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Narrative review

Avoiding resistance development to newer drugs: open research lines

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ABSTRACT

Background: The spread of multidrug-resistant gram-negative bacteria, particularly those with carbapenem-resistant or difficult-to-treat resistance phenotypes, is a major public health threat. New agents offer potent therapeutic options but carry the challenge of preserving their effectiveness against resistance.
Objectives: This narrative review summarizes antimicrobial and non–antimicrobial strategies to prevent or mitigate resistance development to novel agents.
Sources: We searched PubMed-MEDLINE for English-language articles published in the last 5 years.
Content: Among antimicrobial strategies, we reviewed the role of optimising pharmacokinetic/pharmacodynamic targets for novel β-lactam/β-lactamase inhibitor combinations and the impact of combination vs. monotherapy regimens. Achieving aggressive joint pharmacokinetic/pharmacodynamic targets may help prevent resistance, supported by approaches such as continuous infusion of time-dependent agents and therapeutic drug monitoring. Current evidence does not demonstrate a routine benefit of combination therapy over monotherapy for novel drugs; however, available studies are limited in size and quality, and resistance emergence has rarely been a primary endpoint.
Non–antimicrobial strategies reviewed include faecal microbiota transplantation, phage therapy, and active or passive immunisation. These approaches may reduce the burden of multidrug-resistant gram-negative bacteria, particularly in high-risk populations such as immunocompromised patients, those undergoing invasive procedures, or patients with foreign bodies. By lowering pathogen load and transmission, these interventions could enhance the effectiveness of current drugs and limit further resistance development.
Implications: Prevention of resistance to novel β-lactam/β-lactamase inhibitor combinations currently relies on optimized dosing and infusion strategies. The benefit of combination regimens remains uncertain and warrants further investigation, ideally with resistance emergence as a defined endpoint and addressed with appropriate analysis. Non–antimicrobial interventions show promise as adjunctive tools in high-risk settings and merit integration into broader resistance prevention frameworks.
Matteo Rinaldi, Clin Microbiol Infect 2026;32:543

Introduction

The growing spread of difficult-to-treat resistant (DTR) gram-negative bacteria (GNB) represents a remarkable issue for public health [1–3]. In particular, carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and difficult-to-treat resistant *Pseudomonas aeruginosa* (DTR-Pa) have been associated with severe infections in vulnerable patients, with associated significant morbidity and mortality [1–3].

In the past 10 years, new drugs, such as ceftolozane/tazobactam, ceftazidime/avibactam, meropenem/vaborbactam, imipenem/relebactam, and cefiderocol, have been introduced, allowing an improvement in the management and outcome of patients developing such severe infections [4–6]. European guidelines and

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American guidance recommend the use of these new drugs in severe infections, and in complicated urinary or nonurinary infections, respectively, due to CRE and DTR-Pa [7,8]. However, resistance to these new drugs has been emerging [9–12]. Particularly worrisome is the increasing prevalence of resistance to ceftazidime-avibactam in *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacterales*, in particular, in *Klebsiella pneumoniae*, due to the selection of variants generally after a period of exposure, probably suboptimal, to the drug [13].

In this scenario, adopting proper corrective measures could increase the likelihood of preserving the activity of new drugs against CR or DTR-GNB. With these premises, in this review, we will address incoming strategies potentially limiting resistance development to novel agents.

A literature search was conducted on PubMed-MEDLINE, retrieving all types of studies published in English in the last 5 years (until 01 July 2025). Three main areas were identified and discussed according to the available evidence: (a) attainment of aggressive pharmacokinetic/pharmacodynamic (PK/PD) target with novel agents for preventing resistance occurrence; (b) mono- vs. combination therapy; (c) non–antimicrobial strategies including faecal microbiota transplantation (FMT), phage therapy and enhanced immunity approaches.

Antimicrobial strategies

Attaining aggressive PK/PD targets: a novel frontier for minimising resistance development to novel agents

Maximising the attainment of aggressive PK/PD targets may represent a novel frontier for reducing resistance development to novel β-lactam/β-lactamase inhibitor combinations (BL/BLIc). Indeed, a paradigm shift recently emerged with the PK/PD optimisation of β-lactams, considering that moving from conservative to aggressive PK/PD targets, defined as the attainment of free concentrations persisting for 100% of the dosing interval above more than four-fold the MIC of the clinical isolate (i.e. 100%fT > 4xMIC), allowed to prevent breakthrough infections and resistance development in GNB infections [14,15]. In this scenario, a recent meta-analysis including 21 observational studies of empirical and/or targeted treatment with β-lactams in critically ill patients showed that aggressive PK/PD target attainment provided significantly higher clinical cure rate (odds ratio [OR], 1.69; 95% confidence interval, 1.15–2.49), and lower risk of β-lactam resistance development (OR, 0.06; 95% confidence interval, 0.01–0.29) compared with conservative PK/PD target [16]. Furthermore, failure in attaining aggressive PK/PD targets was significantly associated with an increased risk of microbiological failure (OR, 26.08; 95% confidence interval, 8.72–77.95). In regard to novel BL/BLIc, it should be noticed that attaining aggressive joint PK/PD targets, namely, optimising not only β-lactam but also β-lactamase inhibitor PK/PD targets, represents a mandatory issue for both maximising clinical efficacy and minimising resistance development [15–17]. In this scenario, ceftazidime-avibactam may represent the novel BL/BLIc at a higher risk of failure in attaining optimal joint PK/PD target, considering that the fixed 4:1 ratio between ceftazidime and avibactam varies widely according to renal function, leading to higher risk of avibactam underexposure in patients with normal or augmented renal clearance [18].

