Colistin Pharmacokinetics in Burn Patients During Continuous Venovenous Hemofiltration

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Abstract

While colistin is considered a last resort for the treatment of multidrug-resistant Gram-negative bacterial infections, there has been an increase in its use due to the increasing prevalence of drug-resistant infections worldwide. The pharmacology of colistin is complex and pharmacokinetic data are limited, especially in patients requiring renal replacement therapy. As a result, dosing for patients who require renal replacement remains a challenge. Here we present pharmacokinetic data for colistin from two burn patients infected with colistin-susceptible isoclonal Acinetobacter baumannii, 37 and 68 years old, receiving continuous venovenous hemofiltration (CVVH). To our knowledge, we are the first to examine data from both before and during CVVH (for one patient), allowing analysis of the effect of CVVH on colistin pharmacokinetics. PK/PD analysis indicated a dose increase from 1.5 to 2.2 mg/kg colistin base activity on CVVH was insufficient to satisfy the target parameter of AUC:MIC ≥ 60 at an MIC ≥ 1 µg/mL in one patient with residual endogenous renal function. Plasma concentrations of colistin ranged from 0-15 µg/mL, with free colistin ranging from 0.4-2.2 µg/mL. While both patients resolved their clinical infections and survived to discharge, colistin-resistant colonizing isolates resulted from therapy in one patient. The variability observed in colistin concentrations and pharmacokinetic characteristics highlight the importance of pharmacokinetic monitoring of antibiotics in patients undergoing renal replacement therapy.
Introduction

An increase in the prevalence of multidrug-resistant Gram-negative infections worldwide (1, 2), and the lack of new antibiotics for the treatment of multidrug-resistant Gram-negative infections (3), has led to the increased use of polymyxin antibiotics (4), the most common of which are polymyxin B and polymyxin E, also known as colistin. Colistin is a multicomponent lipopeptide, containing predominantly colistin A and colistin B that differ only in the fatty acid chain attached to a cyclic decapeptide moiety (5). To reduce toxicity (3), colistin is administered primarily as the pro-drug, colistin methanesulfonate sodium (CMS), which is produced by sulfomethylation of five amino acid residues in colistin (6). Following parenteral administration, CMS undergoes hydrolysis in vivo to form a complex mixture of colistin and partially sulfomethylated derivatives (3). The rate of CMS conversion to formed colistin has not been well characterized in vivo, but is thought to be slower than the rate of renal CMS elimination by unimpaired kidney function (6). In contrast, formed colistin undergoes predominantly non-renal clearance through mechanisms yet to be elucidated (6).

