Review Article

Treatment Options for Carbapenem-Resistant Gram-Negative Infections

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Summary

Background: Rates of colonization and infection with carbapenem-resistant Gram-negative pathogens are on the rise, particularly in southeastern European countries, and this is increasingly true in Germany as well. The organisms in question include enterobacteriaceae such as Klebsiella pneumoniae and Escherichia coli and non-fermenting bacteria such as Pseudomonas aeruginosa and Acinetobacter baumannii. As the carbapenems have been the gold standard to date for the systemic treatment of serious infections with Gram-negative bacteria, carbapenem resistance presents new and difficult challenges in therapeutic decision-making, particularly because of the high frequency of co-resistance.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed and on other applicable literature.

Results: Multiresistant Gram-negative (MRGN) pathogens are classified in Germany according to their resistance to four different classes of antibiotics; fluoroquinolones, piperacillin, third-generation cephalosporins, and carbapenems. Quadruple MRGN pathogens are resistant to all four groups, triple MRGN pathogens to three of them. There are a number of therapeutic alternatives to carbapenems that can be applied with the aid of sensitive microbiological and/or molecular genetic testing. The following antibiotics are often the only ones that can be used to treat quadruple MRGN pathogens: colistin, aminoglycosides, tigecycline, fosfomycin, ceftazidime/avibactam, and ceftolozan/tazobactam. Carbapenems, too, may still be an option in certain situations. There is also evidence that combinations of antibiotics against which the pathogen is resistant individually can sometimes be a valid treatment option; these include combinations of colistin with one or two carbapenems.

Conclusion: The treatment of severe infection with carbapenem-resistant pathogens should be individualized and carried out in an interdisciplinary framework, in consideration of antibiotic pharmacokinetics and pharmacodynamics in each case. The treatment options are based on evidence from in vitro studies, retrospective studies, and case series, which must be interpreted with caution. Randomized clinical trials are needed to test each of the various combined approaches.

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The availability of effective antibiotics, one of the cornerstones of modern medicine, is increasingly coming under threat owing to the rising resistance rates among members of the Enterobacteriaceae family and the non-fermenting bacteria (e1, e2). Data for 2014 from the Robert Koch Institute (RKI) show that multiresistant gram-negative (MRGN) strains of bacteria have become relatively common in Germany. The 3-MRGN bacteria *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are found in 6.6 to 9.8% of patients on ordinary wards, 11.5 to 13.4% in intensive care units (ICUs), and 3.2 to 7.1% in outpatient departments. To date, 4-MRGN bacteria are rare: they are found in <0.1 to 3.2% of patients on ordinary wards, <0.1 to 7.7% in intensive care units, and <0.1 to 1.5% among outpatients. The rates for *Acinetobacter baumannii* are somewhat higher but the absolute numbers are low (1). The number of cases of 3-MRGN and 4-MRGN pathogens have increased in recent years, particularly in southeastern European countries. In the face of increasing international mobility, this trend may well spread to Germany.

4-MRGN bacteria principally cause urinary tract infections, nosocomial pneumonia, (soft) tissue infections, intra-abdominal infections, and infections of the bloodstream. The treatment of these infections is complex and has not yet been standardized to any great extent. We present the current state of knowledge as reflected in the specialist literature: What treatment options are available, and how strong is the evidence for their efficacy?

Method

A selective survey of PubMed was conducted and further relevant publications were consulted.

Diagnosis

The Enterobacteriaceae (primarily *E. coli* and *K. pneumoniae*) and the non-fermenters *P. aeruginosa* and *A. baumannii* were classified into 3-MRGN and 4-MRGN according to the specifications of the RKI's Committee for Hospital Hygiene and Infection Prevention (*Kommission für Krankenhaushygiene und Infektionsprävention*, KRINKO), depending on their antibiogram for the following four (groups of) antibiotics: fluoroquinolones, piperacillin(/tazobactam), third-generation cephalosporins, and carbapenems. These are the the principal antibiotics used to combat gram-negative "problematic bacteria". 4-MRGN bacteria are resistant to all four groups of antibiotics, 3-MRGN to three groups, and 2-MRGN to two groups (this last category being used only for neonates and children) (2).

