

Review

Novel Antimicrobial Agents for Gram-Negative Pathogens

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Abstract: Gram-negative bacterial resistance to antimicrobials has had an exponential increase at a global level during the last decades and represent an everyday challenge, especially for the hospital practice of our era. Concerted efforts from the researchers and the industry have recently provided several novel promising antimicrobials, resilient to various bacterial resistance mechanisms. There are new antimicrobials that became commercially available during the last five years, namely, cefiderocol, imipenem-cilastatin-relebactam, eravacycline, omadacycline, and plazomicin. Furthermore, other agents are in advanced development, having reached phase 3 clinical trials, namely, aztreonam-avibactam, cefepime-enmetazobactam, cefepime-taniborbactam, cefepime-zidebactam, sulopenem, tebipenem, and benapenem. In this present review, we critically discuss the characteristics of the above-mentioned antimicrobials, their pharmacokinetic/pharmacodynamic properties and the current clinical data.

Keywords: Gram-negative; beta-lactamase; carbapenemases; *Acinetobacter baumannii*; *Enterobacterales*; *Pseudomonas aeruginosa*; pharmacokinetics; pharmacodynamics



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1. Introduction

The spread of multidrug-, extensively drug- and pan drug-resistant Gram-negative bacteria (GNB) in various settings around the world has threatened modern medical practice [1]. The present scarcity of antimicrobial options often makes infections harder to treat. GNB represent four of the six most common pathogens responsible for antimicrobial resistance (AMR) associated mortality (almost a million deaths were attributable to AMR in 2019) [2]. *Enterobacterales* (such as *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus* spp., *Morganella* spp., and *Providencia* spp.) and lactose non-fermenting GNB (such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*) can produce a wide array of beta-lactamases or enzymes that inactivate many beta-lactam antimicrobials [3]. Beta-lactamases are divided into four classes, A to D: classes A, C, D are serine-based enzymes that inactivate the antimicrobial in two steps, while class B, metallo-beta-lactamases (MBL), employ a metal ion, such as Zn²⁺, for a single step drug hydrolysis [4]. Some of the enzymes can inactivate carbapenems and are called carbapenemases.

Many class A carbapenemases are of the *Klebsiella pneumoniae* carbapenemase (KPC) type; this type contains the globally widespread KPC-2 and KPC-3, with resistome amenable to treatment with modern antimicrobials, such as ceftazidime-avibactam (CAZ/AVI). However, there are less commonly encountered KPC-variants with less favorable susceptibility phenotypes and more challenging treatment choices [5]. Moreover, even KPC-2 and KPC-3

can develop mutations during treatment with diverse mechanisms comprising altered KPCs and non-beta-lactamase resistance mechanisms [6,7]. The members of this class of carbapenemases are numerous and expanding [3].

Metallo-beta-lactamases (MBL) can be either plasmid- or chromosomally encoded. Similar to the serine lactamases, they have been disseminated globally and are the most common class in Asia [8]. Notable class members are the active-on-imipenem (IMP), Verona integron-mediated (VIM), and New Delhi metallo-beta-lactamase (NDM) types of enzymes.

Class D enzymes of the oxacillinase (OXA) type (OXA-23, for example) are associated with *Acinetobacter baumannii* resistance, while OXA-48 are associated with that of *Enterobacteriales* resistance [3]. A recent study of *A. baumannii*-related carbapenem-resistance (CR) describes that the addition of novel extrinsic OXA-23 activity to intrinsic oxacillinase OXA-51-like enzyme led to higher minimal inhibitory concentrations (MIC) against imipenem and other beta-lactams, aminoglycosides, and polymyxins [9]. OXA-48-associated resistance is amenable to treatment with CAZ/AVI as avibactam can restore ceftazidime's antimicrobial activity, while many newly launched beta-lactamase inhibitors, such as vaborbactam and relebactam, cannot reinstall beta-lactam action [10].

Regarding the CR phenotypes, USA data have shown that among 450 carbapenem non-susceptible *Enterobacteriales* isolates, a third were non-carbapenemase producers (NCP). The majority of the remaining isolates produced KPC and a few produced MBL enzymes. All the antimicrobials tested showed limited anti-MBL action. However, the respective antimicrobial activity of meropenem/vaborbactam (MER/VARB) and imipenem/cilastatin/relebactam (IMI/CILA/RELE) against NCP exceeded 90% [11]. The significance of the above varies in different geographical regions. Although CR is present globally, the regional differences preclude meaningful clinical comparisons between countries [12]. In addition to the beta-lactamases, many GNB present additional inactivating enzymes to other antimicrobial classes, such as the aminoglycoside-modifying enzymes [13]. Nonetheless, monitoring of resistance through novel microbiological tools, such as whole genome sequencing, may allow better tracking of resistance at a local scale and the discovery of novel resistant traits [14].

Researchers and the industry responded to the challenge by launching novel drugs that are resilient to various resistance mechanisms [15–21]. Moreover, applying knowledge of the pharmacokinetic/pharmacodynamic (pK/pD) characteristics may optimize antimicrobial drug exposure, leading to maximal therapeutic outcomes. In particular, the treating physicians must modify dosing regimens according to the estimated renal clearance. Dose reduction for all, for example, following the commencement of renal replacement therapy, may result in suboptimal therapeutic levels for many patients [22]. On the contrary, total daily dosing must increase whenever there is augmented renal clearance of the administered antimicrobials [23–25]. All the drugs covered in this review, except for eravacycline and omadacycline, are hydrophilic, present a low volume of distribution and protein binding, and are renally cleared [26].

Leading organizations have recently issued recommendations for treating infections associated with difficult-to-treat Gram-negative pathogens. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) strongly recommends monotherapy for the susceptible microorganism, usually KPC, with either CAZ/AVI or MER/VARB. The Infectious Diseases Society of America (IDSA) recommends monotherapy for KPC infections with either one of the two drugs mentioned above or IMI/CILA/RELE. In the case of MBL-*Enterobacteriales*, ESCMID suggests cefiderocol (CEFID) or a combination of two active drugs, as aztreonam-avibactam is currently unavailable. Meanwhile, combining CAZ/AVI with aztreonam is recommended for MBL infections by ESCMID, and IDSA [27,28].

This current review includes novel antimicrobial agents or combinations of existing beta-lactams with novel beta-lactamase inhibitors developed to tackle multidrug-resistant (MDR) GNB, particularly extended beta-lactamase (ESBLs)- and carbapenemase-producing pathogens. Antimicrobial agents active against MDR-GNB approved by the U.S. Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) since

2017, and agents in advanced development, i.e., in phase 3 clinical trials, are presented and critically discussed. The manuscript focuses on the specific characteristics of the novel antimicrobial agents, their pharmacokinetic/pharmacodynamic properties and the current clinical data. Details on the general characteristics of the antimicrobial classes that the presented antibiotics belong to, is beyond the scope of the current manuscript and for further information we refer the reader elsewhere [29].

Methods

New drug approvals (and withdrawals) from FDA and EMA were searched in the relevant webpages for the period 2017–2023 [30–43]. Moreover, the World Health Organization (WHO) 2021 Overview and Analysis of Antibacterial Agents in Clinical and Preclinical Development was used to identify agents in advanced development [44], followed by further extensive search in Medline, Clinicaltrials.org, and in the sites of the relevant pharmaceutical companies.

2. Recently Approved Antimicrobial Agents

The recently approved antimicrobial agents include cefiderocol that is a new siderophore cephalosporin, imipenem-cilastatin-relebactam and meropenem-vaborbactam that are combinations of a carbapenem with novel beta-lactamase inhibitors, the novel glycylcycline eravacycline, the novel tetracycline omadacycline, and the new tetracycline plazomicin. An overview of the main characteristics of these antimicrobial agents is presented in Table 1.

2.1. Cefiderocol

This drug is a modified cephalosporin with a catechol moiety that acts as a siderophore and binds extracellular iron. This drug–iron complex facilitates cefiderocol's entry into the pathogen cell by both porins and the iron transporter system, whereas it is unaffected by efflux pump overexpression. Thus, high periplasmic space concentrations are achieved. Although its spectrum of activity is broad against Gram-negative pathogens, it lacks activity against Gram-positive and anaerobic microorganisms. Meanwhile, the antimicrobial is stable to hydrolysis by serine class A and class B, and MBL enzymes [45]. Limited data demonstrate stability and clinical efficacy against class D, OXA-48-like carbapenemase-resistant *Enterobacterales* (CRE) isolates [46,47]. In contrast to the above, Poirel et al. studied broad-spectrum beta-lactamase-producing *E. coli* and *P. aeruginosa* isogenic strains. Most MBLs and also some extended-spectrum beta-lactamases (ESBL) showed decreased susceptibility to CEFID [48]. *A. baumannii* can acquire CEFID resistance by producing the ESBL-type beta-lactamase PER-1, which is inactivated in vitro by adding avibactam or durlobactam [49]. Finally, a single resistance marker cannot predict non-susceptibility to CEFID, although combined mechanisms can [50]. Overall, it is primarily helpful for treating difficult-to-treat pathogens, such as extensively drug-resistant (XDR) *Enterobacterales*, *P. aeruginosa*, and *A. baumannii*. CEFID retains activity against most ceftazidime-avibactam- and ceftolozane-tazobactam-resistant *P. aeruginosa* isolates [51].

Regarding microbiological diagnosis, susceptibility interpretation can be challenging, and as such it should be tested with broth microdilution using iron-depleted Mueller–Hinton broth [52]. Moreover, a recent European Committee on Antimicrobial Susceptibility Testing (EUCAST) warning recommends against using commercially available cefiderocol tests and suggests disk diffusion MIC determination instead [52].

Table 1. Characteristics of novel approved anti-Gram-negative antimicrobial agents.

Drug	Drug Class	Bacterial Spectrum	Drug Stable to Beta-Lactamase Type					Approval Year/Indication in Adults		Recommendations		Route//Dosage
			KPC	MBL	AmpC	OXA	ESBL	FDA	EMA	IDSA	ESCMID	
Cefiderocol	BL	GNB; not GPB and anaerobes	yes	yes	yes	yes	yes	2019/cUTI, HAP/VAP	2020/aerobic GNB when limited treatment options	CRE: cUTI	CRE #, CRAB, CRPA *	IV//2 g TDS (2 g QDS if augmented renal clearance)
Meropenem/vaborbactam	CP/BLI	GNB, GPB, anaerobes; not MRSA, VRE; VARB cannot enhance activity against <i>A. baumannii</i> and <i>Pseudomonas aeruginosa</i>	yes §	no	yes	no	yes	2017/cUTI	2018/cUTI, cIAI, HAP/VAP, when limited options	CRE: cUTI, infections elsewhere	CRE	IV//4 g TDS
Imipenem/cilastatin/relebactam	CP/BLI	GNB, GPB, anaerobes; not MRSA, VRE; RELE enhances activity against <i>P. aeruginosa</i> , contrary to <i>A. baumannii</i> ; not <i>Morganellaceae</i>	yes	no	yes	no	yes	2019/cUTI and cIAI with limited options, HAP, VAP	2021/HAP/VAP, BSI possibly secondary to pneumonia, when limited options	CRE: cUTI, infections elsewhere CRPA: cUTI	CRPA *	IV//1.25 g QDS
Eravacycline	TC	GNB, GPB, anaerobes; MRSA, VRE active; possibly against <i>A. baumannii</i> ; not <i>P. aeruginosa</i> ; less active against <i>Morganellaceae</i>	-	-	-	-	-	2018/cIAI	2018/cIAI	-	CRAB: No data	IV//1 mg/kg BD
Omadacycline	TC	GNB, atypical, GPB, anaerobes; MRSA, VRE active; may display activity against <i>A. baumannii</i> ; not against <i>P.aeruginosa</i> and <i>Morganellaceae</i>	-	-	-	-	-	2018/CAP, ABSSSI	-	-	CRAB: No data	IV//1st day 200 mg, later 100 mg OD; oral//450 mg for 2 days followed by 300 mg
Plazomicin	AG	Aerobic GNB, ESBL-E, CRE (including MBL); stable against some AG-resistant <i>Enterobacterales</i>	-	-	-	-	-	2018/cUTI	No	-	CRE: cUTI	IV//15 mg/Kg/day

There can be some exceptions to the rule # Inconclusive evidence, conditional. recommendation * Insufficient evidence § Low resistance potential of some KPC variants during treatment; **Abbreviations:** ABSSSI—acute bacterial skin and skin structure infection; AG—aminoglycoside; AmpC—chromosomally encoded beta-lactamase; BL—beta-lactam; BLI—beta-lactamase inhibitor; cIAI—complicated intraabdominal infection; CAP—community-acquired pneumonia; CRAB—carbapenem-resistant *Acinetobacter baumannii*; CP—carbapenem; CRE—carbapenem-resistant Enterobacterales; CRPA—carbapenem-resistant *Pseudomonas aeruginosa*; cUTI—complicated urinary tract infection; EMA—European Medicines Agency; ERA—eravacycline; ESBL—extended spectrum beta-lactamases; ESBL-E—extended spectrum beta-lactamase-producing Enterobacterales; FDA—Food and Drug Administration; GNB—Gram-positive bacteria; GPB—Gram-positive bacteria; HAP—hospital-acquired pneumonia; IMP/CILA/RELE—imipenem/cilastatin/relebactam; IV—intravenous; KPC—*Klebsiella pneumoniae* carbapenemase; MBL—metallo- β -lactamase; MDR—multidrug-resistant; MER/VARB—meropenem/vaborbactam; MRSA—methicillin-resistant *Staphylococcus aureus*; NDM—New Delhi metallo- β -lactamase; OXA—oxacillinase; OMA—omadacycline; PLAZ—plazomicin; OD—once daily; QDS—four times daily; rRNA—ribosomal ribonucleic acid; SD—standard deviation; TC—tetracycline; TDS—thrice daily; VAP—ventilator-acquired pneumonia; VIM—Verona integron-encoded metallo- β -lactamase; VRE—vancomycin-resistant *Enterococcus*.

2.1.1. Pharmacokinetic-Pharmacodynamic Issues

Cefiderocol demonstrates time-dependent killing characteristics and the pK/pD index associated with optimal activity for *Enterobacterales* and *P. aeruginosa* are on average 73% and 77% of fT > MIC in a thigh murine model [53]. CEFID is dosed according to beta-lactam pK/pD characteristics: (1) it is administered via an extended 3 h infusion; (2) dosing has to be increased to 2 g four times daily (QDS) whenever there is augmented renal clearance (>120 mL/min) [33]; (3) the effluent flow rate may help estimate the dose during continuous renal replacement therapy [54].

The lung penetration ratio was assessed in a recent pharmacokinetic model where the study participants received the regular dosing regimen of 2 g thrice daily (TDS). Considering an MIC of ≤ 4 , the probability of CEFID's target attainment of time above MIC in the epithelial lining fluid was 87.5% [53].

Gatti et al. measured trough blood levels of CEFID to study the therapeutic target attainment of 13 critically ill patients with ventilator-associated pneumonia (VAP) and bloodstream infections (BSI) by extensively drug-resistant *A. baumannii* treated with CEFID. The fCmin/MIC at steady state was the measure of drug efficacy and considered optimal if it was ≥ 4 , quasi-optimal when between 1 and 4, and suboptimal if < 1 . The suboptimal ratio was associated with microbiological eradication failure in 80% of the patients [55].

An interesting case report assessed CEFID penetration into the cerebrospinal fluid compartment using two CEFID regimens of 6 and 8 g daily. The drug levels attained were constantly above the minimal inhibitory concentration of the offending pathogen [56].

2.1.2. Clinical Studies

APEKS-NP, a phase 3, multicenter, double-blind, randomized trial, compared the extended, 3 h infusion of 2 g CEFID to that of 2 g meropenem for suspected or proven Gram-negative hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), or VAP, while all non-blindly received linezolid for five days [15]. Regarding the primary outcome of overall 14-day mortality, the CEFID group was non-inferior to the control group, as were the secondary outcomes, notably test-of-cure, i.e., clinical cure or microbiological eradication at 7 ± 2 days.

CREDIBLE-CR, in contrast to the previous report, was an open-label randomized study examining CEFID vs. best available therapy (BAT), according to the treating physician's decision, for severe infections due to CR-GNB [57]. These infections were pneumonia (HAP, HCAP, or VAP), bacteremia, urosepsis, or non-specified sepsis by a suspected or proven CR-GNB. *A. baumannii* was most frequently isolated. The primary study endpoint was clinical cure at day seven following the end of treatment, or eradication of the pathogen in urine, in the case of urosepsis. There were no between-group differences regarding the primary outcome, although the end-of-study (28 ± 3 days) mortality was non-significantly increased in the CEFID group and all-cause mortality was numerically higher in the cefiderocol arm, especially in healthcare-associated pneumonia/HAP/VAP and BSI/sepsis (also at days 14 and 49) [57].

Falcone et al. compared CEFID-containing to colistin-containing regimens in 124 patients with VAP and BSI caused by *A. baumannii*, and performed an inverse probability treatment weighted analysis to examine the effect of the regimen on mortality [58]. In Cox proportional-hazard analysis, the independent predictors for 30-day mortality were septic shock, SOFA score, and age, while receiving CEFID was found protective (hazard ratio 0.32, 95% confidence interval [CI] 0.18–0.57). In subgroup analysis, the effect was confined to BSI, whereas VAP was unaffected by the antibiotic scheme. The colistin group demonstrated higher acute kidney injury rates.

Real-world data on CEFID use for carbapenem-resistant pathogens have recently been published [59]. The authors reported on 172 individuals, including the CREDIBLE-CR patients. Many patients reported adverse events, such as diarrhea or fever, although only four discontinued treatment because of these events [59]. Finally, there is scarce and inconclusive data on the therapeutic potential of combining CEFID with other antibiotics [60].

2.1.3. Approvals

Cefiderocol was approved by FDA in 2019 for complicated urinary tract infection (cUTIs) and in 2020 for HAP/VAP by susceptible pathogens, while in 2020 it was approved by EMA for the same indications.

2.1.4. Molecular Formula

The molecular formula of cefiderocol is $C_{30}H_{34}C_1N_7O_{10}S_2$. For the 2D structure of cefiderocol, please see Figure S1 of the Supplementary material.

2.2. Imipenem–Cilastatin–Relebactam

Relebactam is a novel beta-lactamase inhibitor that potently inhibits class A and class C beta-lactamases. Although chemically related to avibactam, it does not add to imipenem activity against OXA-48 [61]. The drug is formulated as a triple combination—apart from imipenem and relebactam, it contains the renal dehydropeptidase-I inhibitor cilastatin. Although the inhibitor renders most imipenem-non-susceptible KPC-producing *Enterobacteriales* and *P. aeruginosa* isolates susceptible, the metallo-proteinase-producing strains remained non-susceptible to the combination [62]. The combination of IMI/CILA/RELE plus aztreonam was tested against MBL-producing OprD-deficient *P. aeruginosa* isolates and it presented synergy [63]. IMI/CILA/RELE can retain activity against many ceftazidime-avibactam- and ceftolozane-tazobactam-resistant *P. aeruginosa* isolates [51,64].