A summary of studies investigating the relationship between the attainment of aggressive PK/PD target with novel BL/BLIc and selected outcomes is reported in Table 1 [17,18,20–32,36]. Unfortunately, only a few studies assessed the relationship between PK/PD target attainment of novel BL/BLIc and resistance occurrence in GNB infections [23,30].

In the CRE scenario, the most interesting evidence stems from a recent pre-post quasiexperimental study, which assessed the impact of a multidisciplinary approach aiming at maximising the attainment of aggressive ceftazidime-avibactam joint PK/PD target on treatment outcome and resistance development in 228 patients with documented KPC-producing *K. pneumoniae* (KPC-Kp) infections [30]. Specifically, in the postintervention phase, a significantly higher rate of ceftazidime-avibactam administration by continuous infusion (CI) (96.1% vs. 31.9%; $p < 0.001$), a lower adoption of combination therapy (67.2% vs. 15.7%; $p < 0.001$), and a shorter median treatment duration (14 vs. 10 days; p 0.01) was reported, resulting in both a significantly higher microbiological eradication (81.0% vs. 53.0%; $p < 0.001$) and clinical cure rate (70.6% vs. 48.3%; $p < 0.001$) and in a significantly lower 90-day resistance development to ceftazidime-avibactam (5.9% vs. 15.5%; p 0.02). Notably, attaining aggressive ceftazidime-avibactam joint PK/PD target emerged as an independent protective factor for both microbiological failure (OR, 0.03; 95% confidence interval, 0.005–0.20; $p < 0.001$) and 90-day resistance development (OR, 0.07; 95% confidence interval, 0.01–0.69; p 0.023) in the postintervention phase at multivariable analyses.

As for meropenem/vaborbactam, a small case series including eight critically ill patients with documented KPC-Kp ventilator-associated pneumonia receiving CI meropenem-vaborbactam reported that the attainment of aggressive joint PK/PD target (i.e. meropenem 100%$fT_{>4xMIC}$ coupled with vaborbactam area under time-to-concentration curve >24) was associated with microbiological eradication in most of the included cases, with no emergence of resistance occurrence [32].

It should be noticed that a proportion of patients as high as 40% to 60% fail in attaining aggressive PK/PD targets with β-lactams when recommended dosing regimens are administered by intermittent infusion [33–36]. However, when CI administration and a real-time therapeutic drug monitoring (TDM)-guided approach is adopted, the proportion of patients who failed in attaining early aggressive PK/PD targets falls <15% with both traditional and novel β-lactams [17,37]. A recent systematic review with meta-analysis found that independent risk factors for failure in attaining early aggressive PK/PD target with β-lactams were male gender, body mass index (BMI) > 30 kg/m^2, augmented renal clearance, and MIC above the clinical breakpoint, whereas prolonged and/or CI emerged as the only protective factor [16].

Administering novel BL/BLIc by CI and implementing a TDM-guided approach may represent useful tools for maximising the likelihood of attaining aggressive joint PK/PD targets, as recently confirmed [38,39]. Although implementing a TDM-guided approach could be challenging or unfeasible in most settings, it should be noticed that this strategy allowed to recommend dosing adjustments of novel BL/BLIc in more than two-thirds of treatment courses [17]. These strategies should be pursued by clinicians in the treatment of carbapenem resistant or DTR-GNB infections to prevent breakthrough or recurrent infections with resistance development to novel BL/BLIc. Further studies would be warranted for assessing the relationship between the attainment of aggressive PK/PD targets and clinical outcomes according to the site of infection.

Combination treatment

Several studies have demonstrated a synergistic effect *in vitro* of novel BL/BLIc in combination with older antibiotics, including meropenem or imipenem, amikacin, fosfomycin, and colistin [40–45]. Clinical studies investigating the impact of combination therapy over monotherapy with novel drugs are summarized in Table 2 [4,46–54,56–58,60–64,99]. In this regard, several shortcomings should be acknowledged, including the observational

Table 1
Summary of studies investigating the relationship between the attainment of aggressive pharmacokinetic/pharmacodynamic target with novel β-lactams and different outcomes

