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Treatment options for *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* co-resistant to carbapenems, aminoglycosides, colistin and tigecycline. An approach based on the mechanisms of resistance to carbapenems.

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Abstract

The management of carbapenem-resistant infections is often based on colistin, tigecycline, aminoglycosides and their combinations. However, in a recent systematic review we found that Gram-negative bacteria (GNB) co-resistant to carbapanems, aminoglycosides, colistin and tigecycline (CACT-resistant) are increasingly being reported worldwide. Clinical data to guide the treatment of CACT-resistant GNB are scarce and based exclusively on few case reports and small case series but seem to indicate that appropriate (in vitro active) antimicrobial regimens, including newer antibiotics and synergistic combinations, may be associated with lower mortality. In this review we consolidate the available literature to inform clinicians dealing with CACT-resistant GNB about treatment options by considering the mechanisms of resistance to carbapenems. In combination with rapid diagnostic methods that allow fast detection of carbapenemase production, the approach proposed in this review may guide a timely and targeted treatment of patients with infections by CACT-resistant GNB. Specifically, we focus on the three most problematic species, namely *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Several treatment options are currently available for CACT-resistant *K. pneumonia*. Newer β-lactam-β-lactamase combinations, including the combination of ceftazidime/avibactam with aztreonam against metallo-β-lactamase-producing isolates, appear to be more effective compared to combinations of older agents. Options for *P. aeruginosa* (especially metallo-β-lactamase-producing strains) and *A. baumannii* remain limited. Synergistic combination of older agents (e.g. colistin- or fosfomycin-based synergistic combinations) may represent a last resort option but their use against CACT-resistant GNB requires further study.

Keywords; pandrug-resistant, treatment, carbapanemase, *Acinetobacter*, *Klebsiella*, *Pseudomonas*

Introduction

For the management of carbapenem-resistant Gram-negative bacteria (GNB), clinicians often resort to combination therapy based on colistin, aminoglycosides and tigecycline [1, 2]. However, in a recent systematic review of the literature we found that GNB with simultaneous resistance to carbapenems, aminoglycosides, colistin and tigecycline (CACT-resistant), are increasingly being reported worldwide [3]. The CACT-resistance phenotype is predominantly encountered in *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.* It typically affects severely-ill patients and patients in intensive care units, but the potential for hospital-wide dissemination or between health-care facilities has been well-documented [3].

All-cause mortality of patients with infections by CACT-resistant GNB is high (ranging from 20-71%) [3]. The limited available clinical evidence, based on case reports and small case series, seems to indicate that appropriate treatment (based on in vitro susceptibility) with newer antibiotics or synergistic combinations may reduce mortality [3]. However, guidance about treatment options for CACT-resistant bacteria is lacking.

This review aims to consolidate the available literature to inform clinicians dealing with CACT-resistant GNB about the available treatment options by considering the mechanisms of carbapenem resistance of the three most problematic GNB species, namely *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* [3-5].

Rationale for treatment selection based on mechanisms of carbapenem-resistance for CACT-resistant GNB

The mechanisms of resistance to carbapenems (predominantly carbapenemase production, as discussed later) are independent of the mechanisms of resistance to last resort antibiotics such as colistin (resistance predominantly mediated by plasmid- or chromosomal- mediated modification of the lipopolysaccharide [6, 7]), aminoglycosides (predominantly mediated by aminoglycoside modifying enzymes or 16S ribosomal RNA methyltransferases [8]), and tigecycline (predominantly mediated by overexpression of efflux pumps [9, 10]). Therefore, newer β-lactam/β-lactamase Inhibitor antibiotics and combinations that can overcome resistance mediated by carbapenemase production are still useful for CACT-resistant GNB.

The usefulness of an approach based on the mechanism of resistance becomes clearer when laboratory methods to rapidly determine the mechanism of resistance are available to the clinician [11-14]. Delays in determining antimicrobial susceptibility with traditional growth-based laboratory methods, such as broth microdilution, disk diffusion, gradient tests and agar dilution, may result in inappropriate empirical therapy, which may be associated with prolonged hospital stay and increased mortality [3, 15-17]. Rapid diagnostic methods, such as nucleic acid-based tests that detect carbapenemase genes, phenotypic assays that detect hydrolysis of carbapenems including MALDI-TOF mass spectrometry, and immunochromatographic assays, allow faster detection of carbapenemase production and many methods can even determine the most prevalent types of carbapenemases (e.g. KPC, VIM, NDM, OXA-48-like) [13, 14, 18-21]. Many of these methods can be implemented directly on spiked blood cultures [21, 22], allowing

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even earlier identification of the mechanisms of resistance and targeted treatment in a timely manner.

However, considering the limitations of some rapid diagnostic methods regarding the detection of rare or novel β-lactamase variants [21, 23-25], susceptibility to the selected treatment regimen should always be confirmed with traditional growth-based methods. Pending such confirmation (and taking into consideration local epidemiological data) it may be reasonable to use combination empirical therapy for severely-ill patients at risk for carbapenem-resistant infections [15].

Brief overview of the mechanisms of resistance to carbapenems

Understanding the molecular mechanisms of resistance to carbapenems is the most useful first step to guide the treatment of CACT-resistant GNB. Several mechanisms can result in resistance to carbapenems [26]: 1) production of carbapenemases, 2) mutation of porins resulting in reduced outer membrane permeability, 3) overexpression of efflux pumps, 4) target modification (rare). A combination of these mechanisms is also possible. The mechanisms used by each of the three species reviewed here vary significantly in prevalence, not only between different species but also between different countries or regions [8, 27-31].

Carbapenem-resistance in *K. pneumoniae*. Production of carbapenemases, which are typically acquired by horizontal gene transfer, is the predominant mechanism responsible for carbapenem-resistance in *K. pneumoniae* [8, 32]. The type of carbapenemase is highly variable in different geographical regions [8, 27, 28]. Metallo-beta lactamases (MBL) appear to be substantially more prevalent in Asia (especially the Indian subcontinent) and in some European countries. In contrast, OXA-48-like carbapenemases are most prevalent in countries of the Mediterranean Basin, especially Turkey [8, 27]. In United States, Canada, Latin America, China and some European countries (mainly Italy and Greece), KPCs are the most prevalent carbapenemases [8, 27, 33]. The frequency of carbapenemase-negative carbapenem-resistant *K. pneumoniae* is also highly variable in different countries and continents [8, 28, 32]. Porin mutations or efflux pump overexpression (often combined with the production of other beta-lactamases) appear to be responsible for the resistance in carbapenemase-negative *K. pneumoniae* [34-37].

Carbapenem-resistance in *P. aeruginosa*. In contrast to *K. pneumoniae* and other Enterobacteriaceae that acquire carbapenem-resistance predominantly by horizontal gene transfer of carbapenemases, resistance in *P. aeruginosa* is predominantly mediated by chromosomal mutations resulting in loss or reduction of porin OprD, overexpression of the cephalosporinase AmpC and overexpression of efflux pumps [38-40]. For example, only about 20% of carbapenem-resistant *P. aeruginosa* in Europe [38] and 4.3% in Canada [41] produced carbapenemases, predominantly metallo-β-lactamases (specifically VIM and IMP). However, the prevalence of MBL among carbapenem-resistant *P. aeruginosa* is rising [38] and in some settings the majority (70-88%) of carbapenem-resistant *P. aeruginosa* isolates are MBL producers [30, 31]. Furthermore, GES-type carbapenemases are increasingly being reported in *P. aeruginosa* [41-44].

Carbapenem-resistance in *A. baumannii*. Similar to *P. aeruginosa*, reduced membrane permeability and upregulated efflux pumps are important mechanisms of resistance in *A. baumannii* [45, 46]. However, production of Class D carbapenemases (OXA-23 being by far the most widespread in most countries), and less commonly Class A (including KPC and GES) and Class B (MBL) carbapenemases, is the major mechanism of carbapenem resistance in *A. baumannii* [46-48]. In contrast to OXA-48 carbapenemases of Enterobacteriaceae which are inhibited by avibactam, *A. baumannii*'s oxacillinases are resistant to all beta-lactamase inhibitors currently in clinical use, including vaborbactam, relebactam, and avibactam [49-52]. Notably, carbapenem-resistance in *A. baumannii* is rising and in many regions, especially in Europe and the Middle East, the vast majority of *A. baumannii* are resistant to carbapenems [53]. For example, about 80% of *A. baumannii* associated with hospital-acquired infections in Europe are carbapenem-non-susceptible [54, 55].

Options for CACT-resistant *K. pneumoniae*

Several treatment options are available for non-MBL carbapenemase-producing *K. pneumoniae*. Ceftazidime/avibactam [56, 57] is active against both class A (KPC) and Class D (especially OXA-48-like) carbapenemase-producing *K. pneumoniae*, whereas meropenem/vaborbactam [58] and imipenem/relebactam [59] are only active against Class A carbapenemases. A limitation of ceftazidime/avibactam is the potential for emergence of resistance during treatment due to KPC mutations [60-64]. These mutations may reverse the susceptibility to carbapenems [62, 64, 65], but switching to carbapenem monotherapy in such cases may re-select for carbapenem resistance [66]. Meropenem/vaborbactam [67] and imipenem/relebactam [59] remain active against some KPC variants conferring resistance to ceftazidime/avibactam, and against the recently described VEB-25 extended spectrum β-lactamase that has been associated with ceftazidime/avibactam resistance [24]. Furthermore, emergence of resistance may be less likely compared to ceftazidime/avibactam [63, 68]. Finally, several case reports and small series have reported successful treatment of CACT-resistant KPC-producing *K. pneumoniae* with a double carbapenem combination [69-72]. The rationale of this combination is that ertapenem due to its higher affinity with the carbapenemase enzyme acts as a suicide inhibitor, allowing higher levels of the second carbapenem (typically meropenem or doripenem) [69-72]. Optimized two-step administration (intravenous bolus followed by prolonged infusion) of meropenem has also been proposed for carbapenem-resistant isolates with MIC up to 32mg/L (and potentially up to 128mg/L) [73], but clinical data are lacking.

On the other hand, options for MBL-producing *K. pneumoniae* are limited. The novel β-lactam-β-lactamase inhibitor combinations, including ceftazidime/avibactam [56], ceftolozane/tazobactam [74], meropenem/vaborbactam [75] and imipenem/relebactam [52], are inactive against MBL-producing GNB [76]. In contrast, the combination of aztreonam with avibactam may restore activity against MBL-producing isolates [57, 77], because aztreonam is not hydrolyzed by MBLs and avibactam effectively inhibits other beta-lactamases (ESBL, KPC and OXA-48) that can hydrolyze aztreonam. The combination aztreonam-avibactam is not currently available, but the combination of ceftazidime-avibactam plus aztreonam has been used successfully against infections by MBL-producing bacteria [78-81].

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Plazomicin is more active compared to alternative aminoglycosides against carbapenem-resistant Enterobacteriaceae regardless of the mechanism of carbapenem resistance [8], and is active against colistin-resistant Enterobacteriaceae, regardless of the mechanism of polymyxin resistance [82]. However, production of 16S-rRNA-methyltransferases (which confers resistance to plazomicin) is encountered in up to 60% of MBL- producing *K. pneumoniae* [8].

