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Development of a dosing algorithm for meropenem in critically ill patients based on a population pharmacokinetic/pharmacodynamic analysis

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ABSTRACT

Effective antibiotic dosing is vital for therapeutic success in critically ill patients. This work aimed to develop an algorithm to identify appropriate meropenem dosing in critically ill patients. Population pharmacokinetic (PK) modelling was performed in NONMEM®7.3 based on densely sampled meropenem serum samples ($n_{patients} = 48$; $n_{samples} = 1376$) and included a systematic analysis of 27 pre-selected covariates to identify factors influencing meropenem exposure. Using Monte Carlo simulations newly considering the uncertainty of PK parameter estimates, standard meropenem dosing was evaluated with respect to attainment of the pharmacokinetic/pharmacodynamic (PK/PD) target and was compared with alternative infusion regimens (short-term, prolonged, continuous; daily dose, 2000–6000 mg). Subsequently, a dosing algorithm was developed to identify appropriate dosing regimens. The two-compartment population PK model included three factors influencing meropenem pharmacokinetics: the Cockcroft–Gault creatinine clearance ($CLCR_{CG}$) on meropenem clearance; and body weight and albumin on the central and peripheral volume of distribution, respectively; of these, only $CLCR_{CG}$ was identified as a vital influencing factor on PK/PD target attainment. A three-level dosing algorithm was developed (considering PK parameter uncertainty), suggesting dosing regimens depending on renal function and the level (L) of knowledge about the infecting pathogen (L1, pathogen unknown; L2, pathogen known; $L3_{(-MIC)}$, pathogen and susceptibility known; $L3_{(+MIC)}$, MIC known). Whereas patients with higher $CLCR_{CG}$ and lower pathogen susceptibility required mainly intensified dosing regimens, lower than standard doses appeared sufficient for highly susceptible pathogens. In conclusion, a versatile meropenem dosing algorithm for critically ill patients is proposed, indicating appropriate dosing regimens based on patient- and pathogen-specific information.

1. Introduction

Apart from the appropriate choice of an antibiotic based on its antimicrobial spectrum of activity, appropriate dosing is a crucial factor in rational antibiotic therapy [1]. Appropriate dosing regimens, i.e. resulting in effective exposure, have been shown to improve clinical success [2–4]. However, selection of a dosing regimen is challenging especially in critically ill patients owing to (i) pathophysiological changes (e.g. organ dysfunction or altered fluid balance) that may result in altered pharmacokinetics of a drug, and (ii) infections often being caused by less-susceptible bacteria that are commonly encountered in the intensive care setting [5–8]. Therapeutic drug monitoring (TDM) has been suggested to individualise antibiotic dosing in this patient population [9,10]. However, TDM is oftentimes not available in clinical routine to aid the selection of dosing regimens, which is deemed important for the outcome in critically ill patients [11,12]. Meropenem is a broad-spectrum β-lactam antibiotic frequently employed to treat severe infections in intensive care units (ICUs). As a hydrophilic compound with low protein binding (2%), it is mainly eliminated via the kidneys [13]. Meropenem exhibits time-dependent antimi-

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crobial activity, which has been linked to the time period that the meropenem concentration exceeds the minimum inhibitory concentration (MIC) of a pathogen ($T_{>MIC}$) [14]. The approved standard dosing regimens for adults (with intact renal function) include 500 mg up to 2000 mg, administered as short-term intravenous (i.v.) infusions every 8 h (q8h) [15]. Prolonged and continuous infusion of meropenem have been shown to improve the attainment of effective antibiotic exposure and to reduce mortality [16–19]. Continuous infusion, however, poses the risk of meropenem concentrations being always below the MIC when TDM is not performed. Population pharmacokinetic (PK) modelling and simulations have been used to identify meropenem dosing regimens resulting in effective exposure on the basis of pharmacokinetic/pharmacodynamic (PK/PD) target attainment analyses [16,20–22]. However, to the best of our knowledge, no systematic overview of dosing regimens exists considering different levels of information on the infecting pathogen, which varies between hospitals and the stage of antimicrobial treatment. Moreover, the uncertainty in PK parameter estimates of a PK model used for simulations is usually neglected, yet is important to more reliably determine effective antibiotic exposure [23].

Therefore, this work aimed to develop a dosing algorithm suggesting meropenem dosing regimens for the critically ill patient population already at the start of treatment based on the level of knowledge regarding the pathogen. For this purpose, we first sought to develop a population PK model and to conduct a systematic analysis of a large number of potential factors causing PK variability. We further aimed to perform a PK/PD probability of target attainment (PTA) analysis, considering the uncertainty of PK parameters, in order to evaluate standard and alternative dosing schemes and to suggest dosing regimens for different pathogen information levels and patient-specific characteristics.

2. Methods

2.1. Data and patients

A prospective observational study was performed in a heterogeneous population of 48 critically ill patients with severe infections (ClinicalTrials.gov identifier NCT01793012; patient characteristics see Appendix A, Table A1). Written informed consent to participate was obtained from all patients or their legal representatives. Patients received standard dosing of meropenem [1000/2000 mg ($n_{patients}$ = 47/1) as 30-min i.v. infusions q8h]. Dense PK plasma sampling ($n_{samples}$ = 1376) was performed over a period of 4 days and patient-specific data were recorded, the majority longitudinally. For further information regarding patient recruitment (inclusion/exclusion criteria), drug administration, blood sampling and bioanalytical method, please refer to Ehmann et al. [24].

2.2. Population pharmacokinetic modelling

All modelling and simulation activities were performed in NONMEM®7.3 (ICON Development Solutions, Ellicott City, MD, USA), PsN versions 4.4.0–4.6.0 [25] and Piraña versions 2.8.1–2.9.6 [26], utilising the first-order conditional estimation with interaction (FOCE+I) method. Exploratory graphical and statistical data analyses and data visualisation were performed in R versions 3.1.2–3.5.0 (CRAN.R-project.org).

Different PK compartment disposition models with zero-order input and first-order elimination, parameterised in terms of clearance (CL) and volume parameters, were investigated. Interindividual variability (IIV) and interoccasion variability (IOV) were implemented using exponential models. Residual unexplained variability (RUV) was investigated using additive, proportional and combined variability models.

Covariates as potential factors influencing meropenem pharmacokinetics were investigated based on the data of patients without continuous renal replacement therapy (non-CRRT, $n_{patients}$ = 41). Covariate candidates were pre-selected based on graphical evaluation (see Appendix A, Section A.2), prior publications and/or clinical interest. A systematic semi-automated stepwise model development procedure was used (see Appendix A, Sections A.1–A.2). At each step, covariate selection was based on five criteria: statistical significance; reduction in unexplained variability; precision of the covariate effect; clinical relevance; and biological plausibility. The developed PK model was thoroughly evaluated with respect to, e.g., parameter precision and accuracy, robustness and predictive performance (see Appendix A, Section A.5).

2.3. Simulations: evaluation of standard and alternative dosing regimens

The developed population PK model was used for deterministic simulations to explore meropenem exposure given specific covariate combinations. In addition, stochastic Monte Carlo simulations were performed to evaluate the PTA of PK/PD targets and the cumulative fraction of response (CFR) [27] for (i) standard meropenem dosing and (ii) alternative dosing regimens in order to suggest dosing regimens for patients with different clinical characteristics and levels of pathogen information available.