4-MRGN Enterobacteriaceae arise mostly from 3-MRGN strains (extended-spectrum beta-lactamases [ESBL] and/or AmpC beta-lactamases [with quinolone resistance]) via acquisition of a carbapenemase. In Germany, the predominant carbapenemases are OXA-48 (oxacillinase), KPC-2 and KPC-3 (*K. pneumoniae* carbapenemase), VIM-1 (Verona integron-encoded metallo-beta-lactamase), and NDM-1 (New Delhi metallo-beta-lactamase). Carbapenemases are also found in *A. baumannii* and, less frequently, in *P. aeruginosa* (3). The carbapenemases commonly found in Enterobacteriaceae in this country can now be demonstrated simply, quickly, and efficiently by means of molecular diagnostic techniques in both bacterial cultures and patient samples. Recently, systems have come on the market that can also detect carbapenemases in blood cultures. One should consider using such test systems particularly if there is urgent suspicion of severe infection with a 4-MRGN bacterium, so that hygiene precautions and treatment can be modified as necessary. Rapid molecular tests of this kind will probably become part of the clinical routine; however, interpretation of the results and the consequent adjustment of the treatment plan are not a simple matter. The European Centre for Disease Prevention and Control (ECDC) lists the following risk factors for colonization with carbapenem-resistant Enterobacteriaceae (CRE):

- A stay in hospital (at least one night) in the foregoing 12 months
- Dialysis dependence or chemotherapy in the foregoing 12 months
- Known previous CRE colonization
- Epidemiological connection to a CRE-colonized patient

If one or more of these criteria are fulfilled, the ECDC recommends isolation of the patient until screening is negative (4).

Further known risk factors are local prevalence, a known outbreak, age, diabetes mellitus, Charlson index >3, ICU stay, invasive procedures, and treatment with cephalosporins, fluoroquinolones, or carbapenems (5). Owing to the frequency of several of these factors in Germany, preventive isolation on a nationwide basis would be difficult to achieve. The RKI recommends prophylactic isolation of persons suspected as potential carriers of 4-MRGN bacteria after possible contact with the health care system in a highly endemic country or with known carriers (2). The most critical time is the period of at least 24 h between starting a bacterial culture and the result. However, rapid molecular tests could greatly shorten the waiting time.

Treatment options

3-MRGN bacteria

3-MRGN Enterobacteriaceae are susceptible to carbapenems (treatment of choice for severe infections). Depending on the site and severity of the infection, preparations such as trimethoprim/sulfamethoxazole, nitrofurantoin, fosfomycin, aminoglycosides, and possibly even tetracyclines can be used after susceptibility has been demonstrated. In the case of non-fermenting bacteria the situation is more complex and depends on the antibiogram.

4-MRGN bacteria

4-MRGN Enterobacteriaceae are still rare in this country, but are associated with high mortality (bacteremia in 32.1% of cases, nosocomial pneumonia in 33.3%, ventilator-associated pneumonia in 35.0%, and severe urinary tract infection/pyelonephritis in 17.3% [e3]). The bacteria most often responsible in Germany are *K. pneumoniae* with carbapenemases such as OXA-48, KPC-2, and KPC-3, together with *E. coli* and *Enterobacter* spp. They are resistant to carbapenems, piperacillin/tazobactam, third-generation cephalosporins, and usually quinolones. Because of their (almost) total resistance, they are particularly undesirable in patients with severe systemic infections. The antibiotics listed below are options for the treatment of MRGN pathogens and often emerge as the only substances to which 4-MRGN bacteria are susceptible. They all encounter resistance, however, so treatment according to antibiogram findings is recommended *(Table 1)*:

Colistin (polymyxin E)

Colistin acts in a detergent-like manner. Resistance testing is complex, and there may be a higher number of resistant pathogens than is generally realized (e4–e7).

Aminoglycosides

Aminoglycosides are highly efficacious in the urinary tract and for treatment of bacteremia, but less useful against soft tissue and abdominal infections because of their limited tissue penetration (6).

TABLE 1

Antibiotics that are treatment options for multiresistant gram-negative infections (modified from [36–40])

