

Efficient removal of colistin A and B in critically ill patients undergoing CVVHDF and sorbent technologies

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Abstract

Background Colistin pharmacokinetics data are scarce regarding patients undergoing renal replacement therapy (RRT), or even absent as in patients treated with sorbent technologies potentially capable of removing colistin by extensive absorption on many polymeric materials.

Methods Twelve septic shock patients with acute kidney injury (AKI) undergoing RRT [continuous venovenous hemodiafiltration (CVVHDF) $n = 7$, coupled-plasma filtration adsorption-HF (CPFA-HF) $n = 4$, hemoperfusion $n = 1$] treated with colistin methanesulfonate at a dose of 4.5×10^6 U bid were studied. Colistin A (Col-A) and colistin B (Col-B) concentrations on plasma and effluent at time 0, 0.2, 1, 3, 6, 12, 24 and 48 h were determined by the liquid chromatography-tandem mass spectrometry method.

Results With CVVHDF the sieving coefficient was lower for Col-A, peaked early (0.40 for Col-A at 10 min, and 0.59 for Col-B at 3 h) and declined after 48 h (0.22 and 0.30 for Col-A and Col-B, respectively). Colistin's filter clearance

showed a similar pattern, with the highest clearance value of 18.7 ml/min for Col-B at 1 h. With CPFA-HF after the cartridge the Col-A and Col-B levels were negligible (<0.2 mg/l) or not detectable. The sum of the effluent and cartridge clearances reached values of 30 and 40 ml/min for Col-A and Col-B, respectively. With hemoperfusion the postcartridge concentrations for Col-A and Col-B were about 30 % lower than those determined precartridge.

Conclusions During CPFA-HF and CVVHDF, the extent of colistin removal is high, and patients should receive an unreduced dosage. However, due to risk of accumulation in long-term administration colistin plasma levels determination is recommended.

Keywords Colistin sieving coefficient · Colistin extracorporeal removal · CVVHDF · Coupled plasmafiltration adsorption · Hemoperfusion

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Introduction

Colistin (polymyxin E), a re-emerged antibiotic for multidrug-resistant gram-negative bacterial infections [1–4],

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is an antibiotic mixture containing more than 30 components differing in amino-acid and fatty-acid residue composition. The two major components of the mixture are colistin A (polymyxin E1) and colistin B (polymyxin E2) [4]. Colistin A and B have a discrete neuro- and nephrotoxicity [5–8]. To reduce colistine nephro- and neurotoxicity, the drug is currently administered intravenously as sodium colistimethate (CMS), an inactive pro-drug which is hydrolyzed in vivo to the active colistin base moiety [2–4]. The risk of colistin nephrotoxicity proved to be clinically significant after 14 days administration [5]; it appeared to be linked to its cumulative dosage [6], was associated with advancing age and receipt of concurrent nephrotoxic agents [7], and was predicted by the plasma colistin level [8].

Pharmacokinetics and pharmacodynamics of colistin are complex, and data are relatively scarce for critically ill patients with acute kidney injury (AKI) undergoing continuous venovenous hemodiafiltration (CVVHDF) or hemodialysis, which provide inconstant clearance of colistin in addition to endogenous clearance [9–16].

The colistin pharmacokinetics issue has become even more relevant in septic shock patients treated by some new renal replacement therapy (RRT) approaches recently proposed to increase the removal of endotoxin, bacterial products and both pro- and anti-inflammatory mediators [15, 17–19]. These new treatments, including high volume hemofiltration/hemodiafiltration [15], coupled plasmafiltration adsorption (CPFA-HF) [17, 18] and hemoperfusion [19], are potentially capable of removing colistin, due to its hydrophobic character that allows its extensive absorption on many polymeric materials [9, 15]. However, less than 20 cases have been reported so far on conventional continuous RRT (CRRT) accomplished with different membranes [9–16], and no data are available for patients treated with sorbent technologies. Although glomerular filtration rate is the parameter used to guide dose adjustment, kidney disease does affect non-renal clearances, and this aspect has not been adequately considered in most pharmacokinetic studies [20].