Novel β-lactam Author/y	Study design	*N*	Isolates	Types of infection	Dosing regimens	Selected PK/PD target	Intervention/ exposure	Proportion of patients attaining selected PK/PD target	Outcomes	Resistance occurrence
Ceftolozane-tazobactam										
Gatti et al. [23], 2025	Pre-post quasiexperimental	85	PA	HAP/VAP 55.3% BSI 31.8% HAP/VAP + BSI 12.9%	LD + MD by CI in 100% of cases in both pre- (median MD 9 g/day) and postintervention period (median MD 4.5 g/day)	Aggressive PK/PD target Ceftolozane fC_{ss}/ MIC >4[a]	Adoption of a TDM-guided ECPA strategy in postintervention phase for maximizing the attainment of aggressive ceftolozane PK/PD target	100.0%	Pre vs. post Microbiological eradication: 56.3% vs. 75.8% (p 0.10) Clinical cure 50.0% vs. 62.2% (p 0.26)	Pre vs. post 30-day resistance development 18.8% vs. 10.8% (p 0.37)
Gatti et al. [17], 2025	Retrospective observational cohort	44	PA 85.4% ESBL-E 14.6%	HAP/VAP 45.9% BSI 43.2% HAP/VAP + BSI 2.7% IAI 2.7% IAI + BSI 2.7% UTI 2.7%	LD + MD by CI (97.7%) MD by II over 1h (2.3%)	Aggressive joint PK/PD target Ceftolozane fC_{ss}/ MIC >4[a] Tazobactam fC_{ss}/ C_T > 1	Attainment of aggressive PK/PD target by means of a TDM-guided ECPA strategy	100.0%	Microbiological failure 23.3% Clinical failure 40.9% No significant association with failure in attaining PK/PD target	NA
Olivet et al. [20], 2025	Case series	2	DTR-PA	BSI 100.0%	LD 3g over 1h MD 9 g/day by CI	Aggressive PK/PD target Ceftolozane fC_{ss}/ MIC >4[a]	Attainment of aggressive PK/PD target	100.0%	Microbiological failure 0.0%	NA
Venuti et al. [21], 2023	Case series	4	DTR-PA	HAP 100.0%	9 g/day by CI	Aggressive PK/PD target Ceftolozane fC_{ss}/ MIC >4[a]	Attainment of aggressive PK/PD target	100.0%	Microbiological failure 0.0% Clinical failure 25.0%	NA
Navarrete-Ruoco et al. [22], 2022	Retrospective cohort study	40	DTR-PA	HAP/VAP 40.0% UTI 25.0% IAI 12.5% other 12.5%	MD 3g q8h by CI (75%) MD 3g q8h by EI over 4h (5%) MD 3g q8h by II over 1h (20%)	Aggressive PK/PD target Ceftolozane fC_{ss} or fC_{min}/MIC >4[a]	Attainment of aggressive PK/PD target	87.5%	Clinical failure 17.5% Relationship with failure in attaining PK/PD target not assessed	NA
Sheffield et al. [24], 2020	Case series	4	PA	BSI 50.0% HAP 25.0% CNS 25.0%	LD 3g over 1h MD 3-6 g/day CI according to renal function	Aggressive PK/PD target Ceftolozane fC_{ss}/ MIC >4[a]	Attainment of aggressive PK/PD target	100.0%	Clinical failure 0.0%	NA
Ceftazidime-avibactam										
Gatti et al. [30], 2025	Pre-post quasiexperimental	228	KPC-Kp	BSI 45.9% HAP/VAP 10.6% HAP/VAP + BSI 9.6% IAI 7.8% UTI 7.3% IAI + BSI 6.9% UTI + BSI 5.0% BJI 3.2% SSTI 2.3% BJI + BSI 1.4%	MD by II over 2h (68.1%) and LD + MD by CI (31.9%) in the pre-intervention period; MD by II over 2h (3.9%) and LD + MD by CI (96.1%) in the postintervention period	Aggressive joint PK/PD target Ceftazidime fC_{ss}/ MIC >4[a] Avibactam fC_{ss}/ C_T > 1	Antimicrobial stewardship multidisciplinary approach in postintervention phase consisting in favouring the administration of ceftazidime-avibactam by CI (96.1%), adopting a TDM-guided ECPA strategy (73.5%),	81.3%	Pre vs. post Microbiological eradication: 53.0% vs. 81.0% (p < 0.001) Clinical cure 48.3% vs. 70.6% (p < 0.001) At multivariate analysis aggressive joint PK/PD target attainment as an independent	Pre vs. post 90-day resistance development 15.5% vs. 5.9% (p 0.02) At multivariate analysis aggressive joint PK/PD target attainment as an independent predictor of reduced risk of 90-day resistance

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Table 1 (*continued*)

