Abdul-Aziz et al. Critical Care (2017) 21:283
DOI 10.1186/s13054-017-1871-2

Critical Care

EDITORIAL Open Access

Identifying "at-risk" patients for sub-optimal beta-lactam exposure in critically ill patients with severe infections

Mohd H. Abdul-Aziz[1,2], Jeffrey Lipman[1,3*] and Jason A. Roberts[1,3,4,5]

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Keywords: Augmented renal clearance, Critically ill, Meropenem, Pharmacokinetic, Pharmacodynamic, Risk assessment tool

Pathophysiological changes affecting drug pharmacokinetics

Mortality due to severe infections in the intensive care unit (ICU) remains high despite recent therapeutic advancements [1]. However, appropriate antibiotic administration (including spectrum of activity and therapeutic exposure) is rarely a straightforward process in ICU patients as they commonly develop extreme pathophysiological changes that can alter antibiotic pharmacokinetics and consequently affect drug exposure in this population. The volume of distribution and drug clearance are the pharmacokinetic parameters of greatest relevance to determining drug dosing requirements, and both parameters may be significantly deranged during critical illness [2, 3]. Furthermore, ICU pathogens are relatively different from those in the general wards as they commonly have reduced antibiotic susceptibility [4]. Despite profound physiological and pharmacokinetic differences to the non-critically ill population, critically ill patients are typically given conventional antibiotic dosing regimens, which increase the likelihood of therapeutic failures and the emergence of bacterial resistance [5].

Optimal pharmacodynamic index for maximal beta-lactam activity

Beta-lactam antibiotics display time-dependent pharmacodynamics, whereby the time for which the free (unbound) drug concentrations remain above the minimum inhibitory concentration ($fT_{>MIC}$) best characterises bacterial killing [6]. Specifically, the $\%fT_{>MIC}$ value needed for bactericidal activity is between 40 and 70% for these antibiotics. However, emerging clinical data from critically ill patients suggest that these patients may benefit from higher and longer antibiotic exposures [7, 8]. It has since been suggested that beta-lactam concentrations should be maintained as at least four or five times the MIC for extended periods during each dosing interval (e.g. 90–100% $T_{>4\times MIC–5\times MIC}$) to maximise patient outcomes, including suppressing the emergence of resistant bacteria [9]. Nevertheless, achieving this aggressive pharmacokinetic/pharmacodynamic target is not easy in critically ill patients, particularly when standard beta-lactam dosing is applied.

Pharmacokinetic/pharmacodynamic derangements during critical illness

The DALI study has reported significant variability in beta-lactam exposures in critically ill patients [5]. In this study, whilst plasma beta-lactam concentrations could vary by up to 500-fold, pharmacokinetic/pharmacodynamic exposures varied by more than 1000-fold. Approximately one-fifth of the DALI cohort failed to achieve even the most conservative pharmacokinetic/pharmacodynamic target (50% $fT_{>MIC}$) with standard beta-lactam dosing and these patients were 32% more likely to demonstrate negative outcomes (e.g. prolonged antibiotic courses).

* Correspondence: j.lipman@uq.edu.au
[1]Faculty of Medicine, University of Queensland Centre for Clinical Research (UQCCR), The University of Queensland, Building 71/918 Royal Brisbane & Women's Hospital, Brisbane, QLD 4029, Australia
[3]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia
Full list of author information is available at the end of the article

The complexity of beta-lactam dosing in critically ill patients has been characterised recently by Ehmann et al. [10] in their prospective, observational, single-centre pharmacokinetic study. In this study, 48 critically ill patients with severe sepsis were recruited, with the investigators evaluating the pharmacokinetic/pharmacodynamic target attainment of standard meropenem dosing (1000/2000 mg every 8 hours as a 30-min infusion) in critically ill patients. The investigators then developed a tool that may improve meropenem exposure in this population. Large variation in meropenem concentration was observed in this study, corroborating the findings of earlier studies [2, 5, 11, 12]. The pharmacokinetic/pharmacodynamic target attainment of the cohort was relatively poor; only 56% and 48% of the cohort achieved the tested pharmacokinetic/pharmacodynamic targets of 50% $fT_{>4\times MIC}$ and 100% $fT_{>MIC}$, respectively, against the MIC susceptibility breakpoint of 2 mg/L. It is also noteworthy that the investigators had chosen to use two aggressive pharmacokinetic/pharmacodynamic targets as opposed to the conventional target for optimal beta-lactam activity (50% $fT_{>MIC}$). Furthermore, the MIC values were assumed from population estimates (EUCAST MIC breakpoints), inflating the magnitudes of target non-attainment in their analysis.

Sub-therapeutic beta-lactam exposure and the influence of renal function

As the beta-lactams are predominantly cleared by the kidney, elevated renal function may likely lead to sub-optimal antibiotic exposure, particularly when conventional dosing regimens are used [2, 13]. Patients with severe infections commonly develop a systemic inflammatory response syndrome, which increases renal blood flow and glomerular filtration rates. These factors enhance renal clearance of some drugs, a phenomenon referred to as augmented renal clearance (ARC). A measured creatinine clearance (CL_{CR}) ≥ 130 ml/min has been used to correlate ARC with sub-optimal antibiotic exposures [13]. Although ARC is highly prevalent in most ICUs [14], most clinicians fail to address the phenomenon, persisting with conventional beta-lactam dosing that is likely flawed, particularly when less susceptible pathogens are present.

In their study, Ehmann et al. [10] observed that increasing estimated CL_{CR} significantly reduced the likelihood of pharmacokinetic/pharmacodynamic target attainment. This further highlights that those patients who are at risk for ARC, usually those with apparently "normal" renal function, have to be identified earlier so that dose modification can be made earlier [2, 13]. In this respect, the investigators are certainly heading in the right direction with their proposed solution. They have developed a practical tool in commonly used software (Microsoft Excel) to predict the risk of target non-attainment for non-RRT critically ill patients. This free and easy-to-use risk assessment tool, the MeroRisk Calculator, would be able to predict the likelihood of achieving 100% $T_{>MIC}$ with standard meropenem dosing by inputting the CL_{CR} of a patient or its determinants together with the MIC of a known or suspected pathogen. The calculated risk of target non-attainment is displayed with a three-colour coding system and at-risk patients are highlighted in red, which should prompt clinicians to alter dosing for such patients. Although the MeroRisk Calculator was developed based on a broad range of CL_{CR} (25–255 ml/min), the prediction uncertainty increases for the extremes of renal function due to the limited number of patients representing this sub-population. The tool also provides a graphical illustration of the relationship between estimated CL_{CR} and the predicted meropenem exposure which therefore describes the degree of uncertainty around their prediction.

This promising tool, however, can be improved upon. It was developed based on the Cockcroft–Gault CL_{CR}, but the measured CL_{CR} is likely to be more appropriate in the ICU, particularly in patients with ARC [15]. Severity of illness may influence meropenem exposure, particularly in terms of the volume of distribution, and its impact should be incorporated into the Calculator. Actual MIC must be provided for accurate prediction as opposed to population estimates. The MeroRisk Calculator should be refined to also include other patient sub-groups, namely ECMO and RRT patients, in the prediction model.

Conclusion

Conventional beta-lactam dosing is flawed in critically ill patients. Useful tools such as the MeroRisk Calculator need to be comprehensively evaluated clinically, and if successful should be added into clinical practice to guide effective antibiotic dosing.

Abbreviations

ARC: Augmented renal clearance; CL_{CR}: Creatinine clearance; DALI: Defining Antibiotic Levels in Intensive care unit patients; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; MIC: Minimum inhibitory concentration; RRT: Renal replacement therapy; $T_{>MIC}$: Time for which drug concentration remains above the minimum inhibitory concentration during a dosing interval

Acknowledgements

Not applicable.

Funding

JAR is funded by a Career Development Fellowship from the Australian National Health and Medical Research Council (APP1048652), the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP1099452) and a Practitioner Fellowship (APP11117065).

Availability of data and materials

Not applicable.

Authors' contributions
MHA-A, JAR, and JL drafted the manuscript. MHA-A, JAR and JL critically revised the manuscript. All authors read and approved the final manuscript.