Recently, we implemented the quantitative evaluation of colistin A and B using high pressure liquid chromatography-tandem mass spectrometry (HPLC–MS/MS), and obtained preliminary data from 4 patients undergoing CVVHDF [21]. Subsequently, we kept investigating the distribution of colistin between plasma and effluent in further patients treated with CRRT and sorbent technology. The results presented here reveal that sorbent technology is associated to an efficient clearance of colistin through the polysulfone filter and cartridge, and pose the question of colistin maintenance dosage for these patients.

Subjects and methods

Patients

Twelve critically ill patients, median (interquartile range) age 60 (39.5–81.5) years, with septic shock according to current definitions [22] were studied. All patients presented systemic infection sustained by a strain of multiresistant gram-negative bacteria with only residual sensitivity to colistin and suffered from AKI needing RRT [23]. Patients received the conventional pharmacological therapy including crystalloid solutions, broad-spectrum antibiotics, diuretics, vasopressor agents and colistin as part of their standard care. The causes of the primary injury, the causative bacteria, the administered antibiotics, the severity of illness score, and the outcome are reported in Table 1.

Out of 12 patients, seven were treated by CVVHDF (group CVVHDF, *n* 7 sessions), four by CPFA-HF (group CPFA-HF, *n* 4 sessions) and one patient with hemoperfusion cartridge (*n* 2 sessions). Preliminary data from three patients of group CVVHDF were part of the validation of the HPLC–MS/MS method described in [21].

All patients started CVVHDF or CPFA-HF with the citrate anticoagulation protocol [24, 25] to prevent their high bleeding risk (defined as the bleeding alert at catheter insertion site, tracheostomy, gastrointestinal tract, or in surgical wounds) or due to frank bleeding necessitating transfusion of red packed cells.

The study protocol was in accordance with the principles contained in the Helsinki Declaration. Informed written consent was obtained from either a close relative or a legal representative.

CVVHDF protocol

CVVHDF procedures were carried out with a Multifiltrate apparatus (Fresenius Medical Care AG, Bad Homburg, Germany) equipped with a high flux polysulfone filter (AV1000, Fresenius Medical Care) at a blood flow rate of 120 ml/min. Fluid infusion, dialysate flow rates and citrate anticoagulation were done as previously described [24].

CPFA-HF protocol

CPFA-HF was performed by a five-pump CRRT machine [Lynda, Bellco, Mirandola, (MO), Italy] equipped with a polyethersulfone plasmafilter (0.45 m², MPS 05, Bellco) placed in series with a highly permeable polyethersulfone hemodialyzer (1.4 m², BLS814G, Bellco). The plasma was produced at a rate of 15–20 % blood flow, and subsequently underwent absorption on an unselective hydrophobic resin cartridge [17, 18, 25].

Table 1 Clinical data and outcome of patients treated by CVVHDF, CPFA-HF and hemoperfusion

No.	Age (years)/sex	Diagnosis	Weight/height (kg/cm)	Albumin gr/L	Infective agent Hemoculture	Antibiotics	SOFA Score	Exitus
Group CVVHDF								
1	58/M	Burns 40 %	110/180	25.6	Ac. Baumannii	Mero/levo/rifa	11	Yes
2	89/M	Burns 40 %	72/174	24.3	Ac. Baumannii	Fluco/pip-tazo	13	Yes
3	62/M	Pneumonia	85/180	27.2	Kl. Pneumoniae	Vanco	11	No
4	79/M	Fascitis	102/165	29.5	Ac. Baumannii	Linez/fluco/mero/rifa	12	Yes
5	27/M	Burns 70 %	72/180	22.5	Ac. Baumannii	Linez/fluco/mero/rifa	12	Yes
6	85/M	Burns 35 %	84/178	27.1	Ac. Baumannii	Amika/vanco	12	Yes
7	84/F	Burns 30 %	65/168	21.1	Ac. Baumannii	Linez/vorico/rifa	18	Yes
Group CPFA-HF								
8	40/M	Burns 65 %	71/175	26.5	Ac. Baumannii	Levo/linez/pip-tazo	11	No
9	39/M	Burns 50 %	89/180	34.5	Kl. Pneumoniae	Vanco/rifa/cotrim/cefep	14	No
10	72/M	Fascitis	104/180	19.4	Kl. Pneumoniae	Tige/amik	12	Yes
11	18/M	Polytrauma	95/188	30.5	Kl. Pneumoniae	Mero/cipro	13	No
Hemoperfusion								
12	54/M	Pneumonia	74/174	26.2	Kl. Pneumoniae	Mero/dapto	11	Yes