Due to the complicated nature of CMS conversion to colistin in vivo, a lack of consensus on dosing guidelines (7, 8), and concerns about potential nephrotoxicity (6, 9), colistin has long been considered an agent of last resort for the treatment of Gram-negative infections. As the use of colistin predates modern preclinical testing requirements, pharmacokinetic data for colistin are limited. Given the increasing prevalence of multidrug-resistant Gram-negative infections and global use of colistin (2), more data are needed on the pharmacokinetics of colistin, particularly during continuous renal replacement therapies (CRRT) such as continuous...
venovenous hemofiltration (CVVH), which is being used more often to treat critically ill patients for its hemodynamic compatibility (10-13). Advances in high performance liquid chromatography (HPLC) have allowed for the separation and identification of colistin in biological samples (5, 14-16). Here we report plasma pharmacokinetic data for formed colistin in two burn patients treated for multidrug-resistant *Acinetobacter baumannii* infections undergoing CVVH, one of whom also underwent pharmacokinetic characterization prior to CVVH.
A 68-year-old male with diabetes mellitus and hypertension was transferred to our Burn Intensive Care Unit after suffering 2nd and 3rd degree burns, totaling 11% of the total body surface area (TBSA), to the chest, back and upper extremities, as well as moderate inhalational injury, from a house fire. He arrived mechanically ventilated and during his hospital stay experienced two episodes of ventilator-associated pneumonia (VAP), diagnosed on hospital days (HD) 14 and 30, with serial recovery of *A. baumannii* from the respiratory tract. The initial isolate, recovered on hospital day 12, was tested for colistin susceptibility and demonstrated a minimum inhibitory concentration (MIC) of 0.38 µg/mL by Epsilometer test (Etest) and resistance to all other antimicrobials tested. Additional isolates of *A. baumannii* were recovered from the respiratory tract up to hospital day 70 (Figure S1). Both episodes of VAP were treated with 14 days of IV CMS (Coly-Mycin M, Parkedale Pharmaceuticals, Rochester, MI; 4.4 mg colistin base activity (CBA)/kg/day in two divided doses) and nebulized CMS therapy (75 mg every 8 hours). During the period of VAP treatment with colistin, he also received vancomycin titrated to renal function for skin graft donor site cellulitis and levofloxacin 750mg IV for three days for empiric treatment of sepsis prior to the second episode of VAP (HD 26). During the second episode, empiric imipenem-cilastatin was added for Gram-negative rods recovered in bronchoalveolar lavage cultures, found to be MDR/carbapenem-resistant *A. baumannii* and pan-susceptible *Klebsiella pneumoniae*. In addition to colistin, the patient received imipenem-cilastatin for 10 days.
On the date of pharmacokinetic sampling (HD 23, day 10 of the initial course of systemic and day 7 of nebulized CMS therapy), the patient received both IV CMS (2.2 mg CBA/kg every 12 hours, infused over 30 minutes) and nebulized CMS (75 mg every 8 hours). During sampling, the patient received CVVH (which was indicated for renal support) at a delivered dose of 38.1 mL/kg/hour using a PrismaFlex® device (Gambro, Lakewood, CO) with a HF1400 polyarylethersulfone filter. Replacement fluid (RFP401, NxStage) was infused pre-filter at 2 L/hour and post-filter at 2 L/hour, with a blood flow rate ($Q_b$) of 300 mL/minute and ultrafiltration rate set to zero. 24 hour urine output on the day of sampling was 915 mL (0.2 mL/kg/hour). The patient’s VAP resolved clinically with improvement in chest xray infiltrates and minimal ventilator settings, and he was discharged to an acute respiratory care facility 77 days after admission.

**Patient #2**

A 37-year-old, previously healthy male member of the U.S. military sustained 3rd-degree burns totaling 51% TBSA in a helicopter crash while overseas. After preliminary stabilization care at a combat support hospital, he underwent aeromedical evacuation to the United States and admitted to our Burn Intensive Care Unit 4 days after injury. Acute Kidney Injury (AKI) Network stage 2 (17) and rhabdomyolysis were present upon admission. Orthopedic injuries included fractures of the humerus and patella. Blood cultures drawn upon admission, and subsequently bronchoalveolar lavage fluid, contained *A. baumannii*, susceptible only to colistin with MIC of 0.75 µg/mL, determined by Etest. Additional isolates were recovered from superficial cultures of intact and debrided skin from various body sites (Figure S1).
CMS was infused over 30 minutes at 2.9 mg CBA/kg/day (in 2 divided doses) initially and increased to 4.4 mg CBA/kg/day (2 divided doses) after CVVH was prescribed at 35 mL/kg/hour for therapy of AKI with metabolic acidosis. CMS was also given by nebulizer three times daily (75 mg every 8 hours). During colistin therapy he also received empiric treatment with vancomycin titrated to renal function and imipenem-cilastatin 250-500mg every 6 hours, although the recovered A. baumannii isolates were resistant to imipenem. In addition, doxycycline 100mg daily was given for terminal malaria prophylaxis. During pharmacokinetic sampling, the patient received CVVH at a delivered dose of 28.4 ± 3.7 mL/kg/hour using a NxStage® device (NxStage Medical, Lawrence, MA) with a CAR500 polyethersulfone filter. Replacement fluid (RFP401, NxStage) was infused pre-filter only at 3 L/hour, with a Qb of 250 mL/minute and ultrafiltration rate of 300 mL/hour. 24 hour urine output on the day of sampling was 2263 mL (0.9 mL/kg/hour). Patient 2 survived to hospital discharge 154 days after admission with no clinical evidence of recurrent VAP. However, additional colonizing isolates of A. baumannii were recovered including a colistin-resistant isolate (MIC 24 µg/mL) from the respiratory tract (HD 47) which appeared to revert to colistin-susceptible (MIC 1 µg/mL on HD 52). An isolate with high-level colistin resistance (MIC >256 g/mL) was recovered on a rectal surveillance swab on HD 101. Both colistin-resistant isolates remained resistant to all other first-line antimicrobials, and all isolates shared the identical PFGE pattern (Figure S1).
Materials and Methods