Authors' information
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Author details
[1]Faculty of Medicine, University of Queensland Centre for Clinical Research (UQCCR), The University of Queensland, Building 71/918 Royal Brisbane & Women's Hospital, Brisbane, QLD 4029, Australia. [2]School of Pharmacy, International Islamic University Malaysia, Kuantan, Malaysia. [3]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia. [4]Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia. [5]Department of Pharmacy Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.

Received: 4 October 2017 Accepted: 24 October 2017
Published online: 21 November 2017

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DOI 10.1186/s13054-017-1829-4

Critical Care

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Role of renal function in risk assessment of target non-attainment after standard dosing of meropenem in critically ill patients: a prospective observational study

Lisa Ehmann[1,2†], Michael Zoller[3†], Iris K. Minichmayr[1,2], Christina Scharf[3], Barbara Maier[4], Maximilian V. Schmitt[5], Niklas Hartung[1,6], Wilhelm Huisinga[6], Michael Vogeser[4], Lorenz Frey[3], Johannes Zander[4] and Charlotte Kloft[1*]

Abstract

Background: Severe bacterial infections remain a major challenge in intensive care units because of their high prevalence and mortality. Adequate antibiotic exposure has been associated with clinical success in critically ill patients. The objective of this study was to investigate the target attainment of standard meropenem dosing in a heterogeneous critically ill population, to quantify the impact of the full renal function spectrum on meropenem exposure and target attainment, and ultimately to translate the findings into a tool for practical application.

Methods: A prospective observational single-centre study was performed with critically ill patients with severe infections receiving standard dosing of meropenem. Serial blood samples were drawn over 4 study days to determine meropenem serum concentrations. Renal function was assessed by creatinine clearance according to the Cockcroft and Gault equation ($CLCR_{CG}$). Variability in meropenem serum concentrations was quantified at the middle and end of each monitored dosing interval. The attainment of two pharmacokinetic/pharmacodynamic targets ($100\%T_{>MIC}$, $50\%T_{>4\times MIC}$) was evaluated for minimum inhibitory concentration (MIC) values of 2 mg/L and 8 mg/L and standard meropenem dosing (1000 mg, 30-minute infusion, every 8 h). Furthermore, we assessed the impact of $CLCR_{CG}$ on meropenem concentrations and target attainment and developed a tool for risk assessment of target non-attainment.

Results: Large inter- and intra-patient variability in meropenem concentrations was observed in the critically ill population ($n = 48$). Attainment of the target $100\%T_{>MIC}$ was merely 48.4% and 20.6%, given MIC values of 2 mg/L and 8 mg/L, respectively, and similar for the target $50\%T_{>4\times MIC}$. A hyperbolic relationship between $CLCR_{CG}$ (25–255 ml/minute) and meropenem serum concentrations at the end of the dosing interval (C_{8h}) was derived. For infections with pathogens of MIC 2 mg/L, mild renal impairment up to augmented renal function was identified as a risk factor for target non-attainment (for MIC 8 mg/L, additionally, moderate renal impairment).

Conclusions: The investigated standard meropenem dosing regimen appeared to result in insufficient meropenem exposure in a considerable fraction of critically ill patients. An easy- and free-to-use tool (the MeroRisk Calculator) for assessing the risk of target non-attainment for a given renal function and MIC value was developed.

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* Correspondence: charlotte.kloft@fu-berlin.de
Johannes Zander and Charlotte Kloft share senior authorship.
†Equal contributors
[1]Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Kelchstrasse 31, 12169 Berlin, Germany
Full list of author information is available at the end of the article

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Trial registration: Clinicaltrials.gov, NCT01793012. Registered on 24 January 2013.

Keywords: β-Lactam, Intensive care, Pharmacokinetics/Pharmacodynamics, Target attainment, Renal function, Risk assessment tool, Continuous renal replacement therapy

Background

Severe infections remain a major issue in the intensive care unit (ICU) because of their high prevalence and high mortality rates among critically ill patients [1]. Hence, rational antibiotic therapy is especially important in this vulnerable population. Apart from an appropriate activity spectrum and early initiation of antibiotic therapy, a dosing regimen leading to adequate therapeutic antibiotic concentrations and exposure is crucial [2–5]. Adequate antibiotic exposure not only has been found to improve clinical success but also has been suggested to reduce resistance development [6, 7]. At the same time, pathophysiological changes in critically ill patients, including organ dysfunction or altered fluid balance, might substantially influence antibiotic concentrations and increase the risk of inadequate antibiotic exposure. As a second challenge, infections in these patients are often caused by pathogens with lower susceptibility (i.e., higher minimum inhibitory concentration [MIC]) than in other clinical settings [8–11].

Meropenem is a broad-spectrum carbapenem β-lactam antibiotic frequently used to treat severe bacterial infections in critically ill patients, such as those with severe pneumonia, complicated intra-abdominal infections, complicated skin and soft tissue infections, or sepsis [12]. For these indications, the approved standard dosing regimens for adults (intact renal function [RF]) include 500 mg or 1000 mg administered as short-term infusions every 8 h; for other indications, doses up to 2000 mg are recommended [12]. Meropenem is a hydrophilic molecule with very low plasma protein binding of approximately 2% [13]. It is excreted primarily via the kidney, predominantly by glomerular filtration but also by active tubular secretion [14]. Meropenem has been shown to be readily dialysable and effectively removed by haemodialysis [15–17]. As a β-lactam antibiotic, meropenem shows time-dependent activity; that is, its antibacterial activity is linked to the percentage of time that meropenem concentrations exceed the MIC value of a pathogen ($\%T_{>MIC}$) [18]. The attainment of the pharmacokinetic/pharmacodynamic (PK/PD) index $\%T_{>MIC}$ has been associated with clinical success in patients treated with meropenem [19–21]. For example, Ariano et al. demonstrated that the probability of clinical response was 80% when $\%T_{>MIC}$ was 76–100 in febrile neutropenic patients with bacteraemia but only 36% when $\%T_{>MIC}$ was between 0 and 50 [20].

Previous studies have revealed large inter-patient variability in meropenem concentrations after standard dosing in critically ill patients [22–24], which resulted in inadequate meropenem exposure in a relevant fraction of patients [23, 25]. However, in most of these studies, only limited numbers of patients and/or rather homogeneous patient sub-groups have been investigated. Hence, the identified variability in meropenem exposure might not have adequately reflected a typically heterogeneous critically ill population. In previous analyses, RF has been shown to be a major cause of variability in meropenem exposure [23, 24, 26–31] and, as a consequence, to be influential on the attainment of specific target concentrations [25, 32, 33]. However, the impact of kidney function on target attainment has been assessed primarily for distinct RF classes but not yet in a coherent quantitative framework for a population covering the full spectrum of RF ranging from dialysis/severe renal impairment (RI) to augmented renal clearance.

The aims of this study were (1) to quantify inter- and intra-individual variability of meropenem serum concentrations in a heterogeneous critically ill population covering the full spectrum of RF classes after meropenem standard dosing, (2) to investigate the attainment of two different PK/PD targets, (3) to assess the impact of RF on meropenem exposure and consequently target attainment and (4) ultimately to develop an easy-to-use risk assessment tool allowing identification and quantification of the risk of target non-attainment for a particular patient on the basis of the patient's RF.

Methods

Clinical study

This prospective observational study was conducted at three ICUs within the Department of Anaesthesiology, University Hospital, LMU Munich, Germany. The study protocol (ClinicalTrials.gov identifier NCT01793012) was approved by the Institutional Review Board of the Medical Faculty of the LMU Munich, Germany. Criteria for inclusion comprised the presence of severe infection (confirmed or suspected by clinical assessment), age ≥ 18 years and therapy with meropenem (including possible de-escalation; clinical assessment independent from the study). Patients were excluded in case of a planned hospitalisation < 4 days or meropenem administration > 48 h prior to study start. Written informed consent to participate was obtained from all patients or their legal

representatives. All patients received standard doses of meropenem as 30-minute infusions three times per day (*see* Additional file 1: Study design, Figure S1a). Multiple arterial blood samples were collected for the quantification of meropenem concentrations over a study period of 4 days. Intensive sample collection was performed during all three dosing intervals of study day 1 and during the first dosing interval of study days 2–4. An additional single minimum meropenem concentration (C_{min}) sample before the next dose was collected for the third dosing interval of days 2 and 3. The planned sampling time points per intensively monitored dosing interval were as follows: 15 minutes, 30 minutes, 1.5 h, 4 h, and 8 h (directly before next dose; C_{min}) after the start of infusion (*see* Additional file 1: Study design, Figure S1b). The exact sampling time points were recorded by the medical staff. In addition, patient-specific data such as diagnosis, demographics, disease scores and laboratory data (e.g., serum creatinine) were recorded during the study period. Creatinine clearance was estimated according to the Cockcroft and Gault equation ($CLCR_{CG}$ [34]) on the basis of daily measured serum creatinine (Jaffe assay):

$$\mathrm{CLCR_{CG}}\left[\frac{\mathrm{ml}}{\mathrm{min}}\right] = \frac{(140 - \mathrm{age\ [years]}) \cdot \mathrm{body\ weight[kg]}}{72 \cdot \mathrm{serum\ creatinine}\left[\frac{\mathrm{mg}}{\mathrm{dl}}\right]} \cdot (0.85\ \mathrm{if\ female})$$

In addition, pathogens identified in specimens collected from the patients (between 3 days before and 3 days after the study period) were recorded.