Several options are also available for carbapenemase-negative carbapenem-resistant *K. pneumoniae*. Isolates with outer membrane permeability changes (typically OmpK35 and OmpK36 porin mutations) often remain susceptible to ceftazidime/avibactam [83, 84], meropenem/vaborbactam [85] and imipenem/relebactam [59, 86], albeit with higher MICs. Plazomicin is also active against the majority (95%) of carbapenemase-negative carbapenem-resistant Enterobacteriaceae [8].

Other potential options for CACT-resistant *K. pneumoniae* include eravacycline, fosfomycin and cefiderocol. Eravacycline is more potent compared to tigecycline, and may be active against some tigecycline-resistant strains (especially considering the current EUCAST susceptibility breakpoint for tigecycline) [87, 88] . Successful use of fosfomycin against extensively drug-resistant *K. pneumoniae* has been reported in small case series, often in combination with other antimicrobials [89, 90]. Despite concerns about development of resistance during treatment, this does not appear to be a problem in clinical practice possibly because fosfomycin resistance may carry a biological fitness cost [91, 92].

Finally, synergistic combinations, such as colistin-based combinations [93, 94] or combination of fosfomycin with carbapenems [90, 95] may prove useful last-resort options, but pharmacodynamic/pharmacokinetic (PK/PD) and clinical studies are lacking, especially against isolates co-resistant to all components of the combinations [3]. Synergistic combinations based on ceftazidime/avibactam (combined with fosfomycin + aztreonam or meropenem) have also been reported for the treatment of ceftazidime/avibactam-resistant strains [24]. Combinations exploiting multiple heteroresistance is another interesting option and appear to be effective against pan-resistant *K. pneumoniae* based on in vitro and in vivo animal data [96].

Based on the above evidence synthesis, treatment options for CACT-resistant *K. pneumoniae* are summarized in Figure 1.

Options for CACT-resistant *P. aeruginosa*

In contrast to CACT-resistant *K. pneumoniae*, meropenem-vaborbactam and plazomicin are not useful for CACT-resistant *P. aeruginosa*. The activity of meropenem-vaborbactam is similar to that of meropenem alone [58] and plazomicin is not better than older aminoglycosides against *P. aeruginosa* [8].

On the other hand, ceftazidime/avibactam and ceftolozane/tazobactam may retain activity against selected CACT-resistant *P. aeruginosa* strains. Both are less prone to outer membrane permeability changes (porin loss/ efflux pumps) and neither is affected by AmpC (ceftolozane is stable against AmpC and avibactam restores the activity of ceftazidime by inhibition of AmpC) [97, 98]. Therefore, both ceftazidime/avibactam and ceftolozane/tazobactam remain highly active (81-92% [97, 99-102]) against non-MBL carbapenem-resistant *P. aeruginosa*, but susceptibility may be much lower (41-48% [42, 99]) in isolates co-resistant to multiple anti-

pseudomonal beta-lactams (ceftazidime, piperacillin/tazobactam and cefepime). Generally, ceftolozane/tazobactam appears to be more potent than ceftazidime/avibactam in non-carbapenemase producing *P. aeruginosa* [97, 98], and has been used successfully against ventilator-associated pneumonia by CACT-resistant *P. aeruginosa* [103].

Resistance to ceftazidime/avibactam and ceftolozane/tazobactam is usually the result of structural modifications of AmpC (in addition to overexpression) or horizontally acquired carbapenemases [104, 105]. Imipenem-relebactam, another option against non-MBL producing *P. aeruginosa* [106], is not affected by AmpC mutations that confer resistance to ceftazidime/avibactam and ceftolozane/tazobactam [106]. However, GES-producing P. aeruginosa strains are resistant to both imipenem/relebactam [43, 44] and ceftolozane/tazobactam [42, 107], but may be susceptible against ceftazidime/avibactam [42, 107].

Neither imipenem/relebactam nor ceftolozane/tazobactam or ceftazidime/avibactam are active against MBL-producing *P. aeruginosa* [52, 56, 74]. Furthermore, in contrast to MBL-producing *K. pneumoniae*, aztreonam/avibactam cannot overcome resistance against most MBL-producing *P. aeruginosa* due to mechanisms of resistance to aztreonam independent of beta-lactamases [108]. Nevertheless, the combination of ceftazidime/avibactam with aztreonam may be useful against selected strains, with intermediate/borderline MICs to aztreonam or ceftazidime/avibactam [79, 109]. Cefiderocol on the other hand is stable to hydrolysis by all carbapenemases (including MBL and OXA) and is not affected by porin/efflux pumps mutations [110-112]. It is therefore a useful option when everything else is ineffective.

Fosfomycin has also been used successfully against CACT-resistant *P. aeruginosa* [89]. However, alternative antibiotics (if available) may be preferable given the risk of emergence of resistance during treatment with fosfomycin [113]. High-dose amikacin (25-50mg/kg/day) may also be an option for CACT-resistant *P. aeruginosa* with borderline resistance to amikacin (MIC=16mg/dl) [114]. Optimized two-step administration of meropenem (as described above for *K. pneumoniae*) may also be an option but clinical data are lacking [73]. Finally, various synergistic combinations (e.g. based on colistin [115, 116], fosfomycin [117, 118] or aminoglycosides [42]) may represent a last resort treatment option. The combination of ceftolozane-tazobactam with amikacin [42] or fosfomycin [117] may be effective based on in vitro evidence.

Based on this evidence synthesis, treatment options for CACT-resistant *P. aeruginosa* are summarized in Figure 2.

Options for CACT-resistant *A. baumannii*

Options for CACT-resistant *A. baumannii* are limited. This is reasonable considering the multiple concurrent mechanisms of resistance in *A. baumannii*, including reduced membrane permeability, increased efflux and Class B and D carbapenemase production. None of the new β-lactam-β-lactamase inhibitor combinations (meropenem/vaborbactam, imipenem/relebactam, ceftazidime/avibactam, ceftolozane/tazobactam, aztreonam/avibactam) are active against carbapenem-resistant *A. baumannii* [58, 119-122]. Furthermore, plazomicin does not have better activity compared to alternative aminoglycosides [8], and *A. baumannii* appears to be intrinsically resistant to fosfomycin [92, 123].

Potential currently available options for CACT-resistant *A. baumannii* include minocycline, eravacycline and cefiderocol. Eravacycline is more potent compared to tigecycline and may be an option against some tigecycline-resistant *A. baumannii* strains [88, 124-126]. Minocycline has also been proposed as an option and has been used against carbapenem-resistant isolates [127], but its role and activity against CACT-resistant isolates is unclear, especially considering that its susceptibility breakpoints are unclear [128] and the lack of modern PK/PD studies and randomized controlled trials [129]. Finally, cefiderocol is active against most *A. baumannii*, but cefiderocol-resistant strains have already been reported [110]. Ampicillin/sulbactam and trimethoprim/sulfamethoxazole have been used against carbapenem-resistant *A. baumannii* [126, 130-132], but their role and activity against CACT-resistant isolates is less clear.

Until cefiderocol or other new antibiotics (such as combinations with Class D carbapenemase inhibitors [49]) become widely available, or in cases of cefiderocol-resistance, synergistic combinations may represent the only option for CACT-resistant *A. baumannii*. Colistin-based synergistic combination (e.g. with rifampicin, carbapenems, ampicillin/sulbactam, fosfomycin, glycopeptides, tigecycline and minocycline) are the most studied but have been tried predominantly against carbapenem-resistant colistin-susceptible *A. baumannii*, and clinical benefit has not yet been found in most studies [2, 133-138]. Differences between in vitro and in vivo conditions, such as insufficient drug concentrations, insufficient exposure time to synergistic concentrations, host immune-pathogen interactions and fitness cost associated with colistin resistance have been proposed as potential explanations [134, 135, 139, 140].

Nevertheless, colistin-based combinations may be useful for the management of CACT-resistant *A. baumannii* based on in-vitro and animal studies [115, 138, 141-143] and limited clinical data [144-149]. Notable is the synergy between colistin and agents that are not active against Gram-negative bacteria (such as linezolid and vancomycin) suggesting that colistin may exert a sub-inhibitory permeabilizing effect that allows increased entry of other drugs into the bacteria [141, 150]. High-dose ampicillin-sulbactam combined with meropenem and colistin is another promising combination [144, 151, 152], and has been used successfully against CACT-resistant *A. baumannii* ventilator-associated pneumonia [144]. The combination of colistin with rifampicin has also been used successfully against colistin-resistant *A. baumannii* pneumonia [145], and colistin-resistant *A. baumannii* postsurgical meningitis [147, 148].

Tigecycline-based combinations have also been proposed, but have predominantly been studied against tigecycline-susceptible strains, or in combination with an in vitro active agent (predominantly colistin) [153]. Although data regarding tigecycline-based combinations against CACT-resistant GNB are limited, such combinations are often used in clinical practice given the lack of other options [149, 154]. Synergistic combinations with minocycline may also prove useful [138], but currently available data are very limited.

In summary, older agents (including minocycline, ampicillin/sulbactam and trimethoprim/sulfamethoxazole) may be an option against CACT-resistant *A. baumannii* if in vitro active, and have been used mainly in combination with other agents. Among newer (currently approved) agents, eravacycline and cefiderocol are other options. If none of the above options are active, or where newer agents are not yet available, colistin- and tigecycline-

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based synergistic combinations may prove useful, but their role against CACT-resistant strains remains understudied.

Selecting between the different options

Randomized controlled trials providing robust evidence to guide the selection of one agent over the other are lacking [3, 63, 155]. Approval of newer antimicrobials is usually based on non-inferiority trial designs, which have several limitations including insufficient power to assess the superiority of one antimicrobial over the other and even the possibility of bias favoring non-inferiority [155]. Furthermore, trials of new antimicrobials are often conducted in patients with carbapenem-susceptible infections and their results are extrapolated to patients with more resistant infections based on in vitro susceptibility data [12, 155]. Post-marketing adaptive randomized controlled trial designs have been proposed to assess newer antimicrobials for patients with multidrug-resistant GNB infections, who were not included in earlier phase studies [155]. Use of rapid diagnostic methods, combined with utilization of algorithms guided by mechanisms of resistance (such as those proposed here), may guide a more efficient targeting of newer antimicrobials in clinical trials [12, 155].

The available evidence, predominantly based on real rife observational data, suggests the superiority of newer β-lactam-β-lactamase combination regimens such as ceftazidime/avibactam, meropenem/vaborbactam or imipenem/relebactam over older antimicrobial options (including colistin, aminoglycosides, tigecycline and their combinations) against carbapenem-resistant bacteria [63, 156-160]. Furthermore, in a recent multicenter observational study the combination of ceftazidime/avibactam with aztreonam was associated with significantly lower clinical failure, mortality and length of stay compared to other active agents (including combinations of colistin, tigecycline, aminoglycosides and fosfomycin) for bloodstream infection by MBL-producing Enterobacterales (predominantly *K. pneumoniae*) [81]. Moreover, ceftazidime/avibactam has been used successfully as salvage therapy against infections by carbapenem-resistant K. pneumoniae that have failed various combination regimens [161]. Ceftazidime/avibactam and meropenem/vaborbactam appear to have similar efficacy, although emergence of resistance during treatment is more common with ceftazidime/avibactam monotherapy [68]. Nevertheless, based on limited available data ceftazidime/avibactam monotherapy and combination therapy are associated with similar outcomes [162].

