

Single- and multiple-dose pharmacokinetics and total removal of colistin in critically ill patients with acute kidney injury undergoing prolonged intermittent renal replacement therapy

Julius J. Schmidt^{1*†}, Ann-Kathrin Strunk^{1†}, Sascha David¹, Stefanie M. Bode-Böger², Jens Martens-Lobenhoffer², Wolfgang Knitsch³, Stephan Scherneck⁴, Tobias Welte⁵ and Jan T. Kielstein^{1,6}

¹Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany; ²Institute of Clinical Pharmacology, Otto von-Guericke-University of Magdeburg, Magdeburg, Germany; ³Department of General, Visceral and Transplant Surgery, Hannover Medical School, Hannover, Germany; ⁴Institute of Pharmacology, Toxicology and Clinical Pharmacy, Technical University of Braunschweig, Braunschweig, Germany; ⁵Department of Pulmonary Medicine, Hannover Medical School, Hannover, Germany; ⁶Medical Clinic V | Nephrology | Rheumatology | Blood Purification, Academic Teaching Hospital Braunschweig, Braunschweig, Germany

*Corresponding author. Tel: +49511-532-6319; Fax: +49511-532-2144; E-mail: schmidt.julius@mh-hannover.de
†J. J. S. and A.-K. S. contributed equally to the manuscript and are both considered first authors.

Received 22 July 2018; returned 14 August 2018; revised 5 November 2018; accepted 13 November 2018

Background: Owing to the emerging problem of MDR bacteria, interest in 'old' antibiotics such as colistin has re-emerged. However, research on the dosing of colistin in patients undergoing renal replacement therapy (RRT), such as prolonged intermittent renal replacement therapy (PIRRT), is scarce.

Objectives: The aim of this study was to evaluate single- and multiple-dose pharmacokinetics of colistin and its prodrug colistin methanesulfonate in ICU patients with acute kidney injury (AKI) undergoing PIRRT.

Methods: We performed a prospective clinical pharmacokinetic single- and multiple-dose study. Eight ICU patients with AKI undergoing treatment with PIRRT and receiving intravenous colistin were studied on day 1 and days 5–9 of treatment, depending on the timing of dialysis. Six million IU (MIU) of colistin methanesulfonate was administered 8 h prior to the PIRRT session followed by 3 MIU every 8 h. The study was registered under clinical-trials.gov (NCT02556190).

Results: PIRRT removed a considerable amount of colistin and colistin methanesulfonate with a median dialyser plasma CL of 70.1 mL/min (IQR 36.6–96.2) for colistin and 69.3 mL/min (IQR 56.3–318.7) for colistin methanesulfonate. The median amount of colistin in the total collected dialysate was 154 mg (IQR 105–175), corresponding to about 50% of the daily dose. Median colistin peak concentrations accumulated from 5.79 mg/L (IQR 4.14–8.79) on day 1 to 9.49 mg/L (IQR 8.39–10.41) on days 5–9. C_{max} was significantly and inversely correlated with body weight.

Conclusions: PIRRT eliminates about half of the daily administered colistin dose. Even a 6 MIU loading dose of colistin methanesulfonate may not ensure immediate sufficient colistin plasma levels in all critically ill patients. However, we measured significant colistin accumulation, suggesting that the dose of colistin methanesulfonate should be adjusted according to body weight and RRT intensity.

Introduction

Colistin, a polymyxin antibiotic first introduced in the 1950s, was almost abandoned for decades owing to its nephrotoxicity and neurotoxicity. Its inactive prodrug, colistin methanesulfonate, which is hydrolysed to colistin *in vivo*, is administered for intravenous use. About 79 mg of colistin methanesulfonate or 1 million IU (MIU) convert into 33 mg of colistin. Colistin and colistin methanesulfonate both share a low V (colistin = 0.17 L/kg and colistin

methanesulfonate = 0.19 L/kg). Whereas colistin methanesulfonate is excreted mainly via the kidneys, colistin is eliminated by extra-renal pathways in healthy humans.¹ However, a dose adaptation with regard to the patient's kidney function or the usage of renal replacement therapy (RRT) is necessary.² A molecular weight of 1743 Da for colistin methanesulfonate and 1163 Da for colistin, as well as a protein binding of 55%, allow dialysability of both substances.³ As shown in *in vitro* experiments, colistin has

concentration-dependent bactericidal activity and works best when the bacterial MIC is exceeded many times over.⁴