Moreover, another research group performed time-kill analysis of 13 *K. pneumoniae* and *E. coli* isolates, co-harboring MBL and serine beta-lactamases and found that they were resistant to IMI/CILA/RELE (100%) and aztreonam (85%), when each antibiotic was given alone. However, when combined, they were synergistic against 11/13 of the isolates [65]. E-test may be used for observing synergy, although the data are premature [66].

Finally, the intrinsic resistance of the family *Morganellaceae* (*Proteus* spp., *Morganella* spp., and *Providencia* spp.) to imipenem is unaffected by the inhibitor [67,68].

2.2.1. Pharmacokinetic-Pharmacodynamic Issues

Unbound relebactam 24 h area under the concentration time curve to IMI/CILA/RELE MIC (fAUC/MIC) can best prognosticate the drug's antimicrobial efficacy. A ratio value of 7–7.5 can predict a 2-log₁₀ kill of *P. aeruginosa* strains, based on hollow fiber, and a neutropenic murine thigh model [69].

Population pK/pD modeling, based on clinical study data, confirmed that the renal function-based recommended scheme is sufficient for treatment [70]. The recommended dose for normal renal function dose, 1.25 g four times daily infused over 30 min, could achieve a probability of target attainment (PTA) of 93% at a MIC ≤ 2 , even in the case of augmented renal clearance (>130 mL/min) [24].

An in vitro pD model used simulated unbound human plasma levels of IMI/CILA/RELE corresponding to the recommended dose of 1.25 QDS, alone or in the presence of colistin or amikacin. IMI/CILA/RELE plus colistin resulted in colony-forming unit (CFU) reductions in some of the studied *P. aeruginosa* isolates, indicative of either synergy or additivity, whereas adding amikacin did not increment the antibacterial IMI/CILA/RELE action [71].

2.2.2. Clinical Studies

RESTORE-IMI 1, a phase 3 multicenter, double-blind trial, studied patients with infections, most commonly urinary tract infection or pneumonia, due to imipenem non-susceptible pathogens. The primary endpoint was a favorable response according to predefined criteria for every infection type [19]. The microbiologically modified intention-to-treat population comprised 31 individuals. *P. aeruginosa* (77.4%) predominated in this cohort. The intervention group received IMI/CILA/RELE, while the control group received imipenem plus colistin. The favorable 28-day clinical response was 71.4% vs. 40%, whereas the respective mortality was 9.5% vs. 30% (both outcomes were non-significantly different).

Concerning adverse events in the safety population ($n = 47$), the treatment-emergent nephrotoxicity was 10.3% vs. 56.3% ($p = 0.002$).

RESTORE-IMI 2 was a phase 3, HAP/VAP, multicenter, double-blind trial comparing IMI/CILA/RELE to piperacillin/tazobactam. Two-thirds of the patients were in the ICU, half ventilated, while the most isolated bacteria were *K. pneumoniae* and *P. aeruginosa*. The modified intention-to-treat population included 531 patients that had received at least a single drug dose and did not solely present Gram-positive cocci at the baseline stain [20]. The study group was non-inferior compared to the control group regarding the primary trial endpoint, i.e., overall mortality, and the key secondary endpoint of favorable clinical response at early follow-up (on days 7–14 following the end of treatment). Meanwhile, the adverse events were similar in both groups.

Kohno et al. evaluated the efficacy and adverse effect profile of IMI/CILA/RELE, in a multicenter, observational non-comparative phase 3 study of 81 patients with cUTIs and complicated intra-abdominal infections (cIAIs). *E. coli*, with favorable resistance phenotype, predominated in this cohort [72]. The drug-related adverse effects were overall 18.5% and primarily infusion-related. The efficacy was excellent and over 80% at the end of treatment.

Rebold et al. examined IMI/CILA/RELE use in 21 more severely ill patients than in the RESTORE-IMI trials. Out of the 21 patients, 16 were in the ICU, with a median APACHE II score of 21.5. Pneumonia, either HAP or VAP, occurred in 52% of individuals, and the predominant microorganism isolated was MDR *P. aeruginosa*. The all-cause 30-day mortality was 33% [73].

2.2.3. Approvals

Imipenem-cilastatin-relebactam was approved by FDA in 2019 for cUTIs and cIAIs, and 2020 for HAP/VAP by susceptible pathogens, while in 2020 it was approved by EMA for HAP/VAP and associated (or suspected to be associated) bacteremia and GNB infections with limited treatment options.

2.2.4. Molecular Formula

The molecular formula of imipenem is $C_{12}H_{17}N_3O_4S$, of cilastatin is $C_{16}H_{26}N_2O_5S$ and of relebactam is $C_{12}H_{20}N_4O_6S$. For the 2D structures, please see Figure S2 of the Supplementary material.

2.3. Meropenem-Vaborbactam

Vaborbactam, a non-antibiotic cyclic boronic acid inhibitor, binds reversibly with meropenem. The complex improves meropenem's stability to class A and C beta-lactamases; however, it is inactive against class B and D lactamases [61]. The inhibitor cannot improve the susceptibility of *P. aeruginosa* to meropenem due to the commonly present NCR, and *A. baumannii* due to the presence of class B and D beta-lactamases [74].

Regarding HAP/VAP isolates, the drug was active against >90% of KPC-producing *Enterobacterales* and 70–80% of *P. aeruginosa* [74,75]. KPC-producing *K. pneumoniae* strains that develop resistance to CAZ/AVI often leads to MER/VARB cross-resistance through increased KPC expression, although some isolates remained susceptible to MER/VARB [76,77]. Indeed, MER/VARB retained the ability to better interact with KPC-2 variants than ceftazidime-avibactam; however, resistance selection was primarily due to NCR [77–79].

2.3.1. Pharmacokinetic-Pharmacodynamic Issues

The vaborbactam fAUC to MER/VARB MIC correlated with antimicrobial activity, while a ratio value of 36 in the hollow fiber infection model can be bactericidal [61]. MER/VARB is primarily renally cleared, and dosing adjustments are needed for patients with renal impairment. Bhavnani et al. performed pK/pD target attainment analyses of the drug's 2 g/2 g dose and the modified dosing that corresponds to impaired renal function. The recommended dosing regimen achieved the target for treating *P. aeruginosa* and *Enterobacterales* over 80% of the time at an MIC value of 4–8 mg/L [80]. Kufel et al.

measured in vivo, in a single patient, the pre-and post-filter levels during continuous renal replacement therapy and found that a dosing schedule of 1 g/1 g TDS may suffice to achieve drug concentrations above the MIC of the pathogen [81].

2.3.2. Clinical Studies

TANGO II, a phase 3, open-label, multicenter study, was prematurely stopped at the prespecified interim analysis as its objectives were met and finally included 77 individuals. MER/VARB was compared to the best available therapy (ceftazidime/avibactam monotherapy or mono-/combination treatment of the following antimicrobial options: colistin, meropenem, aminoglycosides, and tigecycline). The microbiologic-carbapenem-resistant-*Enterobacterales* modified intention-to-treat population, which received at least a single drug dose, included 47 patients. Bacteremia was the most common diagnosis, while KPC-producing *K. pneumoniae* predominated. The study endpoints in the above population were as follows: (1) cure at the end of treatment; (2) test-of-cure at day 7 ± 2 later; and (3) 28-day overall mortality. The respective results were in favor of MER/VARB 65.6% vs. 33.3%, 59.4% vs. 26.7% (both significant), and 15.6% vs. 33.3% (non-significant) [18].

Real-world data on CRE infections (40% were BSI) were reported by Ackley et al. in a multicenter retrospective cohort study of 131 (57.3% critically ill) participants. The dominant mechanism of CR (~75%) was KPC production. The authors compared MER/VARB to CAZ/AVI. Less CAZ/AVI-treated patients received combination therapy with other antimicrobials than MER/VARB patients. Clinical success, a composite outcome of clinical and microbiological favorable endpoints, did not differ between the groups, which also had similar adverse event rates [82].

Alosaimy et al. provided more real-world data about MER/VARB use for CRE and CR *P. aeruginosa* infections. One-hundred twenty-six adult patients were retrospectively studied. They presented significant comorbidities, and half had been ICU residents. They received MER/VARB for at least 72 h and suffered suspected or confirmed MDR-GNB infection. The adverse clinical outcomes of death or readmission on day 30 was significantly lower in the patients who appropriately received MER/VARB earlier (≤48 h from infection onset) than those who received it later (17.6% vs. 38.6%). The adverse rate was low, at 3.2% [83].

Finally, in a retrospective multicenter Italian study, 37 patients with MER/VARB sensitive, KPC-*K. pneumoniae*, infections were treated compassionately with MER/VARB for at least 72 h. Notably, 51.9% of the isolates were CAZ/AVI-resistant. The bloodstream and the lower respiratory tract were the most frequent infection locations. Most patients were critically ill while treatment followed infection onset by five days. The overall hospital mortality was 24.3%. It did not differ between the ceftazidime-resistant and ceftazidime-sensitive subgroups. Recurrent BSI was evident in just three patients after 18 days (median) of treatment, although the isolates remained susceptible to the drug. These patients achieved clinical cure after they received a combination of MER/VARB with a second antimicrobial (colistin or fosfomycin) [84].

2.3.3. Approvals

Meropenem-vaborbactam was approved by FDA in 2017 for cUTIs, including pyelonephritis, and by EMA in 2018 for cUTIs, cIAIs, HAP/VAP, bacteremia associated or suspected to be associated with any of the listed infections, and infections by GNBs with limited treatment options.

2.3.4. Molecular Formula

The molecular formula of meropenem is C₁₇H₂₅N₃O₅S and of vaborbactam is C₁₂H₁₆BNO₅S. For the 2D structures, please see Figure S3 of the Supplementary material.

2.4. Eravacycline

Eravacycline (ERA) is a novel glycylicycline that shares a similar antibacterial spectrum of activity with the other family member, tigecycline. This spectrum covers Gram-positive, Gram-negative, and anaerobic microorganisms, including MDR strains. However, the MIC is 2- to 4-fold less than that of tigecycline. Notably, ERA is inactive against *P. aeruginosa* [85].

2.4.1. Pharmacokinetic-Pharmacodynamic Issues

Eravacycline' efficacy against *Enterobacterales* was examined with a murine thigh infection model. An fAUC/MIC ratio mean (\pm SD) of 5.6 (\pm 5) was associated with a 1-log isolate reduction, while the peak free drug concentration to MIC ratio was correlated with the efficacy [86].

In a phase 1 pK study of ERA, the penetration of the drug into the epithelial lining fluid and alveolar macrophages were evaluated. Interestingly, the levels were 6-fold and 50-fold, respectively, compared to plasma. Therefore, ERA may become an alternative option for treating pneumonia caused by difficult-to-treat GNB [87].

2.4.2. Clinical Studies

IGNITE 1 and IGNITE 4 were the trials that assessed the drug in patients with cIAI who also had an operation or percutaneous drainage within 48 h of diagnosis [16,17].

IGNITE1 was a double-blind, multicenter, non-inferiority trial that compared eravacycline 1mg/kg twice daily (BD) to ertapenem 1 g once daily (OD) for treating hospitalized patients with cIAIs, at least for four days. The primary outcome and clinical cure rate, 25–31 days following the start of treatment, for the microbiological intention-to-treat population, was 86.8% vs. 87.6% [16].

IGNITE4 was a randomized, double-blind, multicenter, non-inferiority (margin of 12.5%) trial of complicated intraabdominal infections in the hospital. It compared ERA 1mg/Kg BD to meropenem 1 g TDS. The overall primary outcome was 90.8% vs. 91.2% for the ERA and meropenem groups, respectively. ERA was not inferior to MER concerning the primary endpoint of infections by ESBL-producing *Enterobacterales*, which were 87.5% vs. 84.6%. The safety profile of ERA was favorable, with class-effect low rates of nausea, vomiting, and diarrhea [17]. Despite the few *A. baumannii* isolates of the above studies, there were all susceptible to ERA.

A Bayesian network meta-analysis compared ERA to seven other commonly administered antimicrobials, including tigecycline, for treating cIAIs. The efficacy and safety of ERA were like the competing drugs. However, in microbiological response, ERA fared better than tigecycline [88].

A meta-analysis of three studies, including IGNITE1 and IGNITE4, showed that ERA was an effective clinical alternative to carbapenem treatment. The nausea rate was increased, although severe adverse effects did not differ between ERA and the carbapenem comparator [89].

Finally, Alosaimy et al. have provided real-world data about treating *A. baumannii* infections (69.5% of the isolates were CR) with ERA. Most patients received combined antimicrobials, while the most frequent diagnosis was pneumonia. Thirty-day mortality was 23.9 (21.9)%, implying that ERA could be another option for treating these challenging infections, which may present mortality in excess of 40%, in the case of BSI and HAP/VAP [90,91].

2.4.3. Approvals

Eravacycline was approved in 2018 by both FDA and EMA for cIAIs.

2.4.4. Molecular Formula

The molecular formula of eravacycline is C₂₇H₃₁FN₄O₈. For the 2D structure of eravacycline, please see Figure S4 of the Supplementary material.

2.5. Omadacycline

Omadacycline (OMA) is a novel aminomethylcycline, a new drug that belongs to the tetracycline class. It demonstrates activity against a broad-spectrum of Gram-positive, Gram-negative, atypical and anaerobic bacteria. Regarding anti-Gram-negative activity, its spectrum includes many members of the *Enterobacterales* family, except for *Proteus*, *Providencia*, and *Morganella* species. Almost half of the carbapenem-non-susceptible *Enterobacterales* isolates remain susceptible to OMA [92]. Although OMA lacks activity against *Pseudomonas* spp. [40,41], it retains activity against some *A. baumannii* isolates [93]. The therapeutic potential of OMA against *A. baumannii* isolates, regardless of their susceptibility to minocycline, was examined in a recent study [94]. The combination of OMA with sulbactam was promising as it showed synergy against 80% of the isolates [94].

2.5.1. Pharmacokinetic-Pharmacodynamic Issues

The in vitro OMA pD indices for five *A. baumannii* and five *E. coli* strains have been recently assessed. Notably, the relevant index for tetracycline action is the fAUC/MIC. The respective ratios for a 24 h static effect were 108.1 ± 38.6 and 25.3 ± 17.2 . Meanwhile, a single dose of 100 mg IV, the licensed daily scheme, resulted in an AUC of 10 mg/L * h [41,95]. Thus, the recommended dose fell short of achieving meaningful anti-Gram-negative activity. Regarding CR *A. baumannii*, higher in vitro exposures simulating 200 mg and 400 mg were tested and were not bactericidal alone; however, these higher exposures presented synergy with meropenem against 3 out of 8 isolates [96].

About human studies, a pK study compared the steady-state concentrations of omadacycline to those of tigecycline in the epithelial lining fluid (ELF) and the alveolar cells (EC). The OMA ratios of ELF/total plasma and EC/total plasma levels were higher for OMA than tigecycline at the dosing schedule recommended by the summary of product characteristics. Meanwhile, OMA unbound plasma levels surpassed those of tigecycline and ERA [97].

2.5.2. Clinical Studies

There is no clinical study of OMA for the treatment of MDR-GNB.

2.5.3. Approvals

Omadacycline was approved in 2018 by FDA for acute bacterial skin and skin structures infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP). The drug application was withdrawn from the EMA [40,41].

2.5.4. Molecular Formula

The molecular formula of omadacycline is $C_{29}H_{40}N_4O_7$. For the 2D structure of omadacycline, please see Figure S5 of the Supplementary material.

2.6. Plazomicin

This novel semi-synthetic aminoglycoside was highly active in vitro against most *Enterobacterales*, *P. aeruginosa*, and *A. baumannii* isolates at an MIC ≤ 4 . The antimicrobial could inhibit most gentamycin, tobramycin, and amikacin-resistant isolates [98]. Moreover, the drug retains in vitro activity against two-thirds of CR isolates, more than MER/VARB and OMA [99]. Of interest, plazomicin may remain active against MBL-producing *Enterobacterales*. However, CRE can produce 16S rRNA methyltransferase, harbored into plasmids which invariably abrogates aminoglycoside use [100,101].

Regarding the susceptibility testing of *Enterobacterales* to plazomicin, a novel gradient diffusion method (E-TEST Plazomicin) was compared to the standard broth microdilution method. The essential between-the-methods agreement was 99% [102].

2.6.1. Clinical Studies

In a multicenter trial of 609 patients, 15 mg/Kg PLAZ, once daily, was compared to MER 1g TDS to treat cUTIs and acute pyelonephritis. The primary endpoint was the composite cure (patients were clinically cured and bacteria were eradicated) on day 5 and days 15 and 19 following therapy commencement (test-of-cure visit) in the microbiologic modified intent-to-treat population (those patients who had a positive urine culture and received at least a study drug dose). PLAZ was non-inferior to MER, while more patients at the test-of-cure visit presented microbiological eradication [103].

Combating Antibiotic-Resistant Enterobacteriaceae (CARE) trial compared PLAZ to COLI for treating BSI and HAP/VAP due to suspected or confirmed CRE. It was prematurely terminated due to poor enrollment. The microbiologically modified intention-to-treat population comprised 37 patients (28 BSI and 9 pneumonia). PLAZ-treated individuals presented lower mortality from day 14 through day 60. The adverse effects were less frequent in the PLAZ (50%) than in the COLI group (81%) [21].

A meta-analysis of three studies (including the above two) confirmed the superiority of PLAZ to the competitors concerning microbiologic recurrence. However, the drug's clinical efficacy for CRE-associated BSI and pneumonia remains undetermined [104].

2.6.2. Approvals

Plazomicin was approved by FDA in 2018 for cUTIs. It is not available in Europe, as the marketing company withdrew its application in 2020 [43].

2.6.3. Molecular Formula

The molecular formula of plazomicin is $C_{25}H_{48}N_6O_{10}$. For the 2D structure of plazomicin, please see Figure S6 of the Supplementary material.

3. Antimicrobials in Phase 3 Clinical Trials

Antimicrobial agents active against MDR-GNB, currently in phase 3 clinical trials include combinations of existing beta-lactams with novel beta-lactamase inhibitors, namely, aztreonam-avibactam, cefepime-enmetazobactam, cefepime-taniborbactam, cefepime-zidebactam; and novel antibiotics, namely, the novel carbapenems sulopenem, tebipenem, and benapenem. An overview of the main characteristics of these antimicrobial agents is presented in Table 2.

3.1. Aztreonam/Avibactam

The drug combines aztreonam's inherent stability to MBLs and avibactam's inhibition of class A and C beta-lactamases. Many CRE strains co-produce MBLs and serine enzymes that can inactivate aztreonam. Indeed, a beta-lactamase inhibitor, such as avibactam, zidebactam, or nacubactam, protects aztreonam from hydrolysis and enhances its anti-MBL activity towards Enterobacterales and, to a lesser extent, towards *P. aeruginosa* [105,106]. The addition of the already commercially available combination of CAZ/AVI could restore aztreonam's activity against MBL-producing Enterobacterales, while *Stenotrophomonas maltophilia* was 100% susceptible to the triple combination, though the tested isolates were limited [107]. A recent large in vitro broth microdilution study confirmed the potent activity of AZT/AVI against Enterobacterales isolates. Notably, all studied CPE producers were inhibited using a concentration threshold of 8 mg/L [108]. Moreover, combined ceftazidime/avibactam/aztreonam was synergetic at inhibiting four out of five *P. aeruginosa* isolates [109]. Finally, AZT/AVI possesses a broader spectrum than CAZ/AVI; however, an *E. coli*-KPC-21-producing strain was resistant to the former while remaining susceptible to the latter combination [110,111].

