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Continuous versus intermittent infusion of antibiotics in Gram-negative multidrug-resistant infections

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Purpose of review
The aim of this review was to perform a critical reappraisal of the real-world evidence supporting administration by prolonged infusion of novel beta-lactams for the management of multidrug-resistant Gramnegative infections.

Recent findings
Real-world evidence support the use of novel beta-lactams by prolonged infusion over intermittent infusion in terms of achieving aggressive pharmacokinetic/pharmacodynamic (PK/PD) target for either maximizing efficacy and clinical outcome or suppressing the emergence of resistance development. Continuous infusion of ceftolozane-tazobactam showed a marked superiority toward both intermittent and extended infusion (EI) in achieving a PK/PD target of 100%$fT_{> 4 \times MIC}$ in infections caused by less-susceptible *Pseudomonas aeruginosa* isolates. No resistance development was found in critically ill or immunocompromised patients treated with EI ceftolozane-tazobactam compared to intermittent infusion. Prolonged infusion of ceftazidime-avibactam was negatively associated with mortality in patients affected by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* infections. Different challenging scenarios (patients showing augmented renal clearance of affected by deep-seated infections) could benefit from prolonged infusion to optimize the efficacy of novel agents.

Summary
Although available data are still limited, real-world evidence regarding mainly ceftolozane-tazobactam and ceftazidime-avibactam could support the administration of novel beta-lactams by prolonged infusion in some specific scenarios in which achievement of aggressive PK/PD target is quite challenging.

Keywords
ceftazidime-avibactam, ceftolozane-tazobactam, multidrug resistance gram-negative infections, novel beta-lactams, prolonged infusion

INTRODUCTION

In the last ten years, many efforts have been performed to optimize antibiotic therapy, and prolonged infusion currently represents a mainstay for the administration of time-dependent antibiotics in the management of critically ill patients [1]. Prolonged infusion encompasses both extended infusion (EI), consisting in antibiotic administration over 3–4 h (approximately 40–50% of the dosing interval), and continuous infusion (CI), consisting in antibiotic administration for the entire dosing interval up to 24 h [2].

Although prolonged infusion would appear to be a novel and innovative concept for antibiotic administration in clinical practice, it was already well characterized since the late 1940 s, when in preclinical models Dr Harry Eagle highlighted the relationship between the pharmacokinetic (PK) properties of antimicrobials and bacterial killing, reporting the advantages of penicillin CI compared to intermittent administration [3]. Although these concepts were neglected during the so-called 'golden age of antibiotic discovery' [4], they were rediscovered by Dr William Craig in the early 1990 s [5], until gaining a key role in current clinical practice.

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KEY POINTS

- Firm evidence supports the use of traditional beta-lactams by prolonged infusion in maximizing the achievement of optimal pharmacokinetic/pharmacodynamic target and improving clinical outcomes in multidrug-resistant gramnegative infections.
- Real-world studies currently support the advantages of prolonged over intermittent infusion of ceftolozane-tazobactam and ceftazidime-avibactam in achieving aggressive pharmacokinetic/pharmacodynamic targets, in reducing mortality rate, and in preventing the occurrence of resistance development in patients affected by *Pseudomonas aeruginosa* or KPC-producing *Enterobacteriaceae* infections.
- The clinical impact of prolonged infusion of novel beta-lactams could be especially relevant in specific challenging scenarios, namely patients who are critically ill or immunocompromised, or have significant renal derangements, or are affected by deep-seated infections caused by less-susceptible isolates.
- A clinical pharmacological approach based on therapeutic drug monitoring and pharmacokinetic/pharmacodynamic optimization should be encouraged to ensure the best use of novel beta-lactams in patients affected by multidrug-resistant gram-negative infections.

The widespread diffusion of multidrug-resistant (MDR) Gram-negative pathogens (e.g., carbapenemase-producing *Enterobacteriaceae* (CPE), MDR or extensively drug-resistant *Pseudomonas aeruginosa,* carbapenem-resistant *Acinetobacter baumannii, and Stenotrophomonas maltophilia*), represents a worrisome health concern [6]. In recent years, several novel antibiotics for the management of MDR Gram-negative infections have been licensed (i.e., ceftolozane-tazo-bactam, ceftazidime-avibactam, meropenem-vabor-bactam, imipenem-relebactam, cefiderocol) [7▪]. Additionally, some older agents (i.e., fosfomycin or carbapenems) showed promising results in this setting, especially when PK/pharmacodynamic (PD) optimization is performed [8,9]. However, in several cases resistance development to novel beta-lactams have been documented [10–12]. Consequently, PK/PD optimization focused at maximizing clinical efficacy and minimizing resistance occurrence should be pursued also for these novel agents [13].