Colistin is a valuable treatment option for critically ill patients in infections with MDR *Pseudomonas aeruginosa* and *Acinetobacter* spp.⁵ However, drug dosing in critically ill patients with concomitant RRT-dependent acute kidney injury (AKI) has not been fully evaluated.⁶ Additionally, drug development is usually focused on lean patients and dose adjustments in possibly obese and volume-overloaded ICU patients are currently underrepresented,⁷ while insufficient dosing may be an important contributing factor to the high mortality rate of septic patients with RRT-dependent AKI.⁸

Prolonged intermittent renal replacement therapy (PIRRT), also known as extended dialysis, is one of the RRT modalities used in critically ill patients. This cost-effective RRT modality is increasingly used on medical ICUs.⁹ Antibiotic dosing during PIRRT requires adapted dosing strategies but pharmacokinetic data regarding antibiotic dosing is scarce, especially with respect to the dosage of colistin in critically ill patients with AKI during PIRRT.¹⁰

The aim of our study is to investigate single- and multiple-dose pharmacokinetics of colistin in critically ill patients with AKI undergoing PIRRT to further dosing recommendations.

Methods

Patients and study protocol

We enrolled eight adult anuric patients [two female and six male, median age = 48 years (IQR 35–63) and median BMI = 20 kg/m² (IQR 18–27); Table 1] with an indication for colistin therapy during dialysis-dependent AKI. Actual body weight (ABW) was assessed at ICU administration; ideal body weight (IBW) and adjusted body weight (AjBW) were calculated using the following equations: $IBW_{men} = 50\text{ kg} + 2.3\text{ kg} \times [\text{height (in)} - 60]$, $IBW_{women} = 45.5\text{ kg} + 2.3\text{ kg} \times [\text{height (in)} - 60]$ and $AjBW = IBW + 0.4 \times (ABW - IBW)$.¹¹ Every patient received a loading dose of 6 MIU of colistin methanesulfonate on day 1, followed by a dose of 3 MIU every 8 h. The drug (Colistimethat-Natrium Infectopharm 1 MIU) was obtained from Infectopharm Arzneimittel GmbH (Heppenheim, Germany). The choice of the antibiotic drug treatment was based on clinical grounds and was at the discretion of the treating physician.

The first dose of colistin methanesulfonate had been infused intravenously over a period of 30 min, 8 h before RRT was started. PIRRT was performed as haemodialysis in all patients using the GENIUS[®] batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany) with a polysulfone high-flux dialyser [F60S (surface area, 1.3 m²), Fresenius Medical Care]. The technical details of the system are explained elsewhere.¹² The prescribed dialysis time was 8 h per session, blood and dialysis flow were set at 200 mL/min and the ultrafiltration rate was adjusted to the patient's clinical needs. Anticoagulation was performed either by heparin or citrate. Vascular access was achieved by a double-lumen catheter inserted either into the internal jugular or the femoral vein.

Ethics

Written informed consent was obtained from each patient or the legal representative of the patient. The study protocol was approved by the Hannover Medical School Ethics Committee (project #6446) and was performed in accordance with the Declaration of Helsinki and German federal guidelines. The study was registered under clinicaltrials.gov (NCT02556190).

Sampling and analysis

Blood samples were taken before the start of the infusion of the loading dose and at the end of the infusion of the drug. The duration of the

Table 1. Patient characteristics of the study cohort, N = 8

Age (years), median (IQR)	48 (35–63)
Female/male, n/n	2/6
Weight (kg), median (IQR)	63 (55–80)
BMI (kg/m ²), median (IQR)	20 (18–27)
SAPS II, median (IQR)	63 (52–71)
Discharge/death during hospital stay, n/n	2/6
Daily dialysis dose (L/day), median (IQR)	68.8 (62.6–85)
Treatment time (min), median (IQR)	430 (417–442)
Urine output (mL/day), median (IQR)	0 (0–42)
Volume of ultrafiltration (mL), median (IQR)	1744 (375–2047)
Pathogen detected, n (overall MIC range)	
<i>Pseudomonas</i> spp.	6 (1–2 mg/L)
<i>Klebsiella</i> spp.	3 (0.5–2 mg/L)

SAPS, Simplified Acute Physiology Score.