Bioanalytical method for meropenem concentration

Blood samples were immediately sent to the Institute of Laboratory Medicine, University Hospital, LMU Munich and centrifuged. Serum samples were stored at −80 °C until total meropenem serum concentration was quantified by using a validated liquid chromatography-tandem mass spectrometry method described previously [35]. Briefly, sixfold deuterated meropenem was used as an internal standard, and validation revealed good analytical performance, with an inaccuracy of less than or equal to ± 4% relative error and imprecision ≤ 6% coefficient of variation (CV).

Variability of meropenem concentrations

To quantify inter- and intra-individual variability of meropenem serum concentrations, measured C_{min} values were first analysed without regard to the actual heterogeneous sampling time points or administered doses. Inter-individual variability was evaluated by a summary statistical analysis of all available C_{min} values; for description of intra-individual variability, the ratios of the maximum and minimum C_{min} values $\left(\frac{C_{min\ max}}{C_{min\ min}}\right)$ of all dosing intervals monitored within a patient were statistically summarised. Summary statistics included median, range, 95% CI and %CV.

In order to exclude a potential impact of dose- and sampling time point-related variability on the meropenem minimum concentrations, dose-normalised meropenem concentrations (to a dose of 1000 mg, assuming linear PK) at two specific time points (4 h [C_{4h}] and 8 h [C_{8h}] after infusion start) were calculated, and the variability was evaluated as described above. C_{4h} and C_{8h} values were determined by linear regression (if more than two data points) or linear interpolation (if two data points) of the logarithmised data in the declining phase of each concentration-time profile. In case of a coefficient of determination (R^2) < 0.9, being associated with two distinct phases in the declining part of the concentration-time profile, a separate linear interpolation/regression was performed for each of these phases.

Pharmacokinetic/pharmacodynamic target attainment

To evaluate the achievement of therapeutically adequate meropenem serum concentrations, PK/PD target attainment was assessed for a broad MIC range from 0.25 mg/L to 8 mg/L, with a special focus on MIC 2 mg/L and MIC 8 mg/. The two values are common European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptible/intermediate (S/I) and intermediate/resistant (I/R) MIC breakpoints for relevant bacteria, such as Enterobacteriaceae, *Pseudomonas* spp. or *Acinetobacter* spp. [36]. The target $100\%T_{>MIC}$ (i.e., meropenem serum concentrations exceeding one times the MIC for the entire dosing interval) was selected because it has previously been shown to improve clinical cure and bacteriological eradication in patients with serious bacterial infections treated with β-lactam antibiotics [20, 37]. In accordance with other studies, $50\%T_{>4\times MIC}$ (i.e., meropenem serum concentration exceeding four times the MIC for half of the dosing interval) was chosen as a second target [38–40]. Owing to the negligible protein binding of meropenem (2%), total meropenem serum concentrations were used for all analyses [13, 41].

To evaluate the attainment of the targets $100\%T_{>MIC}$ and $50\%T_{>4\times MIC}$, the predicted C_{4h} and C_{8h} values of each dosing interval were evaluated regarding the achievement of the above-mentioned thresholds (one or four times the MIC breakpoints) for all patients not undergoing continuous renal replacement therapy (CRRT). Additionally, target attainment was evaluated for a dose of 2000 mg meropenem based on the extrapolated C_{4h} and C_{8h} values (assuming linear PK). Dosing was considered adequate if the target was attained in ≥ 90% of the monitored dosing intervals [41].

Impact of renal function on meropenem exposure and target attainment

To investigate the impact of RF on meropenem exposure, $CLCR_{CG}$ was related to C_{4h} and C_{8h} values (at patient level using the median individual $CLCR_{CG}$ of a patient, and at sample level using single $CLCR_{CG}$ values). For non-CRRT patients, the relationship between $CLCR_{CG}$ and C_{8h} values was quantified by weighted linear least squares regression in double logarithmic scale $\left(C_{8h} = \alpha \cdot \frac{1}{(CLCR_{CG})^{\beta}}\right)$. For further details, *see* Additional file 2: Regression model for risk calculation.

Target attainment at sample level was stratified by the following classes of RF or RI on the basis of $CLCR_{CG}$ [42–44]: severe RI 15–29 ml/minute, moderate RI 30–59 ml/minute, mild RI 60–89 ml/minute, normal RF 90–129 ml/minute and augmented RF ≥ 130 ml/minute. All analyses described here and previously were performed using the software R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Risk assessment tool

A tool for the risk assessment of target non-attainment based on the RF was developed using Excel 2016 software with Visual Basic for Applications (Microsoft Corporation, Redmond, WA, USA). In the Excel tool, the quantified $CLCR_{CG}$-C_{8h} relationship for non-CRRT patients, the prediction interval around this relationship and the computation of the risk of target ($100\%T_{>MIC}$) non-attainment for given $CLCR_{CG}$ and MIC values were implemented. For further details, *see* Additional file 2: Regression model for risk calculation.

Results

Clinical study

Patient characteristics

A total of 48 patients (27 male, 21 female) were included in the study (*see* Table 1). Of these patients, 83% suffered from sepsis, which was most frequently caused by pneumonia or peritonitis (75% or 20% of the sepsis patients, respectively). Pathogens detected in the patients comprised Enterobacteriaceae, non-fermenters (e.g., *Pseudomonas* spp.), *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp., *Bacillus* spp., *Clostridium* spp., *Bacteroides* spp., *Mycoplasma* spp., *Candida* spp. and *Aspergillus* spp. The patient group covered broad ranges of age (24–84 years), body mass index (16–49 kg/m^2) and severity of illness (Acute Physiology and Chronic Health Evaluation II [APACHE II] score 11–42). RF determined by $CLCR_{CG}$ was highly variable, ranging from severely impaired to augmented RF (first study day 24.8–191 ml/minute). Seven patients received CRRT, and six patients underwent extracorporeal membrane oxygenation (ECMO). Twenty-eight patients were post-lung or post-liver transplant recipients.

Meropenem dosing and sampling

During the study period, patients were treated with 1000 mg ($n_{patients} = 47$) or 2000 mg ($n_{patients} = 1$) of meropenem administered as 30-minute infusions approximately every 8 h (median 8 h, 95% CI 6.94–9.19 h). A total of 1376 blood samples (median per patient 31) were taken during 349 dosing intervals (median per patient 8, range per patient 4–8). Of the measurements, 23.5% ($n = 324$) were C_{min} samples, which were collected 7.92 h (median) after infusion start (95% CI 6.85–9.08 h). Very few serum concentrations (0.36% of data) revealed an implausible increase in the terminal part of the concentration-time profiles and were therefore excluded from the data analyses (*red* data points in Fig. 1).

Variability of meropenem concentrations

Large inter-individual variability was observed for both the observed C_{min} values (*see* Fig. 2) and the calculated concentrations C_{8h} and C_{4h} (*see* Table 2). Whereas inter-individual variability in C_{min} and C_{8h} was particularly large, varying in both concentrations by up to a factor of approximately 1000 between patients, C_{4h} values were slightly less variable (C_{min} range 0.03–30.0 mg/L, 104 CV%; C_{8h} range 0.0426–30.0 mg/L, 110 CV%; C_{4h} range 0.933–43.3 mg/L, 69.9 CV%). Apart from inter-individual variability, large intra-individual variability was identified (*see* Table 2). Particularly C_{min} (*see* Fig. 1) and C_{8h} values showed large variability, with concentrations varying in median by twofold to more than tenfold within a patient (range of ratios $\frac{C_{min\,max}}{C_{min\,min}}$: 1.3–10.9, range of ratios $\frac{C_{8h\,max}}{C_{8h\,min}}$: 1.22–11.4). Intra-individual variability in C_{4h} values was slightly lower, but the C_{4h} values within a patient still varied up to more than fivefold (range of ratios $\frac{C_{4h\,max}}{C_{4h\,min}}$: 1.10–5.47).