2.3.1. Pharmacokinetic/pharmacodynamic target

The PK/PD target 100%$fT_{>MIC}$ (i.e. unbound meropenem serum concentration exceeding the MIC for 100% of the 24-h period) has been suggested in the literature for β-lactam treatment in critically ill patients [3,28]. In the present work, total meropenem concentrations ($T_{>MIC}$) were evaluated due to the negligibly low protein binding of meropenem (2%) [13]. Furthermore, given the non-achievability of 100%$T_{>MIC}$ when starting the i.v. infusion on the first day of therapy, attainment of 98%$T_{>MIC}$ was assessed, i.e. allowing for a 2% period within 24 h (=30 min) for the increasing part of the concentration–time profile to reach the MIC concentration. For the evaluation of continuous-infusion regimens, a stricter target of 98%$T_{>4\times MIC}$ was selected, which has been suggested previously for different β-lactam antibiotics [29–31].

2.3.2. Probability of target attainment analysis

First, the impact of single covariates on the PTA was investigated for standard meropenem dosing by varying one covariate while fixing the remaining ones to the median value in the population. Furthermore, 'worst-case' and 'best-case' covariate combinations (see Appendix B, Section B.2) were assessed. Second, alternative i.v. short-term infusion (SI), prolonged infusion (PI) and continuous infusion (CI) dosing regimens were investigated (see Table 1).

For each specific covariate combination and dosing regimen, meropenem plasma concentration–time profiles were simulated for 500 patients over 4 treatment days using Monte Carlo simulations. The PTA was computed for treatment days 1 and 4 across the full MIC range from 0.002–512 mg/L [32]. A PTA of ≥90% (i.e. 450 of 500 patients achieving the PK/PD target [33]) was considered adequate. To incorporate PK model parameter uncertainty, each Monte Carlo simulation was repeated 1000 times using the PK parameter sets obtained from a non-parametric bootstrap and the respective PTAs derived (stochastic simulation and estimation (sse) functionality in PsN [23,25]). A PTA of ≥90% for the 5th percentile of the 1000 computed PTAs was considered adequate.

2.3.3. Cumulative fraction of response

Based on the PTA results, the CFR [27] was derived for five pathogens commonly encountered in ICUs, namely *Pseudomonas*

Table 1
Evaluated intravenous dosing regimens of meropenem

Daily dose (mg)	Short-term infusion (SI) over 30 min	Prolonged infusion (PI) over 3 h	Continuous infusion (CI) over 24 h
2000	SI2: 1000 mg q12h	PI2: 1000 mg q12h	–
3000 or 3412.5[a]	SI3: 1000 mg q8h (= standard dosing regimen)	PI3: 1000 mg q8h	CI3 [b]: 3000 mg q24h following initial loading dose of 500 mg over 30 min
6000 or 6875[a]	SI6: 2000 mg q8h	PI6: 2000 mg q8h	CI6[b]: 6000 mg q24h following initial loading dose of 1000 mg over 30 min

SI, short-term infusion; PI, prolonged infusion; CI, continuous infusion; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h.
[a] For CI treatment at day 1, the initial loading dose is included.
[b] Consider to renew the infusion solution dependent on the drug concentration twice or thrice daily (see Supplement of [21]) to ensure the stability of meropenem.

Table 2
Parameter estimates of the developed population pharmacokinetic model[a] of meropenem in non-CRRT critically ill patients ($n = 41$)

Parameter (unit)	Final model estimate (RSE, %; 95% CI[b])	Bootstrap[c] median (95% CI)
Fixed-effects parameters		
CL[d] (L/h)	9.25 (4.60; 8.42–10.1)	9.28 (8.38–10.1)
V_1[e] (L)	7.89 (11.9; 6.05–9.73)	7.92 (6.11–11.5)
Q (L/h)	28.4 (16.1; 19.4–37.4)	28.4 (11.1–38.2)
V_2[f] (L)	16.1 (7.40; 13.8–18.4)	16.1 (11.9–18.4)
$CLCR_{CG}$_CL	0.00977 (9.20; 0.00800–0.0115)	0.00987 (0.00756–0.0114)
$CLCR_{CG}$_INF (mL/min)	154 (6.90; 133–175)	155 (111–178)
WT_V_1	0.945 (16.6; 0.637–1.25)	0.936 (0.531–1.32)
ALB_V_2	−0.202 (36.6; −0.347 to −0.0572)	−0.203 (−0.403 to −0.0521)
Interindividual variability parameters (IIV)		
CL, %CV	27.1 (19.3; 13.2–36.5)	26.3 (17.1–36.7)
V_1, %CV	31.5 (14.3; 20.6–39.8)	30.5 (20.0–40.2)
V_2, %CV	16.9 (18.1; 9.02–22.2)	16.3 (8.07–23.2)
Interoccasion variability parameters [g] (IOV)		
CL, %CV	12.5 (12.0; 9.11–15.2)	12.4 (9.61–15.5)
Residual variability parameters (RUV)		
Proportional, %CV	16.6 (6.60; 14.5–18.7)	16.5 (14.5–18.9)
Additive, SD (mg/L)	0.246 (29.0; 0.106–0.386)	0.234 (0.0932–0.337)

ALB, serum albumin concentration; ALB_V_2, ALB effect on V_2 (linear relationship); CI, confidence interval; CL, clearance; $CLCR_{CG}$, creatinine clearance estimated according to Cockcroft and Gault [35]; $CLCR_{CG}$_CL, $CLCR_{CG}$ effect on CL (linear relationship up to inflection point); $CLCR_{CG}$_INF, $CLCR_{CG}$ value serving as inflection point (see Appendix A, Section A.4); CRRT, continuous renal replacement therapy; %CV, coefficient of variation (calculated as exemplified for IIV: IIV, $\%CV = \sqrt{e^{IIV^2} - 1} \cdot 100$; IIV, interindividual variability; IOV, interoccasion variability; Q, intercompartmental clearance; RSE, relative standard error (RSE of random-effects parameters reported on approximated standard deviation scale); RUV, residual unexplained variability; SD, standard deviation; SE, standard error; V_1, central volume of distribution; V_2, peripheral volume of distribution; WT, body weight; WT_V_1, WT effect on V_1 (power relationship).
[a] Model sketch see Appendix A, Fig. A2.
[b] Computed as: parameter estimate ± 1.96 SE.
[c] Non-parametric bootstrap ($n = 1000$): convergence rate of 89.7%.
[d] CL for median $CLCR_{CG}$ of non-CRRT patients on first study day (80.8 mL/min).
[e] V_1 for median WT of non-CRRT patients (70 kg).
[f] V_2 for median ALB of non-CRRT patients at first study day (2.8 g/dL).
[g] Occasion was defined as monitored meropenem infusion, i.e. in total six occasions.

aeruginosa, Acinetobacter spp., *Escherichia coli, Enterobacter cloacae* and *Klebsiella pneumoniae* [34]. For the two least susceptible pathogens (*P. aeruginosa* and *Acinetobacter* spp.), the CFR was separately calculated for the susceptible (MIC ≤ 2 mg/L) and intermediate (MIC >2 and ≤8 mg/L) distribution of the pathogen population. A CFR of ≥90% for the 5th percentile of the 1000 computed CFRs was considered adequate.

3. Results

3.1. Population pharmacokinetic modelling

A two-compartment PK disposition model with first-order elimination, IIV on clearance (CL) and central and peripheral volume of distribution (V_1 and V_2), IOV on CL, and a combined residual variability model adequately described the PK data (see Table 2).

The final model, which was based on the data of the non-CRRT patients ($n = 41$), included creatinine clearance estimated according to Cockcroft and Gault ($CLCR_{CG}$) [35] on CL, total body weight on V_1, and serum albumin concentration on V_2 implemented as piecewise linear, power and linear relationship, respectively (see Appendix A, Sections A.3–A.4). Covariate inclusion considerably reduced unexplained IIV and IOV to ≤31.5%CV (Table 2) compared with the base model. Model evaluation demonstrated high parameter accuracy and precision, robustness and predictive performance of the developed model (see Appendix A, Section A.5). Application of the final PK model for the CRRT population ($n = 7$) revealed similar PK parameter estimates as for non-CRRT patients (see Appendix, Table A2).