Type	Antibiotic and usual dosage	Dosage in CRE infections *1	Dose reduction in presence of	Toxicity	Clinical considerations
Carbapenems	**Meropenem** *2 1000 mg i. v. every 8 h	2000 mg i. v. over a period of 4 h every 8 h	Impaired renal function	Local (thrombo)phlebitis, allergy, headache, gastrointestinal symptoms, blood count changes, cramp	Close monitoring recommended for allergic reactions and other adverse effects (particularly cramps with high-dose treatment)
	Ertapenem *2 1000 mg every 24 h		Impaired renal function	Gastrointestinal symptoms, local (thrombo)phlebitis, allergic reactions, headache, blood count changes, elevated liver values, fever, cramp	Combination partners in dual carbapenem treatment of carbapenem-resistant strains (see text); close monitoring recommended for allergic reactions and other adverse effects (particularly cramps with combination treatment)
Polymyxin	**Colistin** Loading dose 9–12 million IU; maintenance dosage 6–12 million IU divided into 2 or 3 doses per day *2		Impaired renal function	Nephrotoxicity (50–60%), neurotoxic	Monitoring recommended, particularly for kidney function
Aminoglycosides	**Gentamicin** *2 5 mg/kg BW i. v. 1 x daily	7–10 mg/kg BW *3	Impaired renal function	Nephrotoxicity, ototoxicity	Administration of a single dose each day for as short a time as possible is recommended to optimize the action and minimize adverse effects. Individualized treatment with drug monitoring is recommended, depending on microbiological data (MIC). Aminoglycosides are recommended, particularly for urinary tract infections, owing to renal accumulation.
	Tobramycin *2 5 mg/kg BW i. v. 1 x daily	7–10 mg/kg BW *3			
	Amikacin *2 10 mg/kg BW i. v. 1 x daily	15 mg/kg BW *4			
Glycylcyclines	**Tigecycline** *2 Loading dose 100 mg i. v.; maintenance dosage 50 mg i. v. every 12 h	Loading dose 200 mg i. v.; maintenance dosage 100 mg i. v. every 12–24 h	Liver function disorders	Nausea (26%), vomiting (18%), diarrhea (12%)	Tigecycline accumulates in the intracellular space and in tissue soon after infusion. Not recommended as monotherapy in bacteremia, as peak serum values correspond to the MIC of many resistant gram-negative bacteria. Not recommended for urinary tract infections owing to low renal elimination. Intensified gastrointestinal adverse effects can be expected at higher doses.
Epoxides	**Fosfomycin** Single 3 g dose p.o. *2, *5	3 g p.o. every 2–3 days *5 1–16 g i. v. daily, divided into doses every 6–12 h *6	Impaired renal function	Oral treatment: gastrointestinal symptoms, headache, vaginitis Intravenous: hypokalemia (26%), local pain, heart failure *7	Oral fosfomycin should be used only for (uncomplicated) urinary tract infections. Fosfomycin reaches high concentrations in lung, bone, heart valves, and cerebrospinal fluid.
Cephalosporin + beta-lactamase inhibitor	**Ceftazidime + avibactam** *2 2 g Ceftazidime + 0.5 g avibactam i. v. 3 x daily Newly approved		Impaired renal function	Nausea, vomiting, positive Coombs test	Rapid development of resistance has been described in individual cases; therefore, combination treatment is recommended particularly for severe infections.
	Ceftolozane + tazobactam 1 g Ceftolozane + 0.5 g tazobactam i. v. every 8 h Newly approved	Consider higher dosage (3 x 2 g/1 g daily; see text)	Impaired renal function	Nausea, headache, gastrointestinal symptoms, fever, positive Coombs test, elevated liver values	Less suitable for CRE, good effect against Pseudomonas aeruginosa (depending on antibiogram!)

*1 Very little is known about the safety and efficacy of alternative (higher or prolonged) dosages. We therefore recommend careful consideration of the risks and benefits, in consultation with a pharmacologist if needed.
*2 In empirical treatment, it is recommended to give antibiotics in combination (less risk of inadequate effect and development of resistance).
*3 For bacteria with MIC ≤ 0.5 mg/L, daily doses of 5 mg/kg BW were associated with the highest success rates and the lowest rates of nephrotoxicity. MIC of 1–2 µg/mL may necessitate doses of 7 mg/kg BW. A dose of 10 mg/kg BW may achieve good results in infection by bacteria with an MIC of 4 µg/mL.
*4 At MIC ≤ 4 µg/mL, 15 mg/kg BW may be adequate; higher doses may be necessary for higher MIC.
*5 Oral fosfomycin should be used only for uncomplicated urinary tract infections.
*6 It has been reported that intravenous administration of 16 g daily, divided into 2 doses, can achieve the pharmacokinetic target values for pathogens with MIC up to 35 µg/mL. Isolates with higher MIC may need higher doses of up to 20 g daily, but the data on this are sparse.
*7 Rapid infusion over a 30-min period may be associated with hypokalemia; heart failure can be caused by the high salt content of the infusate.

BW, Body weight; CRE, carbapenem-resistant Enterobacteriaceae; IU, international unit; i. v., intravenous; MIC, minimal inhibitory concentration; p.o. oral

Tigecycline

Tigecycline is a bacteriostatic glycylcycline with good tissue penetration but low serum concentrations. The intermittently reported high mortality (50% versus 7.7% in the comparison group for ventilator-associated pneumonia with bacteremia) may have been due to underdosing or the setting of unfavorable limits for testing, so a higher dosage is recommended for severe infection (e8–e13). *P. aeruginosa* is viewed as resistant to tigecycline. Some strains of *A. baumannii* show susceptibility in vitro, but there are no EUCAST clinical threshold values (EUCAST, European Committee on Antimicrobial Susceptibility Testing) (e14).

Fosfomycin (epoxide)

Rapid emergence of resistance is a problem with fosfomycin, especially when used alone (rates of up to 18%). There are no EUCAST clinical threshold values for *P. aeruginosa* and *A. baumannii*. Intravenous administration may have dangerous adverse effects, particularly hypokalemia, hypernatremia, and heart failure (e15, e16).