Pharmacokinetic/pharmacodynamic target attainment

For infections in non-CRRT patients with pathogens of MIC 2 mg/L, both investigated targets were attained in approximately half of the dosing intervals monitored, with slightly higher attainment for the $50\%T_{>4\times MIC}$ target (56%) than for the $100\%T_{>MIC}$ target (48%; *see* Table 3). When extrapolating the data to a dose of 2000 mg, target attainment was substantially higher, with 91% and 78% for the targets $50\%T_{>4\times MIC}$ and $100\%T_{>MIC}$, respectively (*see* Additional file 3: PK/PD target attainment, Table S2).

Given an MIC of 8 mg/L, the target $100\%T_{>MIC}$ was attained only in about one-fifth of the monitored

Table 1 Patient characteristics on study day 1

Diagnosis (multiple possible)	Number of patients	Percentage of patients, %
Sepsis	40	83.3
Pneumonia	30	75.0[1]
Hospital-acquired pneumonia	18	60.0[2]
Community-acquired pneumonia	12	40.0[2]
Peritonitis	8	20.0[1]
Urosepsis	1	2.50[1]
Soft tissue infection	1[3]	2.50[1]
ARDS	7	14.6
Others	6	12.5
Continuous patient characteristics [unit]	**Median**	**5^{th} - 95^{th} Percentile**
APACHE II score [-]	27	13-38
SOFA score [-]	12	4-18
IL-6 concentration [pg/ml]	94.2	24.5-7330
CRP concentration [mg/dl]	9.75	2.10-31.8
$CLCR_{CG}$ [ml/min]	70.8	34.8-160
$CLCR_{CG}$ of patients without CRRT [ml/min]	80.8	24.8-191
$CLCR_{CG}$ of patients with CRRT [ml/min]	54.1	26.5-72.9
Age [years]	55.5	32.0-69.9
Weight [kg]	70.5	47.4-121
BMI [kg/m^2]	24.0	18.4-39.6
Categorical patient characteristics	**Number of patients**	**Percentage of patients, %**
Sex (male)	27	56.3
CRRT	7	14.6
CVVH	1	14.3[4]
CVVHD	3	42.9[4]
CVVHDF	3	42.9[4]
Lung transplantation[5]	19	39.6
Liver transplantation[5]	9	18.8
ECMO	6	12.5

Abbreviations: *APACHE II* Acute Physiology And Chronic Health Evaluation II [53], *ARDS* Acute respiratory distress syndrome, *BMI* Body mass index, $CLCR_{CG}$ Creatinine clearance estimated according to Cockcroft and Gault equation [34], *CRP* C-reactive protein, *CRRT* Continuous renal replacement therapy, *CVVH* Continuous venovenous haemofiltration, *CVVHD* Continuous venovenous haemodialysis, *CVVHDF* Continuous venovenous haemodiafiltration, *ECMO* Extracorporeal membrane oxygenation, *IL-6* Interleukin 6, *SOFA* Sepsis-related Organ Failure Assessment [54]

[1]In relation to total number of patients with sepsis

[2]In relation to total number of patients with pneumonia

[3]Abdominal wall abscess

[4]In relation to total number of patients with CRRT

[5]Transplant within last 28 days

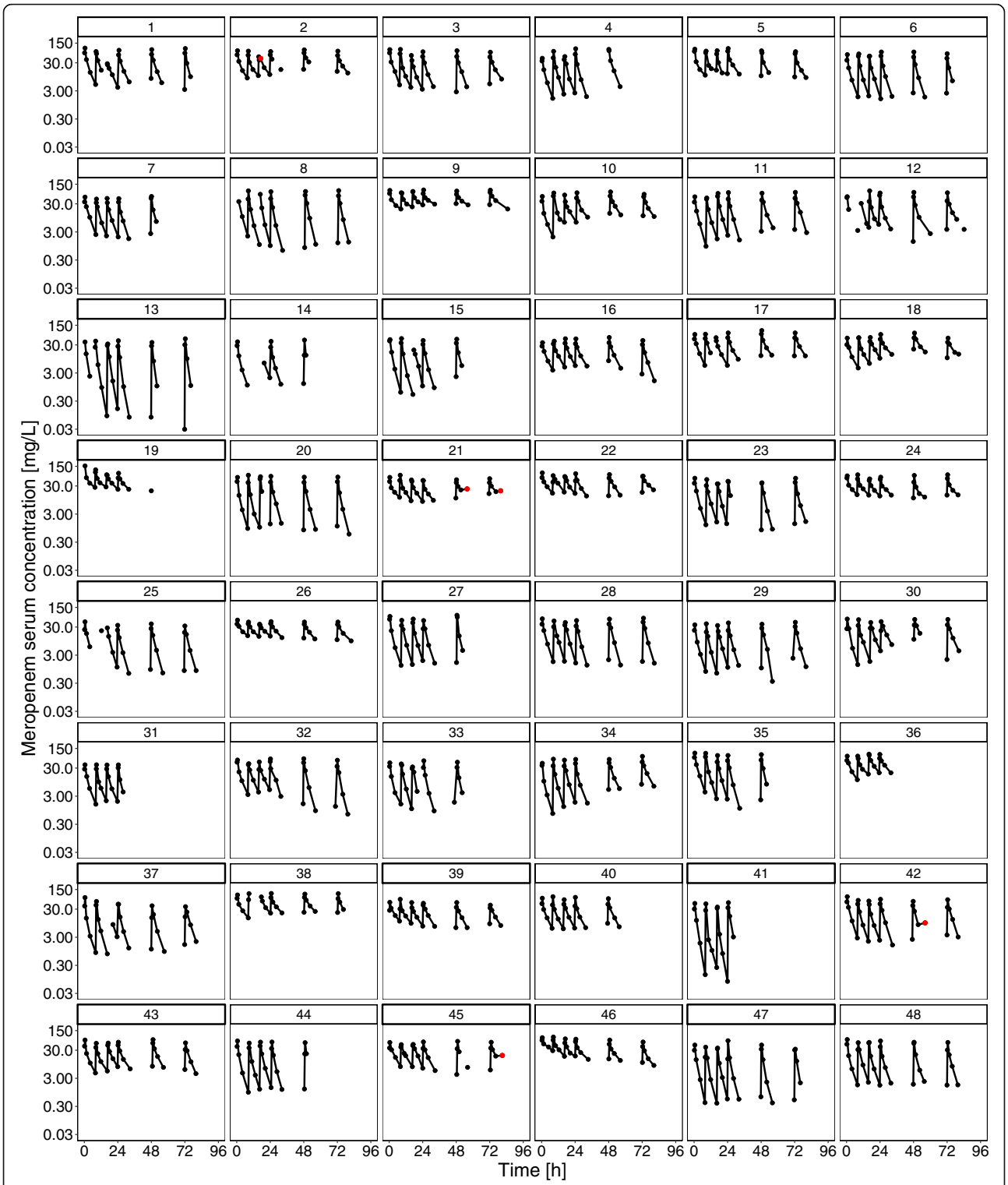

Fig. 1 Individual meropenem serum concentration-time profiles. *Number above individual plot* is patient identifier. *Circles* represent measured meropenem concentrations. *Red circles* represent meropenem concentrations excluded from analyses (0.36%; *see text*). *Lines* represent connection of consecutively sampled meropenem concentrations; that is, gaps represent non-monitored dosing intervals or missing planned meropenem concentration measurements