Novel β-lactam Author/y	Study design	*N*	Isolates	Types of infection	Dosing regimens	Selected PK/PD target	Intervention/ exposure	Proportion of patients attaining selected PK/PD target	Outcomes	Resistance occurrence
							and minimizing the use of combination therapy (15.7%)		predictor of microbiological eradication in postintervention phase (OR, 0.03; 95%CI, 0.005−0.20; $p < 0.001$)	development in postintervention phase (OR, 0.08; 95%CI, 0.02−0.34; $p < 0.001$)
Gatti et al. [17], 2025	Retrospective observational cohort	119	KPC-E 34.9% OXA-48-E 22.2% DTR-PA 17.5% ESBL-E 15.1% CRE 6.3% AmpC-E 4.0%	BSI 46.4% HAP/VAP 18.8% HAP/VAP + BSI 12.5% IAI 4.5% BJI 4.5% IAI + BSI 4.5% UTI 3.6% BJI + BSI 1.8% SSTI 1.8% CNS 0.9% CNS + BSI 0.9%	LD + MD by CI (94.7%) MD by EI over 3h (5.3%)	Aggressive joint PK/PD target Ceftazidime fC_{ss}/ MIC >4[a] Avibactam fC_{ss}/ $C_T > 1$	Attainment of aggressive PK/PD target by means of a TDM-guided ECPA strategy	83.9%	Microbiological failure 14.0% Clinical failure 29.2% Higher risk of microbiological failure ($p < 0.001$) and clinical failure ($p < 0.001$) in patients with aggressive PK/PD target nonattainment	NA
Han et al. [25], 2025	Retrospective observational cohort	23	CR-Kp 78.3% DTR-PA 21.7%	HAP/VAP 53.9% IAI 15.4% UTI 7.7% other 23.0%	MD 2.5 q8h over 2h II adjustment according to renal function	Aggressive joint PK/PD target Ceftazidime fC_{min}/ MIC >4[a] Avibactam fC_{min}/ $C_T > 1$	Attainment of aggressive joint PK/ PD target	69.6%	Clinical failure 34.8% Patients having clinical failure had a significant lower proportion of optimal joint PK/PD target attainment compared with those having clinical cure (12.5% vs. 100.0%; $p < 0.001$)	NA
Curtiaud et al. [26], 2024	Retrospective observational cohort	14	DTR-PA 78.6% ESBL-E 14.3% OXA-48-E 7.1%	VAP 100.0%	MD 0.625g-2.5 q8h over 2h II	Aggressive joint PK/PD target Ceftazidime fC_{min}/ MIC >4[a] Avibactam fC_{min}/ $C_T > 1$	Attainment of aggressive joint PK/ PD target	35.7%	Clinical failure 78.6% Relationship with failure in attaining PK/PD target not assessed	NA
Xu et al. [27], 2024	Case series	7	CR-Kp 57.1% DTR-PA 42.9%	CNS 100.0%	MD 1.25g-2.5 q8h over 2h II	Aggressive joint PK/PD target Ceftazidime fC_{min}/ MIC >4[a] Avibactam fC_{min}/ $C_T > 1$	Attainment of aggressive joint PK/ PD target	42.9%	Microbiological failure 28.6% Clinical failure 0.0%	NA
Gatti et al. [18], 2023	Retrospective observational cohort	58	KPC-Kp 31.0% OXA-48-E 31.0% DTR-PA 24.1% CRE 13.9%	BSI 41.4% HAP/VAP 19.0% HAP/VAP + BSI 17.2% IAI + BSI 12.1% IAI 5.2% SSTI 1.7% CNS 1.7% CNS + BSI 1.7%	LD 2.5g over 2h MD 0.625g-2.5g q8h CI according to renal function	Aggressive joint PK/PD target Ceftazidime fC_{ss}/ MIC >4[a] Avibactam fC_{ss}/ $C_T > 1$	Attainment of aggressive PK/PD target by means of a TDM-guided ECPA strategy	91.4%	At multivariate analysis failure in aggressive joint PK/ PD target attainment as the only independent predictor of microbiological	Overall 3.4%

									failure (OR, 11.11; 95%CI, 1.31–93.98; p 0.023)	
Xu et al. [28], 2023	Case series	4	CR-Kp 50.0% DTR-PA 50.0%	CNS 50.0% VAP 25.0% IAI 25.0%	MD 2.5 q8h over 2h II	Aggressive joint PK/PD target Ceftazidime fC_{min}/MIC >4[a] Avibactam fC_{min}/C_T > 1	Attainment of aggressive joint PK/PD target	25.0%	Microbiological failure 75.0% Microbiological eradication only in the patient who attained aggressive joint PK/PD target	NA
Fresan et al. [29], 2023	Retrospective observational cohort	31	Targeted 83.9% DTR-PA 80.8% ESBL-Kp 19.2%	HAP/VAP 67.7% UTI 12.9%	MD 0.625g q12h-3.75g q12 h by CI	Aggressive PK/PD target Ceftazidime fC_{ss}/MIC >4[a] Avibactam PK/PD target not assessed	Attainment of aggressive ceftazidime PK/PD target Joint PK/PD target not assessed	83.9%	Clinical failure 33.3% The percentage of patients attaining aggressive ceftazidime PK/PD target was higher in those who achieved clinical cure (18/26 [69.2%]) compared with those with clinical failure (2/5 [40%])	0.0%
Gatti et al. [31], 2023	Case series	10	DTR-PA 40.0% KPC-Kp 30.0% OXA-48-Kp 20.0% CRE 10.0%	BSI 50.0% VAP 40.0% VAP + BSI 10.0%	LD 2.5g over 2h MD 0.625g-2.5g q8h CI according to renal function	Aggressive joint PK/PD target Ceftazidime fC_{ss}/MIC >4[a] Avibactam fC_{ss}/C_T > 1	Attainment of aggressive PK/PD target by means of a TDM-guided ECPA strategy	80.0%	Microbiological failure 20.0%	10.0%
Meropenem-vaborbactam										
Gatti et al. [17], 2025	Retrospective observational cohort	47	KPC-Kp 87.8% ESBL-E 9.8% CRE 2.4%	BSI 34.1% HAP/VAP 29.3% IAI 12.2% HAP/VAP + BSI 9.8% VAP + IAI 7.3% UTI + BSI 2.4% UTI 2.4% BJI + BSI 2.4%	LD + MD by CI (78.6%) MD by EI over 3h (21.4%)	Aggressive joint PK/PD target Meropenem fC_{ss}/MIC >4[a] Vaborbactam AUC/C_T > 24	Attainment of aggressive PK/PD target by means of a TDM-guided ECPA strategy	84.4%	Microbiological failure 25.0% Clinical failure 37.5% No significant association with failure in attaining PK/PD target	NA
Gatti et al. [32], 2023	Case series	8	KPC-Kp	VAP 50.0% VAP + IAI 37.5% VPA + BSI 12.5%	LD 2g/2g over 3h MD 1g/1g q8h CI or 2g/2g q8h CI according to renal function	Aggressive joint PK/PD target Meropenem fC_{ss}/MIC >4[a] Vaborbactam AUC/C_T > 24	Attainment of aggressive PK/PD target by means of a TDM-guided ECPA strategy	100.0%	Microbiological failure 12.5%	0.0%
Cefiderocol										
Gatti et al. [17], 2025	Retrospective observational cohort	53	CRAB 57.1% DTR-PA 18.6% SM 12.9% KPC-E 2.9% OXA-48-E 2.9% ESBL-E 2.9% VIM-Kp 1.4% AmpC-E 1.4%	BSI 39.1% HAP/VAP 34.4% HAP/VAP + BSI 12.5% BJI 6.3% IAI + BSI 1.6% BJI + BSI 1.6% SSTI 1.6% CNS 1.6% CNS + BSI 1.6%	LD + MD by CI (50.0%) MD by EI over 3h (50.0%)	Aggressive PK/PD target Cefiderocol fC_{ss}/MIC >4[a]	Attainment of aggressive PK/PD target by means of a TDM-guided ECPA strategy	83.9%	Microbiological failure 39.6% Clinical failure 48.5% Higher risk of clinical failure (p 0.006) in patients with aggressive PK/PD target nonattainment	NA