Table 2. Characteristics of novel anti-Gram-negative antimicrobial agents in phase 3 clinical trials.

Drug	Drug Class	Bacterial Pectrum	Drug Stable to Beta-Lactamase Type					Potential Indications	Ongoing Trials (Phase 3)	Route//Dosage	Comment
			KPC	MBL	AmpC	OXA	ESBL				
Aztreonam/avibactam	MB/BLI	GNB; less effective against MBL-producing <i>P. aeruginosa</i>	yes	yes	yes	yes	yes	cIAI, HAP, VAP, cUTI, BSI	NCT03580044	IV // 500/167 mg loading dose, 1500/500 mg QDS	Combination that covers both serine and MBL carbapenemases
Cefepime/enmetazobactam	BL/BLI	GNB, GPB; ineffective against <i>A. baumannii</i> , CRE, and MRSA	no	no	yes/no	no	yes	cUTI, HAP, VAP	NCT03687255	IV // 2 g/500 mg TDS	Excellent class A, anti-ESBL activity; Potential carbapenem-sparing drug; Penetrates ELF easily
Cefepime/zidebactam	BL/BLI	GPB (not MRSA); GNB (not <i>A. baumannii</i>)	yes	yes	yes	yes	yes	cUTI	NCT04979806	IV // 2 g/1 g TDS	Phase 3 study recruiting patients
Cefepime/taniborbactam	BL/BLI	GPB (not MRSA), GNB, (not <i>A. baumannii</i>)	yes	yes	yes	yes	yes	cUTI	NCT03840148	IV // 2 g/0.5 g TDS	Preliminary results from phase 3 cUTI study: comparable efficacy to MER
Sulbactam/durlobactam	BL/BLI	GNB, particularly <i>Acinetobacter</i> spp.; active against <i>Burkholderia cepacia</i> ; not <i>P. aeruginosa</i>	yes	no	yes	yes	yes	<i>Acinetobacter</i> infections	NCT03894046	1 g/1 g QDS	Phase 3, pneumonia and BSI study. Better clinical cure and less nephrotoxicity than colistin (preliminary results)
Sulopenem	CP	GPB (not MRSA); GNB (not <i>P.aeruginosa</i> , <i>Stenotrophomonas maltophilia</i> , <i>B. cepacia</i>)	no	no	yes	no	yes	cUTI, uUTI, cIAI	NCT03357614, NCT03358576	Oral // sulopenem etzadroxil 500 mg/probenecid 500 mg BD; IV // 1000 mg OD	Phase 3 trial of uncomplicated UTI, recruiting patients
Tebipenem	CP	GPB (not MRSA); GNB (not <i>P.aeruginosa</i> , <i>A. baumannii</i>)	no	no	yes	no	yes	cUTI	NCT03788967	Oral // 600 mg TDS	Excellent anti-ESBL activity
Benapenem	CP	Like other CPs	no	no	yes	no	yes	cUTI	NCT04505683	IV // 1000 mg OD	Excellent anti-ESBL activity

Abbreviations: AmpC—chromosomally encoded beta-lactamase; BD—twice daily; BL—beta-lactam; BLI—beta-lactamase inhibitor; BSI—bloodstream infection; CP—carbapenem; CR—Carbapenem resistant; CRE—Carbapenem-resistant Enterobacteriaceae; cIAI—complicated intraabdominal infections; cUTI—complicated urinary tract infections; ELF—epithelial lining fluid; ESBL—Extended Spectrum Beta-Lactamase; GNB—Gram-positive bacteria; GPB—Gram-positive bacteria; HAP—hospital acquired pneumonia; KPC—*Klebsiella pneumoniae* carbapenemase; MB—monobactam; MER—meropenem; MBL—metallo- β -lactamases; MDR—Multidrug-resistant; OD—once daily; OXA—oxacillinase; QDS—four times daily; TDS—thrice daily; VAP—ventilator associated pneumonia.

3.1.1. Pharmacokinetic-Pharmacodynamic Issues

Smith et al. examined, in vitro and in vivo, an NDM-1 and a CTX-M co-producing *K. pneumoniae* infection using hollow fiber and neutropenia rabbit models. They studied the sequelae by adding polymyxin B to the aztreonam-CAZ/AVI combination. In the presence of polymyxin B, they demonstrated enhanced bacterial killing and reduced inflammation, while suppressing resistance [112].

Aztreonam, co-administered with CAZ/AVI, was studied in healthy subjects which resulted in reduced AZT clearance. Meanwhile, continuously infused AZT was associated with severe hepatic transaminase elevations [113].

A phase 2 open-label multicenter study of AZT/AVI for cIAs compared three dosing regimens for pK/pD target attainment. The regimen that prevailed and presented no safety concerns was the 500 mg/167 mg loading dose followed by the 1500 mg/500 mg QDS, as a 3 h infusion [114].

3.1.2. Clinical Studies

A phase 3 study of AZT/AVI vs. best available treatment for severe infections due to MBL-producing bacteria is still recruiting participants (NCT03580044) [115].

In the meantime, combining a beta-lactam/beta-lactamase inhibitor with aztreonam is viable for MBL-targeted treatment. A recent systematic review summarized the CAZ/AVI-avibactam's clinical use against MBL-producing pathogens [105]. Ninety-four patients, 83% with bacteremia, were administered the combination, almost exclusively (99%) as targeted therapy. Two studies that included data from 128 patients, half with this combination vs. half with other active treatments, were meta-analyzed. The pooled crude 30-day mortality was 19% vs. 44%, (odds ratio 0.33, 95% [CI] 0.13–0.66); however, the mortality of the comparator group is driven by colistin-containing regimens, where 21 out of 36 patients died [105].

3.1.3. Molecular Formula

The molecular formula of aztreonam is $C_{13}H_{17}N_5O_8S_2$ and of avibactam is $C_7H_{11}N_3O_6S$. For the 2D structures, please see Figure S7 of the Supplementary material.

3.2. Cefepime/Enmetazobactam

Cefepime/enmetazobactam (CEFI/ENM) is a β -lactam/ β -lactamase inhibitor combining cefepime, a fourth-generation cephalosporin, with enmetazobactam (formerly AAI101), a novel extended-spectrum β -lactamase inhibitor. Enmetazobactam structurally resembles tazobactam but possesses a methyl group on the triazole ring that enhances its activity against β -lactamases. Cefepime's susceptibility rates are expanded from 2% to 98% with the combination of enmetazobactam, which exhibits potent activity against class A ESBL-producing bacteria [116]. Enmetazobactam only weakly inhibited class D OXA-10 and OXA-48 and moderately inhibited the class C β -lactamase. MBLs, including NDM-1, are not inhibited by enmetazobactam [116]. Although some activity against KPCs is reported in the literature, these results have not been confirmed by other studies, and currently, CEFI/ENM cannot be used against carbapenem non-susceptible strains [116–119]. It has no activity against *A. baumannii* and *S. maltophilia* and should not be used against AmpC-producing *Pseudomonas* strains [116]. Notably, enmetazobactam addition did not alter the efficacy of cefepime against *P. aeruginosa* isolates collected in the US and Europe, as the MIC₉₀ for both cefepime and CEFI/ENM was 16 μ g/mL [118].

3.2.1. Pharmacokinetic-Pharmacodynamic Issues

The pharmacokinetic-pharmacodynamic index that was best associated with potency against ESBL-producing isolates of *K. pneumoniae* was the time above free threshold concentration, fT > CT [120]. Specifically, 44% fT > 2 μ g/mL of enmetazobactam was needed for 1-log₁₀ bioburden reduction, combined with a cefepime pK/pD target of 40 to 60% fT > CEFI/ENM MIC [120]. The dosing regimen supported in the literature is 2 g/500 mg

of CEFI/ENM administered every 8 h [119–121]. A phase 1 clinical trial has completed recruitment, and results are expected concerning the pK parameters and safety of the combination in patients with various degrees of renal impairment (NCT03680352) [122].

Cefepime and enmetazobactam exhibited adequate penetration into the epithelial lining fluid, with AUC plasma: AUC ELF ratios of 61% and 53%, respectively, in healthy subjects, while ELF exposure estimates of both combination components were strongly correlated [121]. In a neutropenic murine pneumonia model, the AUC ELF: AUC plasma ratios were 73% and 62%, respectively [123].

3.2.2. Clinical Studies

The combination has been studied in a phase 3 clinical trial (ALLIUM trial), where CEFI/ENM was non-inferior to piperacillin/tazobactam in treating cUTIs. The study was superior to the control drug in terms of clinical cure and microbiological eradication; the overall success rate was 79.1% vs. 58.9%, (95% [CI] 14.3%–27.9%) [124]. CEFI/ENM was administered 2 g/500 mg TDS as a 2 h infusion. Interestingly, *Clostridioides difficile* infections were noted more often in CEF/ENM group [124].

By the end of 2022, a marketing authorization will be submitted to EMA, while the FDA has granted CEF/ENM with qualified Infectious Disease Product and Fast Track designation. Regarding HAP and VAP, EMA has allowed the company to seek approval without conducting a Phase 3 study with this indication, based on adequate intrapulmonary penetration of the drug into the ELF [121,124].

In summary, cefepime/enmetazobactam is a better option for treating cUTIs than piperacillin/tazobactam and has a potential role as a carbapenem-sparing regimen because it possesses excellent activity against ESBL-producing *Enterobacterales*.

3.2.3. Molecular Formula

The molecular formula of cefepime is $C_{19}H_{24}N_6O_5S_2$ and of enmetazobactam is $C_{11}H_{14}N_4O_5S$. For the 2D structures, please see Figure S8 of the Supplementary material.

3.3. Cefepime/Zidebactam

In addition to being a novel β -lactamase inhibitor, zidebactam (WCK 5107) is also active against beta-lactamase when it binds to Penicillin Binding Protein 2 (PBP2) of *Enterobacterales* and *P. aeruginosa* [125]. The simultaneous inactivation of PBP2 and PBP3 by zidebactam and cefepime confers a strong and rapid bactericidal potential to the combination. Zidebactam is active in vitro against a wide range of β -lactamases from classes A, B, C, and D, including KPC, MBLs, and OXA-48 carbapenemases [126]. The MIC₅₀ and MIC₉₀ values for cefepime/zidebactam (CEFI/ZIDE) against carbapenemase-producing isolates were 0.5 and 16 μ g/mL, respectively, showing enhanced activity compared with other commonly used agents (imipenem, amikacin, polymyxin B, ceftolazone-tazobactam, and piperacillin-tazobactam). The MIC₅₀ and MIC₉₀ values against class B-producing- and class D-producing-carbapenemases were 2 and 32 μ g/mL, and 2 and 16 μ g/mL, respectively [127]. In another study, 86.1% of the CRE strains and 89.8% of CR-K. *pneumoniae* isolates were inhibited by CEFI/ZIDE at 2 mg/L [128]. In contrast, most CRE and CR-*P. aeruginosa* isolates were susceptible to CEFI/ZIDE [129]. At MICs \leq 8 mg/L, only 34% of CR-A. *baumannii* isolates were sensitive to CEFI/ZIDE [130]. Additionally, CEFI/ZIDE has shown promising activity against *S. maltophilia* and *Burkholderia cepacia* [131].

3.3.1. Pharmacokinetic-Pharmacodynamic Issues

CEFI/ZIDE demonstrates time-dependent killing characteristics and the $ft > MIC$ is the pK/pD index associated with efficacy [132]. CEFI/ZIDE is administered 2 g/1 g every 8 h, as an 1 h infusion, and dose adjustment is required for patients with renal impairment as the drug is renally excreted [133].

In a neutropenic mouse *A. baumannii* lung infection model, the addition of zidebactam to cefepime achieved the 1-log₁₀ kill endpoint with a reduced $ft > MIC$ as low as

15.5% [134]. Similarly, adding zidebactam to cefepime in a neutropenic mouse *Enterobacteriales* pneumonia model achieved a target of 31% T > MIC and the 1-log₁₀ endpoint [132].

Regarding pneumonia treatment potential, the total plasma/ELF penetration ratio for CEFI/ZIDE ranged from 0.3 to 0.5 [134], while in another study, the penetration into ELF was 50% and 70% for cefepime and zidebactam, respectively [132].

In vivo efficacy of CEFI/ZIDE has been shown in neutropenic murine lung and thigh infection models against CR-*A. baumannii* and MDR-*P. aeruginosa* [135,136].

3.3.2. Clinical Studies

Currently, a phase 3 clinical trial (NCT04979806) is recruiting patients to compare cefepime-zidebactam to meropenem for treating hospitalized adults with cUTIs or acute pyelonephritis [137].

3.3.3. Molecular Formula

The molecular formula of cefepime is C₁₉H₂₄N₆O₅S₂ and of zidebactam is C₁₃H₂₁N₅O₇S. For the 2D structures, please see Figure S9 of the Supplementary material.

3.4. Cefepime/Taniborbactam

Taniborbactam (VNRX-5133) is a novel, boronate derivative, β-lactamase inhibitor that directly inhibits Ambler class A, B, C, and D enzymes. It exhibits promising in vitro activity against OXA-48, KPC, and MBL-CRE isolates [138]. Differential susceptibility profiles of the MBL subclasses to the cefepime/taniborbactam (CEFI/TANI) combination have been described—CEFI/TANI is highly active against VIM-producing *Enterobacteriales* [138]. Recent data demonstrate that taniborbactam restores cefepime's activity against NDM-producing strains [138]. In an in vitro study from Spain, 90% of meropenem-resistant (MIC > 8 mg/L) *Enterobacteriales* were susceptible to CEFI/TANI, including KPC-, MBL-, and OXA-48-type producers. CEFI/TANI was the most active agent against OXA-48-type and MBL-producing isolates compared to ceftazidime-avibactam, ceftolozane-tazobactam, IMI/CILA/RELE, and MER/VARB [139]. Notably, taniborbactam remains active against novel KPC-variants, which are resistant to CAZ/AVI. However, the accumulation of mutations can confer CEFI/TANI non-activity against *K. pneumoniae* [140].

Comparing isolates' susceptibility to CEFI/TANI with that of CEFI/ZIDE demonstrated that 84.1% of KPC- and 75% of MBL-producing isolates had a MIC ≤ 2 mg/L vs. 100% and 96.4%, respectively [138]. CEFI/TANI showed high in vitro activity against VIM-producing *Enterobacteriales*, but no significant activity against IMP-producing, while further research is needed to assess activity against NDM-producing strains [117].

Concerning anti-*Pseudomonas* activity, CEFI/TANI had the highest efficacy compared with CAZ/AVI, ceftolozane-tazobactam, IMI/CILA/RELE, and MER/VARB, with 68% of strains being susceptible to CEFI/TANI. In particular, bla_{GES} isolates and MBL-producing strains were the most susceptible isolates [139]. However, although it presented activity against *S. maltophilia*, it failed to do so against *A. baumannii* [141].

3.4.1. Pharmacokinetic-Pharmacodynamic Issues

The pK/pD index best associated with taniborbactam inhibitory activity was fAUC₀₋₂₄/MIC in a neutropenic murine thigh infection model [141].

The dosing regimen of CEFI/TANI suggested for phase 3 trials was 2 g/0.5 g TDS as a 2 h infusion [141]. Cefepime's and taniborbactam's pharmacokinetics are similar, and both are primarily excreted in the urine. Dose adjustment is needed for different degrees of renal impairment because increased plasma concentrations of drugs are noted as renal function decreases [142]. In a murine cUTI model, cefepime/taniborbactam was effective against cefepime-resistant *Enterobacteriales*, *P. aeruginosa*, and *S. maltophilia* clinical isolates with MICs ≤ 32 mg/L [143].

3.4.2. Clinical Studies

Currently, a phase 3 clinical trial (NCT03840148) comparing CEFI/TANI with meropenem in cUTIs has completed recruitment, and results are pending [144]. The developing company released a press report stating that CEFI/TANI was non-inferior to meropenem, as 70% of participants belonging to the microbiological intent-to-treat population who received the study drug had a clinical and microbiologic response at the test-of-cure visit vs. 58% of the control subjects [112].

In summary, cefepime/zidebactam and cefepime/taniborbactam may constitute significant new weapons in our armamentarium against, at least, cUTIs [120,145] caused by a wide range of MDR-GNB, including infections caused by CRE isolates expressing MBLs and OXA-type enzymes.

3.4.3. Molecular Formula

The molecular formula of cefepime is $C_{19}H_{24}N_6O_5S_2$ and of taniborbactam is $C_{19}H_{28}BN_3O_5$. For the 2D structures, please see Figure S10 of the Supplementary material.

3.5. Sulbactam-Durlobactam

Sulbactam is a widely used first-generation β -lactamase inhibitor, which also possesses intrinsic β -lactam activity against *A. baumannii*. Durlobactam (ETX2514) is a novel diazabicyclooctenone β -lactamase inhibitor that effectively inhibits class A, C, and D β -lactamases. Although it lacks anti-MBL activity, it possesses a wide range of anti-D activity against the OXA family of enzymes [146]. The combination of sulbactam and durlobactam (SUL/DUR) exhibits potent inhibition against MDR *Acinetobacter* species. An in vitro study reported that 96.9% of CR-A. *baumannii* isolates were susceptible to SUL/DUR [147], while in another study of 141 (55% colistin-resistant) CR-A. *baumannii* clinical isolates, only 11 (8%) were resistant to SUL/DUR [148]. Regarding the sensitive isolates, the MIC₅₀ and MIC₉₀ were 0.5 mg/L and 4 mg/L, respectively [148]. Notably, in a Greek in vitro study, SUL/DUR's activity against CR-A. *baumannii* was enhanced by adding imipenem, which further lowered the MIC₉₀ of SUL/DUR two-fold [149].

3.5.1. Pharmacokinetic-Pharmacodynamic Issues

The optimal target attainment against *Acinetobacter* species was an SUL/DUR dosing scheme of 1 g/1 g QDS via a prolonged, 3 h infusion [150]. Meanwhile, SUL/DUR is renally cleared, and dosing should be reduced in patients with severe renal dysfunction, while it can be removed by hemodialysis [151]. Adequate intrapulmonary penetration is achieved, with an ELF to total plasma ratio of 55% for sulbactam and 37% for durlobactam [151].

3.5.2. Clinical Studies

In a phase 2 clinical trial, including 80 patients with cUTIs, SUL/DUR was administered, combined with imipenem-cilastatin, as 1 g/1 g intravenously QDS and was well-tolerated. The most common negative events reported were headache, diarrhea, nausea, and phlebitis, and no serious adverse events occurred. Although no *A. baumannii* infection was detected, the overall rates of success in the microbiologically modified intention-to-treat (m-MITT) population were similar in both groups (SUL/DUR plus imipenem-cilastatin vs. placebo plus imipenem-cilastatin), while in patients with imipenem-resistant pathogens ($n = 7$) response rates were higher than placebo (100% vs. 75%) [152].