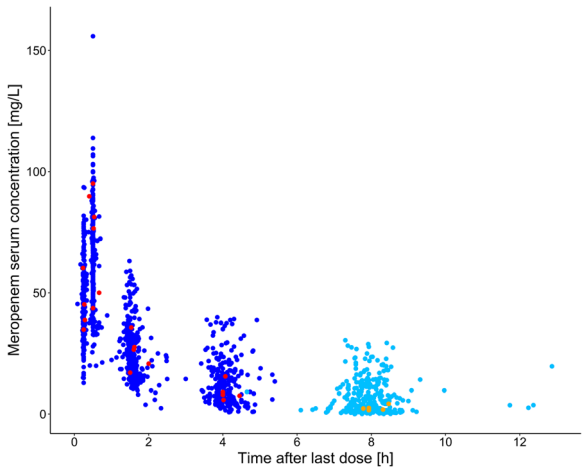

Fig. 2 Meropenem serum concentrations vs. time after last dose ($n = 48$ patients). *Dark blue/red circles* represent concentrations of patients treated with 1000 mg/2000 mg meropenem. *Light blue/orange circles* represent measured meropenem serum concentration values at the end of the actual dosing interval among patients treated with 1000 mg/2000 mg meropenem

meropenem dosing intervals; attainment of the target 50%$T_{>4\times MIC}$ was very low (7%; *see* Table 3). When extrapolating to a dose of 2000 mg, the attainment of 100%$T_{>MIC}$ was approximately twice as high as for a dose of 1000 mg (38.1% vs. 20.6%); the attainment of 50%$T_{>4\times MIC}$ was even about four times as high (27.4% vs. 7.17%) (*see* Additional file 3: PK/PD target attainment, Table S2). For doses of 1000 mg and 2000 mg, target attainment for the full MIC range from 0.25 mg/L to 8 mg/L is summarised in Additional file 3: PK/PD target attainment.

Impact of renal function on meropenem exposure and target attainment

In addition to the large inter- and intra-patient variability in meropenem exposure (i.e., C_{4h} values [*see* Fig. 3a, *y*-axis] and C_{8h} values [*see* Fig. 3b, *y*-axis]), large variability was also observed for RF, with representatives in all RF classes from severe RI to augmented RF (*see* Fig. 3, *x*-axes). In addition to the 41 non-CRRT patients, 7 CRRT patients were investigated. Whereas RF was stable (i.e., constant RF class) within the monitored study period for half of the patients ($n = 24$), RF of the other half changed between two ($n_{patients} = 21$) or even three ($n_{patients} = 3$) classes of RF. Already at the patient level, a strong dependency between median individual $CLCR_{CG}$ and C_{4h} (*see* Fig. 3a1) and C_{8h} (*see* Fig. 3b1) of the patients was found, interestingly also for the CRRT patients (*see* Fig. 3a2, b2). Also of note, in patients undergoing ECMO, meropenem concentrations were comparable with non-ECMO patients regarding their median individual $CLCR_{CG}$. Moreover, within most of the individuals with changing RF, the same tendency of higher meropenem exposure for decreased RF was observed; for example, patient 34 had worsening of RF and at the same time increasing meropenem exposure across the 4 study days (*see grey tick mark label* in Fig. 3a1, b1). At the sample level (i.e., when relating all single $CLCR_{CG}$ values as a continuous variable to meropenem exposure [C_{8h}]), a distinct relation was found, which was described by the hyperbolic function $C_{8h} = 40363 \cdot \frac{1}{(CLCR_{CG})^{2.27}}$ (*see* Fig. 3c; without C_{8h} values of patient 36). Four C_{8h} values of one patient (patient 36) were excluded from the regression because they were considerably larger than those of the remaining patients with similar RF; when including the four values of this patient, the predicted C_{8h} values in the investigated $CLCR_{CG}$ range changed only negligibly for all metrics (quantified $CLCR_{CG}$-meropenem exposure relationship, 95% CI, 95% prediction interval) (*see* Additional file 2: Regression model for risk calculation, Figure S2).

In non-CRRT patients, stratification of target attainment by the RF classes identified augmented RF to mild RI ($CLCR_{CG} > 130–60$ ml/minute) as a risk factor for

Table 2 Inter- and intra-individual variability of meropenem concentrations at specific time points

Variability level	C_X (N)	Median	2.5^{th} – 97.5^{th} Percentile
Inter-individual	*N=Number of C_X values*	*Meropenem concentration (C_X) [mg/l]*	
	C_{min} (320)	3.74	0.348-25.0
	C_{8h} (265)	3.41	0.133-24.1
	C_{4h} (265)	11.1	2.08- 39.3
Intra-individual	*N=Number of C_X ratios*	*Meropenem $\left(\frac{C_{X\_max}}{C_{X\_min}}\right)$ ratio in individual patient*	
	C_{min} (48)	2.00	1.35-7.87
	C_{8h} (48)	2.17	1.29-7.22
	C_{4h} (48)	1.60	1.17-3.70

Abbreviations: C_{min} Measured meropenem serum concentration at end of actual dosing interval, C_X Meropenem serum concentration at specific time point X of concentration-time profile

Table 3 Pharmacokinetic/pharmacodynamic target attainment for all patients not receiving continuous renal replacement therapy and stratified by renal function

Target	Renal function class	$N_{Patients}$[1]	$N_{C_x\ samples}$	PK/PD target attainment for	
				MIC=2 mg/l	MIC=8 mg/l
$50\%T_{>4xMIC}$			$C_X=C_{4h}$	$C_{4h} \geq 4x2$ mg/l, % ($N_{C_{4h}\ samples}$)	$C_{4h} \geq 4x8$ mg/l, % ($N_{C_{4h}\ samples}$)
	All	41	223	56.1 (125)	7.17 (16)
	Severe RI	1	5	100 (5)	100 (5)
	Moderate RI	12	72	93.1 (67)	12.5 (9)
	Mild RI	11	62	59.7 (37)	1.61 (1)
	Normal RF	13	60	26.7 (16)	1.67 (1)
	Augmented RF	4	24	0 (0)	0 (0)
$100\%T_{>MIC}$			$C_X=C_{8h}$	$C_{8h} \geq 2$ mg/l, % ($N_{C_{8h}\ samples}$)	$C_{8h} \geq 8$ mg/l, % ($N_{C_{8h}\ samples}$)
	All	41	223	48.4 (108)	20.6 (46)
	Severe RI	1	4	100 (4)	100 (4)
	Moderate RI	12	72	91.7 (66)	51.4 (37)
	Mild RI	12	65	46.2 (30)	4.62 (3)
	Normal RF	11	57	14 (8)	3.51 (2)
	Augmented RF	5	25	0 (0)	0 (0)

Abbreviations: $CLCR_{CG}$ Creatinine clearance estimated according to Cockcroft and Gault equation [34], *CRRT* Continuous renal replacement therapy, C_X Concentration at specific time point X of concentration-time profile, *I/R* Intermediate/resistant, *PK/PD* Pharmacokinetic/pharmacodynamic, *RF* Renal function, *RI* Renal impairment, *S/I* Susceptible/intermediate

[1]Patients were assigned to a renal function class on the basis of their median individual $CLCR_{CG}$ at the time of C_{4h} or C_{8h} determination

non-attainment of both targets (target attainment 0–46.2% for $100\%T_{>MIC}$, 0–59.7% for $50\%T_{>4\times MIC}$) (*see* Table 3) for infections with pathogens of MIC 2 mg/L. Given an MIC of 8 mg/L, meropenem treatment resulted in reliable target attainment only in the presence of severe RI ($CLCR_{CG}$ 15–29 ml/minute); thus, already moderate RI ($CLCR_{CG}$ 30–59 ml/minute) was identified as a risk factor for target non-attainment (target attainment for moderate RI 51.4% for $100\%T_{>MIC}$, 12.5% for $50\%T_{>4\times MIC}$).