3.2. Simulations: evaluation of standard and alternative dosing regimens

PTA analysis based on the standard meropenem dosing regimen ($n_{simulated\ patients} = 52\ 500\ 000$) indicated an increasing risk of target non-attainment (i.e. decreased PTA) for patients with increasing $CLCR_{CG}$ (see Fig. 1; Table 3), decreasing body weight and increasing albumin (see Appendix B, Figs B2 and B3, Table B1). Of the three covariates, $CLCR_{CG}$ (see Table 3; Fig. 1) revealed by far the strongest impact on PTA and CFR (see Appendix B, Section B.2). Differences in PTA between treatment days 1 and 4 were marginal (see Appendix B, Figs B2 and B3).

Given the importance of $CLCR_{CG}$, dosing simulations and evaluation of PTA and CFR were performed for varying $CLCR_{CG}$ values for the eight selected alternative dosing regimens (see Table 1; Appendix B, Section B.3; $n_{simulated\ patients} = 72\ 000\ 000$).

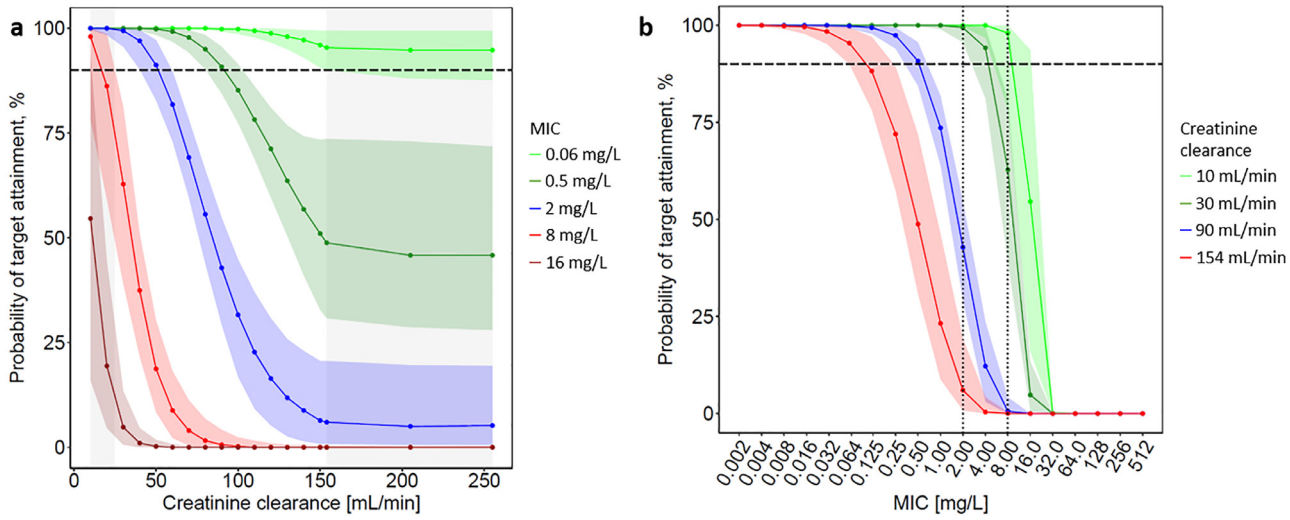

Fig. 1. Probability of target attainment (PTA) versus (a) $CLCR_{CG}$ and (b) MIC on the first day of standard meropenem treatment. Evaluated for the PK/PD target 98%$T_{>MIC}$ and standard meropenem treatment of 1000 mg 30-min intravenous infusion every 8 h. Varied $CLCR_{CG}$ but body weight and albumin fixed to median of first study day (i.e. 70 kg, 2.8 g/dL). Dashed horizontal line = PTA of 90%; coloured dots and lines + shaded areas = median + 90% CI of the 1000 PTA values derived from the 1000 Monte Carlo simulations considering PK parameter uncertainty; grey shaded area = extrapolated covariate range not covered by the study population or $CLCR_{CG} \geq 154$ mL/min (= inflection point of $CLCR_{CG}$–CL relationship). CI, confidence interval; $CLCR_{CG}$, creatinine clearance estimated according to Cockcroft and Gault [35]; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.

Table 3
(A) Probability of target attainment (PTA) and (B) cumulative fraction of response (CFR) for the first day of meropenem standard treatment

A: Probability of target attainment[a]

$CLCR_{CG}$[b] [mL/min]	Probability of target attainment, %																													
	MIC [mg/L]																													
	0.06			0.12			0.25			0.5			1			2			4			8			16			32		
	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95
10	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99.6	100	100	96.8	100	100	78.2	98	100	16	54.6	93.6	0	0	0.8
20	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	98.4	100	100	90.6	99	100	59.2	86.2	98.6	4.6	19.4	44.4	0	0	0
30	100	100	100	100	100	100	100	100	100	99.8	100	100	99	100	100	95.6	99.4	100	81.2	94.2	99.4	39	62.8	81.2	0.6	4.8	13.4	0	0	0
40	100	100	100	100	100	100	99.8	100	100	99.4	100	100	97.6	99.6	100	90.2	97	99.6	68.8	82.6	93.2	21.6	37.4	51	0	1	4.6	0	0	0
50	100	100	100	99.8	100	100	99.6	100	100	98.4	99.8	100	94.6	98.4	99.8	82.8	91.2	97.2	52.4	65.6	77	8.39	18.7	30.2	0	0.2	1.8	0	0	0
60	99.8	100	100	99.6	100	100	98.8	99.8	100	96.8	99.2	100	90	95.6	98.8	73	81.8	89.8	34.8	47.2	57.8	2.2	8.8	18.2	0	0	0.8	0	0	0
70	99.8	100	100	99.4	100	100	98	99.6	100	94.2	97.8	99.6	84.2	90.6	96	59.6	69.2	78.2	19.4	31.8	43.4	0.4	4	11.2	0	0	0.4	0	0	0
80	99.6	100	100	98.8	99.8	100	96.4	98.8	100	90.2	95	98.4	75.4	83	90	43.8	55.6	66.2	8.19	19.9	32.2	0	1.6	6.8	0	0	0.2	0	0	0
90	99.2	99.8	100	97.8	99.4	100	94	97.4	99.4	84.4	90.8	95.6	64	73.6	81.8	29.2	42.8	54.8	3	12.2	23.6	0	0.6	4.2	0	0	0	0	0	0
100	98.6	99.8	100	96.2	98.8	100	90	95.2	98.4	77.4	85.2	91.4	51.4	63.2	73.4	16.8	31.6	44.8	1	7	17.2	0	0.2	2.4	0	0	0	0	0	0
110	97.8	99.4	100	94.4	97.6	99.4	85.8	92	96.6	68.8	78.2	86.2	39.4	53	65.2	9.2	22.7	37	0.39	4.1	12.6	0	0	1.6	0	0	0	0	0	0
120	96.6	98.8	100	92	96.2	98.8	81	87.6	94	59.6	71.2	81	28.4	44.1	58.2	5.2	16.4	30.8	0	2.4	9.6	0	0	1	0	0	0	0	0	0
130	95	98	99.8	88.6	94	98	74.2	83.4	91.8	50.4	63.6	76.8	19.4	36	52	2.6	11.8	25.8	0	1.4	7.2	0	0	0.6	0	0	0	0	0	0
140	93	97.2	99.6	85	91.8	97.6	67.8	78.8	90.4	41	56.8	74.2	14	29.8	49.2	1.4	8.8	23	0	0.8	6.2	0	0	0.6	0	0	0	0	0	0
150	90.6	96	99.4	80.2	89.4	97.2	60	74.4	89.4	32.8	51	73.4	9.99	24.5	46.6	0.8	6.4	20.6	0	0.6	5	0	0	0.4	0	0	0	0	0	0
≥154	90	95.4	99.4	78.2	88.2	97.4	57.4	72	89.6	30.8	48.8	73.6	8.79	23.2	47	0.79	6	20.6	0	0.4	4.6	0	0	0.4	0	0	0	0	0	0