A phase 3 clinical trial (NCT03894046) evaluating the efficacy and safety of intravenous SUL/DUR, compared with colistin in HAP, VAP, and bacteremia caused by *A. baumannii-calcoaceticus complex* has completed recruitment, and results were announced in October 2021. All patients had received imipenem/cilastatin as a background antimicrobial, and approximately 95% of *Acinetobacter* isolates were resistant to carbapenem. Sulbactam-durlobactam was non-inferior to colistin, and the 28-day all-cause mortality was 19% and 32.3%, respectively. The combination presented a better clinical cure at the test-of-cure visit and fewer nephrotoxicity events than colistin [153].

In summary, sulbactam-durlobactam is a potential option for treating severe infections caused by carbapenem-resistant *A. baumannii* infections as it retains activity against OXA-enzymes, which are often responsible for that resistance phenotype.

3.5.3. Molecular Formula

The molecular formula of sulbactam is C₈H₁₁NO₅S and of durlobactam is C₈H₁₁N₃O₆S. For the 2D structures, please see Figure S11 of the Supplementary material.

3.6. Sulopenem

Sulopenem is a synthetic thiopenem β -lactam antimicrobial targeting PBP [154]. It has activity against ESBL-producing and AmpC-producing *Enterobacterales* [155]. Additionally, sulopenem exhibits excellent in vitro activity against urinary isolates of *E. coli*, which is not affected by resistance to trimethoprim-sulfamethoxazole and ciprofloxacin [156]. Sulopenem exhibited excellent in vitro activity against *Enterobacterales* isolated from the urine of Canadian patients, with MIC₉₀ values ranging from 0.06 to 0.5 mg/L, for all species tested [155]. Additionally, similar to meropenem, it retained its activity against trimethoprim-sulfamethoxazole and ciprofloxacin non-susceptible *E. coli* strains, MDR-*E. coli* (defined as resistant to ≥ 3 agents from different antimicrobial classes), and AmpC- and ESBL-producing *E. coli* isolates, with MIC values ranging from 0.015 to 0.12 μ g/mL [156]. It is not active against *P. aeruginosa*, *S. maltophilia*, and *B. cepacia*.

3.6.1. Pharmacokinetic-Pharmacodynamic Issues

Sulopenem, similarly to other carbapenems, demonstrates time-dependent bacterial kill activity. The optimal fT/MIC varied according to the studied pathogen; for example, a 2-log₁₀ kill of a ESBL-producing *K. pneumoniae* isolate, in an immunocompetent murine thigh infection model, ranged from 12% to 28% [154].

Sulopenem can be administered both intravenously (CP-70,429) and orally as a pro-drug, sulopenem etzadroxil (PF-03709270), enabling therapy on an outpatient basis, as well as a step-down therapy from intravenous (IV) to oral administration. Oral bioavailability ranges from 20.1% to 33.6% and improves substantially when the drug is co-administered with food and probenecid. Concentrations achieved in urine vary, as approximately 35.5% of the 1000 mg dose was recovered in urine [154].

Sulopenem etzadroxil 500 mg/probenecid g is administered twice daily as a bilayer tablet, while IV sulopenem is given as 1000 mg once daily and reduced to 250 mg once daily in patients with CrCl < 30 mL/min [157]. Like most β -lactams, a high percentage of time free concentrations that is above the MIC (%fT > MIC) is considered the desired pD target [154], and as a result, sulopenem 1 g IV was infused over 3 h in a phase 3 clinical trial [157].

3.6.2. Clinical Studies

Sulopenem's role in treating uncomplicated and complicated UTIs, and complicated intra-abdominal infections has been studied in phase 3 clinical trials. The authors of the first trial compared IV sulopenem followed by oral sulopenem to IV ertapenem followed by oral ciprofloxacin or amoxicillin-clavulanate for cUTIs. Sulopenem was not non-inferior to the comparator regimen regarding the overall clinical and microbiological response (67.8% vs. 73.9%). It exhibited high clinical success rates (89.4% for sulopenem, and 88.4% for ertapenem). However, microbiological success was lower than ertapenem (71.2% vs. 78.0%), as asymptomatic bacteriuria after completion of therapy was a more common finding in the study group, mainly due to better eradication of quinolone-susceptible pathogens with oral ciprofloxacin following IV ertapenem. In patients with ciprofloxacin-resistant isolates, overall success and asymptomatic bacteriuria rates were similar between the two groups. The most common adverse events reported were headache and diarrhea [157].

In uncomplicated UTIs, overall, oral sulopenem etzadroxil/probenecid was non-inferior, though it was superior to ciprofloxacin when treating ciprofloxacin-resistant

pathogens [157]. However, in July 2021, the FDA denied a New Drug Application for sulopenem etzadroxil/probenecid for treating adult women with uncomplicated UTIs due to quinolone non-susceptible uropathogens, and additional data were requested to support the approval. A new phase 3 clinical trial (REnewed ASsessment of Sulopenem in uncomplicated UTI caused by Resistant *Enterobacterales* (REASSURE), NCT05584657) has started recruiting patients for the evaluation of oral sulopenem compared to amoxicillin/clavulanate for treating adult women with uncomplicated UTI [158]. Upon its completion, the company plans to resubmit a New Drug Application to the FDA in 2024.

Concerning cAIs, according to the results announced from the SURE 3 clinical trial (Sulopenem for Resistant Enterobacteriaceae (SURE) 3 trial) on December 2019, sulopenem missed the primary endpoint and its non-inferiority to ertapenem was not established [159]. In summary, sulopenem may have a role in the inpatient and step-down therapy of cUTIs caused by ESBL, AmpC *Enterobacterales*, and quinolone-resistant isolates.

3.6.3. Molecular Formula

The molecular formula of sulopenem is C₁₂H₁₅NO₅S₃. For the 2D structure of sulopenem, please see Figure S12 of the Supplementary material.

3.7. Tebipenem

Tebipenem/pivoxil hydrobromide (SPR994) is an orally bioavailable carbapenem prodrug. Tebipenem is the active form with activity against *Enterobacterales* pathogens, including MDR strains [160]. It is less active against *P. aeruginosa* and inactive against KPC- and MBL-producing *Enterobacterales*. Specifically, tebipenem's MIC₅₀ was ≤0.06 µg/mL for ESBL and AmpC-producing isolates of *E. coli* and *K. pneumoniae*, while it was >2 µg/mL for *P. aeruginosa* [161].

3.7.1. Pharmacokinetic-Pharmacodynamic Issues

It is administered orally with a dose of 600 mg TDS, achieving bioavailability of 50–60%, and it shows time-dependent bactericidal efficacy [162,163]. It is primarily excreted through the kidneys, achieving high urine concentration. Around 38–64% of the administered dose (600 mg) is recovered from urine, and plasma concentrations increase significantly with varying degrees of renal impairment, requiring a dose adjustment for creatinine clearance below 50 mL/min [164]. Efficient intrapulmonary penetration of tebipenem in healthy subjects was reported in a phase 1 trial (NCT04710407) [162], raising the question of whether the drug can be used in lower tract respiratory infections caused by MDR strains.

3.7.2. Clinical Studies

ADAPT-PO, a phase 3 clinical trial, has been recently completed. According to the results, oral tebipenem pivoxil hydrobromide was non-inferior to IV ertapenem for treating patients with cUTIs and acute pyelonephritis concerning the primary endpoint of overall response at the test-of-cure visit (58.8% and 61.6% of the patients, respectively). The overall response at the end-of-treatment visit was 97.3% in the tebipenem pivoxil hydrobromide group and 94.5% in the ertapenem group. The development of asymptomatic bacteriuria was the main reason for the decrease in response rates from the test-of-cure to the end-of-treatment visit. Additionally, the efficacy was similar in both groups regarding fluoroquinolone-resistant, ESBL-producing, and trimethoprim-sulfamethoxazole-resistant strains [165].

However, in June 2022, FDA rejected Spero Therapeutics' application for approval of tebipenem for outpatient treatment of cUTIs, requesting further investigations, and subsequently, the company suspended commercialization activities.

In summary, with its oral formulation, tebipenem may be a therapeutic option in patients with community-acquired UTIs caused by ESBL and AmpC-producing *Enterobacterales*, as well as quinolone- and trimethoprim/sulfamethoxazole-resistant strains.

3.7.3. Molecular Formula

The molecular formula of tebipenem is C₁₆H₂₁N₃O₄S₂. For the 2D structure of tebipenem, please see Figure S13 of the Supplementary material.

3.8. Benapenem

Benapenem is a novel carbapenem with activity against ESBL-producing *Enterobacteriales*. It exhibited in vitro activity against ESBL-producing *E. coli*, *K. pneumoniae*, and *Enterobacter cloacae* strains with an MIC₉₀ ≤ 0.5 µg/mL [166].

3.8.1. Pharmacokinetic-Pharmacodynamic Issues

Its bacteriostatic and bactericidal effect depends on the percentage of time that the free drug concentration remains above the MIC (%fT > MIC). A target of %fT > MIC above 60% is proposed to ensure bactericidal efficacy [166]. According to results from phase 1 trials, benapenem has a long half-life period, similar to ertapenem, can be administered as a 1000 mg OD dose, and is well tolerated [167]. In a pD study evaluating benapenem, administration in patients with mild to moderate renal impairment, the authors recommended no dose adjustment in mild to moderate renal impairment, as plasma concentrations did not increase significantly in patients with renal dysfunction [168].

3.8.2. Clinical Studies

A phase 2/3 clinical trial (NCT04505683) has completed recruitment to evaluate the efficacy and safety of benapenem in cUTIs. Recently, Sihuan Pharmaceutical has licensed out the rights of benapenem to New Asia Pharmaceutical [169].

3.8.3. Molecular Formula

The molecular formula of benapenem is C₂₂H₂₈N₄O₇S₂. For the 2D structure of benapenem, please see Figure S14 of the Supplementary material.

4. Discussion

Critically ill patients with sepsis require prompt and appropriate empirical antimicrobial treatment. If the patient has recently received carbapenem treatment or is colonized with CR-pathogens, and a rational initial regimen is the combination of two non-beta lactam drugs, such as colistin, aminoglycoside, tigecycline, or fosfomycin, we must cover for potential CRE and non-fermenter pathogens [170]. Alternatively, when we have evidence for a CRE infection, but we do not know the resistance phenotype, we can initially treat with a novel beta-lactam/beta-lactamase inhibitor plus aztreonam. When the susceptibility test results become available, we can de-escalate treatment accordingly [171].

According to ESCMID recommendations for targeted treatment of GNBs, monotherapy with MER/VARB, or CEFID in patients with susceptible bacteria is strongly encouraged, though based on insufficient evidence [28]. Monotherapy is possibly the best approach to treat KPC-producing *Enterobacteriales*, as MER/VARB, CEFID, and IMI/CILA/RELE present over 90% in vitro activity against these isolates. Thus, choosing the best anti-KPC active drug can be challenging. MER/VARB showed in vitro possible reduced potential for resistance development compared to CAZ/AVI [172]. Meanwhile, many KPC-mutants that developed increased MIC to CAZ/AVI also presented increased MICs to CEFID [5]. KPC mutations can develop resistance to IMI/CILA/RELE, and cross-resistance to MER/VARB [173]. However, KPC is not the only mechanism for CR. Unfortunately, many beta-lactamase-producing microorganisms can produce up to four beta-lactamases and carry determinants for many antimicrobial classes beyond beta-lactams [92,174]. Nonetheless, the aminoglycosides, polymyxins, and high-dose tigecycline could increase coverage if combined with the beta-lactams [175,176].

For the OXA-48-like-producing *Enterobacteriales*, CEFID can be used. Notably, there has recently been a shift from KPC- to MBL-carbapenemases after the launch of modern, KPC-active, beta-lactam/beta-lactamase inhibitors [177]. MBL-production often added onto

other class beta-lactamase-production, limits the novel treatment options to just two: CEFID and CAZ/AVI plus aztreonam. Moreover, there is scarce in vitro data on the synergistic potential of combining IMI/CILA/RELE with aztreonam. Plazomicin remains an option for treating MBL-associated cUTIs or can be used compassionately if available. Finally, we are eagerly waiting the launch of AZT/AVI, CEFI/ZIDE, and CEFI/TANI for treating MBL-CRE infections.

A. baumannii, despite the in vitro susceptibility, proved resilient to CEFID, as more CEFID-treated patients died than those who received the comparator, which is the best available treatment. Novel tetracycline class drugs comprise ERA and OMA. ERA has been successfully studied for treating cIAs, although real-world data provide limited data for its use against CR-*A. baumannii* pneumonia. OMA is a more intriguing prospect: it presents higher levels in the blood and lung compartments than other modern tetracycline antimicrobials. It might be used for treating *A. baumannii* if combined with other available drugs. However, it has not been tested yet. Meanwhile, SUL/DURL presents anti-OXA activity and can be a valuable treatment option when available.

CEFID and IMI/CILA/RELE may cover even CAZ/AVI- and ceftolozane-resistant *P. aeruginosa* isolates and are conditionally recommended for CRPA infections [28].

Meanwhile, the treating physicians should be vigilant about resistance in vivo and repeat susceptibility testing as resistance to the novel drugs may evolve through various mechanisms [178].

A systems-based, machine learning approach revealed: (i) a plasmid carrying multiple resistance genes; (ii) the beta-lactam concentration yielding 50% of maximum killing; and (iii) hypotension ranked most important for 30-day mortality. The combination of drugs might have benefited the patients by enhancing bacterial killing and decreasing bacterial regrowth [179]. Moreover, little is known about the bacterial inoculum effect on these novel drugs' therapeutic efficacy [180]. At the usual inocula of 10^5 CFU/mL, many bacteria were susceptible to MER/VARB (70%) and CEFID (85%), and IMI/CILA/RELE (45%). At a higher inocula of 10^7 , the susceptibility got worse at 50%, 12%, and 28%. All the above may indicate that in severe infections failing to improve rapidly, adding a second drug might benefit the patient outcomes.

In summary, CEFID presents the widest in vitro Gram-negative spectrum that includes CRE, CRPA, MBLs and CRAB. However, clinical data showed a numerically increased mortality in CEFID's arm compared to BAT for nosocomial pneumonia and BSI/sepsis, and further clinical research is needed to establish its clinical efficacy, especially for MBL-producing and CRAB. The above mentioned carbapenemases classes B (MBLs) and D (OXA), and CRAB are not included in the spectrum of IMI/CILA/RELE and MER/VARB, which retain stability to carbapenemases classes A and C. CEFID and IMI/CILA/RELE cover more *P. aeruginosa* strains than MER/VARB. Notably, although relebactam enhances imipenem action, vaborbactam cannot improve meropenem's anti-*Pseudomonas* activity. ERA targets an extensive spectrum of intestinal bacteria plus *A. baumannii*. It was clinically studied and licensed for treating cIAs which revealed that it has poor pK in the urinary tract and is not indicated for cUTIs. OMA use against *A. baumannii*, is not warranted, and despite its in vitro activity, its efficacy in critically ill patients remains to be studied. PLAZ is indicated for cUTIs in patients with no or limited alternative options, and it is more active against *Enterobacterales*, including CREs, than non-lactose-fermenters (inactive in vitro against *A. baumannii* and *S. maltophilia* and variable activity against *P. aeruginosa*).

Among the phase 3 antimicrobials, AZT/AVI, CEFI/ZIDE, and CEFI/TANI can target several MBL-producing CREs, while SUL/DUR presents the sole antibacterial agent with promising activity against *A. baumannii*. CEFI/ENM displays excellent anti-ESBL activity coupled with adequate lung penetration. Finally, sulopenem, tebipenem, and biapenem are novel carbapenems targeting ESBL-producing *Enterobacterales*, without anti-*Pseudomonas* activity; notably, sulopenem and tebipenem are the first-class members that can also be administered orally.

Detailed comparison of the novel branded antibiotics and the antibiotics in phase 3, are presented in Tables 1 and 2, respectively.

The highlights of the manuscripts are presented in Appendix A.

5. Conclusions

The number of new antimicrobial agents are not keeping up pace with antimicrobial resistance development and patients' needs. Their vast majority represent modifications of existing chemical structures, addressing specific mechanisms of resistance, rather than new drug classes with unique mechanisms of actions.

Most of the recently approved agents and those in late-stage clinical development can withstand the inactivation by serine-beta-lactamase enzymes. However, the global spread of metallo-beta-lactamase-producing GNBs and of carbapenemases-producing *A. baumannii* remain the hardest challenges to address and represent an unmet clinical need, as very few of these novel agents possess in vitro activity and potential clinical effectiveness against these difficult-to-treat pathogens.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/antibiotics12040761/s1>, Figure S1: Cefiderocol; Figure S2: Imipenem-Cilastatin-Relebactam; Figure S3: Meropenem—Vaborbactam; Figure S4: Eravacycline; Figure S5: Omadacycline; Figure S6: Plazomicin; Figure S7: Aztreonam—Avibactam; Figure S8: Cefepime—Enmetazobactam; Figure S9: Cefepime—Zidebactam; Figure S10: Cefepime—Taniborbactam; Figure S11: Sulbactam—Durlobactam; Figure S12: Sulopenem; Figure S13: Tebipenem; Figure S14: Benapenem. References [181,182] are cited in the supplementary materials.

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Abbreviations

ABSSSIs: Acute Bacterial Skin and Skin Structures Infections; AG: aminoglycoside; AMEs: aminoglycosides-modifying enzymes; AMR: antimicrobial resistance; APACHE II: Acute Physiology and Chronic Evaluation II; AZT/AVI: aztreonam/avibactam; BAT: best available treatment; BSI: blood-stream infections; CAZ/AVI: ceftazidime-avibactam; CABP: community-acquired bacterial pneumonia; CEFI/ENM, cefipime/enmetazobactam; CEFI/TANI, cefipime/taniborbactam; CEFI/ZIDE, cefipime/zidebactam; CEFID: cefiderocol; CFU: colony-forming unit; cIAI: complicated intraabdominal infection; COLI: colistin; CR: carbapenemase-resistance; CRPA: carbapenemase-resistant *Pseudomonas aeruginosa*; CRE: carbapenemase-resistant *Enterobacteriales*; CTX-M, cefotaxime-hydrolyzing-Munich; cUTI: complicated urinary tract infection; ELF: epithelial lining fluid; EC: alveolar cells; ERA: eravacycline; ESBL: extended-spectrum beta-lactamases; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; EUCAST: European Committee on Antimicrobial Susceptibility Testing; fAUC/MIC: 24 h area under the concentration time curve for the drug to microbe's minimal inhibitory concentration ratio; fT/MIC: total time the drug concentration is above the minimal inhibitory concentration for the microbe to microbe's minimal inhibitory concentration ratio; fCmin/MIC: the ratio of the total time the trough drug concentration is above the minimal inhibitory concentration to microbe's minimal inhibitory concentration; %fT > MIC: the percentage of time that the drug concentration is above the microbe's minimal inhibitory concentration; GNB: Gram-negative

bacteria; HAP: hospital-acquired pneumonia; HCAP: healthcare-associated pneumonia; ICU: intensive care unit; IMI/CILA/RELE: imipenem/cilastatin/relebactam; IMP: active-on-imipenem; KPC: *Klebsiella pneumoniae*, carbapenemase-producing; MBL: metallo-beta-lactamases; MDR: multidrug-resistant; MER/VARB: meropenem/vaborbactam; MIC: minimal inhibitory concentration; NCP: non-carbapenemase producers; NDM: New Delhi metallo- β -lactamase; OMA: omadacycline; OprD: outer membrane porin D; OXA: oxacillinase; PER-1: *Pseudomonas* extended resistant; pK/pD: pharmacokinetic/pharmacodynamic; PLAZ: plazomicin; PTA: probability of target attainment; QDS: four times daily; rRNA: ribosomal ribonucleic acid; SUL/DUR: sulbactam-durlobactam; SOFA: sequential organ failure assessment; TDS: three times daily; VIM: Verona integron-mediated; VAP: ventilator-associated pneumonia; XDR, extensively drug-resistant.