CVVHDF continuous venovenous hemodiafiltration, CPFA-HF coupled-plasma filtration adsorption-HF, SOFA sequential organ failure assessment score, *Ac. Baumannii* Acinetobacter baumannii, *Kl. Pneumoniae* Klebsiella pneumoniae, *Mero* meropenem, *Levo* levofloxacin, *Rifa* rifampycin, *Fluco* fluconazol, *Pip-Tazo* Piperacillin-Tazobactam, *Linez* linezolid, *Amik* amikacin, *Vanco* vancomycin, *Cotrim* cotrimoxazole, *Cefep* cefepime, *Vorico* voriconazol, *Tige* tigecycline, *Cipro* ciprofloxacin, *Dapto* daptomycin

For the hemofiltration treatment, a sterile bicarbonate-calcium containing solution was infused in postdilution at a rate of 1,500 ml/h. The circuit anticoagulation was done by a calcium-free citrate-containing solution infused in predilution mode at 25–30 % blood flow [25].

Hemoperfusion protocol

One patient underwent hemoperfusion using a Polymyxin-B Fiber cartridge (Toraymyxin, Toray Industries, Tokyo, Japan) following the manufacturer's instructions [19]. The treatment lasted for 2 h and a further treatment was repeated 24 h later (QB 120 ml/min). As anticoagulation, we followed the manufacturer's protocol which indicated as sole anticoagulant a heparin bolus dose of 2,000 U at the start of the hemoperfusion session.

Colistin methanesulphonate infusion and sampling protocol

Colistin methanesulphonate [Colimicina, UCB Pharma SpA, Pianezza (TO), Italy] was administered by i.v. infusion over 60 min at a dose of 4.5×10^6 U [2] in 250 ml of a normal saline solution every 12 h. Since no specific recommendations based on clinical evidence were prescribed for patients undergoing CRRT, standard colistin methanesulphonate (CMS) dose was adopted [26]. All biological samples were collected after the 3rd day of therapy at the steady state condition of colistin pharmacokinetics.

The samples were collected at time 0, 10 min, 1, 3, 6, 12, 24 and 48 h after the beginning of the CVVHDF session, and at time 0, 1, 3, 6, and 9 h for the CPFA-HF sessions. Infusion of colistin was done during the first hour of CPFA-HF.

Samples were drawn from systemic arterial blood, circuit venous line, effluent line and in the CPFA-HF session from precartridge line and postcartridge line, immediately stored at -22 °C and analyzed within a week. In addition, in burn patient *n*. Eight treated with colistin for 24 days we sequentially determined systemic arterial blood on the 1st and 2nd CPFA-HF (at day 6 and 7 of colistin therapy) and on the 6th and 7th CPFA-HF (day 16 and 17 of colistin therapy) (see Fig. 3).

Pharmacokinetic parameters including sieving coefficient (SC), effluent clearance (Clear_effl, ml/min), filter clearance (Clear_filter, ml/min) and cartridge clearance (Clear_cartridge, ml/min) were calculated with standard formula (see supplementary material).

Determination of colistin in plasma and ultrafiltrate

Colistin A and B were determined using the HPLC–MS/MS method described in detail in a previous study [21]. The analytical methods for plasma and ultrafiltrate samples were validated following the common procedures recommended by the Guideline on bioanalytical method validation of the European Medicines Agency [27].

Statistical methods

The software program Statistica (Statistica 6.1, StaSoft Inc, Tulsa, OK, USA) was used for descriptive statistics, ANOVA with the Duncan multicomparison test, Student's test, and linear regression analysis for quantitative variables and graphs. Values were expressed as median (interquartile range). p values <0.05 were considered statistically significant.