Carbapenems

At minimum inhibitory concentration (MIC) just within the realm of resistance, a high-dose carbapenem may still exert a residual action (e17, e18). Arguments have been advanced for and against dual carbapenem treatment, where a high-affinity carbapenem (ertapenem) is given to bind and exhaust the pathogen's carbapenemases so that a second carbapenem can have a bactericidal effect.

Ceftazidime/avibactam

The recently approved combination of ceftazidime and avibactam was developed to combat bacterial resistance caused by ESBL and carbapenemases. Avibactam inhibits Ambler class A and C beta-lactamases and some members of class D. In-vitro studies have shown efficacy (up to 98%) of ceftazidime/avibactam against carbapenem-resistant enterobacteria with KPC and OXA-48 carbapenemases. These are the most frequently occurring types of Enterobacteriaceae in Germany; some pathogens, however, have type B carbapenemases (VIM, NDM), which are not inhibited by avibactam (e19–e20). Ceftazidime/avibactam is also effective against some strains of carbapenem-resistant *P. aeruginosa* (e21). Case reports and a few studies have shown promising results, but some patients have failed to respond and development of resistance has been described (7–12).

Ceftolozane/tazobactam

The combination of ceftolozane and tazobactam has also recently been licensed for use. Ceftolozane exhibits high efficacy against *P. aeruginosa*, while tazobactam inhibits many class A and some class C lactamases. Together, they work well (MIC ≤ 2 mg/L) against many Enterobacteriaceae (*E. coli* 97.7%, *K. pneumoniae* 87.3%), but have a weaker effect against multiresistant strains (ESBL: *E. coli* 78.9%, *K. pneumoniae* 63.6%) (e22). Ceftolozane/tazobactam is effective against *P. aeruginosa*, even when the bacterium is resistant to third-generation cephalosporins and/or carbapenems (e21–e23). Early clinical studies have demonstrated the success of the treatment (13). For severe infections, particularly in the lungs, a higher dosage may be necessary, e.g., 3 × 2 g/L g. Dosages at this level have not yet received approval and are currently under investigation in a phase-3 study (14, 15).

Combination treatments

Combination treatments aim to take advantage of synergies to achieve bactericidal effects at concentrations below the respective MIC of the substances concerned. For example, antibiotics that destroy the cell wall can facilitate penetration by other antibiotics, in effect lowering their MIC. If this "joint" MIC is below the values attainable in vivo, a clinically beneficial result is feasible. In vitro, synergies can be quantified by, for instance, checkerboard tests and time-kill curves. Synergistic actions have been convincingly demonstrated for carbapenem-resistant Enterobacteriaceae (particularly *K. pneumoniae*), *A. baumannii*, and *P. aeruginosa* (16). A small number of studies have examined the efficacy of these synergistic effects in vivo, but they are largely retrospective and feature considerable limitations *(eTable 1)*.

An observational multicenter cohort study on CRE bloodstream infections failed to demonstrate either a statistically significant advantage of combination treatment or any effect at all of in vitro active antibiotic treatment (17). Another retrospective multicenter study showed superiority of in vitro active treatment over inadequate treatment (hazard ratio, HR 0.45; 95% confidence interval [0.33; 0.62]); however, only in the stratified subgroup with high mortality score were combination treatments significantly more effective (mortality 48% versus 62%, p = 0.02) (18). A further retrospective multicenter study on CRE infections showed a trend towards a better outcome with the use of at least two antibiotics known to be effective against the index CRE pathogen (odds ratio, OR, for clinical recovery 1.58 [0.78; 3.17]; OR for 28-day mortality 0.62 [0.28; 1.37]) (19).

Combination with tigecycline

A meta-analysis on the efficacy of tigecycline revealed a benefit of combination treatment (30-day mortality: OR 1.83 [1.07; 3.12]) and a tendency towards superiority of high-dose treatment (200 mg at first, followed by 100 mg every 12 h) over the standard dosage (100 mg at first, followed by 50 mg every 12 h) (30-day mortality: OR 2.25 [0.55; 9.24]) (20).

Combination with polymyxin

One meta-analysis compared colistin monotherapy with combination treatments in multiresistant *A. baumannii* infections. Although microbiological

TABLE 2

Overview of treatment options by pathogen and resistance patterns (modified from [e51])