B: Cumulative fraction of response[a]

$CLCR_{CG}$[b] [mL/min]	Cumulative fraction of response, %																													
	Full MIC distribution[c]															MIC distribution of susceptible pathogens[c]						MIC distribution of intermediate pathogens[c]								
	Escherichia coli			*Klebsiella pneumonia*			*Enterobacter cloacae*			*Pseudomonas aeruginosa*			*Acinetobacter spp.*			*Pseudomonas aeruginosa*			*Acinetobacter spp.*			*Pseudomonas aeruginosa*			*Acinetobacter spp.*					
	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95	P0.05	P0.5	P0.95			
10	100	100	100	99.8	99.9	100	99.8	99.9	100	91.2	95.2	98	88.2	94	99.1	100	100	100	99.9	100	100	88.2	99.1	100	89.5	99.2	100			
20	100	100	100	99.8	99.8	99.9	99.7	99.8	99.9	88.8	92.1	94.6	85.4	89.1	92.8	99.7	100	100	99.6	100	100	76.1	93.1	99.4	78.3	94	99.5			
30	100	100	100	99.7	99.8	99.8	99.6	99.7	99.8	86.4	89.4	91.4	83	86	88.2	99.3	99.9	100	98.8	99.9	100	61.7	79.7	91	64.7	81.9	92.3			
40	100	100	100	99.6	99.7	99.8	99.5	99.6	99.7	83.7	86.6	88.7	80.4	83.5	85.5	98.2	99.6	100	97.1	99.2	99.9	47	61.7	73.7	50.4	65	76.7			
50	100	100	100	99.5	99.6	99.7	99.4	99.5	99.6	80.5	83.7	86	77	80.6	83.1	96.5	98.6	99.6	94.5	97.7	99.3	32	43.9	55.3	35.2	47.3	58.7			
60	99.9	100	100	99.2	99.5	99.6	99.1	99.4	99.5	76.9	80.4	83.1	72.9	76.9	80	93.8	96.8	98.6	90.8	94.8	97.5	19.7	29.4	39.5	22.1	32.2	42.3			
70	99.9	99.9	100	99.1	99.4	99.5	98.8	99.3	99.4	72.9	76.9	80.2	68	72.5	76.4	90.3	94	96.6	85.7	90.5	94.2	10.6	18.9	28.5	12	20.9	30.8			
80	99.8	99.9	100	98.8	99.3	99.4	98.3	99	99.3	68.2	72.9	77	62.1	67.5	72.2	85.3	90.1	93.8	79	85	89.9	4.4	11.4	20.5	4.99	12.8	22.3			
90	99.6	99.9	99.9	98.2	99	99.3	97.6	98.6	99.1	63	68.5	73.3	55.8	62.2	67.6	79.2	85.3	90.1	71.3	78.7	84.8	1.61	6.83	14.6	1.83	7.67	16			
100	99.4	99.9	99.9	97.5	98.8	99.1	96.6	98.2	98.8	57.4	63.9	69.5	49.4	56.7	63.1	72.3	79.9	86	63.2	72.2	79.5	0.537	3.85	10.4	0.61	4.35	11.4			
110	99.2	99.7	99.9	96.6	98.2	99	95.5	97.4	98.5	52.1	59.1	65.7	43.6	51.4	58.8	65.6	74.2	81.6	55.9	65.6	74.4	0.21	2.2	7.51	0.238	2.5	8.31			
120	98.8	99.6	99.8	95.4	97.6	98.8	94	96.5	98.1	46.9	54.6	62.2	38.4	46.7	55	59.1	68.7	77.5	49.2	59.6	69.7	0	1.29	5.62	0	1.46	6.24			
130	98.2	99.3	99.8	93.9	96.7	98.6	92.1	95.4	97.7	41.6	50.3	59.2	33.5	42.3	51.7	52.5	63.2	74	42.9	54	65.7	0	0.752	4.15	0	0.853	4.62			
140	97.5	99.1	99.8	92.1	95.9	98.3	90	94.3	97.4	37.1	46.5	57.6	29.5	38.6	50	46.7	58.5	72.1	37.7	49.4	63.6	0	0.43	3.61	0	0.488	4.01			
150	96.7	98.8	99.8	89.9	94.8	98.2	87.5	93	97.1	32.6	43.1	56.5	25.7	35.3	48.7	41.1	54.2	70.8	32.9	45.2	62.1	0	0.322	2.87	0	0.366	3.2			
≥154	96.2	98.7	99.8	89.2	94.3	98.2	86.7	92.3	97.2	31.3	41.8	56.7	24.6	34.2	48.9	39.4	52.6	71	31.5	43.8	62.2	0	0.215	2.66	0	0.244	2.96			

CL, clearance; $CLCR_{CG}$, creatinine clearance estimated according to Cockcroft and Gault [35]; MIC, minimum inhibitory concentration; P0.05, 5th percentile; P0.5, 50th percentile (median); P0.95, 95th percentile; PD, pharmacodynamic; PK, pharmacokinetic.

[a] PTA and CFR evaluated for the PK/PD target 98%$T_{>MIC}$ and standard meropenem treatment of 1000 mg 30-min intravenous infusion every 8 h. PTA and CFR are given for varied values of $CLCR_{CG}$ as well as for selected MICs and are presented as the median (P0.5) and 5th (P0.05) and 95th percentile (P0.95) of the 1000 PTA values derived from the 1000 Monte Carlo simulations considering PK parameter uncertainty.

[b] Body weight and albumin fixed to median value of first study day (i.e. 70 kg and 2.8 g/dL).

[c] According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [32].

Colour coding: green, CFR or PTA ≥90%; yellow, CFR or PTA 80% to <90%; orange, CFR or PTA >50% to <80%; red, CFR or PTA ≤ 50%; grey shaded values, extrapolated $CLCR_{CG}$ range not covered by the study population or $CLCR_{CG} \geq 154$ mL/min (= inflection point of $CLCR_{CG}$–CL relationship).