Clinical data for other options (including fosfomycin, eravacycline, minocycline, plazomicin, cefiderocol, synergistic combinations) against carbapenem-resistant bacteria are still limited. The results of the prematurely terminated CARE trial seem to favor plazomicin over colistin-based combinations, although the number of patients enrolled was very small [163]. Data for the use of eravacycline against carbapenem-resistant infections are limited [164], but appears to be a good options extrapolating from trials of carbapenem-susceptible infections [165]. Minocycline has shown favorable efficacy compared to older options against carbapenem-resistant *A. baumannii* [127, 166], but the activity minocycline against tigecycline-resistant strains is unclear considering the lack of modern PK/PD studies and unclear susceptibility breakpoints [128, 129]. Intravenous fosfomycin has been used successfully against extensively drug-resistant and CACT-resistant GNB based on small case series [89, 90]. Cefiderocol has been

used successfully as a last resort option, but the limited available data against carbapenem-resistant bacteria are conflicting [167]. Finally, several in vitro studies have evaluated synergistic combinations, but clinical data against isolates co-resistant to all components of the combinations are limited to small series or case reports [3, 144, 145, 147-149].

Conclusions

Understanding the molecular mechanisms of resistance and the local epidemiology of these mechanisms is crucial in guiding decision-making when selecting appropriate (in vitro active) antimicrobials for the management of CACT-resistant GNB. This understanding becomes particularly useful in the presence of laboratory methods that can rapidly determine the molecular mechanisms of resistance. Several such methods are available, including lower-cost phenotypical assays, and are suitable for microbiology laboratories of any capacity. This review shows that several treatment options are available against CACT-resistant *K. pneumoniae* and against non-MBL CACT-resistant *P. aeruginosa*, but controlled trials to guide the selection of one agent over the other are still lacking. On the contrary, options for MBL-producing *P. aeruginosa* and CACT-resistant *A. baumannii* are limited. Cefiderocol and other novel agents under development are promising future options. Until new agents become widely available in clinical practice, more research (including PK/PD and outcome studies) on the effectiveness of synergistic combinations might help.

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References

1. Papst L, Beović B, Pulcini C, Durante-Mangoni E, Rodríguez-Baño J, Kaye KS et al. Antibiotic treatment of infections caused by carbapenem-resistant Gram-negative bacilli: an international ESCMID cross-sectional survey among infectious diseases specialists practicing in large hospitals. Clin Microbiol Infect 2018;24:1070-6. 10.1016/j.cmi.2018.01.015
2. Piperaki ET, Tzouvelekis LS, Miriagou V, Daikos GL. Carbapenem-resistant Acinetobacter baumannii: in pursuit of an effective treatment. Clin Microbiol Infect 2019;25:951-7. 10.1016/j.cmi.2019.03.014
3. Karakonstantis S, Kritsotakis EI, Gikas A. Pandrug-resistant Gram-negative bacteria: a systematic review of current epidemiology, prognosis and treatment options. J Antimicrob Chemother 2019;75:271–82. 10.1093/jac/dkz401
4. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1-12. 10.1086/595011
5. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. The Lancet Infectious Diseases 2018;18:318-27. https://doi.org/10.1016/S1473-3099(17)30753-3

6. Aghapour Z, Gholizadeh P, Ganbarov K, Bialvaei AZ, Mahmood SS, Tanomand A et al. Molecular mechanisms related to colistin resistance in Enterobacteriaceae. Infect Drug Resist 2019;12:965-75. 10.2147/idr.S199844
7. El-Sayed Ahmed MAE-G, Zhong L-L, Shen C, Yang Y, Doi Y, Tian G-B. Colistin and its role in the Era of antibiotic resistance: an extended review (2000–2019). Emerging Microbes & Infections 2020;9:868-85. 10.1080/22221751.2020.1754133
8. Castanheira M, Deshpande LM, Woosley LN, Serio AW, Krause KM, Flamm RK. Activity of plazomicin compared with other aminoglycosides against isolates from European and adjacent countries, including Enterobacteriaceae molecularly characterized for aminoglycoside-modifying enzymes and other resistance mechanisms. J Antimicrob Chemother 2018;73:3346-54. 10.1093/jac/dky344
9. Shankar C, Nabarro LEB, Anandan S, Veeraraghavan B. Minocycline and Tigecycline: What Is Their Role in the Treatment of Carbapenem-Resistant Gram-Negative Organisms? Microb Drug Resist 2017;23:437-46. 10.1089/mdr.2016.0043
10. Pournaras S, Koumaki V, Spanakis N, Gennimata V, Tsakris A. Current perspectives on tigecycline resistance in Enterobacteriaceae: susceptibility testing issues and mechanisms of resistance. Int J Antimicrob Agents 2016;48:11-8. 10.1016/j.ijantimicag.2016.04.017
11. Yasmin M, Fouts DE, Jacobs MR, Haydar H, Marshall SH, White R et al. Monitoring Ceftazidime-Avibactam (CAZ-AVI) and Aztreonam (ATM) Concentrations in the Treatment of a Bloodstream Infection Caused by a Multidrug-Resistant Enterobacter sp. Carrying both KPC-4 and NDM-1 Carbapenemases. Clin Infect Dis 2019;10.1093/cid/ciz1155
12. Bassetti M, Ariyasu M, Binkowitz B, Nagata TD, Echols RM, Matsunaga Y et al. Designing A Pathogen-Focused Study To Address The High Unmet Medical Need Represented By Carbapenem-Resistant Gram-Negative Pathogens - The International, Multicenter, Randomized, Open-Label, Phase 3 CREDIBLE-CR Study. Infect Drug Resist 2019;12:3607-23. 10.2147/idr.S225553
13. Banerjee R, Humphries R. Clinical and laboratory considerations for the rapid detection of carbapenem-resistant Enterobacteriaceae. Virulence 2017;8:427-39. 10.1080/21505594.2016.1185577
14. Dortet L, Tandé D, de Briel D, Bernabeu S, Lasserre C, Gregorowicz G et al. MALDI-TOF for the rapid detection of carbapenemase-producing Enterobacteriaceae: comparison of the commercialized MBT STAR®-Carba IVD Kit with two in-house MALDI-TOF techniques and the RAPIDEC® CARBA NP. J Antimicrob Chemother 2018;73:2352-9. 10.1093/jac/dky209
15. Gutierrez-Gutierrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Pano-Pardo JR et al. Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. Lancet Infect Dis 2017;17:726-34. 10.1016/s1473-3099(17)30228-1
16. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. BMC Infect Dis 2017;17:279. 10.1186/s12879-017-2383-z
17. Du X, Xu X, Yao J, Deng K, Chen S, Shen Z et al. Predictors of mortality in patients infected with carbapenem-resistant Acinetobacter baumannii: A systematic review and meta-analysis. Am J Infect Control 2019;47:1140-5. 10.1016/j.ajic.2019.03.003
18. Tamma PD, Simner PJ. Phenotypic Detection of Carbapenemase-Producing Organisms from Clinical Isolates. J Clin Microbiol 2018;56:10.1128/jcm.01140-18
19. Mentasti M, Prime K, Sands K, Khan S, Wootton M. Rapid detection of IMP, NDM, VIM, KPC and OXA-48-like carbapenemases from Enterobacteriales and Gram-negative non-fermenter

bacteria by real-time PCR and melt-curve analysis. Eur J Clin Microbiol Infect Dis 2019;38:2029-36. 10.1007/s10096-019-03637-5
20. Hoyos-Mallecot Y, Cabrera-Alvargonzalez JJ, Miranda-Casas C, Rojo-Martin MD, Liebana-Martos C, Navarro-Mari JM. MALDI-TOF MS, a useful instrument for differentiating metallo-beta-lactamases in Enterobacteriaceae and Pseudomonas spp. Lett Appl Microbiol 2014;58:325-9. 10.1111/lam.12203
21. Baeza LL, Pfennigwerth N, Greissl C, Gottig S, Saleh A, Stelzer Y et al. Comparison of five methods for detection of carbapenemases in Enterobacterales with proposal of a new algorithm. Clin Microbiol Infect 2019;25:1286.e9-.e15. 10.1016/j.cmi.2019.03.003
22. Meier M, Hamprecht A. Systematic Comparison of Four Methods for Detection of Carbapenemase-Producing Enterobacterales Directly from Blood Cultures. J Clin Microbiol 2019;57:10.1128/jcm.00709-19
23. Gaibani P, Lombardo D, Foschi C, Re MC, Ambretti S. Evaluation of five carbapenemase detection assays for Enterobacteriaceae harbouring blaKPC variants associated with ceftazidime/avibactam resistance. J Antimicrob Chemother 2020;10.1093/jac/dkaa079
24. Galani I, Karaiskos I, Souli M, Papoutsaki V, Galani L, Gkoufa A et al. Outbreak of KPC-2-producing Klebsiella pneumoniae endowed with ceftazidime-avibactam resistance mediated through a VEB-1-mutant (VEB-25), Greece, September to October 2019. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2020;25:2000028. 10.2807/1560-7917.ES.2020.25.3.2000028
25. Gill CM, Lasko MJ, Asempa TE, Nicolau DP. Evaluation of the EDTA-Modified Carbapenem Inactivation Method for Detecting Metallo-β-Lactamase-Producing Pseudomonas aeruginosa. J Clin Microbiol 2020;58:10.1128/jcm.02015-19
26. Eichenberger EM, Thaden JT. Epidemiology and Mechanisms of Resistance of Extensively Drug Resistant Gram-Negative Bacteria. Antibiotics (Basel, Switzerland) 2019;8:37. 10.3390/antibiotics8020037
27. van Duin D, Doi Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. Virulence 2017;8:460-9. 10.1080/21505594.2016.1222343
28. Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasevic AT et al. Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis 2017;17:153-63. 10.1016/s1473-3099(16)30257-2
29. Kazmierczak KM, de Jonge BLM, Stone GG, Sahm DF. In vitro activity of ceftazidime/avibactam against isolates of Pseudomonas aeruginosa collected in European countries: INFORM global surveillance 2012-15. J Antimicrob Chemother 2018;73:2777-81. 10.1093/jac/dky267
30. Karampatakis T, Tsergouli K, Politi L, Diamantopoulou G, Iosifidis E, Antachopoulos C et al. Molecular Epidemiology of Endemic Carbapenem-Resistant Gram-Negative Bacteria in an Intensive Care Unit. Microb Drug Resist 2019;25:712-6. 10.1089/mdr.2018.0266
31. Saharman YR, Pelegrin AC, Karuniawati A, Sedono R, Aditianingsih D, Goessens WHF et al. Epidemiology and characterisation of carbapenem-non-susceptible Pseudomonas aeruginosa in a large intensive care unit in Jakarta, Indonesia. Int J Antimicrob Agents 2019;54:655-60. 10.1016/j.ijantimicag.2019.08.003
32. Galani I, Karaiskos I, Karantani I, Papoutsaki V, Maraki S, Papaioannou V et al. Epidemiology and resistance phenotypes of carbapenemase-producing Klebsiella pneumoniae in Greece, 2014 to 2016. Eurosurveillance 2018;23:1700775. doi:https://doi.org/10.2807/1560-7917.ES.2018.23.30.1700775

33. Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. The Lancet Infectious diseases 2013;13:785-96. 10.1016/S1473-3099(13)70190-7
34. Baroud M, Dandache I, Araj GF, Wakim R, Kanj S, Kanafani Z et al. Underlying mechanisms of carbapenem resistance in extended-spectrum beta-lactamase-producing Klebsiella pneumoniae and Escherichia coli isolates at a tertiary care centre in Lebanon: role of OXA-48 and NDM-1 carbapenemases. Int J Antimicrob Agents 2013;41:75-9. 10.1016/j.ijantimicag.2012.08.010
35. Doumith M, Ellington MJ, Livermore DM, Woodford N. Molecular mechanisms disrupting porin expression in ertapenem-resistant Klebsiella and Enterobacter spp. clinical isolates from the UK. J Antimicrob Chemother 2009;63:659-67. 10.1093/jac/dkp029
36. Pulzova L, Navratilova L, Comor L. Alterations in Outer Membrane Permeability Favor Drug-Resistant Phenotype of Klebsiella pneumoniae. Microb Drug Resist 2017;23:413-20. 10.1089/mdr.2016.0017
37. Dupont H, Gaillot O, Goetgheluck A-S, Plassart C, Emond J-P, Lecuru M et al. Molecular Characterization of Carbapenem-Nonsusceptible Enterobacterial Isolates Collected during a Prospective Interregional Survey in France and Susceptibility to the Novel Ceftazidime-Avibactam and Aztreonam-Avibactam Combinations. Antimicrob Agents Chemother 2015;60:215-21. 10.1128/AAC.01559-15
38. Castanheira M, Deshpande LM, Costello A, Davies TA, Jones RN. Epidemiology and carbapenem resistance mechanisms of carbapenem-non-susceptible Pseudomonas aeruginosa collected during 2009–11 in 14 European and Mediterranean countries. J Antimicrob Chemother 2014;69:1804-14. 10.1093/jac/dku048
39. Botelho J, Grosso F, Peixe L. Antibiotic resistance in Pseudomonas aeruginosa - Mechanisms, epidemiology and evolution. Drug Resist Updat 2019;44:100640. 10.1016/j.drup.2019.07.002
40. Castanheira M, Mills JC, Farrell DJ, Jones RN. Mutation-driven β-lactam resistance mechanisms among contemporary ceftazidime-nonsusceptible Pseudomonas aeruginosa isolates from U.S. hospitals. Antimicrob Agents Chemother 2014;58:6844-50. 10.1128/aac.03681-14
41. McCracken MG, Adam HJ, Blondeau JM, Walkty AJ, Karlowsky JA, Hoban DJ et al. Characterization of carbapenem-resistant and XDR Pseudomonas aeruginosa in Canada: results of the CANWARD 2007-16 study. J Antimicrob Chemother 2019;74:iv32-iv8. 10.1093/jac/dkz285
42. Galani I, Papoutsaki V, Karantani I, Karaiskos I, Galani L, Adamou P et al. In vitro activity of ceftolozane/tazobactam alone and in combination with amikacin against MDR/XDR Pseudomonas aeruginosa isolates from Greece. J Antimicrob Chemother 2020;10.1093/jac/dkaa160
43. Karlowsky JA, Lob SH, Kazmierczak KM, Hawser SP, Magnet S, Young K et al. In vitro activity of imipenem/relebactam against Gram-negative ESKAPE pathogens isolated in 17 European countries: 2015 SMART surveillance programme. J Antimicrob Chemother 2018;73:1872-9. 10.1093/jac/dky107
44. Young K, Painter RE, Raghoobar SL, Hairston NN, Racine F, Wisniewski D et al. In vitro studies evaluating the activity of imipenem in combination with relebactam against Pseudomonas aeruginosa. BMC Microbiol 2019;19:150. 10.1186/s12866-019-1522-7
45. Wong D, Nielsen TB, Bonomo RA, Pantapalangkoor P, Luna B, Spellberg B. Clinical and Pathophysiological Overview of Acinetobacter Infections: a Century of Challenges. Clin Microbiol Rev 2017;30:409-47. 10.1128/cmr.00058-16
46. Bonnin RA, Nordmann P, Poirel L. Screening and deciphering antibiotic resistance in Acinetobacter baumannii: a state of the art. Expert Rev Anti Infect Ther 2013;11:571-83. 10.1586/eri.13.38

47. Pournaras S, Dafopoulou K, Del Franco M, Zarkotou O, Dimitroulia E, Protonotariou E et al. Predominance of international clone 2 OXA-23-producing-Acinetobacter baumannii clinical isolates in Greece, 2015: results of a nationwide study. Int J Antimicrob Agents 2017;49:749-53. 10.1016/j.ijantimicag.2017.01.028
48. Hamidian M, Nigro SJ. Emergence, molecular mechanisms and global spread of carbapenem-resistant Acinetobacter baumannii. Microbial genomics 2019;5:e000306. 10.1099/mgen.0.000306
49. Mohd Sazlly Lim S, Sime FB, Roberts JA. Multidrug-resistant Acinetobacter baumannii infections: Current evidence on treatment options and the role of pharmacokinetics/pharmacodynamics in dose optimisation. Int J Antimicrob Agents 2019;53:726-45. 10.1016/j.ijantimicag.2019.02.016
50. Mushtaq S, Vickers A, Woodford N, Livermore DM. WCK 4234, a novel diazabicyclooctane potentiating carbapenems against Enterobacteriaceae, Pseudomonas and Acinetobacter with class A, C and D β-lactamases. J Antimicrob Chemother 2017;72:1688-95. 10.1093/jac/dkx035
51. Barnes MD, Kumar V, Bethel CR, Moussa SH, O'Donnell J, Rutter JD 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. 10.1128/mBio.00159-19
52. Zhanel GG, Lawrence CK, Adam H, Schweizer F, Zelenitsky S, Zhanel M et al. Imipenem-Relebactam and Meropenem-Vaborbactam: Two Novel Carbapenem-beta-Lactamase Inhibitor Combinations. Drugs 2018;78:65-98. 10.1007/s40265-017-0851-9
53. Lob SH, Hoban DJ, Sahm DF, Badal RE. Regional differences and trends in antimicrobial susceptibility of Acinetobacter baumannii. Int J Antimicrob Agents 2016;47:317-23. 10.1016/j.ijantimicag.2016.01.015
54. Suetens C, Latour K, Kärki T, Ricchizzi E, Kinross P, Moro ML et al. Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017. Euro Surveill 2018;23:1800516. 10.2807/1560-7917.ES.2018.23.46.1800516
55. Karampatakis T, Antachopoulos C, Tsakris A, Roilides E. Molecular epidemiology of carbapenem-resistant Acinetobacter baumannii in Greece: an extended review (2000-2015). Future Microbiol 2017;12:801-15. 10.2217/fmb-2016-0200
56. Karlowsky JA, Kazmierczak KM, Bouchillon SK, de Jonge BLM, Stone GG, Sahm DF. In Vitro Activity of Ceftazidime-Avibactam against Clinical Isolates of Enterobacteriaceae and Pseudomonas aeruginosa Collected in Latin American Countries: Results from the INFORM Global Surveillance Program, 2012-2015. Antimicrob Agents Chemother 2019;10.1128/aac.01814-18
57. Jayol A, Nordmann P, Poirel L, Dubois V. Ceftazidime/avibactam alone or in combination with aztreonam against colistin-resistant and carbapenemase-producing Klebsiella pneumoniae. J Antimicrob Chemother 2018;73:542-4. 10.1093/jac/dkx393
58. Castanheira M, Huband MD, Mendes RE, Flamm RK. 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. 10.1128/AAC.00567-17
59. Haidar G, Clancy CJ, Chen L, Samanta P, Shields RK, Kreiswirth BN et al. Identifying Spectra of Activity and Therapeutic Niches for Ceftazidime-Avibactam and Imipenem-Relebactam against Carbapenem-Resistant Enterobacteriaceae. Antimicrob Agents Chemother 2017;61:10.1128/aac.00642-17

60. Winkler ML, Papp-Wallace KM, Bonomo RA. Activity of ceftazidime/avibactam against isogenic strains of Escherichia coli containing KPC and SHV beta-lactamases with single amino acid substitutions in the Omega-loop. J Antimicrob Chemother 2015;70:2279-86. 10.1093/jac/dkv094
61. Livermore DM, Warner M, Jamrozy D, Mushtaq S, Nichols WW, Mustafa N et al. In vitro selection of ceftazidime-avibactam resistance in Enterobacteriaceae with KPC-3 carbapenemase. Antimicrob Agents Chemother 2015;59:5324-30. 10.1128/aac.00678-15
62. Shields RK, Chen L, Cheng S, Chavda KD, Press EG, Snyder A et al. Emergence of Ceftazidime-Avibactam Resistance Due to Plasmid-Borne blaKPC-3 Mutations during Treatment of Carbapenem-Resistant Klebsiella pneumoniae Infections. Antimicrob Agents Chemother 2017;61:10.1128/aac.02097-16
63. Pogue JM, Bonomo RA, Kaye KS. Ceftazidime/Avibactam, Meropenem/Vaborbactam, or Both? Clinical and Formulary Considerations. Clin Infect Dis 2019;68:519-24. 10.1093/cid/ciy576
64. Mueller L, Masseron A, Prod'Hom G, Galperine T, Greub G, Poirel L et al. Phenotypic, biochemical and genetic analysis of KPC-41, a KPC-3 variant conferring resistance to ceftazidime-avibactam and exhibiting reduced carbapenemase activity. Antimicrob Agents Chemother 2019;63:10.1128/aac.01111-19
65. Haidar G, Clancy CJ, Shields RK, Hao B, Cheng S, Nguyen MH. Mutations in blaKPC-3 That Confer Ceftazidime-Avibactam Resistance Encode Novel KPC-3 Variants That Function as Extended-Spectrum beta-Lactamases. Antimicrob Agents Chemother 2017;61:10.1128/aac.02534-16
66. Shields RK, Nguyen MH, Press EG, Chen L, Kreiswirth BN, Clancy CJ. In Vitro Selection of Meropenem Resistance among Ceftazidime-Avibactam-Resistant, Meropenem-Susceptible Klebsiella pneumoniae Isolates with Variant KPC-3 Carbapenemases. Antimicrob Agents Chemother 2017;61:10.1128/aac.00079-17
67. Wilson WR, Kline EG, Jones CE, Morder KT, Mettus RT, Doi Y et al. 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. 10.1128/AAC.02048-18
68. Ackley R, Roshdy D, Meredith J, Minor S, Anderson WE, Capraro GA et al. Meropenem-Vaborbactam versus Ceftazidime-Avibactam for Treatment of Carbapenem-Resistant Enterobacteriaceae Infections. Antimicrob Agents Chemother 2020;64:10.1128/aac.02313-19
69. Oliva A, D'Abramo A, D'Agostino C, Iannetta M, Mascellino MT, Gallinelli C et al. Synergistic activity and effectiveness of a double-carbapenem regimen in pandrug-resistant Klebsiella pneumoniae bloodstream infections. J Antimicrob Chemother 2014;69:1718-20. 10.1093/jac/dku027
70. Souli M, Karaiskos I, Masgala A, Galani L, Barmpouti E, Giamarellou H. Double-carbapenem combination as salvage therapy for untreatable infections by KPC-2-producing Klebsiella pneumoniae. Eur J Clin Microbiol Infect Dis 2017;36:1305-15. 10.1007/s10096-017-2936-5
71. Emre S, Moroğlu Ç, Yıldırmak T, Şimşek F, Arabacı Ç, Özkaya Ö et al. Combination antibiotic therapy in pan-resistant klebsiella pneumoniae infection: A report of two cases. Klimik Dergisi 2018;31:169-72. 10.5152/kd.2018.40
72. Oliva A, Mascellino MT, Cipolla A, D'Abramo A, De Rosa A, Savinelli S et al. Therapeutic strategy for pandrug-resistant Klebsiella pneumoniae severe infections: short-course treatment with colistin increases the in vivo and in vitro activity of double carbapenem regimen. Int J Infect Dis 2015;33:132-4. 10.1016/j.ijid.2015.01.011