infusion was always 30 min. In addition, blood samples were taken 0.5, 1, 2, 4 and 6 h after the end of the infusion of the loading dose, directly before the next infusion of colistin (8 h after the first infusion) and at the end of the second infusion. Further samples were taken before the start of PIRRT and 0.25, 0.5, 1, 2, 4 and 6 h after the start of the PIRRT, as well as before the end of PIRRT. Moreover, a blood sample at the end of the third drug infusion was taken. To determine the dialyser CL (CL_{dial}), pre- and post-dialyser blood samples were drawn 30 min after the start of PIRRT and towards the end of the dialysis session. Lastly, we took a trough level after 24 h, as well as samples from the dialysate and ultrafiltration. For the collection of the pre- and post-dialyser samples, ultrafiltration was stopped in order to avoid measurement errors. The measurements mentioned above were performed during the first colistin treatment day (single-dose pharmacokinetics) as well as after five days of colistin therapy (multiple-dose pharmacokinetics).

The CL_{dial} was calculated based on the plasma perfusion rate and extraction ratio $(C_a - C_v)/C_a$, using the equation $CL_{dial} = Q_e \times (C_a - C_v)/C_a$, where Q_e is the effective plasma perfusion rate of the dialyser [dialyser blood flow rate $\times (1 - \text{haematocrit})$] and C_a and C_v are arterial and venous dialyser plasma drug concentrations, respectively.

Samples were centrifuged immediately at 1500 g for 15 min at 4°C. Plasma was separated and stored at –80°C until analysis.

Chemical assays

Colistin and colistin methanesulfonate concentrations were determined separately by HPLC combined with tandem MS (LC-MS/MS),¹³ as recently used in its modified form¹⁴ in the Institute of Clinical Pharmacology, Otto-von-Guericke-University of Magdeburg, Germany.

Statistical analysis

Calculations were computed in R (R Core Team 2016), version 3.3.1 or GraphPad Prism. AUC was calculated using the trapezoidal rule. All data are reported as median and IQR unless stated otherwise. Non-continuous data were compared performing a Wilcoxon–Mann–Whitney test; significance level was set to $P < 0.05$.

Results

Four of the eight patients enrolled in the study died prior to the second study treatment. Two further patients died after receiving the second study treatment. Two patients were discharged alive. All

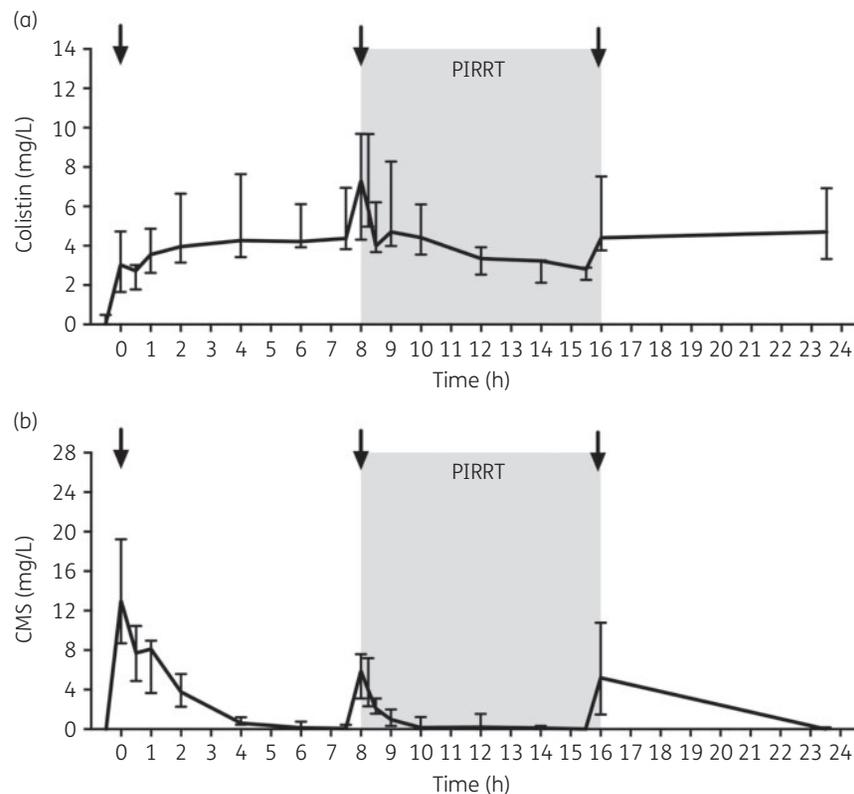


Figure 1. Time course of colistin (a) and colistin methanesulfonate (b) during single-dose pharmacokinetics. Arrows mark the colistin methanesulfonate dosing intervals. Data from $n = 8$ represented by median (IQR). CMS, colistin methanesulfonate.

