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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*

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## 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].

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**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-

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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].

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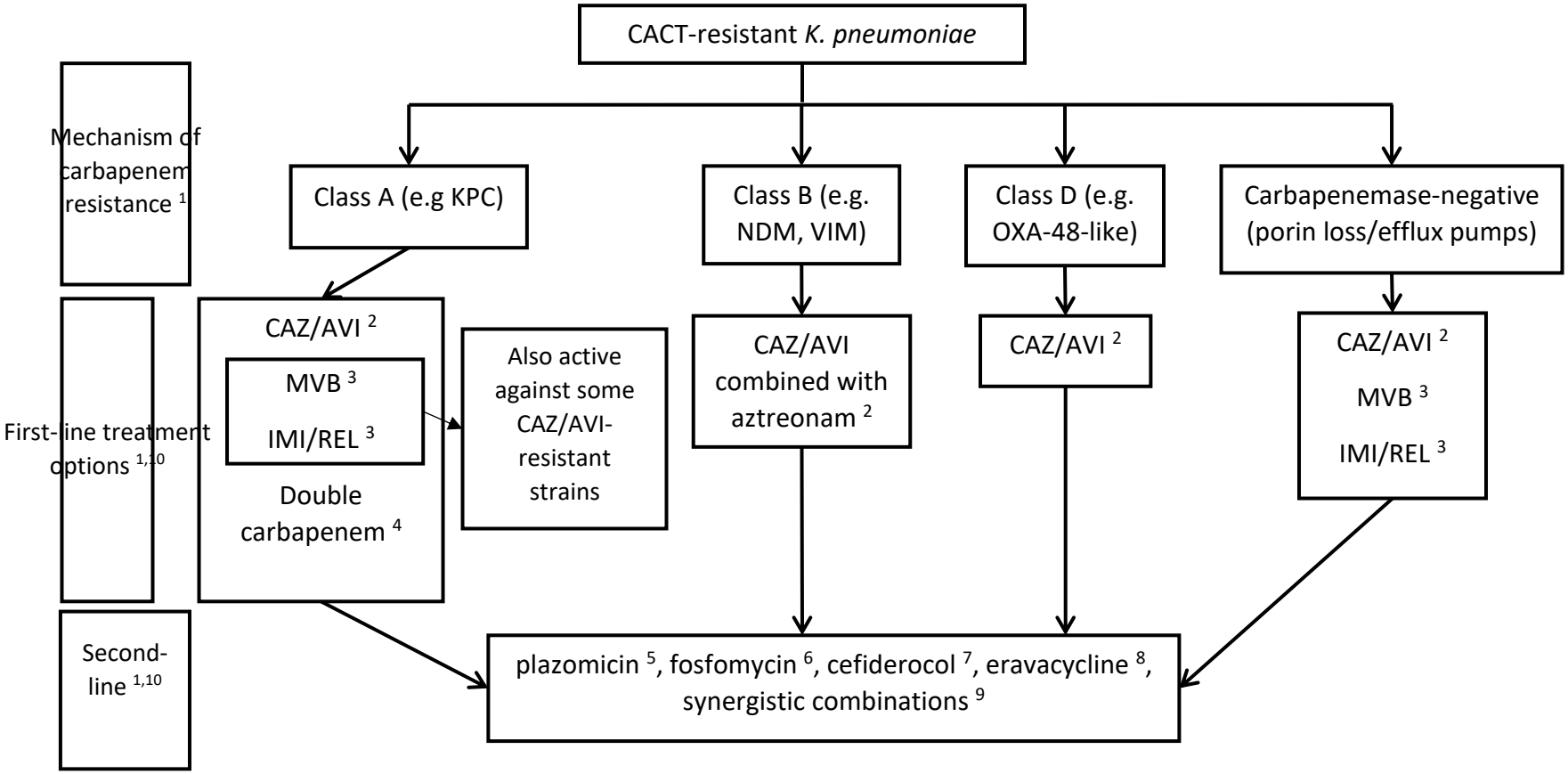
Figure 1. Treatment options for CACT-resistant *K. pneumoniae* depending on the mechanism of resistance to carbapenems




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].