73. Song X, Wu Y, Cao L, Yao D, Long M. Is Meropenem as a Monotherapy Truly Incompetent for Meropenem-Nonsusceptible Bacterial Strains? A Pharmacokinetic/Pharmacodynamic Modeling With Monte Carlo Simulation. Front Microbiol 2019;10:2777. 10.3389/fmicb.2019.02777
74. Garcia-Fernandez S, Garcia-Castillo M, Bou G, Calvo J, Cercenado E, Delgado M et al. Activity of ceftolozane-tazobactam against Pseudomonas aeruginosa and Enterobacterales isolates recovered in Intensive Care Units in Spain: The SUPERIOR multicentre study. Int J Antimicrob Agents 2019;10.1016/j.ijantimicag.2019.02.004
75. Pfaller MA, Huband MD, Mendes RE, Flamm RK, Castanheira M. In vitro activity of meropenem/vaborbactam and characterisation of carbapenem resistance mechanisms among carbapenem-resistant Enterobacteriaceae from the 2015 meropenem/vaborbactam surveillance programme. Int J Antimicrob Agents 2018;52:144-50. 10.1016/j.ijantimicag.2018.02.021
76. Karaiskos I, Galani I, Souli M, Giamarellou H. Novel beta-lactam-beta-lactamase inhibitor combinations: expectations for the treatment of carbapenem-resistant Gram-negative pathogens. Expert Opin Drug Metab Toxicol 2019;15:133-49. 10.1080/17425255.2019.1563071
77. Kazmierczak KM, Bradford PA, Stone GG, de Jonge BLM, Sahm DF. In Vitro Activity of Ceftazidime-Avibactam and Aztreonam-Avibactam against OXA-48-Carrying Enterobacteriaceae Isolated as Part of the International Network for Optimal Resistance Monitoring (INFORM) Global Surveillance Program from 2012 to 2015. Antimicrob Agents Chemother 2018;62:e00592-18. 10.1128/aac.00592-18
78. Shaw E, Rombauts A, Tubau F, Padulles A, Camara J, Lozano T et al. Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing Klebsiella pneumoniae infection. J Antimicrob Chemother 2018;73:1104-6. 10.1093/jac/dkx496
79. Davido B, Fellous L, Lawrence C, Maxime V, Rottman M, Dinh A. Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome beta-Lactam Resistance Conferred by Metallo-beta-Lactamases in Enterobacteriaceae and Pseudomonas aeruginosa. Antimicrob Agents Chemother 2017;61:e01008-17. 10.1128/aac.01008-17
80. Emeraud C, Escaut L, Boucly A, Fortineau N, Bonnin RA, Naas T et al. Aztreonam plus clavulanate, tazobactam or avibactam for the treatment of metallo-beta-lactamase-producing-Gram negative related infections. Antimicrob Agents Chemother 2019;63:e00010-19. 10.1128/aac.00010-19
81. Falcone M, Daikos GL, Tiseo G, Bassoulis D, Giordano C, Galfo V et al. Efficacy of ceftazidime-avibactam plus aztreonam in patients with bloodstream infections caused by MBL- producing Enterobacterales. Clin Infect Dis 2020;10.1093/cid/ciaa586
82. Denervaud-Tendon V, Poirel L, Connolly LE, Krause KM, Nordmann P. Plazomicin activity against polymyxin-resistant Enterobacteriaceae, including MCR-1-producing isolates. J Antimicrob Chemother 2017;72:2787-91. 10.1093/jac/dkx239
83. Pages JM, Peslier S, Keating TA, Lavigne JP, Nichols WW. Role of the Outer Membrane and Porins in Susceptibility of beta-Lactamase-Producing Enterobacteriaceae to Ceftazidime-Avibactam. Antimicrob Agents Chemother 2015;60:1349-59. 10.1128/aac.01585-15
84. Shields RK, Clancy CJ, Hao B, Chen L, Press EG, Iovine NM et al. Effects of Klebsiella pneumoniae carbapenemase subtypes, extended-spectrum beta-lactamases, and porin mutations on the in vitro activity of ceftazidime-avibactam against carbapenem-resistant K. pneumoniae. Antimicrob Agents Chemother 2015;59:5793-7. 10.1128/aac.00548-15
85. Yasmin M, Marshall S, Jacobs M, Rhoads DD, Rojas LJ, Perez F et al. 610. Meropenem-vaborbactam (MV) In Vitro Activity Against Carbapenem-Resistant Klebsiella pneumoniae (CRKP) Isolates with Outer Membrane Porin Gene Mutations. Open Forum Infectious Diseases 2019;6:S285-S. 10.1093/ofid/ofz360.679

86. Canver MC, Satlin MJ, Westblade LF, Kreiswirth BN, Chen L, Robertson A et al. Activity of Imipenem-Relebactam and Comparator Agents against Genetically Characterized Isolates of Carbapenem-Resistant Enterobacteriaceae. Antimicrob Agents Chemother 2019;63:e00672-19. 10.1128/aac.00672-19
87. Zhanel GG, Baxter MR, Adam HJ, Sutcliffe J, Karlowsky JA. In vitro activity of eravacycline against 2213 Gram-negative and 2424 Gram-positive bacterial pathogens isolated in Canadian hospital laboratories: CANWARD surveillance study 2014–2015. Diagn Microbiol Infect Dis 2018;91:55-62. https://doi.org/10.1016/j.diagmicrobio.2017.12.013
88. Morrissey I, Olesky M, Hawser S, Lob SH, Karlowsky JA, Corey GR et al. In Vitro Activity of Eravacycline against Gram-Negative Bacilli Isolated in Clinical Laboratories Worldwide from 2013 to 2017. Antimicrob Agents Chemother 2020;64:e01699-19. 10.1128/AAC.01699-19
89. Pontikis K, Karaiskos I, Bastani S, Dimopoulos G, Kalogirou M, Katsiari M et al. Outcomes of critically ill intensive care unit patients treated with fosfomycin for infections due to pandrug-resistant and extensively drug-resistant carbapenemase-producing Gram-negative bacteria. Int J Antimicrob Agents 2014;43:52-9. 10.1016/j.ijantimicag.2013.09.010
90. Perdigao Neto LV, Oliveira MS, Martins RCR, Marchi AP, Gaudereto JJ, da Costa L et al. Fosfomycin in severe infections due to genetically distinct pan-drug-resistant Gram-negative microorganisms: synergy with meropenem. J Antimicrob Chemother 2019;74:177-81. 10.1093/jac/dky406
91. Kaye KS, Rice LB, Dane AL, Stus V, Sagan O, Fedosiuk E et al. Fosfomycin for Injection (ZTI-01) Versus Piperacillin-tazobactam for the Treatment of Complicated Urinary Tract Infection Including Acute Pyelonephritis: ZEUS, A Phase 2/3 Randomized Trial. Clin Infect Dis 2019;10.1093/cid/ciz181
92. Falagas ME, Athanasaki F, Voulgaris GL, Triarides NA, Vardakas KZ. Resistance to fosfomycin: Mechanisms, Frequency and Clinical Consequences. Int J Antimicrob Agents 2019;53:22-8. https://doi.org/10.1016/j.ijantimicag.2018.09.013
93. Brennan-Krohn T, Pironti A, Kirby JE. Synergistic Activity of Colistin-Containing Combinations against Colistin-Resistant Enterobacteriaceae. Antimicrob Agents Chemother 2018;62:e00873-18. 10.1128/aac.00873-18
94. MacNair CR, Stokes JM, Carfrae LA, Fiebig-Comyn AA, Coombes BK, Mulvey MR et al. Overcoming mcr-1 mediated colistin resistance with colistin in combination with other antibiotics. Nature Communications 2018;9:458. 10.1038/s41467-018-02875-z
95. Erturk Sengel B, Altinkanat Gelmez G, Soyletir G, Korten V. In vitro synergistic activity of fosfomycin in combination with meropenem, amikacin and colistin against OXA-48 and/or NDM-producing Klebsiella pneumoniae. J Chemother 2020;1-7. 10.1080/1120009x.2020.1745501
96. Band VI, Hufnagel DA, Jaggavarapu S, Sherman EX, Wozniak JE, Satola SW et al. Antibiotic combinations that exploit heteroresistance to multiple drugs effectively control infection. Nature Microbiology 2019;4:1627-35. 10.1038/s41564-019-0480-z
97. Buehrle DJ, Shields RK, Chen L, Hao B, Press EG, Alkrouk A et al. Evaluation of the In Vitro Activity of Ceftazidime-Avibactam and Ceftolozane-Tazobactam against Meropenem-Resistant Pseudomonas aeruginosa Isolates. Antimicrob Agents Chemother 2016;60:3227-31. 10.1128/aac.02969-15
98. Wi YM, Greenwood-Quaintance KE, Schuetz AN, Ko KS, Peck KR, Song J-H et al. Activity of Ceftolozane-Tazobactam against Carbapenem-Resistant, Non-Carbapenemase-Producing Pseudomonas aeruginosa and Associated Resistance Mechanisms. Antimicrob Agents Chemother 2017;62:e01970-17. 10.1128/AAC.01970-17