Materials

All drugs and chemicals were reagent grade from Sigma (St. Louis, MO) unless otherwise noted.

Pharmacokinetic Sampling and Analysis

Pharmacokinetic sampling of single dose curves was performed following surrogate informed consent as part of an ongoing prospective observational pharmacokinetics (PK) and pharmacodynamics (PD) study in trauma and burn patients approved by our Institutional Review Board. 3 mL of whole blood was sampled at 0 (pre-dose), 1, 2, 4, 8, and 12 hours from the start of infusion. Samples obtained during CVVH therapy included pre-filter blood and ultrafiltrate. Plasma was separated from whole blood by centrifugation at 2000 x g for 10 minutes at 4°C, and the plasma or ultrafiltrate was immediately frozen at -80°C until analysis. Pharmacokinetic parameters were estimated by non-compartmental analysis using WinNonLin software, version 6.3 (Pharsight, Cary, NC). The total (bound + free) colistin AUC$_{24}$:MIC $\geq$60, derived from a large population pharmacokinetic analysis (18), was selected as the target value to determine adequacy of therapy. When calculating the sieving coefficient ($S_c$), pre-filter blood concentrations were multiplied by the following factor to correct for the dilution effects of pre-filter replacement fluids: $Q_b/(Q_b+Q_{rep})$, representing pre-filter flow rates of blood ($Q_b$) and replacement fluid ($Q_{rep}$). The $S_c$ was calculated as the ratio of the area under the curve (AUC) for the time-concentration curve for the ultrafiltrate to the dilution-corrected AUC of plasma (19, 20).
Sample Preparation

Colistin derivatization and isolation from plasma was performed as previously described (15). Briefly, 200 µl plasma was spiked with netilmicin (100 ng, internal standard) and loaded under vacuum onto a solid phase extraction column (SepPak® C18, Waters, Milford, MA) previously conditioned with methanol (1 mL) and 1% sodium bicarbonate (1 mL, pH 10). After washing with sodium bicarbonate (500 µl), 30 µl of freshly-prepared 9-fluorenylmethyl chlorformate (FMOC) was added and drawn into the extraction column. The derivatization reaction was allowed to proceed for 10 minutes before drying the column under vacuum. Reaction products were eluted with acetone (900 µl) and mixed with sodium borate (0.2M, 600 µl, pH 8.5). 20 µl of each sample was assayed by HPLC. Calibration curves were prepared by creating solutions of blank human plasma containing 0.1 to 10 µg/mL CBA, which were processed in parallel to the samples. Free (unbound) colistin was determined by filter centrifugation (Centrifree UF 30 kDa, Millipore, Billerica, MA) of plasma at 1500 x g for 30 minutes. Despite reports of extensive nonspecific binding to membranes of similar chemistry but smaller (10 kDa) pore size (21), our pilot studies recovered 100% of a 1 µg/mL solution of colistin in phosphate buffered saline.