Table 4
Three-level dosing algorithm[a] for the first day of meropenem treatment in critically ill patients. The proposed eight dosing regimens[b] cover three different infusion durations: short-term infusion (SI: SI2, SI3, SI6), prolonged infusion (PI: PI2, PI3, PI6) and continuous infusion (CI: CI3, CI6); and cover three different daily doses: 2000 mg (light blue: SI2, PI2), 3000 mg (blue: SI3, PI3, CI3[c]) and 6000 mg (pink: SI6, PI6, CI6[d]). For detailed description of the eight dosing regimens, refer to Table 1

Level 1: Pathogen unknown

$CLCR_{CG}$[e] [mL/min]	Dosing regimen: Pathogen unknown; Non-species related EUCAST PK/PD breakpoint [34]					
	S breakpoint (MIC=2 mg/L)			R breakpoint (MIC=8 mg/L)		
	SI	PI	CI	SI	PI	CI
10	SI2	PI2	CI3[c]	SI6	PI6	CI6[d]
20	**SI3**	PI3	CI3[c]	SI6	PI6	-
30	**SI3**	PI3	CI3[c]	-	PI6	-
40	**SI3**	PI3	CI3[c]	-	-	-
50	SI6	PI3	CI3[c]	-	-	-
60	SI6	PI6	CI3[c]	-	-	-
70	-	PI6	CI3[c]	-	-	-
80	-	PI6	CI3[c]	-	-	-
90	-	-	CI6[d]	-	-	-
100	-	-	CI6[d]	-	-	-
110	-	-	CI6[d]	-	-	-
120	-	-	CI6[d]	-	-	-
130	-	-	CI6[d]	-	-	-
140	-	-	CI6[d]	-	-	-
150	-	-	CI6[d]	-	-	-
≥154	-	-	CI6[d]	-	-	-

Level 2: Pathogen known

$CLCR_{CG}$[e] [mL/min]	Dosing regimen: Pathogen known; Full MIC distribution[f]														
	Escherichia coli			*Klebsiella pneumonia*			*Enterobacter cloacae*			*Pseudomonas aeruginosa*			*Acinetobacter spp.*		
	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI
10	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI3	CI6[d]	SI6	PI6	-
20	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI6	PI6	CI6[d]	SI6	PI6	-
30	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI6	PI6	CI6[d]	SI6	PI6	-
40	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI6	PI6	-	-	PI6	-
50	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	-	PI6	-	-	-	-
60	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	-	-	-	-	-	-
70	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	-	-	-	-	-	-
80	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	-	-	-	-	-	-
90	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI2	CI3[c]	-	-	-	-	-	-
100	SI2	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	-	-	-	-	-	-
110	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	-	-	-	-	-	-
120	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	-	-	-	-	-	-
130	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	-	-	-	-	-	-
140	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	-	-	-	-	-	-
150	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	SI6	PI3	CI3[c]	-	-	-	-	-	-
≥154	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	SI6	PI3	CI3[c]	-	-	-	-	-	-

Level $3_{(-MIC)}$: Pathogen and susceptibility known

$CLCR_{CG}$[e] [mL/min]	Dosing regimen: Pathogen and susceptibility known; MIC distribution of susceptible pathogens[f]						MIC distribution of intermediate pathogens[f]					
	Pseudomonas aeruginosa			*Acinetobacter spp.*			*Pseudomonas aeruginosa*			*Acinetobacter spp.*		
	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI
10	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI6	PI3	CI6[d]	SI6	PI3	CI6[d]
20	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI6	PI6	CI6[d]	SI6	PI6	CI6[d]
30	SI2	PI2	CI3[c]	SI3	PI2	CI3[c]	-	PI6	CI6[d]	SI6	PI6	CI6[d]
40	**SI3**	PI2	CI3[c]	SI3	PI3	CI3[c]	-	PI6	-	-	PI6	-
50	**SI3**	PI3	CI3[c]	SI3	PI3	CI3[c]	-	-	-	-	-	-
60	**SI3**	PI3	CI3[c]	SI3	PI3	CI3[c]	-	-	-	-	-	-
70	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	-	-	-	-	-
80	SI6	PI3	CI3[c]	SI6	PI3	CI3[c]	-	-	-	-	-	-
90	SI6	PI3	CI3[c]	-	PI6	CI3[c]	-	-	-	-	-	-
100	-	PI6	CI3[c]	-	PI6	CI3[c]	-	-	-	-	-	-
110	-	PI6	CI3[c]	-	PI6	CI3[c]	-	-	-	-	-	-
120	-	PI6	CI3[c]	-	-	CI3[c]	-	-	-	-	-	-
130	-	-	CI3[c]	-	-	CI3[c]	-	-	-	-	-	-
140	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-
150	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-
≥154	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-

Level $3_{(+MIC)}$: MIC value known

$CLCR_{CG}$[e] [mL/min]	Dosing regimen: MIC value known; MIC [mg/L]																																			
	0.004			0.008			0.015			0.03			0.06			0.12			0.25			0.5			1			2			4			8			16		
	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI	SI	PI	CI
10	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI6	CI6[d]	-	-	-
20	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI6[d]	SI6	PI6	-	-	-	-
30	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI6[d]	-	PI6	-	-	-	-
40	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI6	CI6[d]	-	-	-	-	-	-
50	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI6	CI6[d]	-	-	-	-	-	-
60	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI6	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-
70	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-
80	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-
90	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-	-	-	-
100	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-	-	-	-
110	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-	-	-	-
120	SI2	PI2	CI3[c]	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-	-	-	-
130	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-	-	-	-
140	SI2	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-	-	-	-
150	**SI3**	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	SI6	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI3[c]	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-	-	-	-
≥154	**SI3**	PI2	CI3[c]	**SI3**	PI2	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	**SI3**	PI3	CI3[c]	-	PI3	CI3[c]	-	PI6	CI3[c]	-	-	CI3[c]	-	-	CI3[c]	-	-	CI6[d]	-	-	-	-	-	-	-	-	-

CFR, cumulative fraction of response; CI, continuous infusion; CL, clearance; $CLCR_{CG}$, creatinine clearance estimated according to Cockcroft and Gault [35]; EUCAST, European Committee on Antimicrobial Susceptibility Testing; i.v., intravenous; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PI, prolonged infusion; PK, pharmacokinetic; PTA, probability of target attainment; q8h, every 8h; q12h, every 12 h; q24h, every 24 h; R, resistant; S, susceptible; SI, short-term infusion.
[a]The algorithm is currently intended for clinical research and requires further validation in future clinical studies.
[b]Lowest possible dosing regimen for which the 5th percentile of the 1000 Monte Carlo simulations considering PK parameter uncertainty achieved CFR ≥ 90% (for Level 2, Level $3_{(-MIC)}$) or PTA ≥ 90% (for Level 1, Level $3_{(+MIC)}$). For SI and PI, the PK/PD target $98\%T_{>MIC}$ was evaluated, and for CI the $98\%T_{>4\times MIC}$ was evaluated.
[c]For first day of treatment, daily dose of 3412.5 mg including loading dose.
[d]For first day of treatment, daily dose of 6875 mg including loading dose.
[e]Body weight and albumin fixed to median of first study day (i.e. 70 kg and 2.8 g/dL).
[f]EUCAST MIC distribution [32].
Grey shaded areas: extrapolated covariate range not covered by the study population or $CLCR_{CG}$ ≥154 mL/min (= inflection point of $CLCR_{CG}$–CL relationship).
Dosing regimens: SI2: 1000 mg, 30-min i.v. infusion, q12h; SI3: 1000 mg, 30-min i.v. infusion, q8h (= standard dosing; highlighted in bold); SI6: 2000 mg, 30-min i.v. infusion, q8h; PI2: 1000 mg, 3-h i.v. infusion, q12h; PI3: 1000 mg, 3-h i.v. infusion, q8h; PI6: 2000 mg, 3-h i.v. infusion, q8h; CI3: 3000 mg, q24h, following 500 mg, 30-min loading dose; CI6: 6000 mg, q24h following 1000 mg, 30-min loading dose.
For CI regimens (CI3, CI6), consider to renew the infusion solution dependent on the drug concentration twice or thrice daily (see Supplement of [21]) to ensure the stability of meropenem.

Based on the results of the PTA and CFR analyses (PK/PD target for SI and PI, $98\%T_{>MIC}$; for CI, $98\%T_{>4\times MIC}$) for treatment day 1, a three-level dosing algorithm was developed (Table 4) allowing to identify the lowest short-term, prolonged and continuous-infusion regimen resulting in adequate PTA/CFR (i.e. 5th percentile of 1000 computed PTA/CFR values ≥90%) based on a patient's $CLCR_{CG}$ and the level of knowledge about the pathogen:

- 'Level 1' (L1): pathogen unknown, i.e. based on predefined non-species-related PK/PD breakpoints [34];
- 'Level 2' (L2): pathogen known;
- 'Level $3_{(-MIC)}$' ($L3_{(-MIC)}$): pathogen and susceptibility (i.e. susceptible, intermediate) known; and
- 'Level $3_{(+MIC)}$' ($L3_{(+MIC)}$): MIC known.