patients received a median dialysis dose of 68.8 L/day (62.6–85) during the study period. The median dialysis time during the study was 430 min (417–442) per day. Median blood and counter-current dialysate flow were 200 mL/min. Peak levels after the colistin methanesulfonate loading dose of 6 MIU were 13.02 mg/L (8.7–19.24) for colistin methanesulfonate and 5.79 mg/L (4.14–8.79) for colistin (Figure 1a and b). Additional pharmacokinetic key parameters are given in Table 2. After five to nine treatment days with 3 MIU of colistin methanesulfonate every 8 h, colistin methanesulfonate peak levels were 10.23 mg/L (8.12–12.32) and colistin peak levels 9.49 mg/L (8.39–10.41) (Figure 2a and b). We found a total amount of 154 mg (105–175) colistin in the collected dialysate per treatment. No significant amounts of colistin methanesulfonate could be detected in the spent dialysate. Colistin AUC_{0-24} was 104.7 mg·h/L (80.6–148.7) on the first treatment day and 149 mg·h/L (106.9–189.2) in steady-state. Plasma CL_{dial} was 70.1 mL/min (36.6–96.2) for colistin and 69.3 mL/min (56.3–318.7) for colistin methanesulfonate. A colistin median trough concentration of 5.77 mg/L (4.15–7.68) was measured in the multiple-dose analysis. Figure 3 shows correlations of single-dose colistin AUC as well as C_{max} levels and ABW [Figure 3a, $r^2_{AUC} = 0.29$ ($P = 0.17$) and $r^2_{C_{max}} = 0.2$ ($P = 0.03$)], IBW [Figure 3b, $r^2_{AUC} = 0.31$ ($P = 0.15$) and $r^2_{C_{max}} = 0.26$ ($P = 0.01$)] or AjBW [Figure 3c, $r^2_{AUC} = 0.33$ ($P = 0.13$) and $r^2_{C_{max}} = 0.22$ ($P = 0.02$)]. While correlations of body weight and AUC were not significant in this study, C_{max} was significantly and inversely correlated with body weight. Renal side effects could not be evaluated in this patient population already suffering from AKI requiring RRT. However, no patient regained kidney function during the study period.

Discussion

Our study provides prospective data, including the total amount of the eliminated drug and pharmacokinetics of colistin during PIRRT in critically ill patients with AKI. The pharmacokinetic data obtained show the following findings: (i) colistin and colistin methanesulfonate were significantly removed during PIRRT (corresponding to about 50% of the daily administered dose as colistin methanesulfonate 9 MIU is equivalent to colistin base activity 300 mg/day); (ii) even after a loading dose of 6 MIU of colistin methanesulfonate, therapeutic plasma levels of colistin could not be achieved in all patients within the first 8 h of therapy; (iii) body weight showed an inverse correlation to the achieved single-dose peak plasma concentrations (Figure 3), suggesting that colistin prescription needs to be adjusted to body weight in critically ill patients; and (iv) there was an accumulation of colistin as indicated by a rise in colistin peak levels after several days of colistin treatment with 3 MIU every 8 h, which might lead to adverse events. However, no side effects could be detected in our study.

EUCAST determines the MIC for colistin-susceptible pathogens as ≤ 2 mg/L.¹⁵ Therefore, an average steady-state concentration of 2.5 mg/L, resulting in an AUC_{0-24} target of 60 mg·h/L, was suggested as a dosing target in recent population pharmacokinetic modelling.¹⁶ However, recent evidence suggests that $fAUC/MIC$ correlates best with the efficacy of colistin therapy, yet the target $fAUC/MIC$ varies, ranging from 10 to 50 depending on the pathogen species to treat.¹⁷ In an ideal setting, the pharmacokinetic/pharmacodynamic target should be high enough to allow effective