99. Mirza HC, Hortac E, Kocak AA, Demirkaya MH, Yayla B, Guclu AU et al. In Vitro Activity of Ceftolozane-Tazobactam and Ceftazidime-Avibactam against Clinical Isolates of Meropenem-Non-Susceptible Pseudomonas aeruginosa: A Two-Center Study. J Glob Antimicrob Resist 2019;10.1016/j.jgar.2019.09.016
100. Grupper M, Sutherland C, Nicolau DP. Multicenter Evaluation of Ceftazidime-Avibactam and Ceftolozane-Tazobactam Inhibitory Activity against Meropenem-Nonsusceptible Pseudomonas aeruginosa from Blood, Respiratory Tract, and Wounds. Antimicrob Agents Chemother 2017;61:10.1128/aac.00875-17
101. Sader HS, Mendes RE, Pfaller MA, Shortridge D, Flamm RK, Castanheira M. Antimicrobial Activities of Aztreonam-Avibactam and Comparator Agents against Contemporary (2016) Clinical Enterobacteriaceae Isolates. Antimicrob Agents Chemother 2018;62:e01856-17. 10.1128/aac.01856-17
102. Asempa TE, Nicolau DP, Kuti JL. Carbapenem-Nonsusceptible Pseudomonas aeruginosa Isolates from Intensive Care Units in the United States: a Potential Role for New beta-Lactam Combination Agents. J Clin Microbiol 2019;57:10.1128/jcm.00535-19
103. Alvarez Lerma F, Munoz Bermudez R, Grau S, Gracia Arnillas MP, Sorli L, Recasens L et al. Ceftolozane-tazobactam for the treatment of ventilator-associated infections by colistin-resistant Pseudomonas aeruginosa. Rev Esp Quimioter 2017;30:224-8.
104. Fraile-Ribot PA, Cabot G, Mulet X, Perianez L, Martin-Pena ML, Juan C et al. Mechanisms leading to in vivo ceftolozane/tazobactam resistance development during the treatment of infections caused by MDR Pseudomonas aeruginosa. J Antimicrob Chemother 2018;73:658-63. 10.1093/jac/dkx424
105. Cabot G, Bruchmann S, Mulet X, Zamorano L, Moya B, Juan C et al. Pseudomonas aeruginosa ceftolozane-tazobactam resistance development requires multiple mutations leading to overexpression and structural modification of AmpC. Antimicrob Agents Chemother 2014;58:3091-9. 10.1128/aac.02462-13
106. Fraile-Ribot P, Zamorano L, Orellana R, Barrio-Tofino ED, Sanchez-Diener I, Cortes-Lara S et al. Activity of imipenem/relebactam against a large collection of Pseudomonas aeruginosa clinical isolates and isogenic beta-lactam resistant mutants. Antimicrob Agents Chemother 2019;10.1128/aac.02165-19
107. Poirel L, Ortiz De La Rosa JM, Kieffer N, Dubois V, Jayol A, Nordmann P. Acquisition of Extended-Spectrum β-Lactamase GES-6 Leading to Resistance to Ceftolozane-Tazobactam Combination in Pseudomonas aeruginosa. Antimicrob Agents Chemother 2019;63:10.1128/aac.01809-18
108. Karlowsky JA, Kazmierczak KM, de Jonge BLM, Hackel MA, Sahm DF, Bradford PA. In Vitro Activity of Aztreonam-Avibactam against Enterobacteriaceae and Pseudomonas aeruginosa Isolated by Clinical Laboratories in 40 Countries from 2012 to 2015. Antimicrob Agents Chemother 2017;61:e00472-17. 10.1128/AAC.00472-17
109. Mikhail S, Singh NB, Kebriaei R, Rice SA, Stamper KC, Castanheira M et al. Evaluation of the Synergy of Ceftazidime-Avibactam in Combination with Meropenem, Amikacin, Aztreonam, Colistin, or Fosfomycin against Well-Characterized Multidrug-Resistant Klebsiella pneumoniae and Pseudomonas aeruginosa. Antimicrob Agents Chemother 2019;63:10.1128/aac.00779-19
110. Yamano Y. In Vitro Activity of Cefiderocol Against a Broad Range of Clinically Important Gram-negative Bacteria. Clin Infect Dis 2019;69:S544-s51. 10.1093/cid/ciz827
111. Sato T, Yamawaki K. Cefiderocol: Discovery, Chemistry, and In Vivo Profiles of a Novel Siderophore Cephalosporin. Clin Infect Dis 2019;69:S538-S43. 10.1093/cid/ciz826

112. Dobias J, Dénervaud-Tendon V, Poirel L, Nordmann P. Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens. Eur J Clin Microbiol Infect Dis 2017;36:2319-27. 10.1007/s10096-017-3063-z
113. Walsh CC, McIntosh MP, Peleg AY, Kirkpatrick CM, Bergen PJ. In vitro pharmacodynamics of fosfomycin against clinical isolates of Pseudomonas aeruginosa. J Antimicrob Chemother 2015;70:3042-50. 10.1093/jac/dkv221
114. Layeux B, Taccone FS, Fagnoul D, Vincent JL, Jacobs F. Amikacin monotherapy for sepsis caused by panresistant Pseudomonas aeruginosa. Antimicrob Agents Chemother 2010;54:4939-41. 10.1128/aac.00441-10
115. Vidaillac C, Benichou L, Duval RE. In vitro synergy of colistin combinations against colistin-resistant Acinetobacter baumannii, Pseudomonas aeruginosa, and Klebsiella pneumoniae isolates. Antimicrob Agents Chemother 2012;56:4856-61. 10.1128/aac.05996-11
116. Falagas ME, Bliziotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A. Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. BMC Infect Dis 2005;5:24. 10.1186/1471-2334-5-24
117. Cuba GT, Rocha-Santos G, Cayô R, Streling AP, Nodari CS, Gales AC et al. In vitro synergy of ceftolozane/tazobactam in combination with fosfomycin or aztreonam against MDR Pseudomonas aeruginosa. J Antimicrob Chemother 2020;10.1093/jac/dkaa095
118. Avery LM, Sutherland CA, Nicolau DP. Prevalence of in vitro synergistic antibiotic interaction between fosfomycin and nonsusceptible antimicrobials in carbapenem-resistant Pseudomonas aeruginosa. J Med Microbiol 2019;68:893-7. 10.1099/jmm.0.000984
119. Hsueh SC, Lee YJ, Huang YT, Liao CH, Tsuji M, Hsueh PR. In vitro activities of cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam and other comparative drugs against imipenem-resistant Pseudomonas aeruginosa and Acinetobacter baumannii, and Stenotrophomonas maltophilia, all associated with bloodstream infections in Taiwan. J Antimicrob Chemother 2018;10.1093/jac/dky425
120. Zasowski EJ, Rybak JM, Rybak MJ. The β-Lactams Strike Back: Ceftazidime-Avibactam. Pharmacotherapy 2015;35:755-70. 10.1002/phar.1622
121. Biedenbach DJ, Kazmierczak K, Bouchillon SK, Sahm DF, Bradford PA. In Vitro Activity of Aztreonam-Avibactam against a Global Collection of Gram-Negative Pathogens from 2012 and 2013. Antimicrob Agents Chemother 2015;59:4239-48. 10.1128/AAC.00206-15
122. Testa R, Canton R, Giani T, Morosini MI, Nichols WW, Seifert H et al. In vitro activity of ceftazidime, ceftaroline and aztreonam alone and in combination with avibactam against European Gram-negative and Gram-positive clinical isolates. Int J Antimicrob Agents 2015;45:641-6. 10.1016/j.ijantimicag.2014.12.033
123. Gil-Marques ML, Moreno-Martinez P, Costas C, Pachon J, Blazquez J, McConnell MJ. Peptidoglycan recycling contributes to intrinsic resistance to fosfomycin in Acinetobacter baumannii. J Antimicrob Chemother 2018;73:2960-8. 10.1093/jac/dky289
124. Seifert H, Stefanik D, Olesky M, Higgins PG. In-vitro activity of the novel fluorocycline TP-6076 against carbapenem-resistant Acinetobacter baumannii. Int J Antimicrob Agents 2019;10.1016/j.ijantimicag.2019.10.010
125. Seifert H, Stefanik D, Sutcliffe JA, Higgins PG. In-vitro activity of the novel fluorocycline eravacycline against carbapenem non-susceptible Acinetobacter baumannii. Int J Antimicrob Agents 2018;51:62-4. 10.1016/j.ijantimicag.2017.06.022
126. Nepka M, Perivolioti E, Kraniotaki E, Politi L, Tsakris A, Pournaras S. In Vitro Bactericidal Activity of Trimethoprim-Sulfamethoxazole Alone and in Combination with Colistin against Carbapenem-Resistant Acinetobacter baumannii Clinical Isolates. Antimicrob Agents Chemother 2016;60:6903-6. 10.1128/aac.01082-16

127. Fragkou PC, Poulakou G, Blizou A, Blizou M, Rapti V, Karageorgopoulos DE et al. The Role of Minocycline in the Treatment of Nosocomial Infections Caused by Multidrug, Extensively Drug and Pandrug Resistant Acinetobacter baumannii: A Systematic Review of Clinical Evidence. Microorganisms 2019;7:159. 10.3390/microorganisms7060159
128. Tsakris A, Koumaki V, Dokoumetzidis A. Minocycline susceptibility breakpoints for Acinetobacter baumannii: do we need to re-evaluate them? J Antimicrob Chemother 2019;74:295-7. 10.1093/jac/dky448
129. Zayyad H, Eliakim-Raz N, Leibovici L, Paul M. Revival of old antibiotics: needs, the state of evidence and expectations. Int J Antimicrob Agents 2017;49:536-41. 10.1016/j.ijantimicag.2016.11.021
130. Falagas ME, Vardakas KZ, Roussos NS. Trimethoprim/sulfamethoxazole for Acinetobacter spp.: A review of current microbiological and clinical evidence. Int J Antimicrob Agents 2015;46:231-41. 10.1016/j.ijantimicag.2015.04.002
131. Raz-Pasteur A, Liron Y, Amir-Ronen R, Abdelgani S, Ohanyan A, Geffen Y et al. Trimethoprim-sulfamethoxazole vs. colistin or ampicillin-sulbactam for the treatment of carbapenem-resistant Acinetobacter baumannii: A retrospective matched cohort study. J Glob Antimicrob Resist 2019;17:168-72. 10.1016/j.jgar.2018.12.001
132. Chen H, Liu Q, Chen Z, Li C. Efficacy of sulbactam for the treatment of Acinetobacter baumannii complex infection: A systematic review and meta-analysis. J Infect Chemother 2017;23:278-85. 10.1016/j.jiac.2017.01.005
133. Cai Y, Chai D, Wang R, Liang B, Bai N. Colistin resistance of Acinetobacter baumannii: clinical reports, mechanisms and antimicrobial strategies. J Antimicrob Chemother 2012;67:1607-15. 10.1093/jac/dks084
134. Nutman A, Lellouche J, Temkin E, Daikos G, Skiada A, Durante-Mangoni E et al. Colistin plus meropenem for carbapenem-resistant gram-negative infections: in vitro synergism is not associated with better clinical outcomes. Clin Microbiol Infect 10.1016/j.cmi.2020.03.035
135. Perez F, El Chakhtoura NG, Yasmin M, Bonomo RA. Polymyxins: To Combine or Not to Combine? Antibiotics (Basel) 2019;8:10.3390/antibiotics8020038
136. Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P et al. Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant Acinetobacter baumannii: A Multicenter, Randomized Clinical Trial. Clin Infect Dis 2013;57:349-58. 10.1093/cid/cit253
137. Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant Acinetobacter baumannii infections. Antimicrob Agents Chemother 2014;58:5598-601. 10.1128/aac.02435-13
138. Aranzana-Climent V, Buyck JM, Smani Y, Pachón-Diaz J, Marchand S, Couet W et al. Semi-mechanistic PK/PD modelling of combined polymyxin B and minocycline against a polymyxin-resistant strain of Acinetobacter baumannii. Clin Microbiol Infect 2020;10.1016/j.cmi.2020.01.017
139. Karakonstantis S. Re: 'Colistin plus meropenem for carbapenem-resistant gram-negative infections: in vitro synergism is not associated with better clinical outcomes' by Nutman et al. Clin Microbiol Infect 2020;
140. Karakonstantis S. Re: 'colistin plus meropenem for carbapenem-resistant gram-negative infections: in vitro synergism is not associated with better clinical outcomes' by Nutman et al. Clin Microbiol Infect 10.1016/j.cmi.2020.04.043
141. Bae S, Kim M-C, Park S-J, Kim HS, Sung H, Kim M-N et al. In Vitro Synergistic Activity of Antimicrobial Agents in Combination against Clinical Isolates of Colistin-Resistant Acinetobacter baumannii. Antimicrob Agents Chemother 2016;60:6774-9. 10.1128/AAC.00839-16