The dosing algorithm shall be illustrated for different levels of knowledge about the pathogen by the following example: If starting treatment and suspecting a susceptible infecting pathogen (L1; susceptible breakpoint = 2 mg/L) in patients with $CLCR_{CG}$ = 50

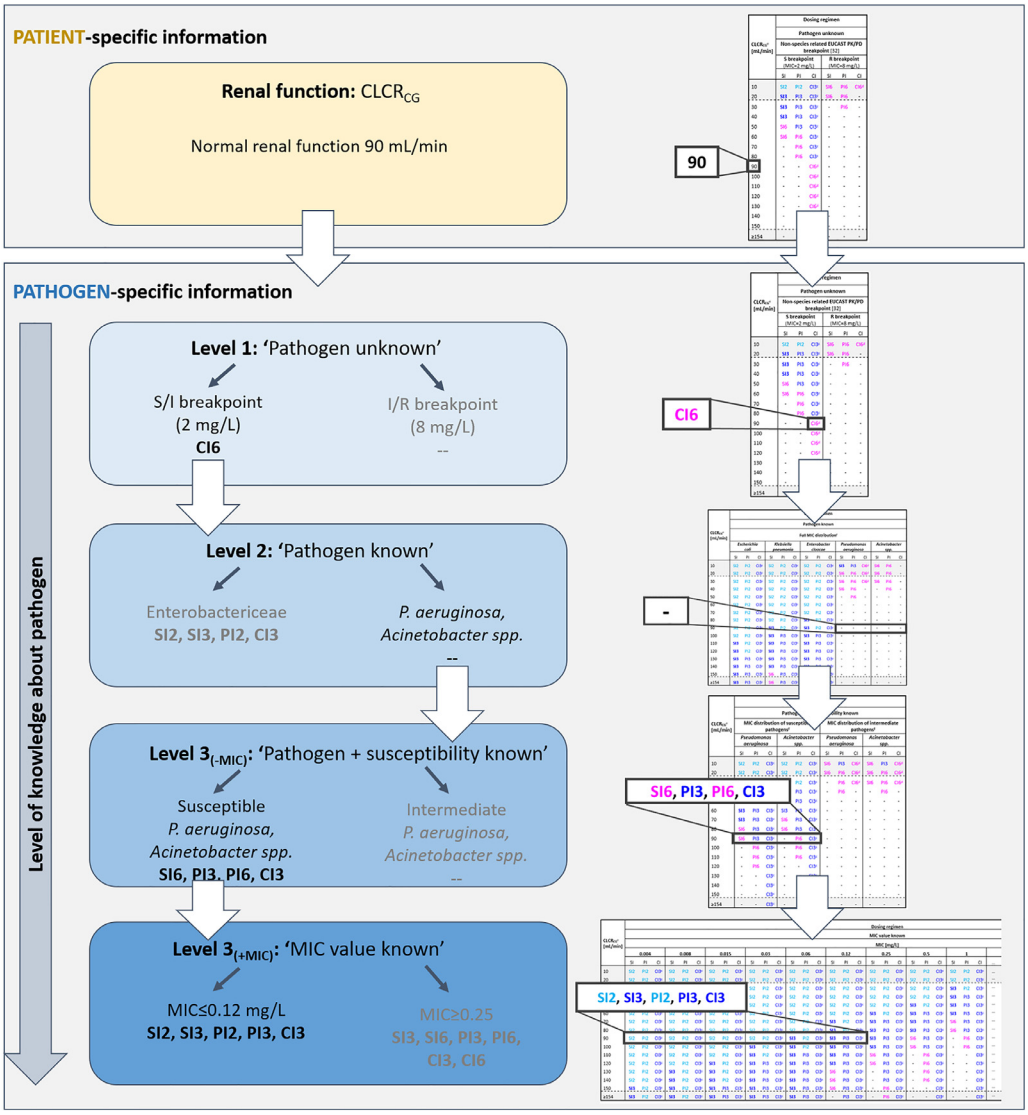

Fig. 2. Example illustrating application of the three-level meropenem dosing algorithm (described in Section 3.2): flow chart (left); and snapshot of parts of the dosing algorithm (see Table 4) relevant for the example given on the left in black font (right). For dosing regimens, see Table 1. For continuous infusion (CI) regimens (CI3, CI6), consider to renew the infusion solution dependent on the drug concentration twice or thrice daily (see supplement of [21]) to ensure the stability of meropenem. $CLCR_{CG}$, creatinine clearance estimated according to Cockcroft and Gault [35]; I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible.

mL/min, the short-term infusion regimen with an increased daily dose of 6000 mg (SI6) would be needed to reach adequate PTA; for the prolonged- and continuous-infusion regimens, 3000 mg daily (PI3/CI3) would be sufficient. For patients with normal renal function ($CLCR_{CG}$ = 90 mL/min; see flow chart, Fig. 2), only the highest investigated continuous-infusion regimen (CI6) would reach adequate PTA. When for the latter patients information on the type of pathogen becomes available (L2), a reduced dosing regimen (SI2/SI3/PI2/CI3) could be selected in case of different Enterobacteriaceae, whereas for *P. aeruginosa* or *Acinetobacter* spp. no regimen appeared appropriate. If additional knowledge of the susceptibility of the pathogen ($L3_{(-MIC)}$) becomes available, e.g. for susceptible *P. aeruginosa*, apart from short-term infusion (SI6), an even lower prolonged infusion (PI3) or continuous infusion (CI3) regimen was found to result in adequate PK/PD target attainment; and for susceptible *Acinetobacter* spp., short-term infusion (SI6), prolonged infusion (PI6) or continuous infusion (CI3) regimens. If the actual MIC is also provided ($L3_{(+MIC)}$) being ≤0.12 mg/L, irrespective of the pathogen but depending on the particular MIC the dosing regimen could be kept or reduced even further (SI2/SI3/PI2/PI3/CI3).

4. Discussion

A three-level meropenem dosing algorithm was generated proposing dosing regimens for meropenem in critically ill patients that aimed to result in effective meropenem exposure by means of a comprehensive population PK/PD analysis. The reliability of the proposed dosing regimens is deemed high as the underlying analysis also considered the uncertainty in the estimated PK model parameters. The investigated dosing regimens are provided in an intuitive tabular overview (Table 4), which considers only $CLCR_{CG}$ as the crucial patient-specific factor for meropenem target attainment. No additional covariates needed to be included as they showed only little impact on the achievement of effective antibiotic exposure. The dosing overview considers different levels of pathogen-specific information (L1, pathogen unknown; L2, pathogen known; $L3_{(-MIC)}$, pathogen and susceptibility known;

$L3_{(+MIC)}$, MIC known) as might be encountered in different clinical settings.