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Table 1 (*continued*)

Novel β-lactam	Author/y	Study design	*N*	Isolates	Types of infection	Dosing regimens	Selected PK/PD target	Intervention/ exposure	Proportion of patients attaining selected PK/PD target	Outcomes	Resistance occurrence
	Gatti et al. [36], 2021	Case series	13	CRAB	VAP 46.2% VAP + BSI 38.5% BSI 15.3%	1.5g-2g q8h over 3h EI	Aggressive PK/PD target Cefiderocol fC_{ss}/MIC >4[a]	Attainment of aggressive PK/PD target by means of a TDM-guided ECPA strategy	38.5%	Microbiological failure 53.8% Trend to higher risk of microbiological failure in patients with VAP when moving from optimal vs. quasi-optimal vs. suboptimal PK/PD target attainment (40.0% vs. 66.7% vs. 100.0%)	NA

AUC, area under time-to-concentration curve; BJI, bone and joint infection; BSI, bloodstream infection; CI, continuous infusion; CNS, central nervous system; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant *Enterobacterales*; C_T, threshold concentration; DTR, difficult-to-treat resistant; E, *Enterobacterales*; ECPA, expert clinical pharmacological advice; EI, extended infusion; ESBL, extended-spectrum β-lactamase; fC_{min}, free trough concentration; fC_{ss}, free steady-state concentration; HAP, hospital-acquired pneumonia IAI, intrabdominal infection; II, intermittent infusion; Kp, *Klebsiella pneumoniae*; LD, loading dose; MD, maintenance dose; NA, not assessed; OR, odds ratio; PA, *Pseudomonas aeruginosa*; PK/PD, pharmacokinetic/pharmacodynamic; SM, *Stenotrophomonas maltophilia*; SSTI, skin and soft tissue infection; TDM, therapeutic drug monitoring; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

[a] fC_{ss}/MIC >4 and fC_{min}/MIC >4 are equivalent to 100%$fT_{>4xMIC}$.

design of all available studies, small sample sizes in most, and the fact that adjusted analyses were performed only for primary endpoints (e.g. all-cause 30-day mortality or composite outcomes of clinical cure, microbiological eradication, and mortality). In contrast, the relationship between combination regimens and resistance emergence was assessed only through descriptive, unadjusted analyses. Well-designed prospective studies are therefore needed to clarify the impact of combination therapy with new BL/BLIc on resistance development.

Another challenge is the marked heterogeneity in the companion drugs used with BL/BLIc across studies. In this regard, fosfomycin deserves a particular mention as it is frequently associated with several new drugs for treating CRE, DTR-Pa, and CRAB. *In vitro* synergy of fosfomycin combinations against CR-GNB assessed by PK/PD and time-kill studies has been explored, showing moderate/high rate of synergy both with old drugs (mainly polymyxins) and novel drugs (mainly ceftazidime-avibactam) [55]. In a matched cohort study including 122 patients, ceftazidime-avibactam + fosfomycin compared with ceftazidime-avibactam with other combinations resulted in a lower rate of subsequent KPC-Kp infections and secondary infections, despite no differences in overall mortality [63]. Among a retrospective cohort of 577 patients treated with ceftazidime-avibactam for CRE infection, fosfomycin + ceftazidime-avibactam was one of the most frequently reported combination regimens, particularly for the treatment of lower respiratory tract infections [4]. However, no significant differences between monotherapy and combination therapy were found for 30-day mortality (26.1% vs. 25%) or resistance development (3.6% vs. 3.4%). In addition, at propensity score adjusted multivariable analysis, combination was not a significant predictor of outcome, whereas the administration of ceftazidime-avibactam by CI was significantly associated with better outcome. In another cohort of 363 patients with gram-negative bloodstream infection (BSI), with a rate of carbapenem-resistant isolates of 36%, adding fosfomycin as a part of combination treatment resulted in significantly lower mortality rates (adjusted hazard ratio [HR], 0.51; 95% confidence interval, 0.28–0.92), but not with other combotherapies (HR, 0.69; 95% confidence interval, 0.44–1.16), especially in severe infections and when fosfomycin was administered within 24 hours from BSI onset [59]. Fosfomycin has been also used in combination with cefiderocol for the treatment of CRAB infections. In a retrospective cohort of 142 CRAB BSIs, no differences between monotherapy and overall combination regimens were reported; however, cefiderocol combined with fosfomycin was found to be protective against 30-day mortality (HR, 0.43; 95% confidence interval, 0.22–0.81) [64]. Similarly, a study evaluating the impact of fosfomycin combination with different drugs for CRE or CRAB infections in critically ill patients demonstrated higher clinical cure, microbiological eradication and lower short-term mortality compared with regimens not containing fosfomycin, especially in KPC-*K. pneumoniae* infections [65]. Thus, receiving fosfomycin combination was independently associated with survival (HR, 0.29; 95% confidence interval, 0.09–0.93, p 0.038).