Currently, firm evidence supports prolonged infusion of traditional beta-lactams (e.g., meropenem, piperacillin-tazobactam, ceftazidime) especially among critically ill and/or immunocompromised patients [14–16]. Additionally, several guidelines recommend prolonged infusion of beta-lactams in the critical care setting [17,18,19▪]. Evidence on the advantages that prolonged infusion of the novel agents may have compared to intermittent infusion in terms of favorable clinical outcome is quite limited.

The aim of this review is to perform a critical reappraisal of the real-world evidence that may support prolonged infusion administration of antimicrobial agents for the treatment of MDR Gram-negative infections, with a focus on clinical data of novel beta-lactams published in the last 18 months.

Rationale for prolonged infusion of novel beta-lactams in the treatment of multidrug-resistant Gram-negative infections

Similarly to old beta-lactams, novel agents exhibit time-dependent bacterial killing, and their efficacy is associated with the percentage of the dosing interval that the unbound concentration is maintained above the minimum inhibitory concentration (MIC) of the targeted pathogen (%$fT_{> MIC}$). The minimum $fT_{> MIC}$ value required for bactericidal activity ranges between 40 and 70% according to experimental studies. However, emerging clinical data suggest that more aggressive PK/PD target up to 100%$fT_{> 4 \times MIC}$ may not only improve clinical efficacy, but also suppress the emergence of resistance [20▪▪,21,22▪▪]. Minimizing the occurrence of resistance development is a key determinant to preserve the activity of novel beta-lactams over time, and this is fundamental as they represent the last resort for the management of MDR Gramnegative infections.

Clinicians have to face two remarkable PK/PD issues when novel beta-lactams are administered in critically ill patients: (1) the wide variations in drug exposure due to the profound pathophysiological alterations commonly affecting volume of distribution and clearance of beta-lactams [1,20▪▪]; (2) the growing prevalence of MDR Gram-negative isolates showing high MIC [23]. In this scenario, administration of novel beta-lactams by intermittent infusion could lead to failure in achieving even the most conservative PK/PD target adopted in pivotal trials. Among novel agents, according to the package insert prolonged infusion over 3 h is allowed only for meropenem-vaborbactam and cefiderocol (Table 1) [13].

Prolonged infusion theoretically allows to achieve and maintain higher %$fT_{> MIC}$, especially in clinical scenarios characterized by extreme pathophysiological alterations (e.g., critically ill patients), deep-seated infections, and/or poor susceptible isolates. Conversely, intermittent infusion leads to unnecessary high peak concentrations followed by an earlier fall below the MIC, resulting in suboptimal achievement of aggressive PK/PD targets (i.e., 100%$fT_{> 4 \times mic}$) [24].

Table 1. Pharmacokinetic/pharmacodynamic targets and infusion modality of novel beta-lactams according to pivotal trials and suggested dosages for maximizing the achievement of aggressive targets

Novel beta-lactams	PK/PD target adopted in pivotal trials	Scheduled infusion modality	PK/PD for suppression of resistance development	Stability in solution	Suggested dosage for maximizing PK/PD target[a]
Cefiderocol	75% $fT_{>MIC}$	Extended infusion over 3h	100% $fT_{> 4–5 \times MIC}$	6h	LD2g MD 2 g q8h prolonged infusion over 4–6 h
Ceftazidime-Avibactam	50% $fT_{>MIC}$	intermittent infusion over 2 h	100% $fT_{> 4–5 \times MIC}$	12h	LD 2 g/0.5 g MD 2 g/0.5 g q8h prolonged infusion over 8 h
Ceftolozane-Tazobactam	30% $fT_{>MIC}$	intermittent infusion over 1 h	100% $fT_{> 4–5 \times MIC}$	24 h	LD 2 g/1 g MD 6 g/3g daily CI
Imipenem-Relebactam	40% $fT_{>MIC}$	intermittent infusion over 0.5 h	100% $fT_{> 4–5 \times MIC}$	3.5 h	500 mg/250 mg q6h prolonged infusion over 3 h
Meropenem-Vaborbactam	45% $fT_{>MIC}$	Extended infusion over 3h	100% $fT_{> 4–5 \times MIC}$	12h	LD 2 g/2 g MD 2 g/2 g q8h prolonged infusion over 8 h

[a]For patients with normal renal function.
CI, continuous infusion; LD, loading dose; MD, maintenance dose; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.