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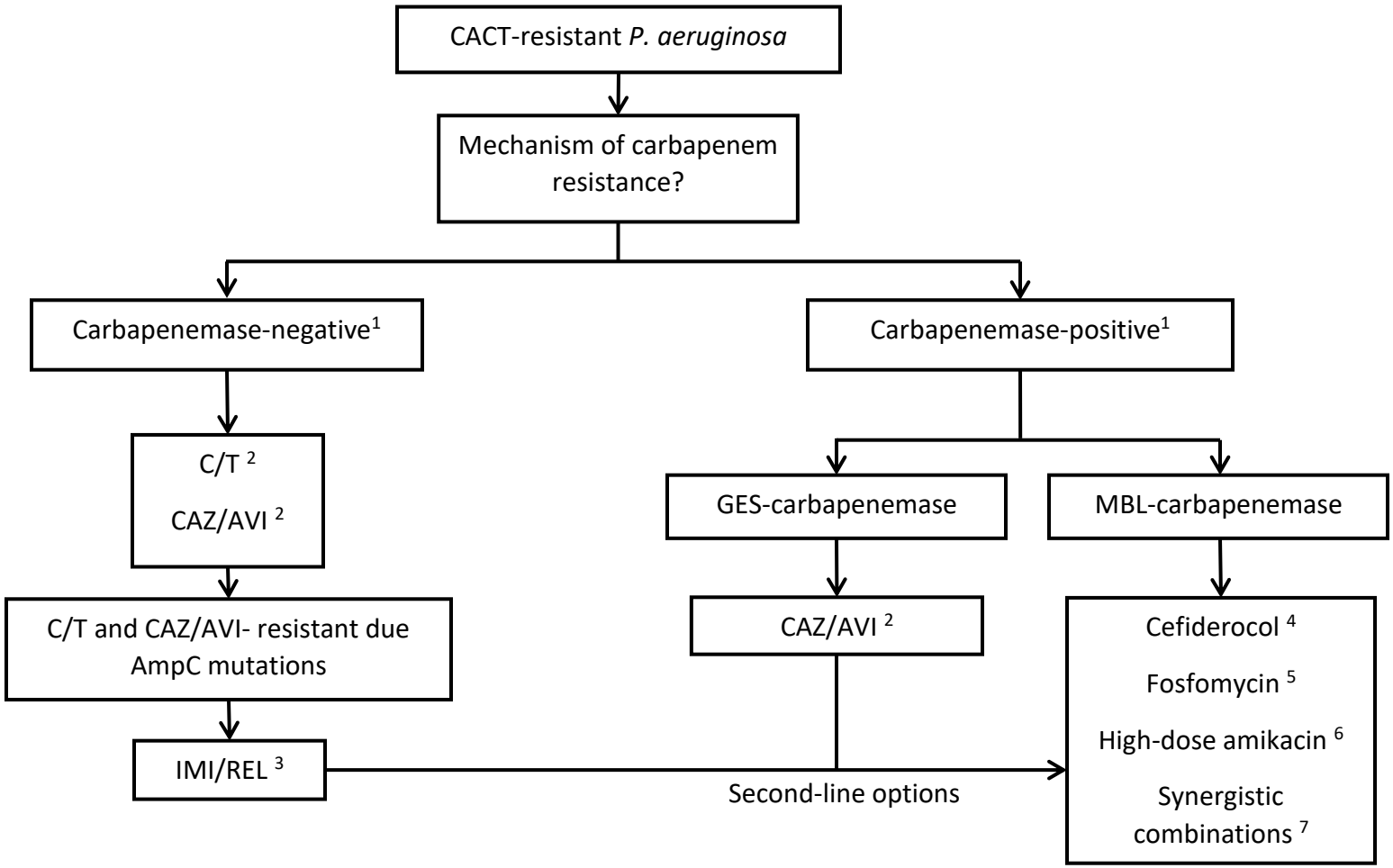
Figure 2. Treatment options for CACT-resistant *P. aeruginosa* depending on the mechanism of resistance to carbapenems




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

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[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].