Nonantibiotic strategies

Faecal microbiota transplantation

FMT has been regarding as an alternative to decolonisation with oral nonabsorbable drugs to reduce the burden of multidrug-resistant organisms (MDRO) in colonized patients at high risk of developing infections (e.g. rectal carriers candidates to stem cell or solid organ transplantation, invasive abdominal procedures, intensive chemotherapy) [66]. This may result in a reduced selective pressure associated with the use of traditional and novel agents possibly limiting resistance development. A recent

Table 2
Studies assessing the impact of combination vs. monotherapy with new drugs for the treatment of carbapenem-resistant or difficult-to-treat resistant gram-negative infections

New drug	Author/y	Study design	Types of infection (main)	Microrganisms	N° mono/N° combo	Combo	Outcome (mono/combo)
Ceftolozane/ tazobactam	Rodríguez-Núñez et al. [46], 2019	Retrospective	LTRI 100%	PsA (XDR 76.7%)	54/36	CST, AMK, FQ, MRM, IMI	30-DM: 22% vs. 36% RE: NA
	Bassetti et al. [47], 2019	Retrospective	LRTI 31.7%	PsA (WT 29.7%, 17.8% MDR, 50.5%, XDR, 2.0% PDR)	65/36	AMG, CST, MRM, IMI	CS: 83.1% vs. 83.3% RE: NA
	Bassetti et al. [48], 2020	Retrospective	LRTI 30.1% cUTI 22.2%	ESBL	26/127	NA	CS: 88.5% vs. 82.7% RE: NA
Ceftazidime/ avibactam	Ackley et al. [49], 2020	Retrospective	BSI 41.9%	CRE (KPC 71.9%)	41/64	CB, AGs, PMB, CST, TGC, FLQ and SXT	90-DM: 22% vs. 31.2% RE: 7.3% vs. 0%
	Càston et al. [50], 2020	Retrospective	BSI 51.1%	CRE (KPC 100%)	34/13	GEN, TGC, CST, FOF + GEN, TGC + GEN	30-DM: 26.5% vs. 15.4% RE: 11.7% vs. 15.4%
	Mishuk et al. [51], 2022	Retrospective	BSI 28.3%	K. pneumoniae 45.7%, PsA 27.4%, Enterobacter 12.2%, E. coli 5.5%, A. baumannii 1.2%	82/154	MEM, CST, TZP, AMK, TGC, GEN, PMB	IH-M: 28.7% vs. 27.7% RE: 2.4% vs. 1.9%
	Shields et al. [52], 2018	Retrospective	BSI 26%	CRE KPC (75%)	17/8	GEN, CST, TGC AMK	RE: 11.3% vs. 8.3%
	Tumbarello et al. [4], 2021	Retrospective	BSI 67.7%	CRE KPC (100%)	165/412	FOF, TGC, GEN, MEM, CST and AMK	30-DM: 26.1% vs. 25% RE: 3.6% vs. 3.4%
	Iannaccone et al. [53], 2020	Retrospective	BSI 100%	CRE KPC (100%)	3/20	TGC, COL, GEN, FOS, and MEM	CS: 66.7% vs. 75% RE: 0% vs. 10%
	Tumbarello et al. [54], 2019	Retrospective	BSI 75.4%	CRE KPC (100%)	29/109	GEN, TGC, COL, FOS, and CAP	30-DM: 40.9% vs. 35.7% RE: 6.9% vs. 0.9%
	Temkin et al. [56], 2017	Retrospective	BSI 68.4%	CRE and CRPA	13/25	NA	MC: 61.5% vs. 64.0% RE: 0% vs. 0%
	Oliva et al. [63], 2022	Retrospective	BSI 100%	CRE KPC (100%)	61/61	FOF, MRM	MC: 76.7% vs. 60.7% RE: 0% vs. 3.3%
	Karaiskos et al. [57], 2021	Prospective	BSI 64.6% LRTI 25.2%	CRE (KPC 95%, OXA-48 5%)		CST, AMG, TGC, FOF	30-DM: 11.8% vs. 27.8% RE: 1.5% vs. 1.3%
Meropenem/ vaborbactam	Ackley et al. [49], 2020	Retrospective	BSI 34.6%	CRE (KPC 76.9%)	22/4	NA	90-DM: 27.3% vs. 25% RE: 0% vs. 0%
	Tumbarello et al. [58], 2024	Retrospective	BSI 50.1% LRTI 31.3%	CRE (KPC 100%)	213/129	FOF, TGC, GEN	30-DM: 30.9% vs. 32.6% RE: NA
Cefiderocol	Falcone et al. [60], 2022	Retrospective	BSI 57.4%	CRAB	14/32	FOF, TGC, ETP	MF: 42.9% vs. 6.3% RE: 28.6% vs. 0%
	Bavaro et al. [64], 2023	Retrospective	BSI 100%	CRAB	43/99	FOF, ASB	30-DM: combo vs. mono HR, 0.81; 95% CI, 0.39−1.66 FOF combo: HR, 0.43; 95% CI, 0.22−0.81) RE: NA
	Giannella et al. [61], 2023	Retrospective	LTRI 65.3% BSI 24.5%	CRAB	49/98	CST, TGC, FOF, MRM, ASB	CS: 61.2% vs. 49% 28-DM: 53.1% vs. 40.8% RE: NA
	Mazzitelli et al. [62], 2023	Retrospective	BSI 56.6% LRTI 43.4%	CRAB	30/30	FOF, TGC, MRM	CS: 76.7% vs. 70% MC: 50% vs. 36.7% 30-DM: 33.3% vs. 53.5% RE: NA
	Rando et al. [99], 2023	Prospective	LRTI 100%	CRAB	12/43	FOF, TGC, ASB, MRM	MF: 56% vs. 52% 28-DM: 42% vs. 44% RE: NA