HPLC Conditions

The concentration of colistin in plasma was determined by HPLC as previously reported (14, 15, 22, 23). Briefly, the HPLC (Dionex Ultimate 3000, Sunnyvale, CA) consisted of a binary pump, sample injection loop, thermal-controlled column compartment (25°C) and UV-diode array with fluorescence detectors. The stationary phase was a reversed phase Luna C18 column.
(150 x 4.6 mm, 100 Å, 5 µm particle size, Phenomenex, Torrance, CA) and the mobile phase consisted of an acetonitrile:methanol:tetrahydrofuran:water mixture (78:10:8:4) run in the isocratic mode at 1 mL/minute. FMOC-colistin was detected by fluorescence using excitation and emission wavelengths of 260 and 315 nm, respectively. The limit of detection for the assay was 100 ng/mL. Colistin peaks in patient samples were identified by their retention times compared to blank human plasma spiked with colistin, and colistin A and B peaks were interpreted according to their elution order previously reported (16). The total colistin concentration was determined by adding the peak areas of colistin A and B and dividing by the peak area of the internal standard.

**Bacterial Characterization**

Isolates of *A. baumannii* were identified using the Vitek 2 (bioMérieux, Durham, NC) and Phoenix (BD, Franklin Lakes, NJ) automated microbiology systems. Colistin MICs were determined by Etest (bioMérieux) following testing and interpretive methods of the Clinical and Laboratory Standards Institute (susceptible, ≤2 µg/mL). Clonal relationships were assessed by pulsed-field gel electrophoresis (PFGE) following the Pulsenet protocol (CDC) with modifications for *Acinetobacter* as previously described (24). Briefly, genomic DNA was digested with Apal (New England Biolabs, Ipswich, MA) for 4 hours at 25°C and separated on a 1% agarose gel in Tris-borate-EDTA buffer. PFGE was performed with a CHEF-DR III system (Bio-Rad, Hercules, CA) and a gradient of 6 V/cm at a 120° angle, with the pulse time increasing from 7 to 20 seconds. Electrophoresis was run at 14°C for 18.5 hours. DNA from *Salmonella enterica* (ATCC BAA-664) was used as a molecular size standard. The gels were stained with 1 mg/mL ethidium bromide,
destained with water, imaged with the U:GENIUS system (Syngene, Fredrick, MD) and analyzed with BioNumerics software (Applied Maths, Austin, TX). The PFGE patterns were interpreted and grouped into pulsed-field types using established criteria (25).
Results

Pharmacokinetic parameters of colistin (Table 1) were estimated using non-compartmental analysis from the time-concentration curves for colistin (Figure 1). In the plasma, the proportions of colistin A and B were approximately 65-68% and 10-14%, respectively, before and during CVVH. Interestingly, colistin B was cleared across the filter membrane slightly more readily than colistin A (difference from plasma, -14.2% for A vs. +16.5% for B). AUC<sub>24</sub>:MIC curves were calculated for hypothetical MICs, indicating that the increased clearance associated with CVVH has the potential to compromise PK/PD targets, particularly with higher MICs and preserved renal function (Figure 2). PFGE analysis of A. baumannii isolates indicated that the same strain was present in all sample locations throughout the duration of the hospital stay for each patient (Dice coefficient ≥95%, Figure S1). Colistin MICs ranged from 0.75 to 1.0 µg/mL for Patient 1. MICs for susceptible isolates from Patient 2 ranged from 0.5 to 1.5 µg/mL, with two colistin-resistant colonizing isolates having MICs from 24 to >256 µg/mL.
Discussion