Appendix A

Highlights—Novel antimicrobial agents (branded during the last 5 years)

- Cefiderocol is a new siderophore cephalosporin approved for cUTIs and HAP/VAP (FDA/EMA), active against lactose-fermenting and non-fermenting GNBs, including ESBL and carbapenemases-producing strains (including OXA-type serine beta-lactamases and MBLs, although further data are needed regarding clinical activity against MBLs).
- Meropenem/vaborbactam is a beta-lactam/beta-lactamases inhibitor combination approved for cUTIs and cIAIs (FDA), HAP/VAP, associated bacteremia and infections due to GNBs with limited treatment options (EMA). It is active against serine-beta-lactamases of class A (including ESBLs and KPCs) and class C (including AmpC) but is inactive against OXA-type beta-lactamases and MBLs.
- Imipenem/cilastatin/relebactam is a triple combination of a beta-lactam with beta-lactamases inhibitors, approved for cUTIs and cIAIs (FDA), HAP/VAP, associated bacteremia and GNBs with limited treatment options (EMA). It is active against lactose-fermenting and non-fermenting GNBs, including strains producing ESBL/KPC/AmpC (including imipenem-R); it is inactive against *A. baumannii*, and MBLs-producing GNBs.
- Eravacycline is a new glycylicycline approved for cIAIs (FDA/EMA), with a wide spectrum of activity against Gram-positive and Gram-negative pathogens, including ESBL-producing *Enterobacterales* (and some CRE strains) and *A. baumannii* (including some CRAB strains). It is inactive against *P. aeruginosa* and *B. cenocepacia*.
- Omadacycline is a novel tetracycline, approved for ABSSI and CABP (FDA), with a broad spectrum of activity against Gram-positive, Gram-negative and atypical bacteria, including ESBL-producing *Enterobacterales* and some CRE, and *A. baumannii* (including some CRAB), while it is inactive against *P. aeruginosa*, *P. mirabilis*, *Providencia* spp., and *M. morgannii*. Its role for ICU patients and against MDR-GNBs, such as CRE/CRAB is not yet established. Omadacycline also has an oral formulation.
- Plazomicin is a new semi-synthetic aminoglycoside approved for cUTIs (FDA), active against GNBs (better activity against lactose-fermenting ones), including CREs and AG-resistant producing several AMEs. It is inactive against *A. baumannii* and *S. maltophilia*, while its activity against *P. aeruginosa* is variable.
- Application of stringent antimicrobial stewardship programs, along with pK/pD optimization, may preclude indiscriminate use of these valuable additions to our antimicrobial armamentarium and prolong their self-lives.

Highlights—Antimicrobials in phase 3 clinical trials

- Aztreonam-avibactam can be a valuable option for the management of MBL-producing *Enterobacterales*.
- Cefepime-enmetazobactam possesses excellent activity against ESBL-producing *Enterobacterales* and can be considered as a carbapenem-sparing regimen in cUTIs, and possibly in VAP/HAP as it exhibits good ELF penetration. MBLs are not inhibited by cefepime-enmetazobactam.

- Cefepime-zidebactam and cefepime-taniborbactam are active against a wide range of β -lactamases from classes A, B, C, and D, conferring them a valuable option against MDR-GNB infections.
- Sulbactam-durlobactam's strong anti-D activity against the OXA family of enzymes, makes it a potential option for carbapenem-resistant *A. baumannii* infections.
- Sulopenem (IV and oral) and tebipenem (oral) may have a role in the treatment of complicated and uncomplicated UTIs caused by ESBL, AmpC *Enterobacterales*, and quinolone-resistant uropathogens.
- Benapenem is another novel carbapenem, currently in phase 2/3 study for cUTIs.

References

- Magiorakos, A.-P.; Srinivasan, A.; Carey, R.B.; Carmeli, Y.; Falagas, M.E.; Giske, C.G.; Harbarth, S.; Hindler, J.F.; Kahlmeter, G.; Olsson-Liljequist, B.; et al. Multidrug-Resistant, Extensively Drug-Resistant and Pandrug-Resistant Bacteria: An International Expert Proposal for Interim Standard Definitions for Acquired Resistance. *Clin. Microbiol. Infect.* **2012**, *18*, 268–281. [[CrossRef](#)] [[PubMed](#)]
- Murray, C.J.; Ikuta, K.S.; Sharara, F.; Swetschinski, L.; Robles Aguilar, G.; Gray, A.; Han, C.; Bisignano, C.; Rao, P.; Wool, E.; et al. Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis. *Lancet* **2022**, *399*, 629–655. [[CrossRef](#)] [[PubMed](#)]
- Tooke, C.L.; Hinchliffe, P.; Bragginton, E.C.; Colenso, C.K.; Hirvonen, V.H.A.; Takebayashi, Y.; Spencer, J. β -Lactamases and β -Lactamase Inhibitors in the 21st Century. *J. Mol. Biol.* **2019**, *431*, 3472–3500. [[CrossRef](#)]
- He, Y.; Lei, J.; Pan, X.; Huang, X.; Zhao, Y. The Hydrolytic Water Molecule of Class A β -Lactamase Relies on the Acyl-Enzyme Intermediate ES* for Proper Coordination and Catalysis. *Sci. Rep.* **2020**, *10*, 10205. [[CrossRef](#)] [[PubMed](#)]
- Hobson, C.A.; Cointe, A.; Jacquier, H.; Choudhury, A.; Magnan, M.; Courroux, C.; Tenaillon, O.; Bonacorsi, S.; Birgy, A. Cross-Resistance to Cefiderocol and Ceftazidime–Avibactam in KPC β -Lactamase Mutants and the Inoculum Effect. *Clin. Microbiol. Infect.* **2021**, *27*, 1172.e7–1172.e10. [[CrossRef](#)]
- Jiang, M.; Sun, B.; Huang, Y.; Liu, C.; Wang, Y.; Ren, Y.; Zhang, Y.; Wang, Y.; Mu, D. Diversity of Ceftazidime-Avibactam Resistance Mechanism in KPC2-Producing *Klebsiella pneumoniae* under Antibiotic Selection Pressure. *IDR* **2022**, *15*, 4627–4636. [[CrossRef](#)]
- Shields, R.K.; Chen, L.; Cheng, S.; Chavda, K.D.; Press, E.G.; Snyder, A.; Pandey, R.; Doi, Y.; Kreiswirth, B.N.; Nguyen, M.H.; et al. Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne *Bla*_{KPC-3} Mutations during Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections. *Antimicrob. Agents Chemother.* **2017**, *61*, e02097-16. [[CrossRef](#)]
- Bahr, G.; González, L.J.; Vila, A.J. Metallo- β -Lactamases in the Age of Multidrug Resistance: From Structure and Mechanism to Evolution, Dissemination, and Inhibitor Design. *Chem. Rev.* **2021**, *121*, 7957–8094. [[CrossRef](#)]
- McKay, S.L.; Vlachos, N.; Daniels, J.B.; Albrecht, V.S.; Stevens, V.A.; Rasheed, J.K.; Johnson, J.K.; Lutgring, J.D.; Sjölund-Karlsson, M.; Halpin, A.L. Molecular Epidemiology of Carbapenem-Resistant *Acinetobacter baumannii* in the United States, 2013–2017. *Microb. Drug Resist.* **2022**, *28*, 645–653. [[CrossRef](#)]
- Bonnin, R.A.; Bernabeu, S.; Emeraud, C.; Creton, E.; Vanparis, O.; Naas, T.; Jousset, A.B.; Dortet, L. Susceptibility of OXA-48-Producing *Enterobacterales* to Imipenem/Relebactam, Meropenem/Vaborbactam and Ceftazidime/Avibactam. *Int. J. Antimicrob. Agents* **2022**, *60*, 106660. [[CrossRef](#)]
- Castanheira, M.; Deshpande, L.M.; Mendes, R.E.; Doyle, T.B.; Sader, H.S. Prevalence of Carbapenemase Genes among Carbapenem-Nonsusceptible *Enterobacterales* Collected in US Hospitals in a Five-Year Period and Activity of Ceftazidime/Avibactam and Comparator Agents. *JAC-Antimicrob. Resist.* **2022**, *4*, dlac098. [[CrossRef](#)]
- Wang, M.; Earley, M.; Chen, L.; Hanson, B.M.; Yu, Y.; Liu, Z.; Salcedo, S.; Cober, E.; Li, L.; Kanj, S.S.; et al. Clinical Outcomes and Bacterial Characteristics of Carbapenem-Resistant *Klebsiella pneumoniae* Complex among Patients from Different Global Regions (CRACKLE-2): A Prospective, Multicentre, Cohort Study. *Lancet Infect. Dis.* **2022**, *22*, 401–412. [[CrossRef](#)]
- Bilinskaya, A.; Linder, K.E.; Kuti, J.L. Plazomicin: An Intravenous Aminoglycoside Antibacterial for the Treatment of Complicated Urinary Tract Infections. *Expert Rev. Anti-Infect. Ther.* **2020**, *18*, 705–720. [[CrossRef](#)]
- Su, M.; Satola, S.W.; Read, T.D. Genome-Based Prediction of Bacterial Antibiotic Resistance. *J. Clin. Microbiol.* **2019**, *57*, e01405-18. [[CrossRef](#)]
- Wunderink, R.G.; Matsunaga, Y.; Ariyasu, M.; Clevenbergh, P.; Echols, R.; Kaye, K.S.; Kollef, M.; Menon, A.; Pogue, J.M.; Shorr, A.F.; et al. Cefiderocol versus High-Dose, Extended-Infusion Meropenem for the Treatment of Gram-Negative Nosocomial Pneumonia (APEKS-NP): A Randomised, Double-Blind, Phase 3, Non-Inferiority Trial. *Lancet Infect. Dis.* **2021**, *21*, 213–225. [[CrossRef](#)]
- Solomkin, J.; Evans, D.; Slepavicius, A.; Lee, P.; Marsh, A.; Tsai, L.; Sutcliffe, J.A.; Horn, P. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-Abdominal Infections in the Investigating Gram-Negative Infections Treated With Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. *JAMA Surg.* **2017**, *152*, 224. [[CrossRef](#)] [[PubMed](#)]
- Solomkin, J.S.; Gardovskis, J.; Lawrence, K.; Montravers, P.; Sway, A.; Evans, D.; Tsai, L. IGNITE4: Results of a Phase 3, Randomized, Multicenter, Prospective Trial of Eravacycline vs Meropenem in the Treatment of Complicated Intraabdominal Infections. *Clin. Infect. Dis.* **2019**, *69*, 921–929. [[CrossRef](#)]

18. Wunderink, R.G.; Giamarellou-Bourboulis, E.J.; Rahav, G.; Mathers, A.J.; Bassetti, M.; Vazquez, J.; Cornely, O.A.; Solomkin, J.; Bhowmick, T.; Bishara, J.; et al. Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial. *Infect. Dis. Ther.* **2018**, *7*, 439–455. [[CrossRef](#)] [[PubMed](#)]
19. Motsch, J.; Murta de Oliveira, C.; Stus, V.; Köksal, I.; Lyulko, O.; Boucher, H.W.; Kaye, K.S.; File, T.M.; Brown, M.L.; Khan, I.; et al. RESTORE-IMI 1: A Multicenter, Randomized, Double-Blind Trial Comparing Efficacy and Safety of Imipenem/Relebactam vs Colistin Plus Imipenem in Patients With Imipenem-Nonsusceptible Bacterial Infections. *Clin. Infect. Dis.* **2020**, *70*, 1799–1808. [[CrossRef](#)]
20. Titov, I.; Wunderink, R.G.; Roquilly, A.; Rodríguez Gonzalez, D.; David-Wang, A.; Boucher, H.W.; Kaye, K.S.; Losada, M.C.; Du, J.; Tipping, R.; et al. A Randomized, Double-Blind, Multicenter Trial Comparing Efficacy and Safety of Imipenem/Cilastatin Versus Piperacillin/Tazobactam in Adults with Hospital-Acquired or Ventilator-Associated Bacterial Pneumonia (RESTORE-IMI 2 Study). *Clin. Infect. Dis.* **2021**, *73*, e4539–e4548. [[CrossRef](#)] [[PubMed](#)]
21. McKinnell, J.A.; Dwyer, J.P.; Talbot, G.H.; Connolly, L.E.; Friedland, I.; Smith, A.; Jubb, A.M.; Serio, A.W.; Krause, K.M.; Daikos, G.L. Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae. *N. Engl. J. Med.* **2019**, *380*, 791–793. [[CrossRef](#)]
22. Matusik, E.; Boidin, C.; Friggeri, A.; Richard, J.-C.; Bitker, L.; Roberts, J.A.; Goutelle, S. Therapeutic Drug Monitoring of Antibiotic Drugs in Patients Receiving Continuous Renal Replacement Therapy or Intermittent Hemodialysis: A Critical Review. *Ther. Drug Monit.* **2022**, *44*, 86–102. [[CrossRef](#)]
23. Kawaguchi, N.; Katsube, T.; Echols, R.; Wajima, T. Population Pharmacokinetic Analysis of Cefiderocol, a Parenteral Siderophore Cephalosporin, in Healthy Subjects, Subjects with Various Degrees of Renal Function, and Patients with Complicated Urinary Tract Infection or Acute Uncomplicated Pyelonephritis. *Antimicrob. Agents Chemother.* **2018**, *62*, e01391-17. [[CrossRef](#)]
24. Fratoni, A.J.; Mah, J.W.; Nicolau, D.P.; Kuti, J.L. Imipenem/Cilastatin/Relebactam Pharmacokinetics in Critically Ill Patients with Augmented Renal Clearance. *J. Antimicrob. Chemother.* **2022**, *77*, 2992–2999. [[CrossRef](#)] [[PubMed](#)]
25. Bakdach, D.; Elajez, R.; Bakdach, A.R.; Awaisu, A.; De Pascale, G.; Ait Hssain, A. Pharmacokinetics, Pharmacodynamics, and Dosing Considerations of Novel β -Lactams and β -Lactam/ β -Lactamase Inhibitors in Critically Ill Adult Patients: Focus on Obesity, Augmented Renal Clearance, Renal Replacement Therapies, and Extracorporeal Membrane Oxygenation. *JCM* **2022**, *11*, 6898. [[CrossRef](#)] [[PubMed](#)]
26. Gatti, M.; Pea, F. Pharmacokinetic/Pharmacodynamic Target Attainment in Critically Ill Renal Patients on Antimicrobial Usage: Focus on Novel Beta-Lactams and Beta Lactams/Beta-Lactamase Inhibitors. *Expert Rev. Clin. Pharmacol.* **2021**, *14*, 583–599. [[CrossRef](#)] [[PubMed](#)]
27. Tamma, P.D.; Aitken, S.L.; Bonomo, R.A.; Mathers, A.J.; van Duin, D.; Clancy, C.J. Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β -Lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-P. *Aeruginosa*). *Clin. Infect. Dis.* **2021**, *72*, e169–e183. [[CrossRef](#)]
28. Paul, M.; Carrara, E.; Retamar, P.; Tängdén, T.; Bitterman, R.; Bonomo, R.A.; de Waele, J.; Daikos, G.L.; Akova, M.; Harbarth, S.; et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Guidelines for the Treatment of Infections Caused by Multidrug-Resistant Gram-Negative Bacilli (Endorsed by European Society of Intensive Care Medicine). *Clin. Microbiol. Infect.* **2022**, *28*, 521–547. [[CrossRef](#)]
29. Niederman, M.; Koulenti, D.; Lipman, J. Antimicrobial Agents with Primary Activity Against Gram-Negative Bacteria. In *Textbook of Critical Care*, 8th ed.; Vincent, J.-L., Moore, F.A., Marini, J.J., Bellomo, R., Eds.; Elsevier: Amsterdam, The Netherlands, 2023; ISBN 978-0-323-75929-8.
30. Food and Drug Administration. Center for Drug Evaluation and Research Development & Approval Process | Drugs. Available online: <https://www.fda.gov/drugs/development-approval-process-drugs> (accessed on 26 March 2023).
31. EMA Medicines. Available online: <https://www.ema.europa.eu/en/medicines> (accessed on 26 March 2023).
32. Food and Drug Administration. FETROJA (Cefiderocol) for Injection, for Intravenous Use. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209445s002lbl.pdf (accessed on 26 March 2023).
33. EMA Fetroja. Available online: <https://www.ema.europa.eu/en/medicines/human/EPAR/fetroja> (accessed on 5 December 2022).
34. Food and Drug Administration. RECARBRIOTM (Imipenem, Cilastatin, and Relebactam) for Injection, for Intravenous Use Initial U.S. Approval: 2019. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212819s002lbl.pdf (accessed on 26 March 2023).
35. EMA Recarbrio. Available online: <https://www.ema.europa.eu/en/medicines/human/EPAR/recarbrio> (accessed on 26 March 2023).
36. Food and Drug Administration. VABOMERE (Meropenem and Vaborbactam) for Injection. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209776lbl.pdf (accessed on 26 March 2023).
37. EMA Vaborem. Available online: <https://www.ema.europa.eu/en/medicines/human/EPAR/vaborem> (accessed on 26 March 2023).
38. Food and Drug Administration. XERAVA (Eravacycline) for Injection. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211109lbl.pdf (accessed on 26 March 2023).