Carbapenemases	Susceptibility/resistance		Treatment options
4-MRGN/carbapenem-resistant Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*)			
Metallo-beta-lactamase (MBL)	Aminoglycoside susceptible		Aminoglycoside + meropenem
	Quinolone susceptible		Quinolone + meropenem
	Aminoglycoside resistent	Colistin susceptible	Colistin + meropenem
		Tigecycline susceptible	Tigecycline + meropenem
		Ceftazidime/avibactam susceptible	Consider ceftazidime/avibactam + aztreonam
Klebsiella pneumoniae carbapenemase (KPC)	Aminoglycoside susceptible		Aminoglycoside + meropenem
	Quinolone susceptible		Quinolone + meropenem
	Aminoglycoside resistant	Colistin susceptible	Colistin + meropenem
		Tigecycline susceptible	Tigecycline + meropenem
		Ceftazidime/avibactam susceptible	Ceftazidime/avibactam
Oxacillinase (OXA-48)		Ceftazidime/avibactam susceptible	Ceftazidime/avibactam
No typing		Colistin susceptible	Colistin + meropenem
		Ceftazidime/avibactam susceptible	Ceftazidime/avibactam
KPC/GES		Fosfomycin susceptible	Consider fosfomycin + meropenem
Salvage therapy	In absence of response	Colistin susceptible	Colistin + ertapenem + meropenem
		Colistin resistant	Ertapenem + meropenem
4-MRGN *Pseudomonas aeruginosa*			
No typing	Ceftolozane/tazobactam susceptible		Ceftolozane/tazobactam (+ colistin)
	Ceftazidime/avibactam susceptible		Ceftazidime/avibactam (+ colistin)
	Ceftolozane/tazobactam and ceftazidime/avibactam resistant		Colistin + meropenem
KPC/GES	Ceftazidime/avibactam susceptible		Ceftazidime/avibactam + colistin
	Ceftazidime/avibactam resistant		Colistin + meropenem
MBL	Aztreonam susceptible		Aztreonam
	Aztreonam resistant		Colistin + meropenem
	Ceftazidime/avibactam and aztreonam susceptible		Ceftazidime/avibactam + aztreonam
4-MRGN *Acinetobacter baumannii*			
	Colistin susceptible		Colistin + meropenem (imipenem)
	Colistin susceptible and tigecycline susceptible		Colistin + tigecycline
	Salvage therapy		Colistin + meropenem + ampicillin/sulbactam
			Colistin + meropenem + tigecycline
	Salvage therapy (alternatives)		Minocycline + meropenem /imipenem (+ colistin)
			Minocycline + colistin

NB: Owing to the limited data and the potential complexity of infections, these suggestions are to be understood as treatment options; the best treatment must be decided on the basis of the individual patient and the bacteria concerned, ideally in an interdisciplinary conference comprising the treating physician together with specialists in infectious disease, clinical microbiologists, and pharmacologists

GES, Guiana extended spectrum; MRGN, multiresistant gram-negative

eradication was significantly higher in the combination group (OR 2.14 [1.48; 3.07]), this benefit was not reflected in mortality (relative risk, RR 0.93 [0.73; 1.17]), length of stay in intensive care, or nephrotoxicity (OR 1.13 [0.74; 1.73]). The greatest limiting factor was the wide heterogeneity of the antibiotic combinations used (21). A meta-analysis that included other gram-negative bacteria concluded that polymyxin monotherapy was inferior to a combination of polymyxin with carbapenem (non-adjusted OR for mortality 1.58 [1.03; 2.42]) and to combinations with tigecycline, aminoglycosides, or fosfomycin (non-adjusted OR 1.57 [1.06; 2.32]) (22). A third meta-analysis, again on the topic of CRE infections, also showed superiority of combinations including polymyxin to treatment with polymyxin alone (OR for mortality 0.36 [0.19; 0.68]) (23). However, the authors of these last two meta-analyses warn against drawing definitive conclusions because of the low data quality (principally due to bias, the retrospective nature of the studies, and the absence of pathogen MIC). A further meta-analysis revealed no statistically significantly greater risk of mortality for colistin monotherapy than for combinations of colistin with carbapenem, tigecycline, or aminoglycosides. Only the heterogeneous subgroup "mixed comparators" showed superiority of combination treatments to colistin alone; however, no valid conclusions could be drawn (24). The only randomized clinical studies compared colistin with colistin + rifampicin—and found no statistically significant difference in mortality (OR 1.06 [0.64; 1.76]).

Combination with carbapenem

A retrospective multicenter study on bloodstream infections by carbapenem-resistant *K. pneumoniae* (CRKP) showed a protective effect of combination treatments including a carbapenem (OR: 0.11 [0.03; 0.43]) (25). Another study, however, found that no benefit was conferred by carbapenem combination treatments. This result was attributed to the high rate of isolates with high MIC for meropenem (86% >16 µg/mL) (17). A pharmacokinetic/pharmacodynamic case study confirmed that antibiotic plasma concentrations measured in vivo did not suffice to achieve a synergistic effect in isolates with a meropenem MIC ≥ 256 mg/L in vitro. However, the results of the study suggested that with the high dosage of meropenem that was used (2 g every 8 h, 3 h continuous infusion), plasma levels were attained that could be effective against isolates with MIC of up to 32 mg/L (e18).