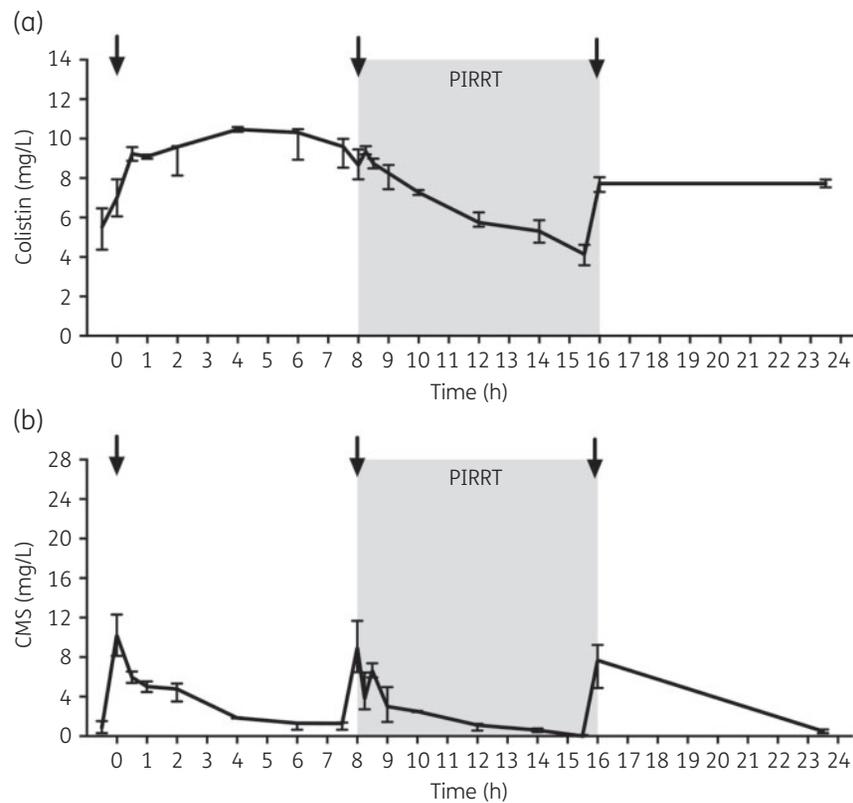


Figure 2. Time course of colistin (a) and colistin methanesulfonate (b) during multiple-dose pharmacokinetics. Arrows mark the colistin dosing intervals. Data from $n = 4$ represented by median (IQR). CMS, colistin methanesulfonate.

treatment of the infection without leading to long-term residual renal failure.

Side effects of colistin therapy mainly include a decrease in kidney function as well as neurotoxicity. Whereas a recent study showed a substantial increase in AKI risk in critically ill patients treated with colistin,¹⁸ data from critically ill patients treated with high doses of colistin showed high clinical cure rates of up to 82% and low renal toxicity after a 9 MIU loading dose and a 9 MIU daily maintenance dose.¹⁹

The elimination of colistin and colistin methanesulfonate by RRT has been understudied, considering how long the drug has been in clinical use. A recent study of 10 patients undergoing intermittent haemodialysis (IHD) showed significant elimination of about 30% of the 5 MIU administered colistin methanesulfonate during one 4 h dialysis.²⁰ Garonzik et al.¹⁶ published pharmacokinetic calculations that underline the need for up to 6-fold higher doses in patients undergoing continuous RRT, compared with IHD patients. The colistin CL in patients undergoing continuous veno-venous haemodiafiltration can be up to 137 mL/min^{21,22} and may result in failing dosing goals when 2 MIU of colistin methanesulfonate are given every 8 h.²³ Recently, a study of eight critically ill patients with IHD showed significant colistin elimination and recommended a dose of 4.5 MIU on IHD days.²⁴ However, although increasingly applied, clinical data on patients receiving PIRRT, a relatively recent RRT method, are absent owing to the high vulnerability of this patient population.

Our data suggest a significant inverse correlation of body weight and peak concentrations on the first prescription day

(Figure 3), which implies a risk of insufficient drug dosing in obese or volume-overloaded ICU patients if a fixed ('one size fits all') dosing approach is followed. Presumably, C_{max} is best correlated with the IBW [$r_{2C_{max}} = 0.26$ ($P = 0.01$)], whereas AUC, in our study, was not significantly correlated with body weight [ABW, $r_{2AUC} = 0.29$ ($P = 0.17$); IBW, $r_{2AUC} = 0.31$ ($P = 0.15$); and AjBW, $r_{2AUC} = 0.33$ ($P = 0.13$)]. As overdosing in obese patients is described when the absolute body weight is used, other forms of weight adjustment should be explored.²⁵ AjBW or IBW guidance in dosing recommendations may be preferable. However, it remains unclear how to best adapt drug dosing of colistin to the body mass of critically ill patients. The number of patients in this study does not allow a firm conclusion other than that the 'one size fits all' approach seems imprudent.