39. EMA Xerava. Available online: <https://www.ema.europa.eu/en/medicines/human/EPAR/xerava> (accessed on 26 March 2023).
40. Food and Drug Administration. NUZYRA (Omadacycline). Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209816_209817lbl.pdf (accessed on 26 March 2023).
41. EMA Nuzyra: Withdrawn Application. Available online: <https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/nuzyra> (accessed on 26 March 2023).
42. Food and Drug Administration. Plazomicin. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210303Orig1s000lbl.pdf (accessed on 26 March 2023).
43. EMA Zemdri: Withdrawn Application. Available online: <https://www.ema.europa.eu/en/medicines/human/withdrawn-applications/zemdri> (accessed on 26 March 2023).
44. 2021 Antibacterial Agents in Clinical and Preclinical Development: An Overview and Analysis. Available online: <https://www.who.int/publications-detail-redirect/9789240047655> (accessed on 26 March 2023).
45. Ong'uti, S.; Czech, M.; Robilotti, E.; Holubar, M. Cefiderocol: A New Cephalosporin Stratagem Against Multidrug-Resistant Gram-Negative Bacteria. *Clin. Infect. Dis.* **2022**, *74*, 1303–1312. [[CrossRef](#)]
46. Longshaw, C.; Roger, E.; Santerre Henriksen, A.; Baba, T.; Nguyen, S.; Yamano, Y. Evidence for Efficacy of Cefiderocol against OXA-48-Containing Isolates from the APEKS-NP and CREDIBLE-CR Trials. *Antimicrob. Agents Chemother.* **2022**, *66*, e01100-22. [[CrossRef](#)]
47. Poirel, L.; Kieffer, N.; Nordmann, P. Stability of Cefiderocol against Clinically Significant Broad-Spectrum Oxacillinases. *Int. J. Antimicrob. Agents* **2018**, *52*, 866–867. [[CrossRef](#)]
48. Poirel, L.; Ortiz de la Rosa, J.-M.; Sadek, M.; Nordmann, P. Impact of Acquired Broad-Spectrum β -Lactamases on Susceptibility to Cefiderocol and Newly Developed β -Lactam/ β -Lactamase Inhibitor Combinations in *Escherichia coli* and *Pseudomonas aeruginosa*. *Antimicrob. Agents Chemother.* **2022**, *66*, e00039-22. [[CrossRef](#)]
49. Liu, X.; Lei, T.; Yang, Y.; Zhang, L.; Liu, H.; Leptihn, S.; Yu, Y.; Hua, X. Structural Basis of PER-1-Mediated Cefiderocol Resistance and Synergistic Inhibition of PER-1 by Cefiderocol in Combination with Avibactam or Durlabactam in *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* **2022**, *66*, e00828-22. [[CrossRef](#)] [[PubMed](#)]
50. Simner, P.J.; Beisken, S.; Bergman, Y.; Ante, M.; Posch, A.E.; Tamma, P.D. Defining Baseline Mechanisms of Cefiderocol Resistance in the Enterobacterales. *Microb. Drug Resist.* **2022**, *28*, 161–170. [[CrossRef](#)]
51. Lasarte-Monterrubio, C.; Fraile-Ribot, P.A.; Vázquez-Ucha, J.C.; Cabot, G.; Guijarro-Sánchez, P.; Alonso-García, I.; Rumbo-Feal, S.; Galán-Sánchez, F.; Beceiro, A.; Arca-Suárez, J.; et al. Activity of Cefiderocol, Imipenem/Relebactam, Cefepime/Taniborbactam and Cefepime/Zidebactam against Ceftolozane/Tazobactam- and Ceftazidime/Avibactam-Resistant *Pseudomonas aeruginosa*. *J. Antimicrob. Chemother.* **2022**, *77*, 2809–2815. [[CrossRef](#)] [[PubMed](#)]
52. Eucast: Cefiderocol Susceptibility Testing. Available online: https://www.eucast.org/eucast_news/news_singleview/?tx_ttnews%5Btt_news%5D=493&cHash=22779384b74c8cf2c55aa3f7fd69d173 (accessed on 3 December 2022).
53. Kawaguchi, N.; Katsube, T.; Echols, R.; Wajima, T. Population Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analyses of Cefiderocol, a Parenteral Siderophore Cephalosporin, in Patients with Pneumonia, Bloodstream Infection/Sepsis, or Complicated Urinary Tract Infection. *Antimicrob. Agents Chemother.* **2021**, *65*, e01437-20. [[CrossRef](#)] [[PubMed](#)]
54. Wenzler, E.; Butler, D.; Tan, X.; Katsube, T.; Wajima, T. Pharmacokinetics, Pharmacodynamics, and Dose Optimization of Cefiderocol during Continuous Renal Replacement Therapy. *Clin. Pharmacokinet.* **2022**, *61*, 539–552. [[CrossRef](#)] [[PubMed](#)]
55. Gatti, M.; Bartoletti, M.; Cojutti, P.G.; Gaibani, P.; Conti, M.; Giannella, M.; Viale, P.; Pea, F. A Descriptive Case Series of Pharmacokinetic/Pharmacodynamic Target Attainment and Microbiological Outcome in Critically Ill Patients with Documented Severe Extensively Drug-Resistant *Acinetobacter baumannii* Bloodstream Infection and/or Ventilator-Associated Pneumonia Treated with Cefiderocol. *J. Glob. Antimicrob. Resist.* **2021**, *27*, 294–298. [[CrossRef](#)]
56. Kufel, W.D.; Abouelhassan, Y.; Steele, J.M.; Gutierrez, R.L.; Perwez, T.; Bourdages, G.; Nicolau, D.P. Plasma and Cerebrospinal Fluid Concentrations of Cefiderocol during Successful Treatment of Carbapenem-Resistant *Acinetobacter baumannii* Meningitis. *J. Antimicrob. Chemother.* **2022**, *77*, 2737–2741. [[CrossRef](#)]
57. Bassetti, M.; Echols, R.; Matsunaga, Y.; Ariyasu, M.; Doi, Y.; Ferrer, R.; Lodise, T.P.; Naas, T.; Niki, Y.; Paterson, D.L.; et al. Efficacy and Safety of Cefiderocol or Best Available Therapy for the Treatment of Serious Infections Caused by Carbapenem-Resistant Gram-Negative Bacteria (CREDIBLE-CR): A Randomised, Open-Label, Multicentre, Pathogen-Focused, Descriptive, Phase 3 Trial. *Lancet Infect. Dis.* **2021**, *21*, 226–240. [[CrossRef](#)]
58. Falcone, M.; Tiseo, G.; Leonildi, A.; Della Sala, L.; Vecchione, A.; Barnini, S.; Farcomeni, A.; Menichetti, F. Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* **2022**, *66*, e02142-21. [[CrossRef](#)] [[PubMed](#)]
59. Sansone, P.; Giaccari, L.G.; Coppolino, F.; Aurilio, C.; Barbarisi, A.; Passavanti, M.B.; Pota, V.; Pace, M.C. Cefiderocol for Carbapenem-Resistant Bacteria: Handle with Care! A Review of the Real-World Evidence. *Antibiotics* **2022**, *11*, 904. [[CrossRef](#)] [[PubMed](#)]
60. Corcione, S.; De Benedetto, I.; Pinna, S.M.; Vita, D.; Lupia, T.; Montrucchio, G.; Brazzi, L.; De Rosa, F.G. Cefiderocol Use in Gram Negative Infections with Limited Therapeutic Options: Is Combination Therapy the Key? *J. Infect. Public Health* **2022**, *15*, 975–979. [[CrossRef](#)] [[PubMed](#)]

61. Zhanel, G.G.; Lawrence, C.K.; Adam, H.; Schweizer, F.; Zelenitsky, S.; Zhanel, M.; Lagacé-Wiens, P.R.S.; Walkty, A.; Denisuik, A.; Golden, A.; et al. Imipenem–Relebactam and Meropenem–Vaborbactam: Two Novel Carbapenem- β -Lactamase Inhibitor Combinations. *Drugs* **2018**, *78*, 65–98. [[CrossRef](#)] [[PubMed](#)]
62. Lob, S.H.; DePestel, D.D.; DeRyke, C.A.; Kazmierczak, K.M.; Young, K.; Motyl, M.R.; Sahm, D.F. Ceftolozane/Tazobactam and Imipenem/Relebactam Cross-Susceptibility among Clinical Isolates of *Pseudomonas aeruginosa* from Patients with Respiratory Tract Infections in ICU and Non-ICU Wards—SMART United States 2017–2019. *Open Forum Infect. Dis.* **2021**, *8*, ofab320. [[CrossRef](#)]
63. O'Donnell, J.N.; Putra, V.; Belfiore, G.M.; Maring, B.L.; Young, K.; Lodise, T.P. In Vitro Activity of Imipenem/Relebactam plus Aztreonam against Metallo- β -Lactamase-Producing, OprD-Deficient *Pseudomonas aeruginosa* with Varying Levels of Pseudomonas-Derived Cephalosporinase Production. *Int. J. Antimicrob. Agents* **2022**, *59*, 106595. [[CrossRef](#)]
64. Karlowky, J.A.; Lob, S.H.; DeRyke, C.A.; Hilbert, D.W.; Wong, M.T.; Young, K.; Siddiqui, F.; Motyl, M.R.; Sahm, D.F. In Vitro Activity of Ceftolozane-Tazobactam, Imipenem-Relebactam, Ceftazidime-Avibactam, and Comparators against *Pseudomonas aeruginosa* Isolates Collected in United States Hospitals According to Results from the SMART Surveillance Program, 2018 to 2020. *Antimicrob. Agents Chemother.* **2022**, *66*, e00189-22. [[CrossRef](#)] [[PubMed](#)]
65. Biagi, M.; Lee, M.; Wu, T.; Shajee, A.; Patel, S.; Deshpande, L.M.; Mendes, R.E.; Wenzler, E. Aztreonam in Combination with Imipenem-Relebactam against Clinical and Isogenic Strains of Serine and Metallo- β -Lactamase-Producing Enterobacterales. *Diagn. Microbiol. Infect. Dis.* **2022**, *103*, 115674. [[CrossRef](#)]
66. Maraki, S.; Mavromanolaki, V.E.; Moraitis, P.; Stafylaki, D.; Kasimati, A.; Magkafouraki, E.; Scoulica, E. Ceftazidime-Avibactam, Meropenem-Vaborbactam, and Imipenem-Relebactam in Combination with Aztreonam against Multidrug-Resistant, Metallo- β -Lactamase-Producing *Klebsiella pneumoniae*. *Eur. J. Clin. Microbiol. Infect. Dis.* **2021**, *40*, 1755–1759. [[CrossRef](#)]
67. Doi, Y. Treatment Options for Carbapenem-Resistant Gram-Negative Bacterial Infections. *Clin. Infect. Dis.* **2019**, *69*, S565–S575. [[CrossRef](#)]
68. Karlowky, J.A.; Lob, S.H.; Akrich, B.; DeRyke, C.A.; Siddiqui, F.; Young, K.; Motyl, M.R.; Hawser, S.P.; Sahm, D.F. In Vitro Activity of Imipenem/Relebactam against Piperacillin/Tazobactam-Resistant and Meropenem-Resistant Non-Morganellaceae Enterobacterales and *Pseudomonas aeruginosa* Collected from Patients with Lower Respiratory Tract Infections in Western Europe: SMART 2018–20. *JAC-Antimicrob. Resist.* **2022**, *5*, dlad003. [[CrossRef](#)]
69. Heo, Y.-A. Imipenem/Cilastatin/Relebactam: A Review in Gram-Negative Bacterial Infections. *Drugs* **2021**, *81*, 377–388. [[CrossRef](#)]
70. Patel, M.; Bellanti, F.; Daryani, N.M.; Noormohamed, N.; Hilbert, D.W.; Young, K.; Kulkarni, P.; Copalu, W.; Gheyas, F.; Rizk, M.L. Population Pharmacokinetic/Pharmacodynamic Assessment of Imipenem/Cilastatin/Relebactam in Patients with Hospital-acquired/Ventilator-associated Bacterial Pneumonia. *Clin. Transl. Sci.* **2022**, *15*, 396–408. [[CrossRef](#)] [[PubMed](#)]
71. Chen, I.H.; Nicolau, D.P.; Kuti, J.L. Imipenem/Cilastatin/Relebactam Alone and in Combination against *Pseudomonas aeruginosa* in the In Vitro Pharmacodynamic Model. *Antimicrob. Agents Chemother.* **2020**, *64*, e01764-20. [[CrossRef](#)] [[PubMed](#)]
72. Kohno, S.; Bando, H.; Yoneyama, F.; Kikukawa, H.; Kawahara, K.; Shirakawa, M.; Aoyama, N.; Brown, M.; Paschke, A.; Takase, A. The Safety and Efficacy of Relebactam/Imipenem/Cilastatin in Japanese Patients with Complicated Intra-Abdominal Infection or Complicated Urinary Tract Infection: A Multicenter, Open-Label, Noncomparative Phase 3 Study. *J. Infect. Chemother.* **2021**, *27*, 262–270. [[CrossRef](#)]
73. Rebold, N.; Morrisette, T.; Lagnf, A.M.; Alosaimy, S.; Holger, D.; Barber, K.; Justo, J.A.; Antosz, K.; Carlson, T.J.; Frens, J.J.; et al. Early Multicenter Experience with Imipenem-Cilastatin-Relebactam for Multidrug-Resistant Gram-Negative Infections. *Open Forum Infect. Dis.* **2021**, *8*, ofab554. [[CrossRef](#)] [[PubMed](#)]
74. Castanheira, M.; Huband, M.D.; Mendes, R.E.; Flamm, R.K. Meropenem-Vaborbactam Tested against Contemporary Gram-Negative Isolates Collected Worldwide during 2014, Including Carbapenem-Resistant, KPC-Producing, Multidrug-Resistant, and Extensively Drug-Resistant Enterobacteriaceae. *Antimicrob. Agents Chemother.* **2017**, *61*, e00567-17. [[CrossRef](#)]
75. Shortridge, D.; Carvalhaes, C.; Deshpande, L.; Castanheira, M. Activity of Meropenem/Vaborbactam and Comparators against Gram-Negative Isolates from Eastern and Western European Patients Hospitalized with Pneumonia Including Ventilator-Associated Pneumonia (2014–19). *J. Antimicrob. Chemother.* **2021**, *76*, 2600–2605. [[CrossRef](#)]
76. Gaibani, P.; Re, M.C.; Campoli, C.; Viale, P.L.; Ambretti, S. Bloodstream Infection Caused by KPC-Producing *Klebsiella pneumoniae* Resistant to Ceftazidime/Avibactam: Epidemiology and Genomic Characterization. *Clin. Microbiol. Infect.* **2020**, *26*, 516.e1–516.e4. [[CrossRef](#)]
77. Wilson, W.R.; Kline, E.G.; Jones, C.E.; Morder, K.T.; Mettus, R.T.; Doi, Y.; Nguyen, M.H.; Clancy, C.J.; Shields, R.K. Effects of KPC Variant and Porin Genotype on the In Vitro Activity of Meropenem-Vaborbactam against Carbapenem-Resistant *Enterobacteriaceae*. *Antimicrob. Agents Chemother.* **2019**, *63*, e02048-18. [[CrossRef](#)]
78. Tsvikovski, R.; Lomovskaya, O. Potency of Vaborbactam Is Less Affected than That of Avibactam in Strains Producing KPC-2 Mutations That Confer Resistance to Ceftazidime-Avibactam. *Antimicrob. Agents Chemother.* **2020**, *64*, e01936-19. [[CrossRef](#)] [[PubMed](#)]
79. Sun, D.; Rubio-Aparicio, D.; Nelson, K.; Dudley, M.N.; Lomovskaya, O. Meropenem-Vaborbactam Resistance Selection, Resistance Prevention, and Molecular Mechanisms in Mutants of KPC-Producing *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **2017**, *61*, e01694-17. [[CrossRef](#)] [[PubMed](#)]