A prospective study of *A. baumannii* bloodstream infection found superiority of carbapenem + colistin to tigecycline + colistin (HR 14-day mortality 6.93 [1.61; 29.78]) for isolates with tigecycline MIC > 2 mg/L (26).

Combination of two carbapenems

The findings of non-controlled case series suggest that combinations of two carbapenems (ertapenem plus prolonged infusion of meropenem or doripenem) can be successful in the treatment of CRKP infections, with clinical cure rates of 39 to 77.8% (27, 28). The association of clinical success with synergy testing in vitro could yield important information (29).

A representative case–control study with good documentation of the treatment schemes reported statistically significantly higher mortality for patients without carbapenem than for patients with dual carbapenem treatment (47.9% versus 29.2%, $p = 0.04$); however, the two groups did not differ significantly with regard to clinical and microbiological cure (30). The authors of a small retrospective study found that addition of colistin to ertapenem and meropenem increased the bactericidal effect in vitro, particularly in the first few hours, but the difference in vivo was not significant (31).

Discussion

In-vitro studies, case reports, and retrospective analyses show promising effects of combination treatments, above all when colistin is given together with substances of other classes and for combinations of ertapenem with another carbapenem. The clinical efficacy of such approaches has, however, not yet been demonstrated with any certainty. Interpretation is hampered by the following major limitations:

- In many studies the specification of bacterial resistance is inadequate. The threshold values above which isolates are categorized as "resistant" differ among various international standards. For instance, an isolate can be classified as "resistant" according to the Clinical and Laboratory Standards Institute (CLSI) standard, but "intermediate" by the EUCAST standard. By definition, "intermediate" means that high-dose therapy can be successful. For studies to be comparable, the MIC of the pathogens concerned should be stated for all antibiotics used, ideally together with details of the detection of the resistance mechanisms.
- Retrospective analysis.
- Heterogeneity of the treatment schemes used. In many studies widely differing combinations of antibiotics are used, each in a small number of patients. Even in studies with clearly defined main comparators, there are often heterogeneous antibiotic "accompanying medications" .

There are signs that combination treatment is beneficial in some constellations. Some studies indicate that colistin should preferably be administered together with another antibiotic. This is controversial, however, and it remains uncertain which preparation constitutes the best colistin combination partner for which pattern of antibiogram.

The benefit of adding carbapenem (when testing shows resistance) in combination with one or more substances of other classes is equally unclear. Retrospective studies have indicated that double carbapenem treatment is beneficial, but due to the various limitations of these studies there is no robust evidence.

One of the few randomized clinical studies on combination treatments showed no additional benefit in terms of mortality from administering rifampicin together with colistin to patients with *A. baumannii* infection, despite previous promising in-vitro results (32). Therefore, the hypotheses generated by experimental studies, case reports, and retrospective investigations should be verified in prospective randomized studies. The pathogens must be clearly defined by MIC measurement, and the administration schemes of the antibiotics used must be (a) described in stringent detail and (b) associated with the antibiograms. Two prospective randomized clinical trials (colistin versus colistin + meropenem) are already under way (33, 34). Furthermore, antibiotic concentrations should be determined by drug monitoring. In this way clinical efficacy could be quantified reliably and treatment failure could be attributed to pharmacokinetic, pharmacodynamic, or bacterial factors. In studies of synergistic effects, the index pathogens must be tested accordingly and the success of treatment must be correlated with the synergy testing.

New antibiotics in clinical studies

The new antibiotics launched in recent years were primarily developed with the aim of overcoming bacterial resistance. An overview of the substances currently in phases 2 to 4 of clinical testing is provided in *eTable 2*.

Multidisciplinary individual treatment

The heterogeneity of the pathogens involved (various species, widely differing resistance profiles) and the diversity of the accompanying factors exhibited by the patients, coupled with the complexity of pharmacokinetics, pharmacodynamics, and drug interactions, make it difficult to formulate general treatment recommendations. An S2k guideline was recently published in Germany, but the authors explicitly refer to the lack of high-quality data from randomized clinical trials (35). Therefore, patient– and pathogen-specific factors should be weighed up on an individual basis in each case. We recommend that whenever possible two or more antibiotics shown to be effective in vitro should be used to treat severe infections with carbapenem-resistant gram-negative bacteria, with due consideration of spectrum of effect, site of effect, indication, and contraindications. One of the antibiotics can be a carbapenem classified as intermediate, in which case we advise giving the maximum appropriate dose. In general, we recommend that the treatment of patients infected with multiresistant pathogens should be managed by an interdisciplinary team including infectious disease specialists, microbiologists, and clinical pharmacologists. This can be established in the framework of antibiotic stewardship (ABS). It is then the responsibility of the ABS team to adjust the antibiotic treatment to the individual patient on the basis of the clinical findings (severity of disease, relevant comorbidities), microbiological efficacy (MIC values), and pharmacodynamics and pharmacokinetics. *Table 2* provides an overview of the treatment options for selected pathogens and patterns of resistance.