Notably, stability in aqueous solution represents a critical issue for implementing prolonged infusion, considering that loss of efficacy may be associated with early antibiotic degradation after reconstitution in aqueous solution. Ceftolozane-tazobactam and meropenem-vaborbactam are stable at room temperature respectively for 24 and 12 h after reconstitution, so that prolonged infusion may be easily performed [25,26]. Likewise, ceftazidime-avibactam is stable for up to 12 h in aqueous solution, according to the package insert, and firm evidence support the stability of ceftazidime for 24 h [27]. Although no data on imipenem-relebactam stability exist nowadays, the stability of imipenem in aqueous solution is limited to 3.5 h, and thus only EI over 3 h could be allowed [28].

Novel evidence for the use in prolonged infusion of traditional agents in the treatment of multidrug-resistant Gram-negative infections

Carbapenems still play a key role in the management of MDR Gram-negative infections, whenever MICs of clinical isolates are permissive and PK/PD optimization is applied [29]. Previous real-world evidence showed that administration of high-dose CI meropenem (6–8 g/day) allowed to achieve optimal PK/PD target ($100\%T_{> 1–4 \times MIC}$) for the management of infections caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae* with an MIC up to 64 mg/L [30,31].

Recently, Cojutti *et al* [32]. found that CI meropenem at a dosage ranging between 1 g q8 h over 8 h and 1.25 g q6 h over 6 h allowed the achievement of optimal PK/PD target in terms of steady state concentration [C_{ss}]/MIC ratio $\geq$ 4 against *Enterobac-teriaceae* among febrile neutropenic patients affected by hematological malignancies. Similarly, a CI dosage of 1.5 g q6 h over 6 h was required to achieve aggressive PK/PD target against *P. aeruginosa* [32]. Notably, the approach of adjusting CI meropenem dosage among oncohematologic patients with febrile neutropenia on the basis of real-time therapeutic drug monitoring (TDM) allowed not only to attain aggressive PK/PD target of Css/MIC of 4–8, but also to prevent the occurrence carbapenem-producing *Enterobacteriaceae* (CPE), as documented by the lack of CPE isolates at rectal swab during a 3-month follow-up period [33▪].

Fosfomycin exhibits activity against a considerable proportion of MDR Gram-negative pathogens, and in the last years is becoming an useful option for combination therapy in the management of infections caused by CPE or carbapenem-resistant *P. aeruginosa* and *A. baumannii* [8]. Prolonged or CI has been suggested for fosfomycin according to a better PK/PD optimization compared to intermittent infusion [34,35]. A daily dosage of 16–24 g of fosfomycin in prolonged or CI after a loading dose of 8 g is recommended for the treatment of MDR Gram-negative infections. This approach may allow to maximize the achievement of adequate area under the concentration-to-time curve (AUC)/MIC ratio,

and delay the occurrence of resistant development [34,35].

Real-world evidence for the use in prolonged infusion of novel beta-lactams in the management of multidrug-resistant Gramnegative infections

Current evidence to support the administration of novel agents by prolonged infusion is limited to real-world experiences with ceftolozane-tazobactam and ceftazidime-avibactam. Although meropenem-vaborbactam and cefiderocol administration schedule is by EI over 3 h [13], nowadays no real-world data assessed the potential advantages associated with this.

Real-world evidence concerning the use of ceftolozane-tazobactam in prolonged infusion are summarized in Table 2. Overall, one prospective study, one Monte Carlo simulation study, three retrospective studies, and four case reports [36▪▪, 37,38▪▪,39–44] compared prolonged with intermittent infusion of ceftolozane-tazobactam or reported real-world experiences of ceftolozane-tazobactam prolonged infusion in the management of MDR *P. aeruginosa* infections (including pneumonia, bloodstream infections, complicated urinary or intrabdominal infections, bone or joint infections, meningitis, or skin and soft tissue infections). Pilmis *et al.* [36▪▪] prospectively assessed 72 patients treated with ceftolozane-tazobactam for MDR *P. aeruginosa* infections (26.3% MIC $\geq$4 mg/L; 66.7% pneumonia), of whom 79% was admitted to intensive care unit (ICU), and more than half were immunocompromised. Ceftolozane-tazobactam was administered by intermittent, EI (over 4 h), or CI respectively in 44, 13, and 15 patients. Notably, CI showed a marked superiority toward both intermittent and EI in infections caused by less-susceptible isolates. Aggressive PK/PD target of 100%$fT_{> 4 \times MIC}$ was achieved in all of the patients with infections caused by clinical isolates with an MIC $<$ 4 mg/L regardless of infusion modality. Conversely, only patients who received ceftolozane-tazobactam by CI showed a $>$ 9O% probability of target attainment of 1OO% $fT_{> 4 \times MIC}$ for infections caused by *P. aeruginosa* with an MIC $\geq$ 4 mg/L.