28-DM, 28-day mortality; 30-DM, 30-day mortality; 90-DM, 90-day mortality; AMK, amikacin; ASB, ampicillin/sulbactam; BSI, bloodstream infection; CRAB, Carbapenem-resistant *Acinetobacter baumannii*; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; CRE, Carbapenem-resistant *Enterobacterales*; CS, clinical success; CST, colistin; ETP, ertapenem; FOF, fosfomycin; GEN, gentamycin; HR, hazard ratio; IH-M, in-hospital mortality; IMI imipenem; LRTI, lower respiratory tract infection; MC, microbiological cure; MDR, multidrug resistant; MF, microbiological failure; MRM, meropenem; PDR, pan-drug resistant; PMB, polymyxin-B; PsA, *Pseudomonas aeruginosa*; RE, resistance emergence; TGC, tigecycline; TZP, piperacillin/tazobactam; UTI, urinary tract infection; XDR, extensively drug resistant.

systematic review including ten retrospective or prospective observational studies assessing the efficacy of FMT in 112 patients with documented CRE colonisation (mainly KPC-, OXA-48-, or New Delhi Metallo beta-lactamase (NDM)-producing *K. pneumoniae* or *Escherichia coli*) found a decolonisation rate of 61% at 1 month after FMT and of 78.7% at 6 to 12 months follow-up, with a median decolonisation time ranging from 7 to 24 days [67]. Furthermore, the decolonisation rate associated with FMT was significantly higher than spontaneous decolonisation reported in control groups ranging from 10% to 33%. In an explorative controlled trial to compare bowel preparation plus FMT vs. bowel preparation alone in 11 kidney transplant recipients, FMT resulted in faster MDRO decolonisation and protected study participants from recurrent infection. In some participants, extended-spectrum β-lactamase (ESBL)–producing strains were replaced by non-ESBL strains, suggesting that strain competition rather than eradication may occur after FMT [68]. In a recent randomized feasibility study enrolling patients with invasive infection with extended-spectrum β-lactamase (ESBL-) or CRE and persistent gastrointestinal carriage: 41 were randomized to receive FMT (20) or placebo (21) [69]. Although only three patients were decolonized in the intervention group, a trend towards increased effectiveness of FMT for MDRO eradication with increased proportional engraftment of donor-derived strains was observed. Of note, in patients treated with FMT who failed eradication a shift in species carrying resistance pattern was reported. These findings provide valuable insights into the mechanisms by which FMT may lead to MDRO decolonisation but also to potential harmful effects.

Some experts argued that eradication should not be considered as the only endpoint of FMT therapy, indeed a prospective study including 20 high-risk patients (11 patients with haematological malignancy and nine kidney transplant recipients) with intestinal colonisation by multidrug-resistant (MDR) pathogens or recurrent MDR-infections showed a significant reduction in overall BSIs and in BSIs caused by MDR pathogens, a significantly shorter median inpatient length of stay (28 days vs. 70 days; p 0.0002), and a significant reduction in median carbapenem use (median 4 days vs. 36 days; p 0.0005) after FMT, despite a low rate of eradication [70].

Overall, these preliminary findings may support the potential role of FMT as an adjuvant strategy for reducing the burden of MDRO infections in high-risk patients with documented colonisation [71]. In this context, the development of ad hoc protocols and the involvement of specialized expertise are essential, particularly when managing fragile, often immunocompromised hosts, given that the procedure itself may carry intrinsic infectious risks.