80. Bhavnani, S.M.; Trang, M.; Griffith, D.C.; Lomovskaya, O.; Hammel, J.P.; Loutit, J.S.; Cammarata, S.K.; Dudley, M.N.; Ambrose, P.G.; Rubino, C.M. Pharmacokinetic-Pharmacodynamic Target Attainment Analyses as Support for Meropenem-Vaborbactam Dosing Regimens and Susceptibility Breakpoints. *Antimicrob. Agents Chemother.* **2022**, *66*, e02130-21. [[CrossRef](#)] [[PubMed](#)]
81. Kufel, W.D.; Eranki, A.P.; Paolino, K.M.; Call, A.; Miller, C.D.; Mogle, B.T. In Vivo Pharmacokinetic Analysis of Meropenem/Vaborbactam during Continuous Venovenous Haemodialysis. *J. Antimicrob. Chemother.* **2019**, *74*, 2117–2118. [[CrossRef](#)]
82. Ackley, R.; Roshdy, D.; Meredith, J.; Minor, S.; Anderson, W.E.; Capraro, G.A.; Polk, C. Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant *Enterobacteriaceae* Infections. *Antimicrob. Agents Chemother.* **2020**, *64*, e02313-19. [[CrossRef](#)]
83. Alosaimy, S.; Lagnf, A.M.; Morrisette, T.; Scipione, M.R.; Zhao, J.J.; Jorgensen, S.C.J.; Mynatt, R.; Carlson, T.J.; Jo, J.; Garey, K.W.; et al. Real-World, Multicenter Experience with Meropenem-Vaborbactam for Gram-Negative Bacterial Infections Including Carbapenem-Resistant *Enterobacteriales* and *Pseudomonas aeruginosa*. *Open Forum Infect. Dis.* **2021**, *8*, ofab371. [[CrossRef](#)]
84. Tumbarello, M.; Raffaelli, F.; Cascio, A.; Falcone, M.; Signorini, L.; Mussini, C.; De Rosa, F.G.; Losito, A.R.; De Pascale, G.; Pascale, R.; et al. Compassionate Use of Meropenem/Vaborbactam for Infections Caused by KPC-Producing *Klebsiella pneumoniae*: A Multicentre Study. *JAC-Antimicrob. Resist.* **2022**, *4*, dlac022. [[CrossRef](#)]
85. Livermore, D.M.; Mushtaq, S.; Warner, M.; Woodford, N. In Vitro Activity of Eravacycline against Carbapenem-Resistant *Enterobacteriaceae* and *Acinetobacter baumannii*. *Antimicrob. Agents Chemother.* **2016**, *60*, 3840–3844. [[CrossRef](#)]
86. Thabit, A.K.; Monogue, M.L.; Newman, J.V.; Nicolau, D.P. Assessment of in Vivo Efficacy of Eravacycline against *Enterobacteriaceae* Exhibiting Various Resistance Mechanisms: A Dose-Ranging Study and Pharmacokinetic/Pharmacodynamic Analysis. *Int. J. Antimicrob. Agents* **2018**, *51*, 727–732. [[CrossRef](#)]
87. Connors, K.P.; Housman, S.T.; Pope, J.S.; Russomanno, J.; Salerno, E.; Shore, E.; Redican, S.; Nicolau, D.P. Phase I, Open-Label, Safety and Pharmacokinetic Study To Assess Bronchopulmonary Disposition of Intravenous Eravacycline in Healthy Men and Women. *Antimicrob. Agents Chemother.* **2014**, *58*, 2113–2118. [[CrossRef](#)]
88. Meng, R.; Guan, X.; Sun, L.; Fei, Z.; Li, Y.; Luo, M.; Ma, A.; Li, H. The Efficacy and Safety of Eravacycline Compared with Current Clinically Common Antibiotics in the Treatment of Adults with Complicated Intra-Abdominal Infections: A Bayesian Network Meta-Analysis. *Front. Med.* **2022**, *9*, 935343. [[CrossRef](#)] [[PubMed](#)]
89. Eljaaly, K.; Ortwine, J.K.; Shaikhomer, M.; Almangour, T.A.; Bassetti, M. Efficacy and Safety of Eravacycline: A Meta-Analysis. *J. Glob. Antimicrob. Resist.* **2021**, *24*, 424–428. [[CrossRef](#)]
90. Alosaimy, S.; Morrisette, T.; Lagnf, A.M.; Rojas, L.M.; King, M.A.; Pullinger, B.M.; Hobbs, A.L.V.; Perkins, N.B.; Veve, M.P.; Bouchard, J.; et al. Clinical Outcomes of Eravacycline in Patients Treated Predominately for Carbapenem-Resistant *Acinetobacter baumannii*. *Microbiol. Spectr.* **2022**, *10*, e00479-22. [[CrossRef](#)]
91. Lim, C.; Teparrukkul, P.; Nuntalohit, S.; Boonsong, S.; Nilsakul, J.; Srisamang, P.; Sartorius, B.; White, N.J.; Day, N.P.J.; Cooper, B.S.; et al. Excess Mortality Attributable to Hospital-Acquired Antimicrobial-Resistant Infections: A 2-Year Prospective Surveillance Study in Northeast Thailand. *Open Forum Infect. Dis.* **2022**, *9*, ofac305. [[CrossRef](#)]
92. Zhang, Q.; Neidig, N.; Chu, T.-Y.; Divoky, C.; Carpenter, J.; Lee-Hsiao, C.; Threatt, H.; Sultana, R.; Bush, K. In Vitro Antibacterial Activity of Cefiderocol against Recent Multidrug-Resistant Carbapenem-Nonsusceptible *Enterobacteriales* Isolates. *Diagn. Microbiol. Infect. Dis.* **2022**, *103*, 115651. [[CrossRef](#)]
93. Zhanel, G.G.; Esquivel, J.; Zelenitsky, S.; Lawrence, C.K.; Adam, H.J.; Golden, A.; Hink, R.; Berry, L.; Schweizer, F.; Zhanel, M.A.; et al. Omadacycline: A Novel Oral and Intravenous Aminomethylcycline Antibiotic Agent. *Drugs* **2020**, *80*, 285–313. [[CrossRef](#)]
94. Abbey, T.; Vialichka, A.; Jurkovic, M.; Biagi, M.; Wenzler, E. Activity of Omadacycline Alone and in Combination against Carbapenem-Nonsusceptible *Acinetobacter baumannii* with Varying Minocycline Susceptibility. *Microbiol. Spectr.* **2022**, *10*, e00542-22. [[CrossRef](#)] [[PubMed](#)]
95. Noel, A.R.; Attwood, M.; Bowker, K.E.; MacGowan, A.P. In Vitro Pharmacodynamics of Omadacycline against *Escherichia coli* and *Acinetobacter baumannii*. *J. Antimicrob. Chemother.* **2021**, *76*, 667–670. [[CrossRef](#)] [[PubMed](#)]
96. O'Donnell, J.N.; Putra, V.; Maring, B.L.; Ozer, E.A.; Belfiore, G.M.; Rhodes, N.J. Effect of Omadacycline Alone and in Combination with Meropenem against Carbapenem-Resistant *Acinetobacter baumannii* Isolates. *J. Glob. Antimicrob. Resist.* **2022**, *29*, 147–149. [[CrossRef](#)]
97. Gotfried, M.H.; Horn, K.; Garrity-Ryan, L.; Villano, S.; Tzanis, E.; Chitra, S.; Manley, A.; Tanaka, S.K.; Rodvold, K.A. Comparison of Omadacycline and Tigecycline Pharmacokinetics in the Plasma, Epithelial Lining Fluid, and Alveolar Cells of Healthy Adult Subjects. *Antimicrob. Agents Chemother.* **2017**, *61*, e01135-17. [[CrossRef](#)] [[PubMed](#)]
98. Castanheira, M.; Davis, A.P.; Mendes, R.E.; Serio, A.W.; Krause, K.M.; Flamm, R.K. In Vitro Activity of Plazomicin against Gram-Negative and Gram-Positive Isolates Collected from U.S. Hospitals and Comparative Activities of Aminoglycosides against Carbapenem-Resistant *Enterobacteriaceae* and Isolates Carrying Carbapenemase Genes. *Antimicrob. Agents Chemother.* **2018**, *62*, e00313-18. [[CrossRef](#)]
99. Abd El-Aziz Gadallah, M.; El-sayed, W.M.; Hussien, M.Z.; Elheniedy, M.A.; Maxwell, S.Y. In-Vitro Activity of Plazomicin, Meropenem-Vaborbactam, and Omadacycline against Carbapenem-Resistant Gram-Negative Isolates in Egypt. *J. Chemother.* **2022**, *Online ahead of print*, 1–14. [[CrossRef](#)]
100. Serio, A.W.; Keepers, T.; Krause, K.M. Plazomicin Is Active Against Metallo- β -Lactamase-Producing *Enterobacteriaceae*. *Open Forum Infect. Dis.* **2019**, *6*, ofz123. [[CrossRef](#)] [[PubMed](#)]

101. Arca-Suárez, J.; Rodiño-Janeiro, B.K.; Pérez, A.; Guijarro-Sánchez, P.; Vázquez-Ucha, J.C.; Cruz, F.; Gómez-Garrido, J.; Alioto, T.S.; Álvarez-Tejado, M.; Gut, M.; et al. Emergence of 16S RRNA Methyltransferases among Carbapenemase-Producing Enterobacterales in Spain Studied by Whole-Genome Sequencing. *Int. J. Antimicrob. Agents* **2022**, *59*, 106456. [CrossRef]
102. Blanchard, L.S.; Van Belkum, A.; Dechaume, D.; Armstrong, T.P.; Emery, C.L.; Ying, Y.X.; Kresken, M.; Pompilio, M.; Halimi, D.; Zambardi, G. Multicenter Clinical Evaluation of ETEST Plazomicin (PLZ) for Susceptibility Testing of Enterobacterales. *J. Clin. Microbiol.* **2022**, *60*, e01831-21. [CrossRef] [PubMed]
103. Wagenlehner, F.M.E.; Cloutier, D.J.; Komirenko, A.S.; Cebrik, D.S.; Krause, K.M.; Keepers, T.R.; Connolly, L.E.; Miller, L.G.; Friedland, I.; Dwyer, J.P. Once-Daily Plazomicin for Complicated Urinary Tract Infections. *N. Engl. J. Med.* **2019**, *380*, 729–740. [CrossRef] [PubMed]
104. Yan, K.; Liang, B.; Zhang, G.; Wang, J.; Zhu, M.; Cai, Y. Efficacy and Safety of Plazomicin in the Treatment of Enterobacterales Infections: A Meta-Analysis of Randomized Controlled Trials. *Open Forum Infect. Dis.* **2022**, *9*, ofac429. [CrossRef]
105. Mauri, C.; Maraolo, A.E.; Di Bella, S.; Luzzaro, F.; Principe, L. The Revival of Aztreonam in Combination with Avibactam against Metallo- β -Lactamase-Producing Gram-Negatives: A Systematic Review of In Vitro Studies and Clinical Cases. *Antibiotics* **2021**, *10*, 1012. [CrossRef]
106. Le Terrier, C.; Nordmann, P.; Poirel, L. In Vitro Activity of Aztreonam in Combination with Newly Developed β -Lactamase Inhibitors against MDR Enterobacterales and *Pseudomonas aeruginosa* Producing Metallo- β -Lactamases. *J. Antimicrob. Chemother.* **2022**, *78*, 101–107. [CrossRef]
107. Emeraud, C.; Escaut, L.; Boucly, A.; Fortineau, N.; Bonnin, R.A.; Naas, T.; Dortet, L. Aztreonam plus Clavulanate, Tazobactam, or Avibactam for Treatment of Infections Caused by Metallo- β -Lactamase-Producing Gram-Negative Bacteria. *Antimicrob. Agents Chemother.* **2019**, *63*, e00010-19. [CrossRef]
108. Sader, H.S.; Mendes, R.E.; Arends, S.J.R.; Carvalhaes, C.G.; Castanheira, M. Antimicrobial Activities of Aztreonam-Avibactam and Comparator Agents Tested against Enterobacterales from European Hospitals Analysed by Geographic Region and Infection Type (2019–2020). *Eur. J. Clin. Microbiol. Infect. Dis.* **2022**, *41*, 477–487. [CrossRef] [PubMed]
109. Lee, M.; Abbey, T.; Biagi, M.; Wenzler, E. Activity of Aztreonam in Combination with Ceftazidime–Avibactam against Serine- and Metallo- β -Lactamase–Producing *Pseudomonas aeruginosa*. *Diagn. Microbiol. Infect. Dis.* **2021**, *99*, 115227. [CrossRef] [PubMed]
110. Yu, W.; Xiong, L.; Luo, Q.; Chen, Y.; Ji, J.; Ying, C.; Liu, Z.; Xiao, Y. In Vitro Activity Comparison of Ceftazidime–Avibactam and Aztreonam–Avibactam Against Bloodstream Infections With Carbapenem-Resistant Organisms in China. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 780365. [CrossRef]
111. Ma, K.; Feng, Y.; Zong, Z. Aztreonam-Avibactam May Not Replace Ceftazidime/Avibactam: The Case of KPC-21 Carbapenemase and Penicillin-Binding Protein 3 with Four Extra Amino Acids. *Int. J. Antimicrob. Agents* **2022**, *60*, 106642. [CrossRef]
112. Smith, N.M.; Boissonneault, K.R.; Chen, L.; Petraitis, V.; Petraitiene, R.; Tao, X.; Zhou, J.; Lang, Y.; Kavaliauskas, P.; Bulman, Z.P.; et al. Mechanistic Insights to Combating NDM- and CTX-M-Coproducing *Klebsiella pneumoniae* by Targeting Cell Wall Synthesis and Outer Membrane Integrity. *Antimicrob. Agents Chemother.* **2022**, *66*, e00527-22. [CrossRef] [PubMed]
113. Lodise, T.P.; O'Donnell, J.N.; Balevic, S.; Liu, X.; Gu, K.; George, J.; Raja, S.; Guptill, J.T.; Zaharoff, S.; Schwager, N.; et al. Pharmacokinetics of Ceftazidime-Avibactam in Combination with Aztreonam (COMBINE) in a Phase 1, Open-Label Study of Healthy Adults. *Antimicrob. Agents Chemother.* **2022**, *66*, e00936-22. [CrossRef]
114. Cornely, O.A.; Cisneros, J.M.; Torre-Cisneros, J.; Rodríguez-Hernández, M.J.; Tallón-Aguilar, L.; Calbo, E.; Horcajada, J.P.; Queckenberg, C.; Zettelmeyer, U.; Arenz, D.; et al. Pharmacokinetics and Safety of Aztreonam/Avibactam for the Treatment of Complicated Intra-Abdominal Infections in Hospitalized Adults: Results from the REJUVENATE Study. *J. Antimicrob. Chemother.* **2020**, *75*, 618–627. [CrossRef]
115. Pfizer. *A Prospective, Randomized, Open-Label, Comparative Study to Assess the Efficacy, Safety and Tolerability of Aztreonam-Avibactam (Atm-Avi) and Best Available Therapy for the Treatment of Serious Infections Due to Multi-Drug Resistant Gram-Negative Bacteria Producing Metallo-B-Lactamase (Mbl)*. Available online: clinicaltrials.gov/ct2/show/NCT03580044 (accessed on 26 March 2023).
116. Tselepis, L.; Langley, G.W.; Aboklaish, A.F.; Widlake, E.; Jackson, D.E.; Walsh, T.R.; Schofield, C.J.; Brem, J.; Tyrrell, J.M. In Vitro Efficacy of Imipenem-Relebactam and Cefepime-AAI101 against a Global Collection of ESBL-Positive and Carbapenemase-Producing Enterobacteriaceae. *Int. J. Antimicrob. Agents* **2020**, *56*, 105925. [CrossRef]
117. Vázquez-Ucha, J.C.; Lasarte-Monterrubio, C.; Guijarro-Sánchez, P.; Oviaño, M.; Álvarez-Fraga, L.; Alonso-García, I.; Arca-Suárez, J.; Bou, G.; Beceiro, A. Assessment of Activity and Resistance Mechanisms to Cefepime in Combination with the Novel β -Lactamase Inhibitors Zidebactam, Taniborbactam, and Enmetazobactam against a Multicenter Collection of Carbapenemase-Producing Enterobacterales. *Antimicrob. Agents Chemother.* **2022**, *66*, e01676-21. [CrossRef]
118. Morrissey, I.; Magnet, S.; Hawser, S.; Shapiro, S.; Knechtle, P. In Vitro Activity of Cefepime-Enmetazobactam against Gram-Negative Isolates Collected from U.S. and European Hospitals during 2014–2015. *Antimicrob. Agents Chemother.* **2019**, *63*, e00514-19. [CrossRef]
119. Papp-Wallace, K.M.; Bethel, C.R.; Caillon, J.; Barnes, M.D.; Potel, G.; Bajaksouzian, S.; Rutter, J.D.; Reghal, A.; Shapiro, S.; Taracila, M.A.; et al. Beyond Piperacillin-Tazobactam: Cefepime and AAI101 as a Potent β -Lactam– β -Lactamase Inhibitor Combination. *Antimicrob. Agents Chemother.* **2019**, *63*, e00105-19. [CrossRef] [PubMed]
120. Bernhard, F.; Odedra, R.; Sordello, S.; Cardin, R.; Franzoni, S.; Charrier, C.; Belley, A.; Warn, P.; Machacek, M.; Knechtle, P. Pharmacokinetics-Pharmacodynamics of Enmetazobactam Combined with Cefepime in a Neutropenic Murine Thigh Infection Model. *Antimicrob. Agents Chemother.* **2020**, *64*, e00078-20. [CrossRef]

121. Das, S.; Fitzgerald, R.; Ullah, A.; Bula, M.; Collins, A.M.; Mitsi, E.; Reine, J.; Hill, H.; Rylance, J.; Ferreira, D.M.; et al. Intrapulmonary Pharmacokinetics of Cefepime and Enmetazobactam in Healthy Volunteers: Towards New Treatments for Nosocomial Pneumonia. *Antimicrob. Agents Chemother.* **2020**, *65*, e01468-20. [[CrossRef](#)] [[PubMed](#)]
122. Allecra. Phase 1, Open-Label, Parallel Group, Single-Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of AAI101 with Cefepime in Subjects with Varying Degrees of Renal Function. Available online: clinicaltrials.gov/ct2/show/NCT03680352 (accessed on 26 March 2023).
123. Johnson, A.; McEntee, L.; Farrington, N.; Kolamunnage-Dona, R.; Franzoni, S.; Vezzelli, A.; Massimiliano, M.; Knechtle, P.; Belley, A.; Dane, A.; et al. Pharmacodynamics of Cefepime Combined with the Novel Extended-Spectrum- β -Lactamase (ESBL) Inhibitor Enmetazobactam for Murine Pneumonia Caused by ESBL-Producing *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **2020**, *64*, e00180-20. [[CrossRef](#)] [[PubMed](#)]
124. Kaye, K.S.; Belley, A.; Barth, P.; Lahlou, O.; Knechtle, P.; Motta, P.; Velicitat, P. Effect of Cefepime/Enmetazobactam vs. Piperacillin/Tazobactam on Clinical Cure and Microbiological Eradication in Patients with Complicated Urinary Tract Infection or Acute Pyelonephritis: A Randomized Clinical Trial. *JAMA* **2022**, *328*, 1304. [[CrossRef](#)] [[PubMed](#)]
125. More Cefepime. Available online: <https://www.allecra.com/more-cefepime> (accessed on 4 December 2022).
126. Isler, B.; Harris, P.; Stewart, A.G.; Paterson, D.L. An Update on Cefepime and Its Future Role in Combination with Novel β -Lactamase Inhibitors for MDR Enterobacterales and *Pseudomonas aeruginosa*—Authors' Response. *J. Antimicrob. Chemother.* **2021**, *76*, 3327–3328. [[CrossRef](#)]
127. Thomson, K.; AbdelGhani, S.; Snyder, J.; Thomson, G. Activity of Cefepime-Zidebactam against Multidrug-Resistant (MDR) Gram-Negative Pathogens. *Antibiotics* **2019**, *8*, 32. [[CrossRef](#)]
128. Yang, Y.; Guo, Y.; Yin, D.; Zheng, Y.; Wu, S.; Zhu, D.; Hu, F. In Vitro Activity of Cefepime-Zidebactam, Ceftazidime-Avibactam, and Other Comparators against Clinical Isolates of Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*: Results from China Antimicrobial Surveillance Network (CHINET) in 2018. *Antimicrob. Agents Chemother.* **2020**, *65*, e01726-20. [[CrossRef](#)]
129. Guo, Y.; Han, R.; Jiang, B.; Ding, L.; Yang, F.; Zheng, B.; Yang, Y.; Wu, S.; Yin, D.; Zhu, D.; et al. In Vitro Activity of New β -Lactam- β -Lactamase Inhibitor Combinations and Comparators against Clinical Isolates of Gram-Negative Bacilli: Results from the China Antimicrobial Surveillance Network (CHINET) in 2019. *Microbiol. Spectr.* **2022**, *10*, e01854-22. [[CrossRef](#)]
130. Khan, Z.; Iregui, A.; Landman, D.; Quale, J. Activity of Cefepime/Zidebactam (WCK 5222) against Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* Endemic to New York City Medical Centres. *J. Antimicrob. Chemother.* **2019**, *74*, 2938–2942. [[CrossRef](#)] [[PubMed](#)]
131. Sader, H.S.; Mendes, R.E.; Duncan, L.R.; Carvalhaes, C.G.; Castanheria, M. Antimicrobial Activity of Cefepime/Zidebactam (WCK 5222), a β -Lactam/ β -Lactam Enhancer Combination, against Clinical Isolates of Gram-Negative Bacteria Collected Worldwide (2018–19). *J. Antimicrob. Chemother.* **2022**, *77*, 2642–2649. [[CrossRef](#)] [[PubMed](#)]
132. Lepak, A.J.; Zhao, M.; Andes, D.R. WCK 5222 (Cefepime-Zidebactam) Pharmacodynamic Target Analysis against Metallo- β -Lactamase-Producing Enterobacteriaceae in the Neutropenic Mouse Pneumonia Model. *Antimicrob. Agents Chemother.* **2019**, *63*, e01648-19. [[CrossRef](#)]
133. Preston, R.A.; Mamikonyan, G.; DeGraff, S.; Chiou, J.; Kemper, C.J.; Xu, A.; Mastim, M.; Yeole, R.; Chavan, R.; Patel, A.; et al. Single-Center Evaluation of the Pharmacokinetics of WCK 5222 (Cefepime-Zidebactam Combination) in Subjects with Renal Impairment. *Antimicrob. Agents Chemother.* **2019**, *63*, e01484-18. [[CrossRef](#)] [[PubMed](#)]
134. Bhagwat, S.S.; Periasamy, H.; Takalkar, S.S.; Palwe, S.R.; Khande, H.N.; Patel, M.V. The Novel β -Lactam Enhancer Zidebactam Augments the *In Vivo* Pharmacodynamic Activity of Cefepime in a Neutropenic Mouse Lung *Acinetobacter baumannii* Infection Model. *Antimicrob. Agents Chemother.* **2019**, *63*, e02146-18. [[CrossRef](#)]
135. Avery, L.M.; Abdelraouf, K.; Nicolau, D.P. Assessment of the *In Vivo* Efficacy of WCK 5222 (Cefepime-Zidebactam) against Carbapenem-Resistant *Acinetobacter baumannii* in the Neutropenic Murine Lung Infection Model. *Antimicrob. Agents Chemother.* **2018**, *62*, e00948-18. [[CrossRef](#)]
136. Monogue, M.L.; Tabor-Rennie, J.; Abdelraouf, K.; Nicolau, D.P. In Vivo Efficacy of WCK 5222 (Cefepime-Zidebactam) against Multidrug-Resistant *Pseudomonas aeruginosa* in the Neutropenic Murine Thigh Infection Model. *Antimicrob. Agents Chemother.* **2019**, *63*, e00233-19. [[CrossRef](#)] [[PubMed](#)]
137. Wockhardt. A Phase 3, Randomized, Double-Blind, Multicenter, Comparative Study to Determine the Efficacy and Safety of Cefepime-Zidebactam vs. Meropenem in the Treatment of Complicated Urinary Tract Infection or Acute Pyelonephritis in Adults. Available online: clinicaltrials.gov/ct2/show/NCT04979806 (accessed on 26 March 2023).
138. Piccirilli, A.; Segatore, B.; Brisdelli, F.; Amicosante, G.; Perilli, M. Potent Inhibitory Activity of Taniborbactam towards NDM-1 and NDM-1Q119X Mutants, and in Vitro Activity of Cefepime/Taniborbactam against MBLs Producing Enterobacterales. *Int. J. Antimicrob. Agents* **2021**, *57*, 106228. [[CrossRef](#)] [[PubMed](#)]
139. Hernández-García, M.; García-Castillo, M.; Ruiz-Garrajosa, P.; Bou, G.; Siller-Ruiz, M.; Pitart, C.; Gracia-Ahufinger, I.; Mulet, X.; Pascual, Á.; Tormo, N.; et al. In Vitro Activity of Cefepime-Taniborbactam against Carbapenemase-Producing Enterobacterales and *Pseudomonas aeruginosa* Isolates Recovered in Spain. *Antimicrob. Agents Chemother.* **2022**, *66*, e02161-21. [[CrossRef](#)]
140. Satapoomin, N.; Dulyayangkul, P.; Avison, M.B. *Klebsiella pneumoniae* Mutants Resistant to Ceftazidime-Avibactam Plus Aztreonam, Imipenem-Relebactam, Meropenem-Vaborbactam, and Cefepime-Taniborbactam. *Antimicrob. Agents Chemother.* **2022**, *66*, e02179-21. [[CrossRef](#)]