Interestingly, in a case-control study evaluating 28 patients affected by MDR *P.* aeruginosa infections (46.4% immunocompromised), Tamma *et al.* [38▪▪] found no resistance development in cases receiving ceftolozane-tazobactam in EI (over 3 h; 0% vs. 29%; $P = 0.04$).

Real-world evidence concerning the use of ceftazidime-avibactam in prolonged infusion are summarized in Table 3. Overall, one retrospective cohort study, one case series, and three case reports [45▪▪,46▪,47–49] focused on administration of ceftazidime-avibactam in prolonged infusion for the management of MDR Gram-negative infections. In a multicentric retrospective study, Tumbarello *et al.* [45▪▪] assessed 577 patients receiving ceftazidime-avibactam for the management of KPC-producing *K. pneumoniae* infections (23.7% admitted in ICU; 67.8% bacteraemic). Ceftazidime-avibactam was administered by prolonged infusion over at least over 3 h in 42.6% of cases. Notably, at multivariate analysis administration of ceftazidime-avibactam by prolonged infusion was negatively associated with mortality, thus resulting protective ($P = 0.006$).

Recently, it was shown that in a case series of 10 patients who received ceftazidime-avibactam by CI for the management of MDR Gram-negative infections (including *P. aeruginosa* and KPC-producing *K. pneumoniae*), the aggressive PK/PD target of at least 100%$fT_{> 5 \times MIC}$ was granted in all of the cases [46▪]. Microbiological eradication rate and clinical cure rate were 90% and 80% respectively [46▪].

Overall, these data suggest that administration of ceftolozane-tazobactam and ceftazidime-avibactam by prolonged infusion may be crucial not only for maximizing clinical efficacy, but also for preventing the occurrence of resistance development, as previously reported for traditional beta-lactams [50]. To this regard, it should be recognized that the PK/PD threshold required for resistance suppression against MDR Gram-negative isolates are not yet well established for novel beta-lactams. In this regard, there is only an *in vitro* hollow-fiber infection model that reported how administration of ceftolozane-tazobactam 1.5 g q8 h was associated with larger resistance amplification of MDR *P. aeruginosa* compared to a double dosage (3 g q8 h) [51], probably due to the fact this latter dosage allowed the achievement of higher trough concentration/MIC ratio resulting in suppression of resistance occurrence.

Clinical scenarios benefiting by administration of novel beta-lactams in prolonged infusion

In several challenging scenarios prolonged infusion of novel agents may be crucial for maximizing the achievement of aggressive PK/PD target and minimizing the occurrence of resistance development. Specifically, the following special populations could benefit from administration of novel beta-lactams by prolonged infusion: patients who are criticallyill, who exhibit extreme renal alterations (augmented renal clearance [ARC] or requirementforcontinuous renal replacement therapy [CRRT]), who are affected

Table 2. Real-life evidence supporting the use of ceftolozanetazobactam in prolonged or continuous infusion for the management of multidrug-resistance Gram-negative infections