Risk assessment tool

The developed risk assessment tool, the MeroRisk Calculator (beta version), is provided as Additional file 4 and is compatible with Windows operating systems and Excel version 2010 and onwards. When opening the tool, the user might be asked to enable macros, enable content and add to trusted documents. The MeroRisk Calculator is an easy-to-use, three-step Excel spreadsheet (graphical user interface) which can be used to assess the risk of target non-attainment of the PK/PD index $100\%T_{>MIC}$ for non-CRRT patients (Fig. 4a). In step 1, the user provides either the $CLCR_{CG}$ of a patient or its determinants (sex, age, total body weight, serum creatinine concentration), which will then be used to calculate $CLCR_{CG}$. In step 2, the user provides the MIC value of a determined or suspected infecting pathogen, which is used as the target meropenem concentration. In cases in which the MIC value is not available, no MIC value needs to be provided (for handling of blank MIC entry, *see* next step). In step 3, the MeroRisk Calculator computes the probability ("risk") of target non-attainment for the given $CLCR_{CG}$ and MIC value; if the MIC entry was left blank, the user then has the option to select a EUCAST MIC breakpoint for relevant bacteria [36]. The calculated risk (rounded to integer) of target non-attainment is displayed with the following three-colour coding system: green (≤10%), orange (>10% to < 50%) and red (≥50%). In addition, the tool provides a graphical illustration of the quantified $CLCR_{CG}$-C_{8h} relationship including the 95% prediction interval and predicts, on the basis of provided/calculated $CLCR_{CG}$, the most likely concentration

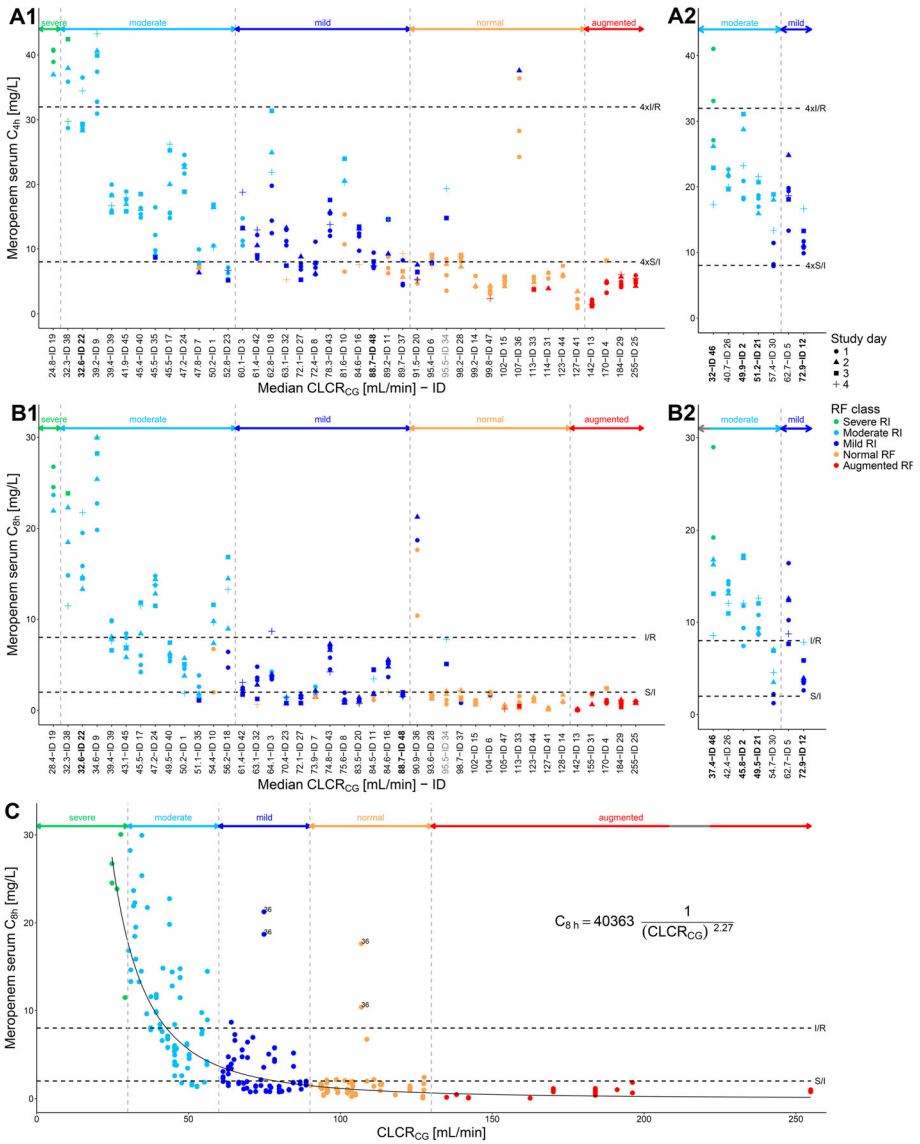

Fig. 3 Relationship between meropenem serum concentration and creatinine clearance. Meropenem serum concentrations 4 h (C_{4h}) (**a1**, **a2**) and 8 h (C_{8h}) (**b1**, **b2**, **c**) after start of infusion in non-CRRT (**a1**, **b1**, **c**) and CRRT (**a2**, **b2**) patients vs. median individual $CLCR_{CG}$ (patient level; **a**, **b**) or vs. all single $CLCR_{CG}$ (sample level; **c**) of the patients. *Tick mark of x-axis* (**a**, **b**) represents median individual $CLCR_{CG}$ at time of determined C_{4h} or C_{8h} value. *Bold tick mark labels* (**a**, **b**) represent ECMO patients. *Grey tick mark labels* (**a1**, **b1**) represent patient example mentioned in "Impact of renal function on meropenem exposure and target attainment" section of main text. *Coloured symbols* (**a-c**) represent renal function class of a patient at time of determined C_{4h} or C_{8h} value. *Shaped symbols* (**a**, **b**) represent study day on which C_{4h} or C_{8h} value was determined. *Dashed vertical lines/horizontal arrows* (**a-c**) represent separation of renal function classes. *Dashed horizontal lines* (**a-c**) represent EUCAST MIC breakpoints for Enterobacteriaceae, *Pseudomonas* spp. or *Acinetobacter* spp. (S/I 2 mg/L, I/R 8 mg/L [36]). *Data points labelled with 36* (**c**) represent four C_{8h} values of patient 36. *Black curve* (**c**) represents quantified hyperbolic relationship between $CLCR_{CG}$ and C_{8h} values, excluding data of patient 36. *Abbreviations: $CLCR_{CG}$* Creatinine clearance estimated according to Cockcroft and Gault [34]; *CRRT* Continuous renal replacement therapy; *C_{4h}* Meropenem serum concentration at 4 h after infusion start; *C_{8h}* Meropenem serum concentration at 8 h after infusion start; *ECMO* Extracorporeal membrane oxygenation; *EUCAST* European Committee on Antimicrobial Susceptibility Testing; *ID* Patient identifier; *I/R* Intermediate/resistant; *MIC* Minimum inhibitory concentration; *S/I* Susceptible/intermediate

to which meropenem concentrations after multiple dosing will decline before the next dosing (C_{8h}) (*see* Fig. 4b; for further details, *see* Additional file 2: Regression model for risk calculation, section 2).

Discussion

We found a strong relationship between RF and meropenem exposure and consequently PK/PD target attainment, and we developed a graphical user tool to predict