142. Lenhard JR, Thamlikitkul V, Silveira FP, Garonzik SM, Tao X, Forrest A et al. Polymyxin-resistant, carbapenem-resistant Acinetobacter baumannii is eradicated by a triple combination of agents that lack individual activity. J Antimicrob Chemother 2017;72:1415-20. 10.1093/jac/dkx002
143. Poulakou G, Renieris G, Sabrakos L, Zarkotou O, Themeli-Digalaki K, Perivolioti E et al. Daptomycin as adjunctive treatment for experimental infection by Acinetobacter baumannii with resistance to colistin. Int J Antimicrob Agents 2018;10.1016/j.ijantimicag.2018.10.024
144. Assimakopoulos SF, Karamouzos V, Lefkaditi A, Sklavou C, Kolonitsiou F, Christofidou M et al. Triple combination therapy with high-dose ampicillin/sulbactam, high-dose tigecycline and colistin in the treatment of ventilator-associated pneumonia caused by pan-drug resistant Acinetobacter baumannii: a case series study. Infez Med 2019;27:11-6.
145. Park HJ, Cho JH, Kim HJ, Han SH, Jeong SH, Byun MK. Colistin monotherapy versus colistin/rifampicin combination therapy in pneumonia caused by colistin-resistant Acinetobacter baumannii: A randomised controlled trial. J Glob Antimicrob Resist 2019;17:66-71. 10.1016/j.jgar.2018.11.016
146. Lertsrisatit Y, Santimaleeworagun W, Thunyaharn S, Traipattanakul J. In vitro activity of colistin mono- and combination therapy against colistin-resistant Acinetobacter baumannii, mechanism of resistance, and clinical outcomes of patients infected with colistin-resistant A. baumannii at a Thai university hospital. Infect Drug Resist 2017;10:437-43. 10.2147/idr.S148185
147. Rodríguez CH, Barberis C, Nastro M, Bombicino K, Granados G, Vay C et al. Impact of heteroresistance to colistin in meningitis caused by Acinetobacter baumannii. J Infect 2012;64:119-21. 10.1016/j.jinf.2011.10.007
148. Rodriguez CH, Bombicino K, Granados G, Nastro M, Vay C, Famiglietti A. Selection of colistin-resistant Acinetobacter baumannii isolates in postneurosurgical meningitis in an intensive care unit with high presence of heteroresistance to colistin. Diagn Microbiol Infect Dis 2009;65:188-91. 10.1016/j.diagmicrobio.2009.05.019
149. Kofteridis DP, Andrianaki AM, Maraki S, Mathioudaki A, Plataki M, Alexopoulou C et al. Treatment pattern, prognostic factors, and outcome in patients with infection due to pan-drug-resistant gram-negative bacteria. Eur J Clin Microbiol Infect Dis 2020;39:965-70. 10.1007/s10096-019-03784-9
150. Leite GC, Oliveira MS, Perdigao-Neto LV, Rocha CK, Guimaraes T, Rizek C et al. Antimicrobial Combinations against Pan-Resistant Acinetobacter baumannii Isolates with Different Resistance Mechanisms. PLoS One 2016;11:e0151270. 10.1371/journal.pone.0151270
151. Lenhard JR, Smith NM, Bulman ZP, Tao X, Thamlikitkul V, Shin BS et al. High-Dose Ampicillin-Sulbactam Combinations Combat Polymyxin-Resistant Acinetobacter baumannii in a Hollow-Fiber Infection Model. Antimicrob Agents Chemother 2017;61:e01268-16. 10.1128/aac.01268-16
152. Qureshi ZA, Hittle LE, O'Hara JA, Rivera JI, Syed A, Shields RK et al. Colistin-resistant Acinetobacter baumannii: beyond carbapenem resistance. Clin Infect Dis 2015;60:1295-303. 10.1093/cid/civ048
153. Li J, Yang X, Chen L, Duan X, Jiang Z. In Vitro Activity of Various Antibiotics in Combination with Tigecycline Against Acinetobacter baumannii: A Systematic Review and Meta-Analysis. Microb Drug Resist 2017;23:982-93. 10.1089/mdr.2016.0279
154. Elsayed E, Elarabi MA, Sherif DA, Elmorshedi M, El-Mashad N. Extensive drug resistant Acinetobacter baumannii: a comparative study between non-colistin based combinations. Int J Clin Pharm 2020;42:80-8. 10.1007/s11096-019-00940-1
155. Lanini S, Ioannidis JPA, Vairo F, Pletschette M, Portella G, Di Bari V et al. Non-inferiority versus superiority trial design for new antibiotics in an era of high antimicrobial resistance: the

case for post-marketing, adaptive randomised controlled trials. The Lancet Infectious Diseases 2019;19:e444-e51. https://doi.org/10.1016/S1473-3099(19)30284-1
156. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV et al. Ceftazidime-Avibactam Is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia. Antimicrob Agents Chemother 2017;61:10.1128/aac.00883-17
157. Falcone M, Bassetti M, Tiseo G, Giordano C, Nencini E, Russo A et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing Klebsiella pneumoniae. Crit Care 2020;24:29. 10.1186/s13054-020-2742-9
158. Bassetti M, Giacobbe DR, Patel N, Tillotson G, Massey J. Efficacy and Safety of Meropenem-Vaborbactam Versus Best Available Therapy for the Treatment of Carbapenem-Resistant Enterobacteriaceae Infections in Patients Without Prior Antimicrobial Failure: A Post Hoc Analysis. Adv Ther 2019;36:1771-7. 10.1007/s12325-019-00981-y
159. van Duin D, Lok JJ, Earley M, Cober E, Richter SS, Perez F et al. Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae. Clin Infect Dis 2018;66:163-71. 10.1093/cid/cix783
160. Kaye KS, Boucher HW, Brown ML, Aggrey A, Khan I, Joeng HK et al. Comparison of Treatment Outcomes between Analysis Populations in the RESTORE-IMI 1 Phase 3 Trial of Imipenem-Cilastatin-Relebactam versus Colistin plus Imipenem-Cilastatin in Patients with Imipenem-Nonsusceptible Bacterial Infections. Antimicrob Agents Chemother 2020;64:10.1128/aac.02203-19
161. Tumbarello M, Trecarichi EM, Corona A, De Rosa FG, Bassetti M, Mussini C et al. Efficacy of Ceftazidime-Avibactam Salvage Therapy in Patients With Infections Caused by Klebsiella pneumoniae Carbapenemase–producing K. pneumoniae. Clin Infect Dis 2018;68:355-64. 10.1093/cid/ciy492
162. Onorato L, Di Caprio G, Signoriello S, Coppola N. Efficacy of ceftazidime/avibactam in monotherapy or combination therapy against carbapenem-resistant Gram-negative bacteria: A meta-analysis. Int J Antimicrob Agents 2019;54:735-40. 10.1016/j.ijantimicag.2019.08.025
163. McKinnell JA, Dwyer JP, Talbot GH, Connolly LE, Friedland I, Smith A et al. Plazomicin for Infections Caused by Carbapenem-Resistant Enterobacteriaceae. N Engl J Med 2019;380:791-3. 10.1056/NEJMc1807634
164. Alosaimy S, Molina KC, Claeys KC, Andrade J, Truong J, King MA et al. Early Experience With Eravacycline for Complicated Infections. Open Forum Infect Dis 2020;7:ofaa071. 10.1093/ofid/ofaa071
165. Alosaimy S, Abdul-Mutakabbir JC, Kebriaei R, Jorgensen SCJ, Rybak MJ. Evaluation of Eravacycline: A Novel Fluorocycline. Pharmacotherapy 2020;40:221-38. 10.1002/phar.2366
166. Chan JD, Graves JA, Dellit TH. Antimicrobial treatment and clinical outcomes of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. J Intensive Care Med 2010;25:343-8. 10.1177/0885066610377975
167. Shields RK. Case Commentary: the Need for Cefiderocol Is Clear, but Are the Supporting Clinical Data? Antimicrob Agents Chemother 2020;64:10.1128/aac.00059-20

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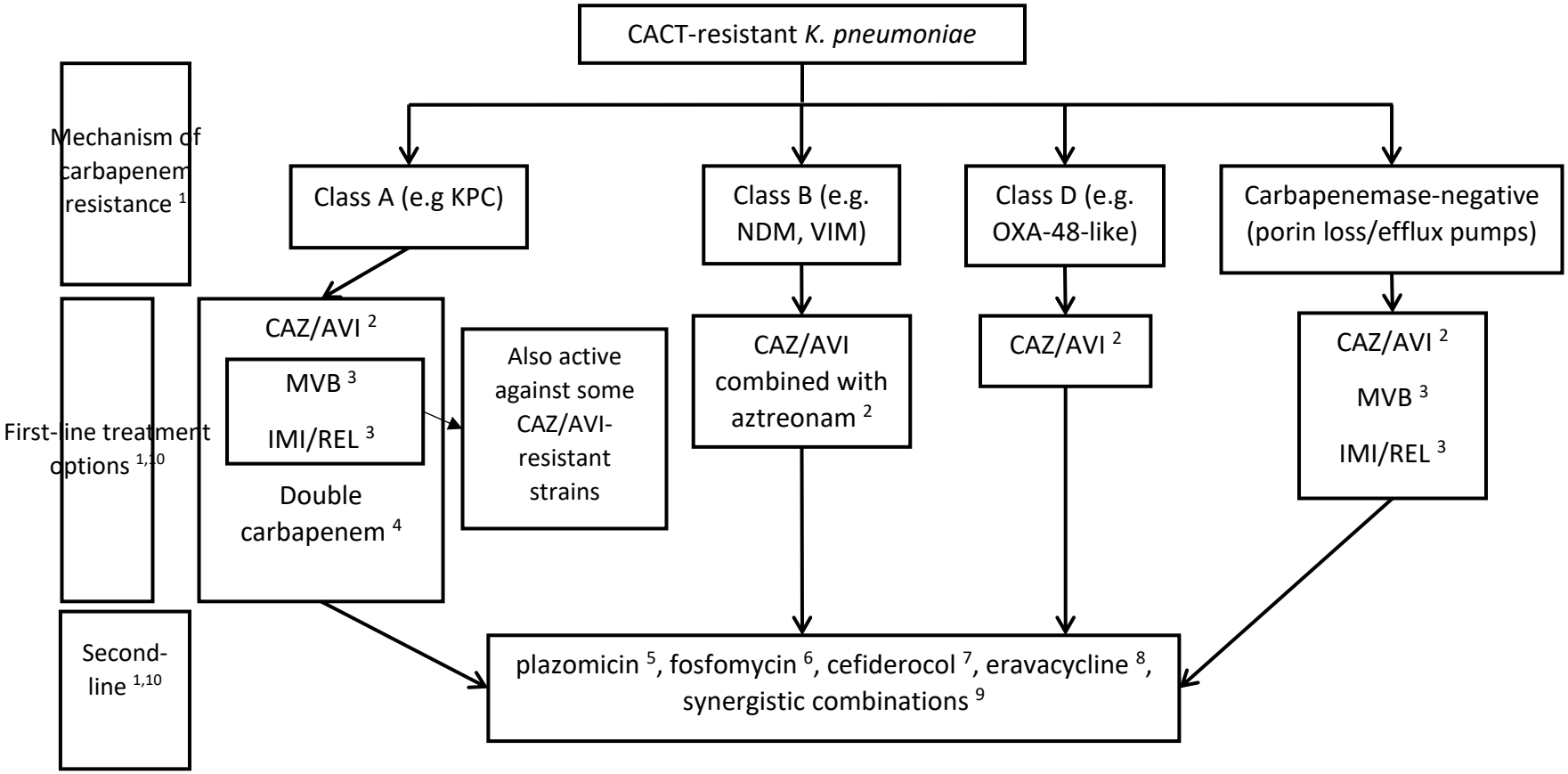
Figure 1. Treatment options for CACT-resistant *K. pneumoniae* depending on the mechanism of resistance to carbapenems