141. Abdelraouf, K.; Almarzoky Abuhussain, S.; Nicolau, D.P. In Vivo Pharmacodynamics of New-Generation β -Lactamase Inhibitor Taniborbactam (Formerly VNRX-5133) in Combination with Cefepime against Serine- β -Lactamase-Producing Gram-Negative Bacteria. *J. Antimicrob. Chemother.* **2020**, *75*, 3601–3610. [CrossRef]
142. Dowell, J.A.; Marbury, T.C.; Smith, W.B.; Henkel, T. Safety and Pharmacokinetics of Taniborbactam (VNRX-5133) with Cefepime in Subjects with Various Degrees of Renal Impairment. *Antimicrob. Agents Chemother.* **2022**, *66*, e00253–22. [CrossRef]
143. Lasko, M.J.; Nicolau, D.P.; Asempa, T.E. Clinical Exposure–Response Relationship of Cefepime/Taniborbactam against Gram-Negative Organisms in the Murine Complicated Urinary Tract Infection Model. *J. Antimicrob. Chemother.* **2022**, *77*, 443–447. [CrossRef] [PubMed]
144. NCT03894046. Available online: <https://www.google.com/search?q=NCT03894046&oeq=NCT03894046&aqs=chrome..69i57j0i546l3j0i30i546j0i546.1576j0j15&sourceid=chrome&ie=UTF-8> (accessed on 4 December 2022).
145. UTIs: Why Did You Have to Go and Make Things so Complicated? Available online: <https://www.contagionlive.com/view/why-did-you-have-to-go-and-make-things-so-complicated-> (accessed on 4 December 2022).
146. Barnes, M.D.; Kumar, V.; Bethel, C.R.; Moussa, S.H.; O'Donnell, J.; Rutter, J.D.; Good, C.E.; Hujer, K.M.; Hujer, A.M.; Marshall, S.H.; et al. Targeting Multidrug-Resistant *Acinetobacter* spp.: Sulbactam and the Diazabicyclooctenone β -Lactamase Inhibitor ETX2514 as a Novel Therapeutic Agent. *mBio* **2019**, *10*, e00159–19. [CrossRef] [PubMed]
147. Karlowsky, J.A.; Hackel, M.A.; McLeod, S.M.; Miller, A.A. In Vitro Activity of Sulbactam–Durlobactam against Global Isolates of *Acinetobacter baumannii*-*Calcoaceticus* Complex Collected from 2016 to 2021. *Antimicrob. Agents Chemother.* **2022**, *66*, e00781–22. [CrossRef] [PubMed]
148. Segatore, B.; Piccirilli, A.; Cherubini, S.; Principe, L.; Alloggia, G.; Mezzatesta, M.L.; Salmeri, M.; Di Bella, S.; Migliavacca, R.; Piazza, A.; et al. In Vitro Activity of Sulbactam–Durlobactam against Carbapenem-Resistant *Acinetobacter baumannii* Clinical Isolates: A Multicentre Report from Italy. *Antibiotics* **2022**, *11*, 1136. [CrossRef] [PubMed]
149. Petropoulou, D.; Siopi, M.; Vourli, S.; Pournaras, S. Activity of Sulbactam-Durlobactam and Comparators Against a National Collection of Carbapenem-Resistant *Acinetobacter baumannii* Isolates from Greece. *Front. Cell. Infect. Microbiol.* **2022**, *11*, 814530. [CrossRef] [PubMed]
150. O'Donnell, J.; Preston, R.A.; Mamikonyan, G.; Stone, E.; Isaacs, R. Pharmacokinetics, Safety, and Tolerability of Intravenous Durlobactam and Sulbactam in Subjects with Renal Impairment and Healthy Matched Control Subjects. *Antimicrob. Agents Chemother.* **2019**, *63*, e00794–19. [CrossRef]
151. Rodvold, K.A.; Gotfried, M.H.; Isaacs, R.D.; O'Donnell, J.P.; Stone, E. Plasma and Intrapulmonary Concentrations of ETX2514 and Sulbactam Following Intravenous Administration of ETX2514SUL to Healthy Adult Subjects. *Antimicrob. Agents Chemother.* **2018**, *62*, e01089–18. [CrossRef]
152. Sagan, O.; Yakubsevitch, R.; Yanev, K.; Fomkin, R.; Stone, E.; Hines, D.; O'Donnell, J.; Miller, A.; Isaacs, R.; Srinivasan, S. Pharmacokinetics and Tolerability of Intravenous Sulbactam-Durlobactam with Imipenem-Cilastatin in Hospitalized Adults with Complicated Urinary Tract Infections, Including Acute Pyelonephritis. *Antimicrob. Agents Chemother.* **2020**, *64*, e01506–19. [CrossRef]
153. Entasis Therapeutics Announces Positive Topline Results for Sulbactam-Durlobactam (SUL-DUR) from Phase 3 ATTACK Trial | Entasis Therapeutics Holdings Inc. Available online: <https://investors.entasistx.com/news-releases/news-release-details/entasis-therapeutics-announces-positive-topline-results> (accessed on 4 December 2022).
154. Zhanel, G.G.; Pozdirca, M.; Golden, A.R.; Lawrence, C.K.; Zelenitsky, S.; Berry, L.; Schweizer, F.; Bay, D.; Adam, H.; Zhanel, M.A.; et al. Sulopenem: An Intravenous and Oral Penem for the Treatment of Urinary Tract Infections Due to Multidrug-Resistant Bacteria. *Drugs* **2022**, *82*, 533–557. [CrossRef]
155. Walkty, A.J.; Karlowsky, J.A.; Baxter, M.R.; Lagace-Wiens, P.R.S.; Adam, H.J.; Zhanel, G.G. In Vitro Activity of Sulopenem against 1880 Bacterial Pathogens Isolated from Canadian Patients with Urinary Tract Infections (CANWARD, 2014–2021). *J. Antimicrob. Chemother.* **2022**, *77*, 3414–3420. [CrossRef] [PubMed]
156. Karlowsky, J.A.; Adam, H.J.; Baxter, M.R.; Denisuk, A.J.; Lagacé-Wiens, P.R.S.; Walkty, A.J.; Puttagunta, S.; Dunne, M.W.; Zhanel, G.G. In Vitro Activity of Sulopenem, an Oral Penem, against Urinary Isolates of *Escherichia coli*. *Antimicrob. Agents Chemother.* **2019**, *63*, e01832–18. [CrossRef]
157. Dunne, M.W.; Aronin, S.I.; Das, A.F.; Akinapelli, K.; Zelasky, M.T.; Puttagunta, S.; Boucher, H.W. Sulopenem or Ciprofloxacin for the Treatment of Uncomplicated Urinary Tract Infections in Women: A Phase 3, Randomized Trial. *Clin. Infect. Dis.* **2022**, *76*, 66–77. [CrossRef]
158. NCT05584657. Available online: <https://www.google.com/search?q=NCT05584657&oeq=NCT05584657&aqs=chrome..69i57j0i546l4.1631j0j15&sourceid=chrome&ie=UTF-8> (accessed on 4 December 2022).
159. Iterum Therapeutics Announces Topline Results from Phase 3 Clinical Trial of Oral and IV Sulopenem for the Treatment of Complicated Intra-Abdominal Infections-Drugs.Com MedNews. Available online: https://www.drugs.com/clinical_trials/iterum-therapeutics-announces-topline-results-phase-3-clinical-trial-oral-iv-sulopenem-complicated-18400.html (accessed on 4 December 2022).
160. Sun, Z.; Su, L.; Cotroneo, N.; Critchley, I.; Pucci, M.; Jain, A.; Palzkill, T. Evaluation of Tebipenem Hydrolysis by β -Lactamases Prevalent in Complicated Urinary Tract Infections. *Antimicrob. Agents Chemother.* **2022**, *66*, e02396–21. [CrossRef]
161. Cotroneo, N.; Rubio, A.; Critchley, I.A.; Pillar, C.; Pucci, M.J. In Vitro and In Vivo Characterization of Tebipenem, an Oral Carbapenem. *Antimicrob. Agents Chemother.* **2020**, *64*, e02240–19. [CrossRef] [PubMed]

162. Rodvold, K.A.; Gotfried, M.H.; Gupta, V.; Ek, A.; Srivastava, P.; Talley, A.; Bruss, J. Plasma and Intrapulmonary Concentrations of Tebipenem Following Oral Administration of Tebipenem Pivoxil Hydrobromide to Healthy Adult Subjects. *Antimicrob. Agents Chemother.* **2022**, *66*, e00590-22. [CrossRef] [PubMed]
163. McEntee, L.; Johnson, A.; Farrington, N.; Unsworth, J.; Dane, A.; Jain, A.; Cotroneo, N.; Critchley, I.; Melnick, D.; Parr, T.; et al. Pharmacodynamics of Tebipenem: New Options for Oral Treatment of Multidrug-Resistant Gram-Negative Infections. *Antimicrob. Agents Chemother.* **2019**, *63*, e00603-19. [CrossRef]
164. Patel, G.; Rodvold, K.A.; Gupta, V.K.; Bruss, J.; Gasink, L.; Bajraktari, F.; Lei, Y.; Jain, A.; Srivastava, P.; Talley, A.K. Pharmacokinetics of Oral Tebipenem Pivoxil Hydrobromide in Subjects with Various Degrees of Renal Impairment. *Antimicrob. Agents Chemother.* **2022**, *66*, e02407-21. [CrossRef]
165. Eckburg, P.B.; Muir, L.; Critchley, I.A.; Walpole, S.; Kwak, H.; Phelan, A.-M.; Moore, G.; Jain, A.; Keutzer, T.; Dane, A.; et al. Oral Tebipenem Pivoxil Hydrobromide in Complicated Urinary Tract Infection. *N. Engl. J. Med.* **2022**, *386*, 1327–1338. [CrossRef] [PubMed]
166. Ji, X.; Xue, F.; Kang, Z.; Zhong, W.; Kuan, I.H.; Yang, X.; Zhu, X.; Li, Y.; Lv, Y. Model-Informed Drug Development, Pharmacokinetic/Pharmacodynamic Cutoff Value Determination, and Antibacterial Efficacy of Benapenem against *Enterobacteriaceae*. *Antimicrob. Agents Chemother.* **2020**, *64*, e01751-19. [CrossRef]
167. Zhao, C.-Y.; Lv, Y.; Zhu, Y.; Wei, M.-J.; Liu, M.-Y.; Ji, X.-W.; Kang, Z.-S.; Xia, Y.-H.; Tian, J.-H.; Ma, Y.; et al. A First-in-Human Safety, Tolerability, and Pharmacokinetics Study of Benapenem in Healthy Chinese Volunteers. *Antimicrob. Agents Chemother.* **2019**, *63*, e02188-18. [CrossRef] [PubMed]
168. Yang, H.; Zhang, M.; Chen, Y.; Ren, H.; Zhang, H.; Yu, C.; Lu, J.; You, L.; Yu, J.; Liang, H.; et al. Pharmacokinetics of Benapenem for Injection in Subjects with Mild to Moderate Renal Impairment. *Eur. J. Clin. Pharmacol.* **2022**, *78*, 1079–1086. [CrossRef]
169. Sihuan Pharmaceutical Holdings Group Ltd. *A Phase 2, Randomized, Double-Blind, Positive-Control, Multicenter, Prospective Study to Assess Efficacy and Safety of Intravenous Benapenem in Patients with Complicated Urinary Tract Infection (CUTI) or Acute Pyelonephritis (AP)*. Available online: clinicaltrials.gov/ct2/show/NCT04505683 (accessed on 23 March 2023).
170. Timsit, J.-F.; Wicky, P.-H.; de Montmollin, E. Treatment of Severe Infections Due to Metallo-Betalactamases *Enterobacteriales* in Critically Ill Patients. *Antibiotics* **2022**, *11*, 144. [CrossRef]
171. Belati, A.; Bavaro, D.F.; Diella, L.; De Gennaro, N.; Di Gennaro, F.; Saracino, A. Meropenem/Vaborbactam Plus Aztreonam as a Possible Treatment Strategy for Bloodstream Infections Caused by Ceftazidime/Avibactam-Resistant *Klebsiella pneumoniae*: A Retrospective Case Series and Literature Review. *Antibiotics* **2022**, *11*, 373. [CrossRef]
172. Pogue, J.M.; Bonomo, R.A.; Kaye, K.S. Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations. *Clin. Infect. Dis.* **2019**, *68*, 519–524. [CrossRef] [PubMed]
173. Findlay, J.; Rens, C.; Poirel, L.; Nordmann, P. In Vitro Mechanisms of Resistance Development to Imipenem-Relebactam in KPC-Producing *Klebsiella pneumoniae*. *Antimicrob. Agents Chemother.* **2022**, *66*, e00918-22. [CrossRef] [PubMed]
174. Boyd, S.E.; Holmes, A.; Peck, R.; Livermore, D.M.; Hope, W. OXA-48-Like β -Lactamases: Global Epidemiology, Treatment Options, and Development Pipeline. *Antimicrob. Agents Chemother.* **2022**, *66*, e00216-22. [CrossRef]
175. Tamma, P.D.; Bergman, Y.; Jacobs, E.B.; Lee, J.H.; Lewis, S.; Cosgrove, S.E.; Simner, P.J. For the Centers for Disease Control and Prevention Epicenters Program Comparing the Activity of Novel Antibiotic Agents against Carbapenem-Resistant Enterobacterales Clinical Isolates. *Infect. Control Hosp. Epidemiol.* **2022**; Ahead of print. [CrossRef]
176. Nulsopapon, P.; Pongchaidecha, M.; Nasomsong, W.; Polwichai, P.; Suphankong, S.; Sirichote, P.; Chaisomboonpan, S.; Santimaleeworagun, W. Antimicrobial Activity Profiles and Potential Antimicrobial Regimens against Carbapenem-Resistant Enterobacterales Isolated from Multi-Centers in Western Thailand. *Antibiotics* **2022**, *11*, 355. [CrossRef]
177. Papadimitriou-Olivgeris, M.; Bartzavali, C.; Lambropoulou, A.; Solomou, A.; Tsiata, E.; Anastassiou, E.D.; Fligou, F.; Marangos, M.; Spiliopoulou, I.; Christofidou, M. Reversal of Carbapenemase-Producing *Klebsiella pneumoniae* Epidemiology from BlaKPC- to BlaVIM-Harboursing Isolates in a Greek ICU after Introduction of Ceftazidime/Avibactam. *J. Antimicrob. Chemother.* **2019**, *74*, 2051–2054. [CrossRef]
178. Sadek, M.; Le Guern, R.; Kipnis, E.; Gosset, P.; Poirel, L.; Dessein, R.; Nordmann, P. Progressive in Vivo Development of Resistance to Cefiderocol in *Pseudomonas aeruginosa*. *Eur. J. Clin. Microbiol. Infect. Dis.* **2022**, *42*, 61–66. [CrossRef] [PubMed]
179. Luterbach, C.L.; Qiu, H.; Hanafin, P.O.; Sharma, R.; Piscitelli, J.; Lin, F.-C.; Ilomaki, J.; Cober, E.; Salata, R.A.; Kalayjian, R.C.; et al. A Systems-Based Analysis of Mono- and Combination Therapy for Carbapenem-Resistant *Klebsiella pneumoniae* Bloodstream Infections. *Antimicrob. Agents Chemother.* **2022**, *66*, e00591-22. [CrossRef] [PubMed]
180. Danjean, M.; Hobson, C.A.; Gits-Muselli, M.; Courroux, C.; Monjault, A.; Bonacorsi, S.; Birgy, A. Evaluation of the Inoculum Effect of New Antibiotics against Carbapenem-Resistant Enterobacterales. *Clin. Microbiol. Infect.* **2022**, *28*, 1503.e1–1503.e3. [CrossRef]
181. PubChem Open Chemistry Database at the National Institutes of Health (NIH), U.S. National Library of Medicine. Available online: <https://pubchem.ncbi.nlm.nih.gov/> (accessed on 7 January 2021).
182. Kim, S.; Chen, J.; Cheng, T.; Gindulyte, A.; He, J.; He, S.; Li, Q.; A Shoemaker, B.; A Thiessen, P.; Yu, B.; et al. PubChem 2023 update. *Nucleic Acids Res.* **2022**, *51*, D1373–D1380. [CrossRef] [PubMed]

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