Author, year and reference	Study design	No. of patients	Antibiotic and dosing	Source of infection and isolates	Severity	Clinical outcomes	Comments
Pilmis *et al.*, 2019 [36▪▪]	Multicentric prospective cohort study	72	44 LOZ-TAZ 2000 mg/1000 mg q8h II (1 -h infusion) 13 2000 mg/1000 mg q8h LOZ-TAZ PI (4-h infusion) 15 2000 mg/1000 mg q8h LOZ-TAZ CI	*P. aeruginosa* 26.3% MIC $\geq$ 4 mg/L 66.7% HAP/VAP 7% primary BSI 5.5% SSTI 5.5% bone and joint infections	79% ICU admission 51.4% immunosuppressed	100% $fT_{> 4 \times MIC}$ achieved by all patients regardless of infusion modality for infections caused by *P. aeruginosa* exhibiting MIC $<$ 4 mg/L Only CI allowed to achieve a PTA >90% of patients with 100% $fT_{> 4 \times MIC}$ in case of *P. aeruginosa* strains exhibiting MIC $\geq$ 4 mg/L	Higher probability of achieving aggressive PK/PD target with LOZ-TAZ in CI compared to II and PI for less-susceptible *P. aeruginosa* strains
Ruiz *et al.*, 2020 [37]	Monte Carlo simulation study	35	LOZ-TAZ 500 mg/250 mg q8h (1-h or 3-h infusion) or 1000 mg/500 mg q8h (1-h or 3-h infusion) or 2000 mg/1000 mg q8h (1-h or 3-h infusion)	*P. aeruginosa* 4 MIC $\leq$ 1 mg/L 5 MIC 1.5 mg/L 13 MIC 2 mg/L 2 MIC 3 mg/L 7 MIC 4 mg/L 3 MIC 8 mg/L 1 MIC 12 mg/L	NA	PTA of reaching 100%T> MIC forCLCr 100 mL/min: 86.4% vs. 82.2% (1000 mg/500 mg q8h 3-h vs. 1 -h infusion) PTA of reaching l00%T> MIC for CLCr 100 mL/min: 95.0% vs. 89.7% (2000 mg/1000 mg q8h 3-h vs. 1-h infusion)	Higher probability of achieving optimal PK/PD target with LOZ-TAZ in EI compared to II in patients with normal renal function
Tamma *et al.*, 2020 [38▪▪]	Retrospective case-control study	28	14 patients with at least 4-fold in *P.* aeruginosa increase in TOL-TAZ MICs after exposure vs. 14 patients without increase in TOL-TAZ MICs 14.3% EI over 3 h 85.7% II over 1h	*P. aeruginosa* all susceptible to TOL-TAZ 19 pneumonia 5 BSI 4 cIAI	10.7% cystic fibrosis 46.4% immunosuppressed 1 7.9% CRRT 7.1% burn	No resistance development occurred in patients receiving LOZ-TAZ in EI (0% vs. 29%; P=0.04]	Prolonged infusion of LOZ-TAZ may prevent the emergence of resistance in *P. aeruginosa* infections
Sheffield *et al.*, 2020 [39]	Monocentric retrospective cohort study	7	LOZ-TAZ 4000 mg/2000 mg CI over 24h (5 patients) or 3000 mg/1500 mg CI over 24h (one patient) or 2000 mg/1000 mg CI over 24h (one patient)	*P. aeruginosa* (all cases) + ESBL-producing *E. coli* (two cases) MIC range: 0.19–1.5 mg/L 4 LVAD infections 2 pneumonia in cystic fibrosis 1 prosthetic joint infections 1 ventriculoperitoneal shunt infection	NA	100.0% clinical resolution	In four patients performing LOZ-TAZ TDM optimal target (100%$fT_{>4\times MIC}$) was achieved

Table 2 (*Continued*)

Author, year and reference	Study design	No. of patients	Antibiotic and dosing	Source of infection and isolates	Severity	Clinical outcomes	Comments
Jones *et al.*, 2020 [40]	Retrospective cohort study	7	LOZ-TAZ 3000 mg/1500 mg CI over 24h (6 patients] or 6000 mg/3000 mg CI over 24h (one patient) in elastomeric pump	*P. aeruginosa* MIC 2 mg/L (2 strains) MIC 8 mg/L (one strain) 3 Pneumonia 2 cUTI 1 BSI 1 Discitis	NA	85.7% clinical cure 100.0% microbiological resolution (only 3 out of 7 isolates were tested)	LOZ-TAZ CI suitable for OPAT in the management of MDR *P. aeruginosa*
Jones *et al.*, 2017 [41]	Case report	1	LOZ-TAZ 3000 mg/1500 mg CI over 24h in elastomeric pump	Carbapenem-resistant *P. aeruginosa* cUTI	NA	Clinical and microbiological cure	First report of LOZ-TAZ CI in OPAT setting
Davis *et al.*, 2019 [42]	Case report	1	LOZ-TAZ 2000 mg/1000 mg LD + 4000 mg/2000 mg CI over 24h	MDR *P. aeruginosa* (MIC 0.19 mg/L) + ESBL-producing *E. coli* (MIC 0.25 mg/L) Pneumonia	Cystic fibrosis in augmented renal clearance (215 mL/min)	Clinical and microbiological cure	LOZ-TAZ CI achieved adequate plasma exposure (25.31 mg/L), although lower compared to patients without cystic fibrosis
Alvarez Otero *et al.*, 2020 [43]	Case report	1	LOZ-TAZ 1000 mg/500 mg LD + 1500 mg/750 mg CI over 24h in elastomeric pump	*P. aeruginosa* MIC 1 mg/L Osteomyelitis	NA	Favorable evolution	LOZ-TAZ CI suitable for OPAT in the management of MDR *P. aeruginosa*
Winans *et al.*, 2021 [44]	Case report	1	LOZ-TAZ 2000 mg/1000 mg LD + 6000 mg/3000 mg CI over 24h	Carbapenem-resistant *P. aeruginosa* Healthcare-associated meningitis	NA	Serum LOZ concentration: 46.6 mg/L CSF LOZ concentration: 38.8 mg/L CSF/serum ratio: 0.83	CI administration of high-dose LOZ-TAZ allowed to achieve adequate CSF concentration