Phage therapy

Phage therapy, first conceived over a century ago, is experiencing a resurgence as a potential solution to manage infections caused by MDRO. Phage therapy consists in using naturally bacteriophages that use lytic viruses able to infect and lyse target bacteria [72]. Through such mechanisms, phages deliver viral genomic material into the bacterial cell, producing new viral particles and resulting in final lysis of the bacterial wall [73]. Although some advantages, such as specificity for the target organism, ability to penetrate biofilms and preservation of the human microbiota, the requirement for strain-specific phages has limited the prompt administration and expansion [74]. As in the last decades a growing interest in phage therapy has been observed, the first randomized controlled phase I/II trial enrolling patients with burn wounds infected with *P. aeruginosa* ended in 2017. The phage cocktail used resulted to be safe, but low concentrations of phage was used, resulting in a slower decrease in bacterial burden [75]. Phages show promising *in vitro* activity against CRE isolates, although clinical trials conducted specifically for CRE infections are lacking [76,77]. Nowadays, evidence of phage therapy as an alternative to conventional antibiotic treatment derives from case reports [78]. Promising results have been reported in CRE infections of the urinary tract, intraabdominal and prosthetic knee [79–81]. Small experiences in solid organ transplant recipients were conducted combining bacteriophages and antibiotics to treat CRE chronic urinary tract infection, epididymitis and lung infection [82–84]. In these case reports, cocktails of phages were administered by different routes, such as intravenous, intrarectal, oral and intravesical. Thus, optimal route of administration, appropriate dosing and timing are crucial to obtain higher cure rates, as well as prophylactic use could be a promising strategy for those patients at highest risk of recurrent CRE infections [85]. However, bacteria may also develop specific resistance mechanisms against phages. Several resistance mechanisms have been reported, including blocking phage attacking, absorption and transcription [86]. Of interest, development of phage resistance may result in restoring of antimicrobial susceptibility, as recently observed [87].

Strategies to enhance immunity

In the last decade, a variety of vaccines, including whole-cell or killed mutant, outer membrane proteins, lipopolysaccharide or conjugate/polysaccharide, have been evaluated for MDR-GNB infections, as well as monoclonal antibodies are under investigation [88,89]. The main challenges in developing vaccines for GNB are the difficult to avoid cross-reactivity with the host microbiome, and the decreased vaccine protective response among immunosuppressed patients [90]. Given such limitations, despite different vaccines showed favourable safety and protective profile, no significant progress has been reported afterward, and none of them have been further approved for use [91]. However, in recent years, new technologies on vaccines for GNB are in development. Among them, there is a new vaccine with revolutionary mechanism of action, being able to target two different porins constantly present on *K. pneumoniae* surface, potentially active against all different strains. The project is currently supported by European Horizon [92], it is expected that a phase IA trial will start during this year. With the same technology, a new vaccine for *P. aeruginosa* for patients with cystic fibrosis and bronchiectasis has been developed. Similarly, new vaccines against *E. coli* and *Acinetobacter* spp. are in the pipeline. Also, monoclonal antibodies targeting specific bacterial proteins responsible for pathogenicity has been evaluated, especially for *P. aeruginosa* infections. One of them, KB001-A was studied in phase I and II trials in patients with pneumonia or chronic lung infections, but did not achieve sufficient efficacy to proceed to phase III [93]. Similarly, a new bispecific antibody targeting *P. aeruginosa* biofilm failed to demonstrate efficacy in phase II trial [94]. Recently, an unbiased monoclonal antibody (mAb) selection method against an hypervirulent carbapenem-producing *Enterobacterales* strain (ST147NDM-1) not bound to a specific antigen, which enabled the isolation of potent bactericidal mAbs from donors who experienced bloodstream infection by ST147NDM-1 has been published [95]. The top candidate mAb, 08O09, was able to provide protection as a prophylactic drug against ST147NDM-1, as well as against other strains with different determinants of carbapenem resistance and virulence (ST231OXA-48 and ST2096OXA-232) in animal models [95]. To give priority of developing new specific vaccines and monoclonal antibodies, informing the strategic allocation of limited resources, an European project named 'PrIMAVeRa' (Predicting the Impact of Monoclonal Antibodies & Vaccines on Antimicrobial Resistance) is ongoing [96].

Finally, antimicrobial peptides (AMPs), which also exert immunomodulatory effects, have gained interest as an alternative therapeutic option for bacterial infections, considering their broad-spectrum antimicrobial activity [97]. Several syndrome-specific phase III trials are in development or have been completed. Some of these agents have demonstrated improved recovery of patients with diabetic foot as well as resolution of sepsis and higher rates of hospital discharge in necrotising soft tissue infections. However, different trials failed for high rates of severe adverse events, especially for AMPs administered via the intravenous route. This issue poses a significant limitation to their application for severe GNB infections, although *in vitro* studies are encouraging [19,98].

Conclusions

Preserving the efficacy of novel agents against MDR-GNB requires their judicious use, with a focus on attaining optimal PK/PD targets through TDM, ensuring adequate exposure not only to β-lactams but also to their β-lactamase inhibitors, particularly avibactam in the ceftazidime-avibactam combination. CI administration of novel BL/BLIc may be universally suggested for minimising the risk of failure in attaining aggressive PK/PD targets, whereas the implementation of a TDM-guided approach should be pursued at least in challenging scenarios (i.e. critically ill patients, occurrence of remarkable pathophysiological alterations, infections caused by strains with borderline susceptibility) also in settings where this approach could be unfeasible. The role of combination therapy in preventing resistance remains uncertain and warrants well-designed prospective studies with resistance emergence as a defined endpoint. In parallel, nonantibiotic approaches are gaining interest, with FMT at advanced stages of clinical investigation. These adjunctive tools hold promise for reducing the burden of MDROs in high-risk patients, potentially limiting antibiotic use and mitigating the risk of new resistance development.

CRediT authorship contribution statement

Milo Gatti and Matteo Rinaldi: Conceptualisation, Methodology, Investigation, and Writing – Original draft preparation. Milo Gatti: Supervision, Reviewing, and Editing. Matteo Rinaldi, Milo Gatti, and Maddalena Giannella: Conceptualisation, methodology, read and approved the final manuscript.

Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

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