy of ERV for *Pseudomonas* spp. [80,141].

4.3. Limitations of the Study

To correctly and safely identify what could interfere with the activity of the novel molecules, a thorough characterization of the strains isolated from patients should be performed. Several studies classified strains only as "carbapenem-resistant" without any other information, thus limiting the conclusions that could be drawn. Other authors characterized the genetic background but have not found significant correlations.

The difference between interpretation standards allows for high heterogeneity of results, thus raising questions regarding the validity of said data. The CLSI evaluation, especially through disk diffusion, provides more false-susceptible results, partly explaining the higher failure rate in some studies. On the other hand, the EUCAST guidelines could allow more false-resistant results. Until these intervals are better defined, depending on the standard used for interpretation, the prevalence of non-susceptible isolates should be cautiously approached.

The lack of data on aztreonam-avibactam is another limitation. Though a promising alternative, this antimicrobial agent has been made available for far too short of an amount of time for proper clinical setting studies to be performed. As such, more data is required in order to determine whether or not aztreonam-avibactam is a suitable alternative to current molecules used in treatment.

5. Conclusions

Novel antibiotic molecules fill a need in the current landscape of antimicrobial resistance. The concerning trend of extended/pan-resistant strains raises concerns throughout the medical field, pushing researchers and medical professionals towards new molecules or new associations among existing molecules.

Eravacycline and cefiderocol present promising results, offering similar or superior results to the already available options, creating new possibilities for patient treatment. However, as we adapt, microorganisms adapt as well, thus enforcing the need for caution in using these last-resort molecules. These antibiotics proved to be efficient, however, the question of longevity remains, one which can only be prolonged through the practice of antimicrobial stewardship and through adequate use based on accurate scientific data.

Aztreonam-avibactam, although efficient in laboratory conditions, has not yielded any real-life experience results. Considering the approval as of April 2024, the global availability of said antibiotic can partly explain the absence of available data. Until the molecule becomes widely available, in vitro evaluation and substituents (i.e., ceftazidime-avibactam + aztreonam) remain usable options, especially for strains exhibiting extended antibiotic resistance or even pan-resistant phenotypes.

More studies are required to draw definite conclusions, nonetheless, the new molecules offer hope for an otherwise grim future.

Supplementary Materials

The additional data and information can be downloaded at: https://media.sciltp.com/articles/others/2505261536526506/JMHD-686-Supplementary-2.xlsx.

Author Contributions

H.O.M., M.A.A., P.M.I.: conceptualization, methodology; H.O.M., C.B.F.: data curation, writing—original draft preparation; H.O.M., C.B.F., C.E.C., D.C., P.D.M.: investigation; M.A.A., P.M.I.: supervision; H.O.M., C.B.F., M.A.A., P.M.I.: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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The authors confirm that the data supporting the findings of this study are available within the article [and/or its supplementary materials].

Conflicts of Interest

The authors declare no conflict of interest.

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