BSI, bloodstream infection; CI, continuous infusion; cIAI, complicated intrabdominal infection; CLCr, creatinine clearance; CRRT, continuous renal replacement therapy; CSF, cerebrospinal fluid; cUTI, complicated urinary tract infection; EI, extended infusion; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; II, intermittent infusion; LD, loading dose; LOZ-TAZ, ceftolozane-tazobactam; LVAD, left-ventricular assistant device; MDR, multidrug resistant; MIC, minimum inhibitory concentration; OPAT, outpatient parenteral antimicrobial therapy; PI, prolonged infusion; PK/PD, pharmacokinetic/pharmacodynamic; PTA, probability of target attainment; SSTI, skin and soft tissue infection; TDM, therapeutic drug monitoring; VAP, ventilator-associated pneumonia.

Table 3. Real-life evidence supporting the use of ceftazidime-avibactam in prolonged or continuous infusion for the management of multidrug-resistance Gram-negative infections

Author, year and reference	Study design	No. of patients	Antibiotic and dosing	Source of infection and isolates	Severity	Clinical outcomes	Comments
Tumbarello *et al.*, 2021 [45▪▪]	Multicentric retrospective cohort study	577	CAZ-AVI 2000 mg/500 mg q8h adjusted for renal impairment 42.6% PI (over 3 or more hours) 57.4% II	KPC-producing *Klebsiella pneumoniae* 391 BSIs 71 cUTIs 59 pneumonia 35 cIAI 21 others	ICU admission 23.7% Solid organ transplantation 14.9% mmunosuppression 7.8% Mechanical ventilation 28.1% Septic shock 17.3%	Mortality was negatively associated with CAZ-AVI administration by PI ($P=0.006$)	Potential survival benefits associated with prolonging CAZ-AVI infusion over 3 or more hours
Goncette *et al.*, 2021 [46▪]	Retrospective case series	10	CAZ-AVI 4000 mg/1000 mg ql2h CI adjusted for renal impairment	MDR *Pseudomonas aeruginosa* (6 isolates) KPC-producing *Klebsiella pneumoniae* (2 isolates) ESBL-producing *Klebsiella pneumoniae* (2 isolates) *Enterobacter aerogenes* (1 isolate) MIC range: 0.25–8 mg/L 30% bacteraemic 4 pneumonia 2 cUTI 2 cIAI 2 bone and joint infections	ICU admission 40% Septic shock 10%	Clinical cure: 80% Microbiological eradication: 90% 30-day mortality rate: 10%	All patients achieved a PK/PD target of 100%$T_{> 5 \times MIC}$ (median 13.3-fold the MIC)
Cowart *etat.*, 2021 [49]	Case report	1	CAZ-AVI 200 mg/kg/day CI + Aztreonam 200 mg/kg/day	*Stenotrophomonas maltophilia* Pneumonia	Cystic fibrosis	Clinical and microbiological cure	TDM-guided dosing adjustment of CAZ-AVI coupled with PI allowed to achieve adequate PK/PD target
Tamma *et al.*, 2018 [48]	Case report	1	CAZ-AVI 50 mg/kg q8h CI (over 8 h)	*Burkholderia cepacia* complex MIC 2 mg/L BSI	ICU admission Septic shock	Clinical and microbiological cure	CAZ-AVI administered by CI is feasible also in paediatric setting
Jacobs *et al.*, 2016 [47]	Case report	1	CAZ-AVI 2000 mg/500 mg q8h EI over 4 h	KPC 3-producing *Klebsiella pneumoniae* MIC 0.5 mg/L BSI	Solid organ transplantation ICU admission CRRT Septic shock	Microbiological cure Death at 37-day due to noninfective complications	First report of CAZ-AVI administration in PI

BSI, bloodstream infection; CAZ-AVI, ceftazidime-avibactam; CI, continuous infusion; cIAI, complicated intrabdominal infection; CRRT, continuous renal replacement therapy; cUTI, complicated urinary tract infection; EI, extended infusion; ESBL, extended-spectrum beta-lactamase; ICU, intensive care unit; II, intermittent infusion; KPC, *Klebsiella pneumoniae*-carbapenemase; MDR, multidrug resistant; MIC, minimum inhibitory concentration; PI, prolonged infusion; PK/PD, pharmacokinetic/pharmacodynamic.