When separated into high and low body-weight groups, our patients did not show a significant difference in AUC/MIC, the preferred therapy target for colistin (median AUC/MIC_{heavy}, 91.6; AUC/MIC_{low}, 149.7; $P = 0.1$). However, two high-body-weight patients did not achieve an AUC/MIC goal of up to 50, while in some patients in the low body-weight group the AUC/MIC was seven times as high (Figure S1, available as [Supplementary data](#) at JAC Online).

Six of our patients suffered from MDR *Pseudomonas* infection. As the breakpoint concentration of 2 mg/L was barely achieved by some of our patients after the loading dose of 6 MIU, the administration of 9 MIU, as recommended by some authors,¹⁹ should be considered even in dialysis-dependent patients with severe infections, especially in cases where *Pseudomonas* spp. with high MIC

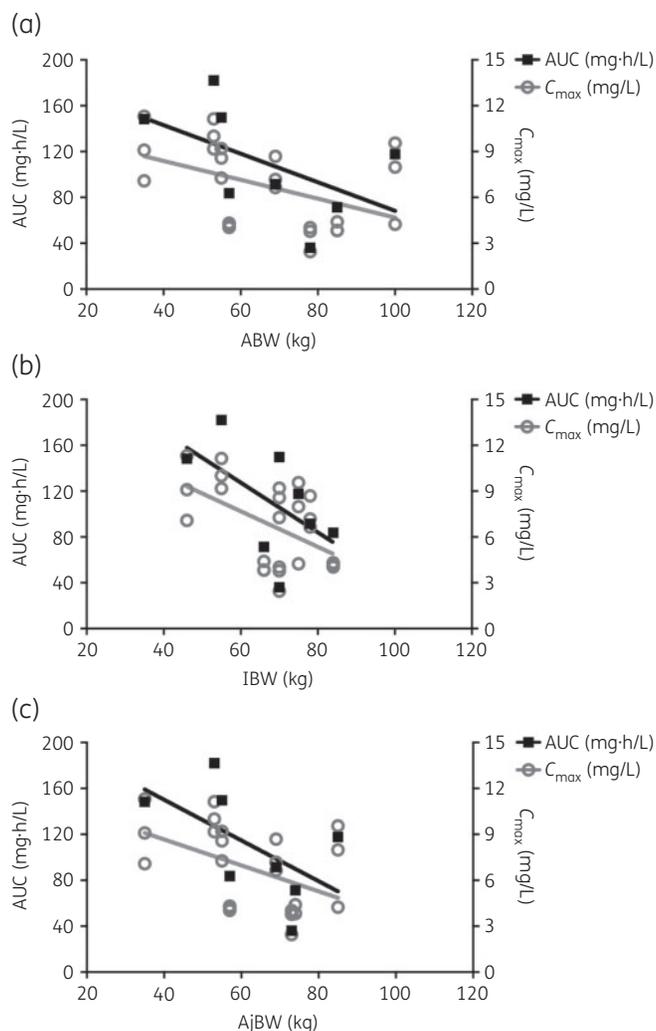


Figure 3. Correlations of single-dose colistin AUC (mg-h/L; left-hand y-axis) as well as C_{max} levels (mg/L; right-hand y-axis) and ABW (a), IBW (b) or AjBW (c).

and/or lung infection have been identified. However, achieving an early therapy goal may be difficult in colistin therapy, as conversion of colistin methanesulfonate into active colistin can be slow in critically ill patients, with maximum concentrations occurring up to 7 h after the dose.¹⁶

Our study has some important limitations. First, we treated our patients in different PIRRT intensities according to their individual needs e.g. volume removal, which reflects the diversity of today's ICU population but, similarly to body weight, may affect the achieved colistin plasma levels. A methodological shortcoming is the fact that owing to the fast conversion of colistin methanesulfonate into colistin, which is reported to continue outside of the blood compartment, the measured amount of colistin in the total spent dialysate that is actually eliminated as colistin methanesulfonate and converted into colistin outside of the patient is unknown. However, as colistin, and not colistin methanesulfonate, is identified as the active bactericidal drug,²⁶ the relevance of this shortcoming is disputable. Population pharmacokinetic studies in critically ill patients with the objective to improve PIRRT dosing recommendations are difficult owing to the