Colistin, approved for parenteral use in the United States as the prodrug colistin methanesulfonate, has seen a resurgence of use in the last decade as a drug of last resort for multidrug-resistant Gram-negative organisms. As it was developed prior to modern regulatory requirements, which include rigorous pharmacokinetic study, significant uncertainties persist regarding its disposition in humans. Methods for the analysis of colistin by HPLC have been described (14-16, 22, 23), resulting in an increase in pharmacokinetic studies in patients. The most comprehensive pharmacokinetic study to date included 851 sample observations from 105 subjects (18), of which 12 were treated with hemodialysis and 4 were treated with CRRT; of these, 3 were treated with continuous venovenous hemodiafiltration (CVVHDF) and one received CVVH. Since CVVHDF uses passive diffusion across a concentration gradient in addition to hemofiltration (the sole method for clearance in CVVH), the equivalence of these modes with respect to CMS/colistin clearance is unknown. Additionally, recent reports have described CMS and colistin pharmacokinetics in patients undergoing CVVHDF (26) and dialysis (27), but to our knowledge this is the first study to report on the pharmacokinetics of colistin in the same individual prior to and during CVVH therapy. Evaluating pharmacokinetic data for colistin before and during CVVH affords the opportunity to directly study the impact of CVVH on colistin pharmacokinetics.

After administration, colistin is a complex mixture of at least 30 hydrolysis products of the pro-drug CMS, with colistin A and B serving as the major products (6, 14). The pharmacokinetic disposition of CMS and colistin in humans is equally complex, especially under
conditions of CVVH therapy, with CMS being cleared renally but colistin being cleared by poorly defined non-renal mechanisms. Additionally, the in vivo rate and extent of conversion from CMS to colistin is unknown, but thought to be slower than the renal clearance of CMS by unimpaired kidneys (6), and there is uncertainty as to whether CMS hydrolysis is spontaneous or enzymatically catalyzed (3, 6). Despite the fact that the CVVH circuit and apparatus can functionally increase the volume of distribution (V_d), the V_d of Patient 1 (during CVVH) was slightly lower than for Patient 2 (without CVVH). This may reflect a reduced circulating plasma volume due to fluid losses from ultrafiltration. CRRT further complicates the situation as data describing the rate of CRRT clearance of CMS and colistin, or to what extent CRRT clearance of CMS may be offset by a reduced glomerular filtration rate, are sparse. Other than monitoring urine output, there are no methods currently available to determine the degree of intrinsic renal function while receiving CRRT. Additionally, there are varying modes of CRRT utilized with varying doses that are prescribed. Use of intermittent modes of renal replacement in many units with hybrid techniques such as sustained low-efficiency dialysis also complicates the picture (28-30). As a result, CMS dosing for patients who require renal replacement remains a challenge.

While this study provides valuable in vivo pharmacokinetic data for colistin in patients undergoing CVVH, and for the first time pharmacokinetic data for colistin from before and during CVVH, some limitations require caution in drawing broad conclusions from this study. The small sample size (two patients) and lack of data for CMS limit the statistical comparisons and reduce the power of analyses. Unfortunately, filter clotting in Patient 2 during CVVH, which may have caused a rise in the plasma colistin concentration prior to clotting, prevented
calculation of the full suite of PK parameters because a terminal clearance slope could not be
determined. Further, although samples were kept cold during analytical procedures, some
spontaneous conversion of CMS to colistin in ultrafiltrate and plasma during or after collection
is possible (14), particularly in the ultrafiltrate that is sampled from fluid collected at ambient
temperature over a long sampling interval. However, concentrations of formed colistin in the
ultrafiltrate were similar at the beginning and end of sampling. Additionally, patients were also
treated with nebulized CMS during CVVH and pharmacokinetic sampling, which could
complicate the interpretation of colistin plasma concentrations, but inhaled colistin has been
shown to have minimal systemic absorption using doses higher than those observed here (31,
32). Due to inherent limitations in the system of care at our facility, we were not able to
ascertain the age of CVVH filters at the time of sampling. This is relevant because the sieving
efficiency of individual filters is known to degrade over time (33), likely as a result of
proteinaceous fouling (34). Thus, newly placed filters in the CVVH circuit may have enhanced
solute clearance relative to older filters. While the delivered CVVH doses during colistin PK
sampling reflect those typically used for renal support (10-13), higher doses have been used for
sepsis and other states of shock (13, 35, 36). The impact of higher CVVH doses on colistin and
other antimicrobials remains to be determined.