For the vulnerable population of critically ill patients, TDM has been recommended for individual dose adjustment [9,10]. However, TDM of antibiotics is still only rarely available in clinical routine, e.g. the recent ADMIN-ICU survey indicated that only 2% of the investigated ICUs implemented TDM for carbapenems [11]. As especially at the start but also during meropenem treatment TDM is mostly not available, reliable dosing recommendations are needed. In contrast to previous suggestions, the present work systematically investigated various dosing regimens for meropenem given different levels of information about the pathogen and furthermoreconsidered PK parameter uncertainty in the underlying simulations [16,20,21]. The developed three-level dosing algorithm (see Table 4) summarises dosing regimens that are likely to result in effective meropenem exposure (i.e. adequate PTA/CFR) based on a patient's renal function and the level of knowledge about a pathogen and hence provides information for different stages of treatment [pathogen and/or antibiogram available or not (yet)] and for different ways of reporting susceptibility in the patient records (susceptible/resistant classification or MIC). Choosing the dosing regimen based on the highest level of knowledge about a pathogen could allow to achieve effective exposure with the potential advantage of more probable or faster cure [2–4] as well as reduced risk of unnecessary high or toxic concentrations and of resistance development and spread. The algorithm is currently intended for clinical research and needs further validation in future clinical studies.

To give an example, in 'Level 1' (pathogen unknown; based on the non-species-related PK/PD breakpoints, e.g. susceptible = 2 mg/L [34]) for patients with normal renal function (CRCL ≥ 90 mL/min) a very high dose is proposed (CI6; see Fig. 2). In such situations, especially when TDM is not available, it is important to closely observe signs and symptoms of toxicity (e.g. neurotoxicity [36]). Depending on the site of infection, the bacterial spectrum may not be fully unknown and an empirical antibiotic treatment may be indicated. However, if the infecting strain is known ('Level 2'), in most cases (for all evaluated Enterobacteriaceae) reduced dosing might be adequate. For the bacteria listed in the algorithm, only for infections with *P. aeruginosa* or *Acinetobacter* spp. none of the investigated dosing regimens was sufficient, which can be explained by the higher proportion of pathogens with intermediate susceptibility or resistance against meropenem [32]. In such situations, combination therapy might be an option for critically ill patients, as already recommended by diverse guidelines if *P. aeruginosa* is a suspected strain in severe infections [37,38].

Overall, the analyses suggested adequate exposure to cover susceptible bacteria (MIC ≤ 2 mg/L) with at least one of the eight investigated dosing regimens in all investigated patients even if displaying augmented renal function. Bacteria with intermediate susceptibility, however, appeared to only be adequately covered in patients with renal insufficiency (MIC = 4 mg/L, $CLCR_{CG}$ ≤ 80 mL/min; MIC = 8 mg/L, $CLCR_{CG}$ ≤ 30 mL/min) using the most intensified dosing regimens (SI6/PI6/CI6). Conversely, for highly susceptible pathogens (e.g. MIC < 0.12 mg/L for $CLCR_{CG}$ = 90 mL/min), even lower than standard dosing appeared to be sufficient, however the advantages or disadvantages of such adaptions to lower dosing have to be further evaluated in prospective clinical trials. Nevertheless, this finding demonstrates the revelance of reporting MIC values even within the low susceptible range.

This systematic PK/PD analysis demonstrated important trends, notably for MIC ≤ 4 mg/L and day 1 of treatment. First, for a given daily dose, continuous-infusion regimens were superior to prolonged, and prolonged to short-term dosing regimens. The superiority of continuous over prolonged infusion was more pronounced than that of prolonged over short-term infusion. Previous investigations for meropenem revealed the feasibility of continuous infusion, despite the reported instability [39,40], at 25 °C if renewing the solution in dependence of the drug concentration twice or thrice daily (see Supplement of [21]). Second, the effect of type of infusion (e.g. continuous versus prolonged) on the achievement of effective exposure was more relevant than the administered total daily dose (e.g. 3000/3412.5 vs. 6000/6875 mg; for continuous infusion ≤14.6% higher total daily doses compared with the other regimens owing to the initial loading dose on day 1). For MIC > 4 mg/L and non-susceptible *P. aeruginosa or Acinetobacter* spp., prolonged rather than continuous-infusion regimens were superior. Note that these findings are based on the evaluation of the selected PK/PD targets (for SI and PI, $98\%T_{>MIC}$; for CI, $98\%T_{>4\times MIC}$). Trends might differ when evaluating other targets (e.g. $50\%T_{>MIC}$ or $50\%T_{>4\times MIC}$) or non-critically ill patient populations.

The PK/PD target of $98\%T_{>MIC}$ was selected for critically ill patients as it has previously been shown to result in improved clinical response in patients receiving β-lactam antibiotics [3,28] and also given the good safety profile of meropenem [41]. For continuous-infusion regimens, an even stricter PK/PD target of $98\%T_{>4\times MIC}$ was selected. This was deemed reasonable in light of the increasing spread of resistance [42] and the raised concerns that plateau-like antibiotic concentrations achieved at steady-state following continuous infusion may, if close to the MIC, favour the selection of resistant strains [43–45]. Notably, even stricter targets have been suggested. For instance, Tam et al. [43] suggested minimum meropenem target concentrations that not only exceed 4 × but 6.2 × MIC to supress in vitro resistance of *P. aeruginosa*. Despite the strict target of $98\%T_{>4\times MIC}$, continuous-infusion regimens were still found to be superior over short-term or prolonged-infusion regimens with respect to the PTA/CFR for MIC ≤ 4 mg/L.

The dosing regimens in the present work were derived based on the results of PTA and CFR analyses and the developed population PK model. To the best of our knowledge, this is the first analysis of meropenem to also consider PK parameter uncertainty in the Monte Carlo simulations [23] underlying the selection of dosing regimens for the dosing algorithm. Compared with the traditional approach not considering PK parameter uncertainty, the dose selection was more conservative (see Appendix B, Section B.4); thus, the results were deemed more reliable, which may be important to ensure effective exposure especially for critically ill patients. The PTA and CFR analyses on treatment days 1 and 4 revealed only little difference given the short elimination half-life of meropenem (study ICU patient, median = 2.27 h), with the results of day 1 being slightly more conservative. Hence, the dosing algorithm, which is provided for the start of treatment, is considered appropriate also during later meropenem treatment.

In contrast to most previous studies on meropenem, we systematically investigated a high number of potential covariate candidates (n = 27). Three covariate–PK parameter relationships ($CLCR_{CG}$ on CL, body weight on V_1, and albumin on V_2) were included in the developed population PK model. Due to the pronounced impact of $CLCR_{CG}$ on the PTA, caused by its strong influence on the descending part of the concentration–time profile, the dosing simulations were performed for varying $CLCR_{CG}$ but fixed body weight and albumin concentration. For patients with extreme body weight and albumin values, however, there might be an additional marginal impact of body weight and albumin that has not been considered in the algorithm. If aiming at additionally taking them into account, the implementation of the developed population PK model in a dosing software (e.g. TDMx [46]) is required, which can ultimately allow to determine an individualised dosing regimen for an individual $CLCR_{CG}$–weight–albumin combination.

In conclusion, we developed a three-level meropenem dosing algorithm, suggesting meropenem dosing regimens for critically ill patients based on their renal function as well as different levels

of knowledge about the pathogen. Additional independent clinical studies will be next necessary to validate the dosing algorithm in order to make it applicable in clinical practice. In addition, further studies investigating clinical outcome, also including toxicity, as well as further pharmacometric exploitations of in vitro information [47] are warranted.

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Declaration of Competing Interest

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Ethical approval

Ethical approval and consent was obtained from the Institutional Review Board of the Medical Faculty of the Ludwig-Maximilians-Universität München (Munich, Germany) [registration no. 428-12].

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.06.016.