Key messages

- Infections by carbapenem-resistant gram-negative bacteria (4-MRGN) are not yet a widespread problem in Germany but are difficult to treat and may have grave consequences.
- A number of different substances are available for the treatment of 4-MGRN, foremost among them aminoglycosides, fosfomycin, colistin, tigecycline, new cephalosporin/beta-lactamase inhibitor combinations and carbapenems).
- To date, the data on evidence-based treatment of these infections come predominantly from in-vitro studies and retrospective clinical studies. Any recommendations are thus of limited strength.
- Prospective randomized clinical trials are required, above all for comparison of different treatments for pathogens with a similar susceptibility pattern.
- Treatment should be guided by the antibiogram. In the case of severe infections, specialists in infectious disease, microbiologists and pharmacologists should be consulted if possible.

Conflict of interest statement
Prof. Wagenlehner has received consultancy fees from Achaogen, Astra Zeneca, Bionorica, MSD, Rempex, Pfizer, Rosen-Pharma, Shionogi, and Vifor; and payments for conducting clinical studies from Achaogen, Astellas, Astra Zeneca, Bionorica, Calixa, Cerexa, Leo-Pharma, Merlion, MSD, Cubist, Rempex, Rosen-Pharma, Shionogi, and Vifor.
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► **Supplementary material**
For eReferences please refer to:
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Treatment Options for Carbapenem-Resistant Gram-Negative Infections

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eTABLE 1

Studies on the efficacy of combination treatments

First author, year	Study type	Studies/ patients	Mortality	Infections	Results/major limitations (selected)
Satlin, 2011 (6)	Multicenter, observational	121 patients	51%	CRE BSI, 90% thereof *K. pneumoniae*	No statistically significant benefit of combination treatment demonstrated, no statistically significant benefit of in vitro active treatment demonstrated (mortality 56% with polymyxin/tigecycline, 33% with aminoglycoside-tigecycline, 62% with carbapenem, 44% without carbapenem versus 38% monotherapy)
Gutiérrez-Gutiérrez, 2017 (18)	Multicenter, retrospective	437 patients	43% (calculated)	BSI from CRE, 86% thereof *K. pneumoniae*	Statistically significantly lower mortality for combination treatment than for monotherapy only in subgroup with high mortality score (48% versus 62%, p = 0.02, overall 34.8% versus 40.9%); statistically significant mortality benefit from in vitro active treatment (HR 0.45; 95% CI [0.33; 0.62])
Alexander; 2017 (19)	Multicenter, retrospective	256 patients	28.1%	cUTI/pyelonephritis, HAP, VAP, BSI	Mortality for active combination treatment 20.8% versus 27.0% for monotherapy (not statistically significant). However, only a small proportion of patients (20.7%) received active combination treatment.
Ni, 2016 (20)	Meta-analysis	26 studies 1328 patients	39.21% (5 studies)	CRE BSI, UTI, HAP	High mortality for tigecycline monotherapy versus combination treatment (OR 1.83 [1.07; 3.12]), especially for BSI (OR 2.12 [1.17; 3.86]); lower intensive care mortality for high-dose tigecycline treatment (OR 12.48 [2.06; 75.43])
Chen, 2015 (21)	Meta-analysis	5 studies 412 patients	49.9% (calculated)	Multiresistant *A. baumannii*	Combination treatment with colistin improves the microbiological effect (OR 2.14 [1.48; 3.07]); however, it achieves no statistically significant improvement in the clinical response rate or intensive care mortality.
Zusman, 2017 (22)	Systematic review with meta-analysis	22 studies	–	Infections with CRE, *A. baumannii* and *P. aeruginosa*	Polymyxin monotherapy is associated with higher mortality than combination of polymyxin with carbapenem (uOR 1.58 [1.03; 2.42]), or with tigecycline, aminoglycosides, or fosfomycin (uOR 1.57 [1.06; 2.32]). The combination of colistin with rifampicin revealed no mortality benefit. Only three RCTs, absence of mortality rates for combination treatment, little information on MIC, selection bias
Ni, 2015 (23)	Meta-analysis	25 studies 1086 patients	33.8–35.7% (depending on study type)	Infections with CRE	No statistically significant superiority of polymyxins over various comparators (OR mortality: 0.79 [0.58; 1.08]), but polymyxin combination treatment was associated with lower mortality than monotherapy (OR 0.36 [0.19; 0.68]) and the control groups (OR 0.49 [0.31; 0.75]); no RCT, insufficient information on MIC, dosage, and treatment duration
Paul, 2014 (24)	Meta-analysis	16 studies	–	Infections with CRKP, *A. baumannii* and *P. aeruginosa*	No statistically significant superiority of colistin combination treatment over monotherapy: the OR for mortality was 0.95 [0.35; 2,54] for monotherapy versus combination with carbapenem, 1.16 [0.41; 3.27] versus combination with tigecycline, and 2.62 [0.91; 7.58] versus combination with aminoglycosides.
Cristina, 2018 (25)	Multicenter, retrospective	213 patients	26.29%	BSI, CRKP	Protective effect of combination treatment with a carbapenem after resistance testing (OR mortality: 0.11 [0.03; 0.43])
Cheng, 2015 (26)	Multicenter, prospective observational	176 patients	25.5% (calculated)	BSI, multiresistant *A. baumannii*	Fourteen-day mortality for colistin/tigecycline 35% versus colistin/carbapenem 15%; the excess mortality was caused by a subgroup with high tigecycline MIC.
De Pascale, 2017 (30)	Two-center case–control study	144 patients	41.7% (calculated)	Invasive infection by CRKP	Mortality for dual carbapenem treatment 29.2% versus non-carbapenem combinations 47.9%; clinical response rate and microbiological eradication showed no statistically significant difference. No data on carbapenem MIC