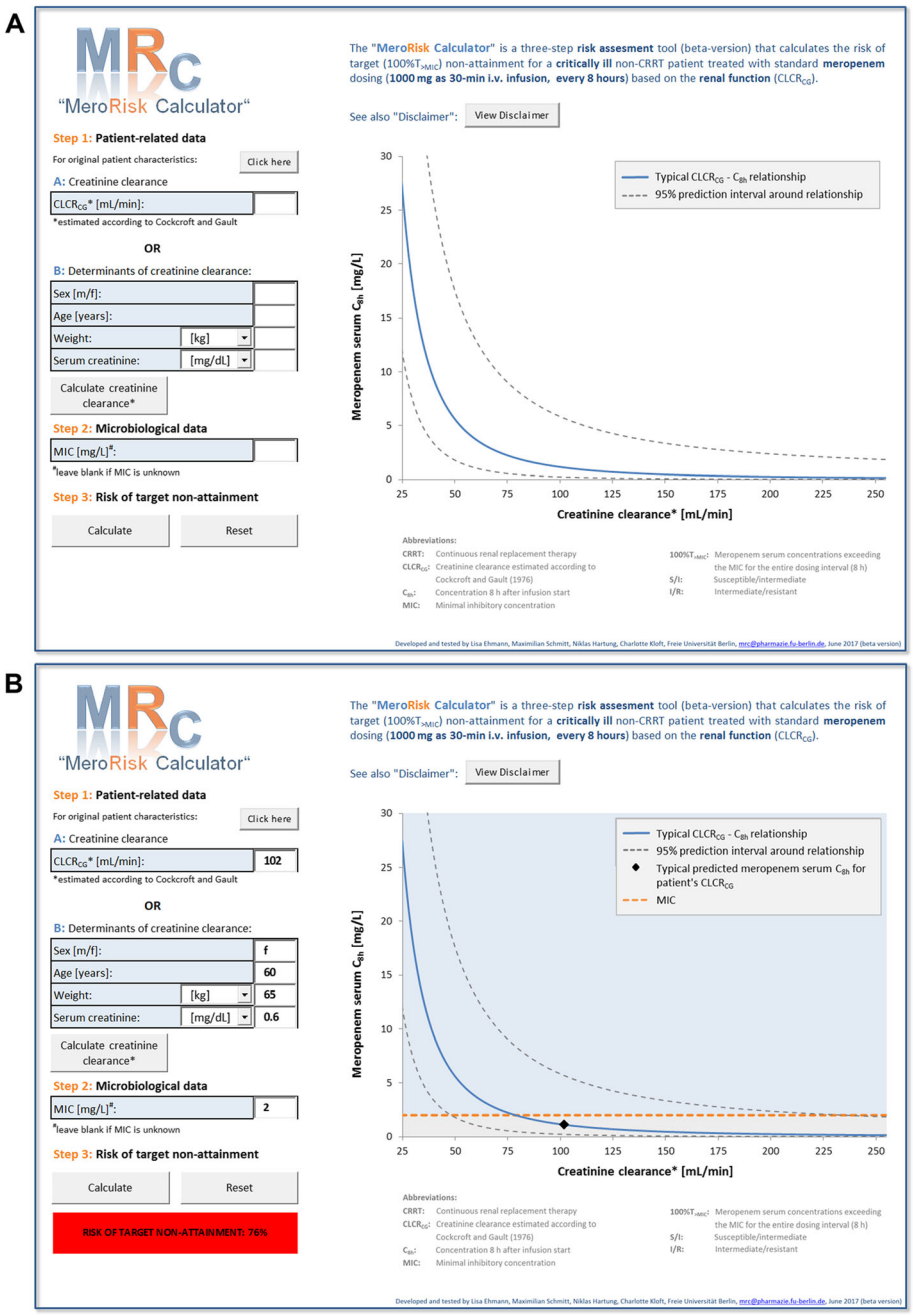

Fig. 4 Graphical user interface of the MeroRisk Calculator. **a** Display when opening the tool (i.e., without any entries). **b** Display after risk calculation for a specific patient: female, aged 60 years, body weight 65 kg, serum creatinine 0.6 mg/dl, infected with pathogen of MIC 2 mg/L. *Abbreviations: $CLCR_{CG}$* Creatinine clearance estimated according to Cockcroft and Gault equation [34], *CRRT* Continuous renal replacement therapy, *C_{8h}* Meropenem serum concentration 8 h after infusion start, *MIC* Minimum inhibitory concentration

the risk of target non-attainment under meropenem standard dosing based on an ICU patient's RF.

This work was focused on the analysis of the standard dosing regimen for meropenem (1000 mg administered as 30-minute infusions every 8 h) as the approved and still most frequently used dosing regimen in ICUs [12, 45]. To best represent the variety of different ICU patients, the analysis was based on extensively sampled data of a prospective observational study including a large number of patients with highly heterogeneous patient-specific factors from different ICUs, though at one single study centre.

We showed large inter-individual variability in meropenem exposure, which was in accordance with previous studies [22, 23]. The larger variability in concentrations of the late phase compared with the earlier phase of the concentration-time profile (variability: C_{min}, $C_{8h} > C_{4h}$) suggested that PK variability was due to variability in drug elimination processes rather than in drug distribution. This finding is supported by population PK analyses that identified larger inter-individual variability on the PK parameter clearance than on volume of distribution [24, 28]. The relatively long observation period of 4 days and the large number of samples collected per patient in our study additionally enabled the quantification of intra-individual variability in meropenem exposure. Its large value led to the hypothesis that meropenem exposure is influenced by certain time-varying patient-specific factors such as confirmed in the present work by longitudinally measured $CLCR_{CG}$.

Our PK/PD analysis demonstrated that meropenem standard dosing did not achieve the desired meropenem PK/PD targets $100\%T_{>MIC}$ and $50\%T_{>4\times MIC}$ in a considerable fraction of patients. For pathogens of MIC 2 mg/L, which represents the upper limit of the susceptible range for many important bacteria [36], meropenem exposure was inadequate in every second dosing interval monitored. In line with our work, Carlier et al. found similar results for the target $100\%T_{>MIC}$ given the same MIC value (target attainment 55%) [25]. For infections with less susceptible bacteria of MIC 8 mg/L (I/R breakpoint [36]), which have been shown to commonly occur in ICUs [8, 9], target non-attainment was high, with four of five dosing intervals resulting in sub-therapeutic concentrations (target $100\%T_{>MIC}$). The target attainment analysis with the two targets $100\%T_{>MIC}$ and $50\%T_{>4\times MIC}$ revealed similar results. Of note, current knowledge on PK/PD targets for meropenem in heterogeneous ICU populations is limited, and a PK/PD target for this special patient population has not been derived yet. In relation to other PK/PD targets derived for meropenem in diverse clinical studies (e.g., $19.2\%T_{>MIC}$ and $47.9\%T_{>MIC}$ [21], $54\%T_{>MIC}$ [19] and $76\text{-}100\%T_{>MIC}$ [20]), the two PK/PD targets selected for our analysis were at the upper end (i.e., stricter). The selection of the higher targets seemed reasonable, given (1) limited knowledge on an adequate PK/PD target for heterogeneous ICU populations and (2) the high severity of illness (median APACHE $II_{first\ study\ day}$ 27) and the high proportion of patients with transplants (~58%) in the evaluated population. Indeed, these targets have been reported to be commonly used in clinical practice for ICU patients [40]. However, owing to the limited knowledge of PK/PD targets in ICU patients, there is a crucial need to explore which PK/PD target is best related to clinical outcome in critically ill patients in a prospective clinical trial. Further analyses should also be aimed at investigating differences in PK/PD targets between, for example, different patient sub-groups (e.g., with vs. without transplants), different states of severity of illness or different types of infecting bacteria (gram-positive vs. gram-negative) in a sufficiently large number of patients.

In line with other studies, we identified RF determined by $CLCR_{CG}$ to influence meropenem exposure [26, 27, 29–31]. On the basis of the large number of longitudinally measured meropenem serum concentrations and $CLCR_{CG}$ values covering the full spectrum of RF classes, we were able to quantify a hyperbolic relationship between $CLCR_{CG}$ and meropenem exposure. The present study also included special patient groups such as CRRT and ECMO patients. For CRRT patients, authors of other publications identified measured CLCR determined via 24-h urine collection [28] or residual diuresis [46] as influencing factors on meropenem exposure, both requiring time-consuming urine collection. Although our analysis included a rather small number of CRRT patients, it revealed $CLCR_{CG}$ as a potential determinant of meropenem exposure which can be assessed more easily and quickly in clinical practice than RF markers determined via 24-h urine collection. This finding requires further investigation with a larger number of patients under a well-designed protocol. For the six ECMO patients, the relationship between $CLCR_{CG}$ and meropenem concentrations did not seem different from that of the remaining patients, suggesting that ECMO therapy did not have a strong impact on meropenem serum exposure. This is in line with findings reported by Donadello et al. showing no significant difference between the PK parameters of ECMO and control non-ECMO ICU patients [47].

The impact of RF on the target attainment was overall in accordance with the results of a recent publication by Isla et al. [33], in which the probability of attaining the target $100\%T_{>MIC}$ was analysed for three specific $CLCR_{CG}$ values: Target attainment was 51% for $CLCR_{CG}$ 35 ml/minute (vs. 51% in our study for $CLCR_{CG}$ range 30–59 ml/minute), 3% for $CLCR_{CG}$ 71 ml/minute (vs. 4.6%, 60–89 ml/minute) and 0% for $CLCR_{CG}$ 100 ml/minute (vs. 3.5%, 90–129 ml/minute) for an MIC 8 mg/L. Because the present study included patients covering the full spectrum of RF classes, additional investigation of target attainment in extreme RF classes (severe RI, augmented RF) was possible. For infections with bacteria of MIC 2 mg/L, augmented RF to mild RI was identified as a risk factor of target non-attainment; given bacteria of MIC 8 mg/L, moderate RI was an additional risk factor. These findings imply the need for dosing intensification in patients identified to be at risk

of target non-attainment, such as by increasing the dose or prolonged up to continuous infusion, which is currently under clinical investigation; whereas some previous studies have associated continuous infusion with improved clinical cure rates [48, 49], others have not shown a difference in clinical outcome when comparing continuous with intermittent dosing [50]. In this PK/PD analysis, the only patient group that reliably reached the PK/PD targets was the subgroup with severe RI. Notably, these patients also received 1000 mg meropenem every 8 h as 30-minute infusions and thus received higher doses than recommended in the summary of product characteristics (half of indicated dose every 12 h for patients with $CLCR_{CG}$ 10–25 ml/minute [12]).