Abbreviations; IMI/REL= imipenem/relebactam, CAZ/AVI= ceftazidime/avibactam, C/T= ceftolozan/tazobactam, MVB= meropenem/vaborbactam

[1] Several rapid methods are available or under development that can detect both the production and the type of carbapenemases [18-21]. Because rare or novel β-lactamase variants may not be detectable by some methods [21, 23-25], susceptibility should always be confirmed with traditional growth-based methods and combination therapy may be reasonable pending such confirmation [15].

[2] CAZ/AVI is active against both Class A and some Class D carbapenemases [56] and is less affected by outer membrane permeability changes (porin mutations or efflux pumps) [83, 84]. CAZ/AVI can be combined with aztreonam to overcome resistance to MBL [78-80]. Notable, however, is the potential for resistance development during treatment due to KPC mutations [60-63] and due to the recently described VEB-25 extended spectrum β-lactamase [24].

[3] MVB and IMI/REL are active against Class A (KPC) carbapemenase-producers but not against Class B or Class D carbapenemase-producers [58, 59]. Both remain active against some KPC variants that confer resistance to CAZ/AVI [67] and against the recently described VEB-25 extended spectrum β-lactamase that has been associated with CAZ/AVI resistance [24]. MVB and IMI/REL may also be active against isolates with porin mutations, but major OmpK35 or OmpK36 disruptions may be associated with resistance [59, 85]. Emergence of resistance may less likely compared to CAZ/AVI monotherapy [63, 68].

[4] Double carbapenem combinations may be useful if CAZ/AVI, MVB and IMI/REL are not available (or not an option due to higher cost) and have been used effectively against KPC-producing CACT-resistant *K. pneumoniae* [69-72].

[5] Plazomicin is active against 93% of KPC-producing, 42% of MBL-producing (co-production of 16S-rRNA-methyltransferases), 87% of OXA-producing, and 95% of carbapenemase-negative carbapenem-resistant Enterobacteriaceae [8].

[6] Fosfomycin has been shown to be effective against XDR/PDR *K. pneumoniae* [89, 90] but its activity is highly variable [92].

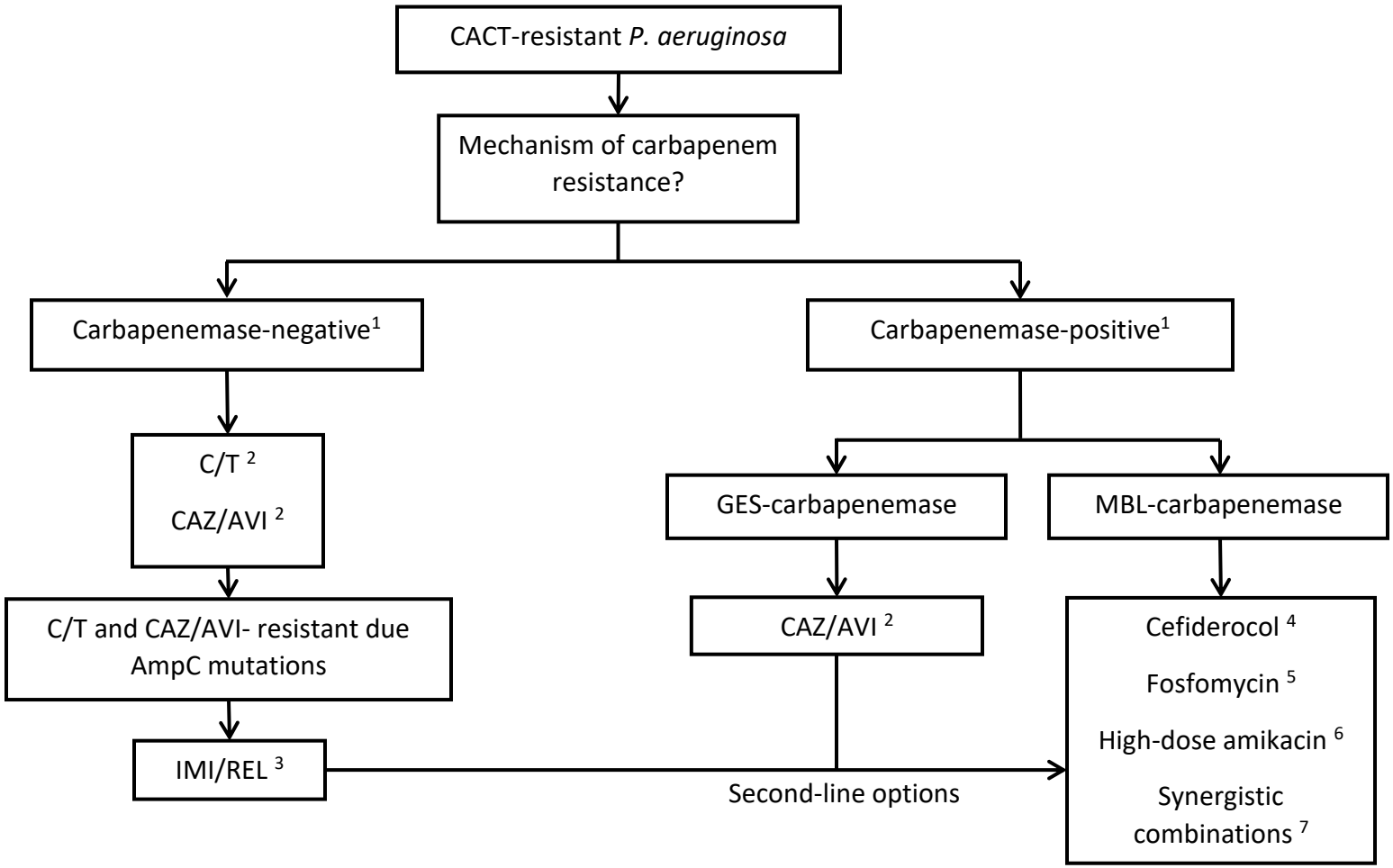
[7] Cefiderocol is stable against hydrolysis by all carbapenemases (including MBL) and its mechanism of bacterial cell entry is independent from porin channels and efflux pumps. Therefore, cefiderocol appears to be a useful option when no other antibiotic is active [110, 111].

[8] Eravacycline is more potent compared to tigecycline and may be active against some tigecycline-resistant strains [87, 88].

[9] Options include combinations based on colistin [93, 94], fosfomycin [90, 95] and ceftazidime/avibactam [24], and combinations exploiting multiple heteroresistance [96].

[10] Newer β-lactams-β-lactamases and the combination of CAZ/AVI with aztreonam have been better studied compared to other options. Furthermore, the available data suggest better outcomes with β-lactam-β-lactamase combinations compared to various combinations of older agents [63, 156-160].

Figure 2. Treatment options for CACT-resistant *P. aeruginosa* depending on the mechanism of resistance to carbapenems



Abbreviations; IMI/REL= imipenem/relebactam, CAZ/AVI= ceftazidime/avibactam, C/T= ceftolozan/tazobactam, MVB= meropenem/vaborbactam

[1] The prevalence of carbapenemases varies substantially in different regions, but may be very high in some settings [29-31, 38]. MBL are the predominant carbapenemases in *P. aeruginosa*, but GES carbapenemases are increasingly being reported [42-44]. Neither IMI/REL nor CAZ/AVI or C/T are active against MBL-producing *P. aeruginosa* [52, 56, 74], while GES carbapenemases may inactivate IMI/REL [43, 44] and C/T [42, 107] but not CAZ/AVI [42, 107]. Because rare or novel β-lactamase variants may not be detectable by some methods [21, 23-25], susceptibility should always be confirmed with traditional growth-based methods and combination therapy may be reasonable pending such confirmation [15].

[2] Both CAZ/AVI and C/T are unaffected by the most common mechanism of resistance in *P. aeruginosa* (OprD porin mutations, overexpression of efflux pumps, overexpression of AmpC) [97, 98]. Resistance to CAZ/AVI and C/T is usually the result of structural modifications of AmpC (+ overexpression of AmpC) or horizontally acquired carbapenemases [104, 105]. GES-type carbapenemases may confer resistance to C/T but not to CAZ/AVI [42].

[3] IMI/REL is unaffected by the most relevant mutation-driven β-lactam resistance mechanisms of *P. aeruginosa* [106]. Moreover, IMI/REL is not affected by AmpC mutations that confer resistance to ceftazidime/avibactam and ceftolozane/tazobactam [106]. IMI/REL is ineffective against MBL- and GES-producing *P. aeruginosa* strains [43, 44].

[4] Cefiderocol is stable against hydrolysis by all carbapenemases (including MBL) and its mechanism of bacterial cell entry is independent from porin channels and efflux pumps. Therefore, cefiderocol appears to be a useful option when no other antibiotic is active [110, 111].

[5] Alternative antibiotics (if available) may be preferable taking into account the concerns for development of resistance during treatment with fosfomycin [92, 113].

[6] High-dose amikacin (25-50mg/kg/day) has been used for CACT-resistant *P. aeruginosa* with amikacin MIC=16mg/dl [114]

[7] Until cefiderocol becomes widely available, synergistic combinations (e.g. based on colistin [115, 116], fosfomycin [117, 118], aminoglycosides [42] and C/T [42, 117]) may sometimes represent the only treatment option, but PK/PD and clinical studies are needed.

Other options are ineffective for CACT-resistant *P. aeruginosa*;

- The activity of MVB against *P. aeruginosa* is similar to that of meropenem alone [58].
- Plazomicin is no better than other aminoglycosides against *P. aeruginosa* [8].
- Similar to other tetracyclines, *P. aeruginosa* is resistant to eravacycline [87].
- Aztreonam/avibactam cannot overcome resistance against most MBL-producing *P. aeruginosa* [108], but may be useful against selected strains with borderline/intermediate MICs to aztreonam or ceftazidime/avibactam [79, 109].