References

[1] Levy Hara G, Kanj SS, Pagani L, Abbo L, Endimiani A, Wertheim HFL, et al. Ten key points for the appropriate use of antibiotics in hospitalised patients: a consensus from the Antimicrobial Stewardship and Resistance Working Groups of the International Society of Chemotherapy. Int J Antimicrob Agents 2016;48:239–46.
[2] Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014;58:1072–83.
[3] Ariano RE, Zelenitsky SA, Nyhlén A, Sitar DS. An evaluation of an optimal sampling strategy for meropenem in febrile neutropenics. J Clin Pharmacol 2005;45:832–5.
[4] Muller AE, Punt N, Moutona JW. Exposure to ceftobiprole is associated with microbiological eradication and clinical cure in patients with nosocomial pneumonia. Antimicrob Agents Chemother 2014;58:2512–19.
[5] Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 2014;14:498–509.
[6] McKenzie C. Antibiotic dosing in critical illness. J Antimicrob Chemother 2011;66:25–31.
[7] Kees MG, Minichmayr IK, Moritz S, Beck S, Wicha SG, Kees F, et al. Population pharmacokinetics of meropenem during continuous infusion in surgical ICU patients. J Clin Pharmacol 2016;56:307–15.
[8] Vossen MG, Ehmann L, Pferschy S, Maier-Salamon A, Haidinger M, Weiser C, et al. Elimination of doripenem during dialysis and pharmacokinetic evaluation of posthemodialysis dosing for patients undergoing intermittent renal replacement therapy. Antimicrob Agents Chemother 2018;62 e02430-17.
[9] Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, et al. Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents 2010;36:332–9.
[10] Felton TW, Hope WW, Roberts JA. How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it? Diagn Microbiol Infect Dis 2014;79:441–7. doi:10.1016/j.diagmicrobio.2014.04.007.
[11] Tabah A, de Waele J, Lipman J, Zahar JR, Cotta MO, Barton G, et al. The ADMIN-ICU survey: a survey on antimicrobial dosing and monitoring in ICUs. J Antimicrob Chemother 2015;70:2671–7.
[12] Kumar A. Early antimicrobial therapy in severe sepsis and septic shock. Curr Infect Dis Rep 2010;12:336–44.
[13] Craig WA. The pharmacology of meropenem, a new carbapenem antibiotic. Clin Infect Dis 1997;24(Suppl 2):S266–75.
[14] Nicolau DP. Pharmacokinetic and pharmacodynamic properties of meropenem. Clin Infect Dis 2008;47(Suppl 1):S32–40.
[15] Pfizer. *Meronem IV 500 mg & 1 g*. https://www.medicines.org.uk/emc/medicine/11215 [Accessed 28 August 2018].
[16] Roberts JA, Kirkpatrick CMJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 2009;64:142–50.
[17] Lal A, Jaoude P, El-Solh AA. Prolonged versus intermittent infusion of β-lactams for the treatment of nosocomial pneumonia: a meta-analysis. Infect Chemother 2016;48:81–90.
[18] Ahmed N, Jen S-P, Altshuler D, Papadopoulos J, Pham VP, Dubrovskaya Y. Evaluation of meropenem extended versus intermittent infusion dosing protocol in critically ill patients. J Intensive Care Med 2018:88506661878426. doi:10.1177/0885066618784264.
[19] Roberts JA, Abdul-Aziz M-H, Davis JS, Dulhunty JM, Cotta MO, Myburgh J, et al. Continuous versus intermittent β-lactam infusion in severe sepsis. a meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med 2016;194:681–91.
[20] Isla A, Canut A, Arribas J, Asín-Prieto E, Rodríguez-Gascón A. Meropenem dosing requirements against Enterobacteriaceae in critically ill patients: influence of renal function, geographical area and presence of extended-spectrum β-lactamases. Eur J Clin Microbiol Infect Dis 2016;35:511–19.
[21] Minichmayr IK, Roberts JA, Frey OR, Roehr AC, Kloft C, Brinkmann A. Development of a dosing nomogram for continuous-infusion meropenem in critically ill patients based on a validated population pharmacokinetic model. J Antimicrob Chemother 2018;73:1330–9.
[22] Tsai D, Stewart P, Goud R, Gourley S, Hewagama S, Krishnaswamy S, et al. Optimising meropenem dosing in critically ill Australian Indigenous patients with severe sepsis. Int J Antimicrob Agents 2016;48:542–6.
[23] Colin P, Eleveld DJ, Jonckheere S, Van Bocxlaer J, De Waele J, Vermeulen A. What about confidence intervals? A word of caution when interpreting PTA simulations. J Antimicrob Chemother 2016;71:2502–8.
[24] Ehmann L, Zoller M, Minichmayr IK, Scharf C, Maier B, Schmitt MV, et al. Role of renal function in risk assessment of target non-attainment after standard dosing of meropenem in critically ill patients: a prospective observational study. Crit Care 2017;21:263.
[25] Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed 2005;79:241–57.
[26] Keizer RJ, van Benten M, Beijnen JH, Schellens JHM, Huitema ADR. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed 2011;101:72–9.
[27] Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother 2005;55:601–7.
[28] McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration ($T_{>MIC}$) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 2008;31:345–51.
[29] Mouton JW, Den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother 1994;38:931–6.
[30] Tam VH, McKinnon PS, Akins RL, Rybak MJ, Drusano GL. Pharmacodynamics of cefepime in patients with Gram-negative infections. J Antimicrob Chemother 2002;50:425–8.
[31] Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 2007;51:1725–30.

[32] European Committee on Antimicrobial Susceptibility Testing. *Meropenem wild type distribution of microorganisms*. https://mic.eucast.org/Eucast2/ [Accessed 4 April 2018].
[33] European Medicines Agency (EMA). Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products. EMA; 2016 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/0722/WC500210982.pdf.
[34] European Committee on Antimicrobial Susceptibility Testing. *Breakpoint tables for interpretation of MICs and zone diameters. Version 8.0, 2018*. http://www.eucast.org/clinical_breakpoints/ [Accessed 4 April 2018].
[35] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[36] Imani S, Buscher H, Marriott D, Gentili S, Sandaradura I. Too much of a good thing: a retrospective study of β-lactam concentration–toxicity relationships. J Antimicrob Chemother 2017;72:2891–7.
[37] Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:e61–111.
[38] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign. Crit Care Med 2017;45:486–552.
[39] Carlier M, Stove V, Verstraete AG, De Waele JJ. Stability of generic brands of meropenem reconstituted in isotonic saline. Minerva Anestesiol 2015;81:283–7.
[40] Wicha SG, Kloft C. Simultaneous determination and stability studies of linezolid, meropenem and vancomycin in bacterial growth medium by high-performance liquid chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 2016;1028:242–8.
[41] Linden P. Safety profile of meropenem. Drug Saf 2007;30:657–68.
[42] Zaman SB, Hussain MA, Nye R, Mehta V, Mamun KT, Hossain N. A review on antibiotic resistance: alarm bells are ringing. Cureus 2017;9:e1403.
[43] Tam VH, Schilling AN, Neshat S, Poole K, Melnick DA, Coyle EA. Optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance of *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2005;49:4920–7.
[44] Boak LM, Li J, Rayner CR, Nation RL. Pharmacokinetic/pharmacodynamic factors influencing emergence of resistance to linezolid in an in vitro model. Antimicrob Agents Chemother 2007;51:1287–92.
[45] Felton TW, Goodwin J, O'Connor L, Sharp A, Gregson L, Livermore J, et al. Impact of bolus dosing versus continuous infusion of piperacillin and tazobactam on the development of antimicrobial resistance in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2013;57:5811–19.
[46] Wicha SG, Kees MG, Solms A, Minichmayr IK, Kratzer A, Kloft C. TDMx: a novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine. Int J Antimicrob Agents 2015;45:442–4.
[47] Wicha SG, Huisinga W, Kloft C. Translational pharmacometric evaluation of typical antibiotic broad-spectrum combination therapies against *Staphylococcus aureus* exploiting in vitro information. CPT Pharmacometrics Syst Pharmacol 2017;6:512–22.