To enable the practical application of the quantified relationship between RF and meropenem exposure and consequently target attainment, we developed a risk assessment tool in a commonly available and known software (*see* Additional file 4: MeroRisk Calculator, beta version). This easy-to-use Excel tool allows assessment of the risk of target non-attainment for non-CRRT patients displaying RF within a broad range (25–255 ml/minute) and receiving standard dosing of meropenem (1000 mg every 8 h as 30-minute infusions). We implemented the risk of target non-attainment of meropenem depending on creatinine clearance according to the Cockcroft and Gault equation ($CLCR_{CG}$ [34]) and not depending on creatinine clearance determined by 24-h urine collection ($CLCR_{UC}$ [51]), because $CLCR_{CG}$ can be assessed more easily in clinical practice, and the relationship between $CLCR_{UC}$ and meropenem exposure was not better than between $CLCR_{CG}$ and meropenem exposure (*see* Additional file 2: Figure S3). To apply the tool, the user needs to provide only the $CLCR_{CG}$ or its determinants (i.e., sex, age, total body weight and the routinely determined laboratory value serum creatinine). In addition, the MIC value of a bacterium determined or suspected in the investigated patient needs to be provided. Should MIC values not be available, the user has the option to select an MIC breakpoint for important pathogens from the EUCAST database. Because only a limited number of patients with augmented RF or severe RI were included in this analysis, the uncertainty of the $CLCR_{CG}$-meropenem exposure relationship implemented in the MeroRisk Calculator is higher for the extremes of the RF spectrum. Furthermore, the user of the tool needs to keep in mind that in addition to $CLCR_{CG}$, other factors might influence meropenem exposure. To visualise the prediction uncertainty (i.e., uncertainty in the $CLCR_{CG}$-meropenem exposure relationship combined with the variability in C_{8h} values) of the calculated meropenem C_{8h} value for a patients $CLCR_{CG}$, the prediction interval around the $CLCR_{CG}$-meropenem exposure relationship is additionally provided in the risk assessment tool. Of particular note, using the MeroRisk calculator does not require the measurement of a meropenem concentration of a patient. In case of available meropenem concentrations in a patient, use of therapeutic drug monitoring is encouraged to aid therapeutic decision making [52]. The current beta version of the MeroRisk Calculator is intended to be used in the setting of clinical research and training. As a next step, comprehensive prospective validation of the risk calculator in clinical research setting is warranted.

Conclusions

Our PK/PD analysis demonstrated large inter- as well as intra-patient variability in meropenem serum exposure after standard dosing in critically ill patients. Standard dosing was likely to result in sub-therapeutic meropenem exposure in a considerable fraction of critically ill patients, especially when assuming infections caused by less susceptible bacteria commonly encountered in these patients. $CLCR_{CG}$ was identified as a vital clinical determinant of meropenem exposure and consequently target attainment. In the future, the newly developed risk assessment tool as a graphical user interface (*see* Additional file 4: MeroRisk Calculator) might, if all requirements are met, be beneficial in clinical practice for therapeutic decision making. An ICU patient's risk of target non-attainment, given his/her RF and the MIC value of the infecting pathogen, would already be accessible when no meropenem concentration measurement is available, such as prior to the start of antibiotic therapy. Our findings indicate that dosing intensification might be needed, depending on a patient's RF and the susceptibility of the infecting pathogen, and that optimised dosing regimens should be further investigated with respect to increased clinical benefit and reduced development of resistance.

Additional files

Additional file 1: Study design.pdf. (PDF 170 kb)
Additional file 2: Regression model for risk calculation.pdf. (PDF 475 kb)
Additional file 3: PK/PD target attainment.pdf. (PDF 65 kb)
Additional file 4: MeroRisk Calculator.xltm. (XLTM 330 kb)

Abbreviations

APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: Acute respiratory distress syndrome; BMI: Body mass index; C_{4h}: Meropenem serum concentration 4 h after infusion start; C_{8h}: Meropenem serum concentration 8 h after infusion start; $CLCR_{CG}$: Creatinine clearance estimated according to Cockcroft and Gault equation; $CLCR_{UC}$: Creatinine clearance determined by 24-h urine collection; C_{min}: Minimum meropenem concentration; CRP: C-reactive protein; CRRT: Continuous renal replacement therapy; CV: Coefficient of variation; CVVH: Continuous venovenous haemofiltration; CVVHD: Continuous venovenous haemodialysis; CVVHDF: Continuous venovenous haemodiafiltration; C_X: Meropenem serum concentrations at specific time points; ECMO: Extracorporeal membrane oxygenation; EUCAST: European Committee on Antimicrobial Susceptibility Testing; I/R: Intermediate/resistant; ICU: Intensive care unit; IL: Interleukin;

MIC: Minimum inhibitory concentration; PD: Pharmacodynamic(s); PK: Pharmacokinetic(s); RF: Renal function; RI: Renal impairment; S/I: Susceptible/intermediate; SOFA: Sepsis-related Organ Failure Assessment; $\%T_{>MIC}$: Percentage of time that drug concentration exceeds the minimum inhibitory concentration; $\%T_{>4\times MIC}$: Percentage of time that drug concentration exceeds four times the minimum inhibitory concentration

Funding
This study was supported by a Mérieux research grant (Institut Mérieux, Lyon, France). The design, collection, analysis and interpretation of data, as well as the writing and publication of the manuscript, were done by the authors without participation or influence from the funding source.

Availability of data and materials
The datasets generated and/or analysed during the present study are not publicly available, but they are available from the corresponding author on reasonable request.

Authors' contributions
MZ, CS, MV, LF and JZ designed the clinical study. MZ, CS and JZ conducted the clinical study. BM, JZ and MV performed assays. LE, IKM and CK designed data analysis. LE and CK analysed data. LE, MVS, NH and CK developed the tool. LE, MZ, IKM, JZ and CK discussed results. LE drafted the manuscript. LE, MZ, IKM, CS, BM, MVS, NH, WH, MV, LF, JZ and CK commented on and approved the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Ethics approval and consent were obtained from the Institutional Review Board of the Medical Faculty of the LMU Munich, Germany (registration number 428-12). Written informed consent to participate was obtained from all patients or their legal representatives.

Consent for publication
Not applicable.

Competing interests
WH declares receiving research grants from an industry consortium (AbbVie Deutschland GmbH & Co. KG, Boehringer Ingelheim Pharma GmbH & Co. KG, Grünenthal GmbH, F. Hoffmann-La Roche Ltd, Merck KGaA and SANOFI). CK declares receiving research grants from an industry consortium (AbbVie Deutschland GmbH & Co. KG, Boehringer Ingelheim Pharma GmbH & Co. KG, Grünenthal GmbH, F. Hoffmann-La Roche Ltd, Merck KGaA and SANOFI) as well as research grants from the Innovative Medicines Initiative-Joint Undertaking (DDMoRe) and Diurnal Ltd. The other authors declare that they have no competing interests.

Publisher's Note

Author details
[1]Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universitaet Berlin, Kelchstrasse 31, 12169 Berlin, Germany. [2]Graduate Research Training Program PharMetrX, Berlin/Potsdam, Germany. [3]Department of Anaesthesiology, University Hospital, LMU Munich, Munich, Germany. [4]Institute of Laboratory Medicine, University Hospital, LMU Munich, Munich, Germany. [5]Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg, Heidelberg, Germany. [6]Institute of Mathematics, Universitaet Potsdam, Potsdam, Germany.

Received: 26 June 2017 Accepted: 29 August 2017
Published online: 21 October 2017

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