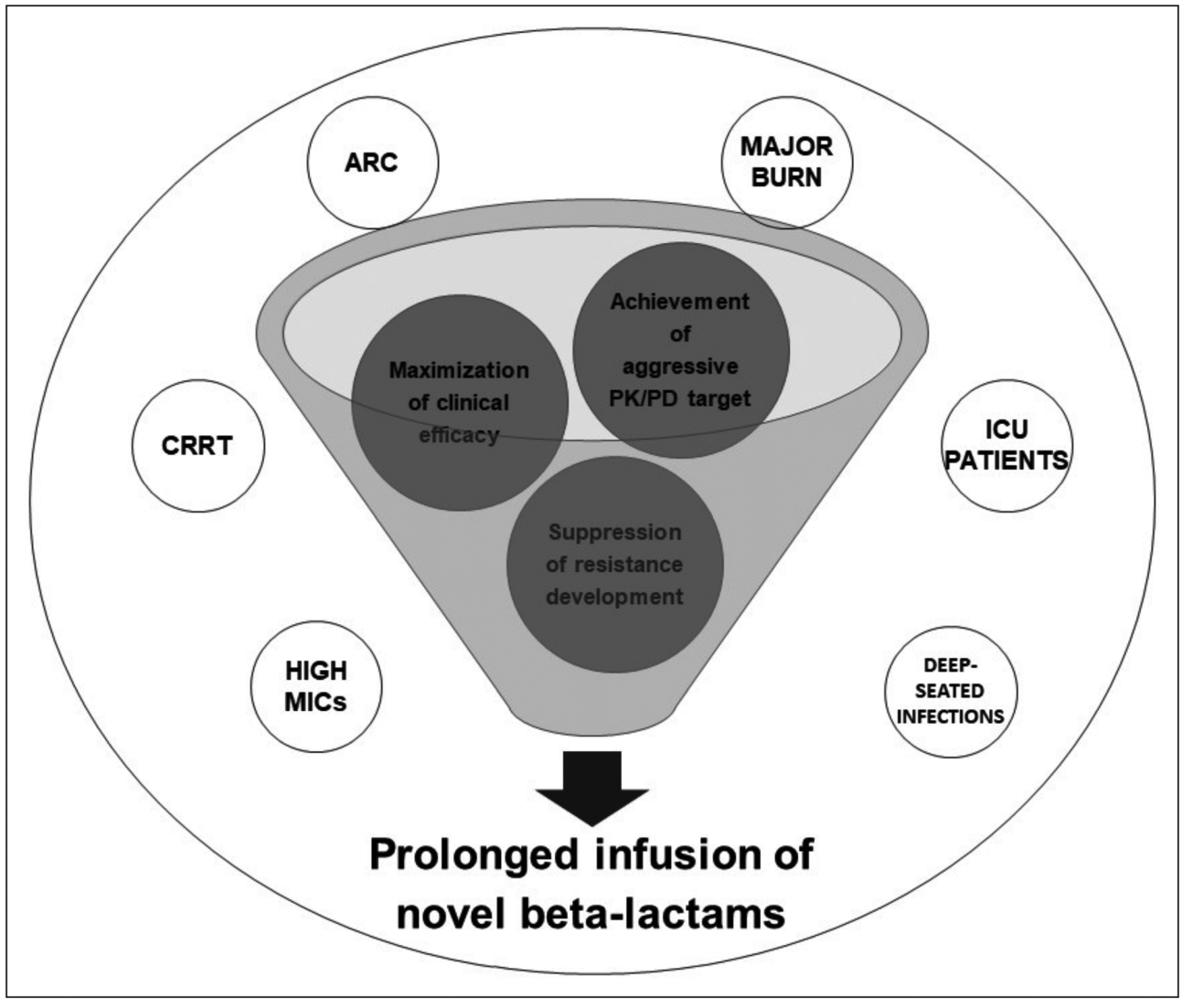

FIGURE 1. Rationale for administering novel beta-lactams by prolonged infusion in challenging clinical scenarios. ARC, augmented renal clearance; CRRT, continuous renal replacement therapy; ICU, intensive care unit; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.

by deep-seated infections (e.g., ventilator-acquired pneumonia [VAP]) and/or by major burns, and in whom the infections are caused by MDR Gram-negative isolates with reduced susceptibility for the novel agents (Fig. 1).

Nowadays, real-world evidence supporting the administration of novel agents by prolonged infusion in these specific scenarios is scarce or absent. However, according to time-dependent bacterial killing and real-world evidence for traditional beta-lactams, it can be assumed that prolonged infusion may represent a key approach for the PK/PD optimization of the novel agents as well.