Table 2. Pharmacokinetic key data of our study population

	Colistin methanesulfonate, median (IQR)	Colistin, median (IQR)
Single dose (day 1, $n = 8$)		
C_{max1} (mg/L)	13.02 (8.7–19.24)	5.79 (4.14–8.79)
C_{max2} (mg/L)	5.91 (3.11–7.59)	7.32 (4.31–9.69)
C_{max3} (mg/L)	5.21 (1.48–10.77)	5.66 (3.98–8.72)
AUC_{0-24} (mg-h/L)	56.5 (16.5–105.6)	104.7 (80.6–148.7)
Multiple dose (days 5–9, $n = 4$)		
C_{max1} (mg/L)	10.23 (8.12–12.32)	9.49 (8.39–10.41)
C_{max2} (mg/L)	8.99 (6.64–11.68)	9.05 (8.6–9.62)
C_{max3} (mg/L)	7.68 (4.89–9.24)	8.13 (7.73–8.26)
AUC_{0-24} (mg-h/L)	64 (58.2–73.2)	149 (106.9–189.2)
CL_{dial} (mL/min)	69.3 (56.3–318.7)	70.1 (36.6–96.2)
Drug amount in dialysate (mg)	NA	154 (105–175)

NA, not available.

limited size of comparable studies.²⁷ Additionally, all of our patients had anuric AKI stage 3, according to the AKI network classification, and remained dependent on dialysis during the study. Therefore, possible nephrotoxicity, resulting in delayed renal recovery, cannot be estimated in this study.

Our data in critically ill patients undergoing PIRRT suggest that a sufficient loading dose (i.e. 6–9 MIU of colistin methanesulfonate in patients with a body weight higher than 70 kg and pathogens with high MIC values) should be administered in critically ill patients, as advised by other studies with intensified loading dose regimens.²⁸ As the advised steady-state colistin AUC_{0-24} of 60 mg-h/L¹⁶ was exceeded owing to the accumulation of colistin during the study period, which correlates with the high colistin peak and trough concentrations measured in our patients, a reduced maintenance dose (i.e. 1.5–2 MIU every 8 h) should be used. We recommend an IBW or AjBW and RRT intensity-adapted dosing regimen, while additional data is needed to determine the exact influence of these parameters on colistin plasma levels.

Acknowledgements

Parts of these data were presented as posters during the Kidney Week 2014 of the American Society of Nephrology (Abstract FR-P0951) and the 16th annual meeting of the German Interdisciplinary Association of Intensive Care and Emergency Medicine (DIVI) in 2016 (Abstract EP08/02).

Funding

This study was supported by internal funding.

Transparency declarations

J. J. S. and J. T. K. received a congress travel grant from 'InfectoPharm Arzneimittel und Consilium GmbH'. All other authors: none to declare.

Supplementary data

Figure S1 is available as [Supplementary data](#) at JAC Online.