A. baumannii, *Acinetobacter baumannii*; BSI, bloodstream infection; CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; CRKP, carbapenem-resistant *Klebsiella pneumoniae;* cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; HR, hazard ratio; *K. pneumoniae*, *Klebsiella pneumoniae*; MIC, minimal inhibitory concentration; OR, odds ratio; *P. aeruginosa*, *Pseudomonas aeruginosa*; RCT, randomized clinical trial; uOR, unadjusted odds ratio; UTI, urinary tract infection; VAP, ventilator-associated pneumonia

eTABLE 2

Antibiotics undergoing clinical testing

Antibiotic substance	Substance class	Development status in Germany	Antibacterial spectrum	Infection indications	Reference(s)
Cefiderocol	Cephalosporin	Phase 2	Gram-negative, non-fermenters, e.g., TEM, CTX-M, SHV, KPC, OXA, VIM, NDM	cUTI	e24–e26
Ceftolozane + tazobactam	Cephalosporin + BLI	Approved	Gram-negative, non-fermenters, TEM, CTX-M, SHV	cUTI, cIAI	e27–e30
Ceftazidime + avibactam	Cephalosporin + BLI	Approved	Gram-negative, non-fermenters, TEM, CTX-M, SHV, KPC, OXA-48	cUTI, cIAI	e31–e33
Ceftaroline + avibactam	Cephalosporin + BLI	Phase 2	Gram-positive, MRSA Gram-negative, TEM, CTX-M, SHV, KPC, OXA-48 (no non-fermenters)	cUTI	e34
Aztreonam + avibactam	Monobactam + BLI	Phase 2	Gram-negative, non-fermenters, TEM, CTX-M, SHV, KPC	cIAI	e35
Meropenem + vaborbactam	Carbapenem + BLI	Phase 3	Gram-positive Gram-negative, non-fermenters, e.g., AmpC, TEM, CTX-M, SHV, KPC	cUTI	e36–e38
Imipenem + relebactam	Carbapenem + BLI	Phase 2	Gram-positive Gram-negative, non-fermenters, e.g., AmpC, TEM, CTX-M, SHV, KPC	cUTI, cIAI	e39
Eravacycline	Fluorocycline	Phase 3	Gram-positive, MRSA, VRE Gram-negative, e.g., KPC, OXA	cIAI	e40, e41
Finafloxacin	Fluoroquinolone	Phase 2	Gram-positive, MRSA Gram-negative	cUTI	e42–e44
Delafloxacin	Fluoroquinolone	Phase 3	Gram-positive, MRSA Gram-negative	ABSSSI, gonorrhea	e42, e45
Zabofloxacin	Fluoroquinolone	Phase 2	Gram-positive, MRSA Gram-negative	CAP	e42, e46
Nemonoxacin	Non-fluorinated quinolone	Phase 2	Gram-positive, MRSA Gram-negative	CAP	e42, e47
Plazomicin	Aminoglycoside	Phase 3	Gram-positive, MRSA Gram-negative (no non-fermenters), e.g., VIM, IMP, KPC, OXA	cUTI, HAP, VAP	e48–e50

ABSSSI, Acute bacterial skin and skin structure infections; BLI, beta-lactamase inhibitor; CAP, community-acquired pneumonia; cIAI, complicated intra-abdominal infections; CTX-M, cefotaximase-Munich; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; IMP, imipenem carbapenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MRSA, methicillin-resistant *Staphylococcus aureus*; NDM, New Delhi metallo-beta-lactamase; OXA, oxacillinase; SHV, sulfhydryl variable beta-lactamase; TEM, Temoneira beta-lactamase; VAP, ventilator-associated pneumonia; VIM, Verona integron-encoded metallo-beta-lactamase; VRE, vancomycin-resistant enterococci