Critically ill or immunocompromised patients (e.g., hematological patients, solid organ transplant recipients) usually have relevant pathophysiological alterations that may affect volume of distribution and clearance of hydrophilic agents, and this may be responsible for antibiotic underexposure and worsening in clinical outcome when conventional dosing regimens are administered [21,52]. Some meta-analyses clearly proved the superiority of prolonged over intermittent infusion of traditional beta-lac-tams in these settings in terms of survival rate and clinical cure rate [14,15,16].

Similarly, major burn victims commonly suffer from extreme PK alterations coupled with skin and soft tissue infections caused by MDR Gram-negative pathogens, including CPE-producing *Enterobacteriaceae,* carbapenem-resistant *P. aeruginosa* and *A. baumannii,* and MDR *S. maltophilia* [53,54]. In this scenario, administration of novel beta-lactams by prolonged infusion may be helpful for achieving more aggressive PK/PD targets, and overcoming the huge

increase in volume of distribution and clearance derangements (including fluid losses from open wounds) that may affect major burns victims [53].

ARC is defined as the occurrence of a measured CLCr $\geq$ 130 mL/min/1.73 m^2 in males and $\geq$ 120 in females coupled with a normal serum creatinine value [55], and may represent a rather common pathophysiological occurrence among some special patient populations, like critically ill patients, those with febrile neutropenia or with subarachnoid hemorrhage. ARC may be a risk factor of underexposure and failure in achieving optimal beta-lactam PK/PD target with beta-lactams, despite the use of high-doses by prolonged infusion. In a prospective observational study including 79 critically ill subjects treated with traditional beta-lactams by CI, ARC patients had higher risk of suboptimal exposure in terms 100%$fT_{< 4 \times MIC}$ and higher rate of therapeutic failure (OR 6.3; 95% CI 1.2–33.2; $P = 0.03$) [56]. Notably, in a phase 1 study carried out among 11 critically ill patients with ARC (median creatinine clearance 214 mL/min), Nicolau *et al.* found that administering ceftolozane-tazobactam at the dosage of 3 g q8 h by intermittent infusion granted the achievement of only 86.4% *f*T>MIC against *P. aeruginosa* isolates with an MIC of 4 mg/L [57▪▪]. Consequently, in patients with ARC administration of high-doses by prolonged infusion should be recommended for granting the achievement of aggressive PK/PD targets [58].

Likewise, also critically ill patients could benefit from the administration of novel beta-lactams by prolonged infusion, especially those who undergo high-flux CRRT and have residual renal function, those with deep-seated infection caused by borderline susceptible isolates [59]. In a population PK study Sime *et al.* reported that among six critically ill patients who underwent continuous venovenous haemodiafiltration, treatment with ceftolozane-tazobactam by prolonged infusion allowed the achievement of higher probability of target attainment considering a PK/PD target of 100%$fT_{>MIC}$ [60▪]. Furthermore, several case reports found that administration of ceftolozane-tazobactam by EI [61,62] or CI [63] allowed the achievement of more aggressive PK/PD targets for both ceftolozane (100% $fT_{> 4 \times MIC}$) and tazobactam (100%T>4 mg/L) in critically ill patients who underwent CRRT.

Another important aspect to deal with is the fact that the penetration rate of novel beta-lactams in epithelial lining fluid (ELF) and alveolar macrophages is quite limited, ranging from 24% for cefiderocol to 63% for meropenem-vaborbactam [64–68]. This may represent an issue among critically ill patients affected by VAP caused by MDR Gram-negative pathogens, and administration of high doses by prolonged infusion may improve PK/PD of novel agents in the ELF, as reported previously for traditional beta-lactams [69].

Real-time TDM-guided clinical pharmacological adivces of novel agents should be encouraged in these challenging scenarios as a helpful approach in dealing with maximization of clinical efficacy and with suppression of resistance development among patients who are affected by MDR gram-negative infections [13,70].

CONCLUSION

Although still limited, real-world data regarding the novel beta-lactams ceftolozane-tazobactam and cef-tazidime-avibactam coupled with firm evidence concerning the traditional ones support administration by prolonged infusion as a valuable approach in dealing with the achievement of aggressive PK/PD target for proper treatment of MDR Gram-negative infections in presence of challenging scenarios.

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Conflicts of interest

F.P. participated in speaker bureau for Angelini, Basilea Pharmaceutica, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Pfzer and Sanofi Aventis, and in advisory board for Angelini, Basilea Pharmaceutica, BeiGene, Correvio, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Novartis, Pfzer, Shionogi and Thermo-Fisher. M.G. have no conflict of interest.
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