References

- 1 Couet W, Grégoire N, Gobin P et al. Pharmacokinetics of colistin and colistimethate sodium after a single 80-mg intravenous dose of CMS in young healthy volunteers. *Clin Pharmacol Ther* 2011; **89**: 875–9.
- 2 Curitis JR, Eastwood JB. Colistin sulphomethate sodium administration in the presence of severe renal failure and during haemodialysis and peritoneal dialysis. *Br Med J* 1968; **1**: 484–5.
- 3 Trotman RL, Williamson JC, Shoemaker DM et al. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis* 2005; **41**: 1159–66.
- 4 Li J, Turnidge J, Milne R et al. In vitro pharmacodynamic properties of colistin and colistin methanesulfonate against *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. *Antimicrob Agents Chemother* 2001; **45**: 781–5.
- 5 Markou N, Apostolakis H, Koumoudiou C et al. Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients. *Crit Care* 2003; **7**: R78–83.
- 6 Goldstein SL, Nolin TD. Lack of drug dosing guidelines for critically ill patients receiving continuous renal replacement therapy. *Clin Pharmacol Ther* 2014; **96**: 159–61.
- 7 Erstad BL. Dosing of medications in morbidly obese patients in the intensive care unit setting. *Intensive Care Med* 2004; **30**: 18–32.
- 8 Uchino S, Kellum JA, Bellomo R et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 2005; **294**: 813–8.
- 9 Fliser D, Kielstein JT. Technology Insight: treatment of renal failure in the intensive care unit with extended dialysis. *Nat Clin Pract Nephrol* 2006; **2**: 32–9.
- 10 Mushatt DM, Mihm LB, Dreisbach AW et al. Antibiotic dosing in slow extended daily dialysis. *Clin Infect Dis* 2009; **49**: 433–7.
- 11 Bauer L. *Applied Clinical Pharmacokinetics*. New York, NY, USA: McGraw Hill - Medical Publishing Division, 2001.
- 12 Kielstein JT, Kretschmer U, Ernst T et al. Efficacy and cardiovascular tolerability of extended dialysis in critically ill patients: a randomized controlled study. *Am J Kidney Dis* 2004; **43**: 342–9.
- 13 Gobin P, Lemaître F, Marchand S et al. Assay of colistin and colistin methanesulfonate in plasma and urine by liquid chromatography-tandem mass spectrometry. *Antimicrob Agents Chemother* 2010; **54**: 1941–8.
- 14 Bode-Böger SM, Schopp B, Tröger U et al. Intravenous colistin in a patient with serious burns and borderline syndrome: the benefits of therapeutic drug monitoring. *Int J Antimicrob Agents* 2013; **42**: 357–60.
- 15 EUCAST. *Breakpoint Tables for Interpretation of MICs and Zone Diameters*. Version 8.0. 2018. <http://www.eucast.org>.
- 16 Garonzik SM, Li J, Thamlikitkul V et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother* 2011; **55**: 3284–94.
- 17 Bergen PJ, Bulitta JB, Forrest A et al. Pharmacokinetic/pharmacodynamic investigation of colistin against *Pseudomonas aeruginosa* using an in vitro model. *Antimicrob Agents Chemother* 2010; **54**: 3783–9.
- 18 Miano TA, Lautenbach E, Wilson FP et al. Attributable risk and time course of colistin-associated acute kidney injury. *Clin J Am Soc Nephrol* 2018; **13**: 542–50.
- 19 Dalfino L, Puntillo F, Mosca A et al. High-dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. *Clin Infect Dis* 2012; **54**: 1720–6.
- 20 Jitmuang A, Nation RL, Koomanachai P et al. Extracorporeal clearance of colistin methanesulfonate and formed colistin in end-stage renal disease patients receiving intermittent haemodialysis: implications for dosing. *J Antimicrob Chemother* 2015; **70**: 1804–11.
- 21 Karvanen M, Plachouras D, Friberg LE et al. Colistin methanesulfonate and colistin pharmacokinetics in critically ill patients receiving continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 2013; **57**: 668–71.
- 22 Li J, Rayner CR, Nation RL et al. Pharmacokinetics of colistin methanesulfonate and colistin in a critically ill patient receiving continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 2005; **49**: 4814–5.
- 23 Markou N, Fousteri M, Markantonis SL et al. Colistin pharmacokinetics in intensive care unit patients on continuous venovenous haemodiafiltration: an observational study. *J Antimicrob Chemother* 2012; **67**: 2459–62.
- 24 Jacobs M, Grégoire N, Mégarbane B et al. Population pharmacokinetics of colistin methanesulfonate and colistin in critically ill patients with acute renal failure requiring intermittent hemodialysis. *Antimicrob Agents Chemother* 2016; **60**: 1788–93.
- 25 Gauthier TP, Wolowich WR, Reddy A et al. Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients. *Antimicrob Agents Chemother* 2012; **56**: 2392–6.
- 26 Bergen PJ, Li J, Rayner CR et al. Colistin methanesulfonate is an inactive prodrug of colistin against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2006; **50**: 1953–8.
- 27 Nation RL, Garonzik SM, Thamlikitkul V et al. Dosing guidance for intravenous colistin in critically-ill patients. *Clin Infect Dis* 2017; **64**: 565–71.
- 28 Menna P, Salvatorelli E, Mattei A et al. Modified colistin regimen for critically ill patients with acute renal impairment and continuous renal replacement therapy. *Chemotherapy* 2018; **63**: 35–8.