A previous analysis, based upon population pharmacokinetics derived from 3 non-
burned CVVHDF patients and one CVVH patient, has suggested that a daily dose of 192 mg CBA
(irrespective of body weight) is necessary for each 1.0 µg/mL steady-state average (C_{ss.avg})
colistin concentration during continuous renal replacement (18). In our series, Patient 1
received 600 mg daily during CVVH but this resulted in plasma C_{ss.avg} above the predicted value
(predicted $C_{\text{ss.avg}}$ 3.1 µg/mL; measured $C_{\text{ss.avg}}$ 9.3 µg/mL). In contrast, the $C_{\text{ss.avg}}$ for Patient 2, who received 450 mg daily during CVVH, was accurately predicted (predicted $C_{\text{ss.avg}}$ 2.3 µg/mL; measured $C_{\text{ss.avg}}$ 2.3 µg/mL). This difference may be attributable to the relatively greater preservation of endogenous renal function in Patient 2, as reflected by urinary output. In addition, potential drug interactions impairing the clearance of colistin are impossible to assess, given that the mechanism for colistin clearance (which is non-renal) remains unknown.

Colistin has been previously reported to have 59-74% protein binding (26-41% unbound fraction) in a series of non-burned critically ill patients (37), whereas we observed slightly higher protein binding in the 80-90% range. The increased protein binding we observed relative to previous reports may be due to prolonged elevation in alpha-1-acid glycoprotein, as occurs in burn patients (38, 39), and to which colistin has moderate binding affinity (40). This highlights the need for further detailed studies examining free colistin pharmacokinetics in burn patients, as a previous population pharmacokinetic model derived from burn patients did not incorporate protein binding data (41), and the unbound fraction has been identified as a relevant PK/PD parameter (42). The pre- and post-CVVH values were similar for Patient 2 (Table 1), suggesting CVVH did not affect the protein binding status of colistin. This highlights the uncertain and variable results of colistimethate dosing and suggests a need for therapeutic drug monitoring to achieve optimal levels during CVVH, particularly for oliguric or anuric patients.

Colistin MIC values before and during therapy were below the CLSI “susceptible” breakpoint of 2 µg/mL. It is notable, therefore, that for Patient 2, an increase in the
colistimethate dose from 2.9 to 4.4 mg CBA/kg/day (2 divided doses) during CVVH was insufficient to achieve AUC$_{24}$:MIC$\geq$60 when the MIC was $\geq$1 µg/mL (Figure 2). Thus, isolates determined to be “susceptible” according to current CLSI interpretive criteria may receive inadequate therapy despite the achievement of predicted plasma concentration. Indeed, Garonzik et al. were prudent to acknowledge that their recommended maintenance doses may not be reliably effective against isolates with colistin MICs above 0.5 µg/mL (18). Published reports of treatment-associated colistin resistance are accumulating in the literature (43-45), perhaps corroborating in vitro data suggesting no regimen of colistin monotherapy (including continuous infusion) can prevent colistin resistance in A. baumannii (46). Additionally, colistin resistance arose in Patient 2 despite concurrent therapy with vancomycin and imipenem, which in vitro data suggest may be able to prevent the emergence of resistance when given concurrently with colistin (46).

Despite its limitations, this case series provides an opportunity to examine the total clearance and fractional CVVH-related clearance rates for colistin and adds to the existing pharmacokinetic data for an increasingly common antibiotic for increasingly common multidrug-resistant bacterial infections. We observed significant variability in colistin concentrations resulting from recommended dosing strategies, with high and low concentration excursions in the setting of CVVH, suggesting risks for toxicity and compromised PK/PD target attainment, respectively. In our opinion, this case series highlights the importance of antibiotic PK/PD monitoring in ICU patients, particularly those undergoing continuous renal replacement therapy.
Acknowledgements

This study was conducted under a protocol reviewed and approved by the U.S. Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol H-09-059. This work was supported by Defense Medical Research & Development Program (DMRDP) Military Infectious Disease Clinical Trial Award (MID-CTA) #D_MIDCTA_I_12_J2_299, and in part by an appointment to the Postgraduate Research Participation Program at the U.S. Army Institute of Surgical Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and USAMRMC. A portion of this material was presented at ID Week 2013, Infectious Diseases Society of America, San Francisco, CA. We gratefully acknowledge the invaluable contributions of Doug Johnson LVN, Kristie Harnisch RN, Crystal Rosemann RN, Lance Ferguson MS and the participating research subjects, without whom this research would not be possible.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.
References


Table 1. Patient information and pharmacokinetic data for colistin in plasma samples from patients undergoing CVVH (Patients 1 and 2B). Pharmacokinetic data for patient 2 was collected before (2A) and during (2B) CVVH therapy.

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<th>Patient 1</th>
<th>Patient 2A</th>
<th>Patient 2B</th>
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<tr>
<td><strong>Age/Gender</strong></td>
<td>68/M</td>
<td>37/M</td>
<td>37/M</td>
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<tr>
<td><strong>% TBSA Burn</strong></td>
<td>11</td>
<td>51</td>
<td>51</td>
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<tr>
<td><strong>CVVH Delivered Dose (mL/kg/h)</strong></td>
<td>38.1 ± 11.0</td>
<td>28.0 ± 3.7</td>
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<td><strong>Weight (kg)</strong></td>
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<td>102.3</td>
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<td>0.9</td>
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<td>NxStage, CAR500</td>
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<td>--</td>
<td>3</td>
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<td>2.2</td>
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<td><strong>Colistin C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</strong></td>
<td>13.6 (2.2 free)</td>
<td>3.4 (0.4 free)</td>
<td>6.7 (0.6 free)</td>
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<td>2.3</td>
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<td><strong>AUC&lt;sub&gt;24&lt;/sub&gt; (h·µg/mL)</strong></td>
<td>222.2 (18.2 free)</td>
<td>55.0 (6.0 free)</td>
<td>100.0 (8.7 free)*</td>
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<td>99.7</td>
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<td><strong>% CVVH Clearance</strong></td>
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<td><strong>% Free Colistin</strong></td>
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<td>13.7 ± 6.4</td>
<td>10.9 ± 4.6</td>
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<td>64.8 ± 1.4</td>
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<td><strong>% Colistin B</strong></td>
<td>14.1 ± 1.7</td>
<td>10.9 ± 4.6</td>
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<td><strong>MIC at which AUC&lt;sub&gt;24&lt;/sub&gt;:MIC≥60</strong></td>
<td>2 µg/mL</td>
<td>0.75 µg/mL</td>
<td>1 µg/mL</td>
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*Only 0 to 8h data available due to filter clotting
Figure 1. Time-concentration curves for CMS and colistin in patients undergoing CVVH. A&B) Concentrations over time in pre-filter plasma for total and free colistin, and ultrafiltrate fluid for Patient 1 (A) and Patient 2 (B). Additionally, colistin concentrations over time before CVVH are shown for Patient 2. For Patient 2, 12 hour sampling could not be performed during CVVH due to filter clotting.
Figure 2. Achievement of the pharmacodynamic target of total colistin AUC\textsubscript{24}:MIC\textsubscript{≥60} (dashed line) versus hypothetical MIC using plasma AUC values in two burn patients, one of whom was sampled before and during CVVH therapy. Solid squares: Patient 1 treated with 2.2 mg CBA/kg with delivered CVVH dose of 38.1 ± 11.0 mL/kg/hour over 12 hours; Solid circles: Patient 2 treated with 1.5 mg CBA/kg without CVVH; Empty circles: Patient 2 treated with 2.2 mg CBA/kg with delivered CVVH dose of 28.0 ± 3.7 mL/kg/hour over 8 hours. Both patients also received nebulized CMS (75 mg every 8 hours) during sampling.