Results

Clinical and dialysis data

The clinical data and outcome of patients treated with colistin are reported in Table 1. Only four patients survived out of 12. Seven patients were severely burned (two survived) and five were admitted to the intensive care unit after a polytrauma event (two survived). Most of patients were affected by multiple infections, and treated with several antibiotics.

Table 2 shows dialysis flow rates in groups CVVHDF, CPFA-HF and Hemoperfusion. Blood flow rates were significantly higher in CPFA-HF than in CVVHDF (100.0 vs. 135.0 ml/min). Also the effluent volumes, obtained by the sum of infusion and dialysate volumes, were significantly different (3,800 vs. 1,550 ml/h, $p < 0.05$). In addition, in group CPFA-HF the rate of treated plasma reached median values higher than 20 ml/min.

Colistin handling in group CVVHDF

SC_{cvvhdf} was significantly lower for colistin A than for colistin B over the entire CVVHDF session (Fig. 1a). SC_{cvvhdf} values peaked (SC_{max}) early during each session ($SC_{max} = 0.40$ at 10 min for colistin A, $SC_{max} = 0.59$ at 3 h for colistin B), and slightly declined after 48 h

($SC_{cvvhdf} = 0.22$ for colistin A and $SC_{cvvhdf} = 0.30$ for colistin B, see Fig. 1a).

Figure 1b and c show the Clear_effl and Clear_filter for colistin A and B, respectively. Most Clear_filter values overlaid Clear_effl values, except for an early peak found 1 h after infusion for both colistin A and B. Declining clearance values were progressively observed, reaching half of the starting values at 48 h.

No correlation between blood flow rate and colistin A sieving coefficient was found (Fig. 5, panel a, n 40 points), whereas a weak negative correlation was present with colistin B sieving coefficient (Fig. 5, panel b, n 40 points).

Colistin handling in group CPFA-HF

During CPFA-HF sessions, the colistin A Cpl_in decreased roughly 4-fold (from basal level of 10.4 to 2.6 mg/l at 9 h) (Fig. 2a). Colistin A and B pre-cartridge levels were about 4 and 2 mg/l, respectively, representing about 50–60 % of the levels present in systemic plasma. Post-cartridge, the colistin levels were lower than 0.2 mg/l (see Fig. 2a), or not detectable any longer (see Fig. 2b).

The extracorporeal plasma clearance of colistin (the sum of the effluent and cartridge clearance) was slightly higher for colistin B than for colistin A, with values of approximately 40 and 30 ml/min, respectively (Fig. 2c, d).

In a burn patient (n . 8) treated with colistin for 24 days the systemic levels for colistin A and B on day 16 and 17 of colistin therapy (6th and 7th CPFA-HF sessions) showed an accumulation with peak values of 20 and 4 mg/l, respectively (Fig. 3b), double in comparison to those determined on day 6 and 7 of colistin therapy (1st and 2nd CPFA-HF) (Fig. 3a).

No correlation between blood flow rate and colistin A and B sieving coefficient was found (Fig. 5, panel c, d, respectively, n 16 points).

Table 2 Dialysis flow rates in patients on CVVHDF (n 7 sessions) and CPFA-HF (n 4 sessions)

	Group CVVHDF	Group CPFA-HF	p^a
Patients (n)	7	4	–
Blood flow rate (ml/min)	100 (100–100)	135 (130–140)	<0.05
Infusion flow rate pre (ml/h)	800 (650–800)	2,300 (2,000–2,300)	<0.05
Infusion flow rate post (ml/h)	–	1,650 (1,000–1,800)	–
Dialysate flow rate (ml/h)	750 (725–900)	–	–
Hematocrit (%)	0.27 (0.25–0.29)	0.34 (0.29–0.38)	<0.05
Plasma flow rate (ml/min)	–	20 (15–25)	–

Data are expressed as median (1st–3rd interquartiles)

CVVHDF continuous venovenous hemodiafiltration, CPFA-HF coupled-plasma filtration adsorption-HF

^a Student's test between groups CVVHDF (n 40) and CPFA-HF (n 16)

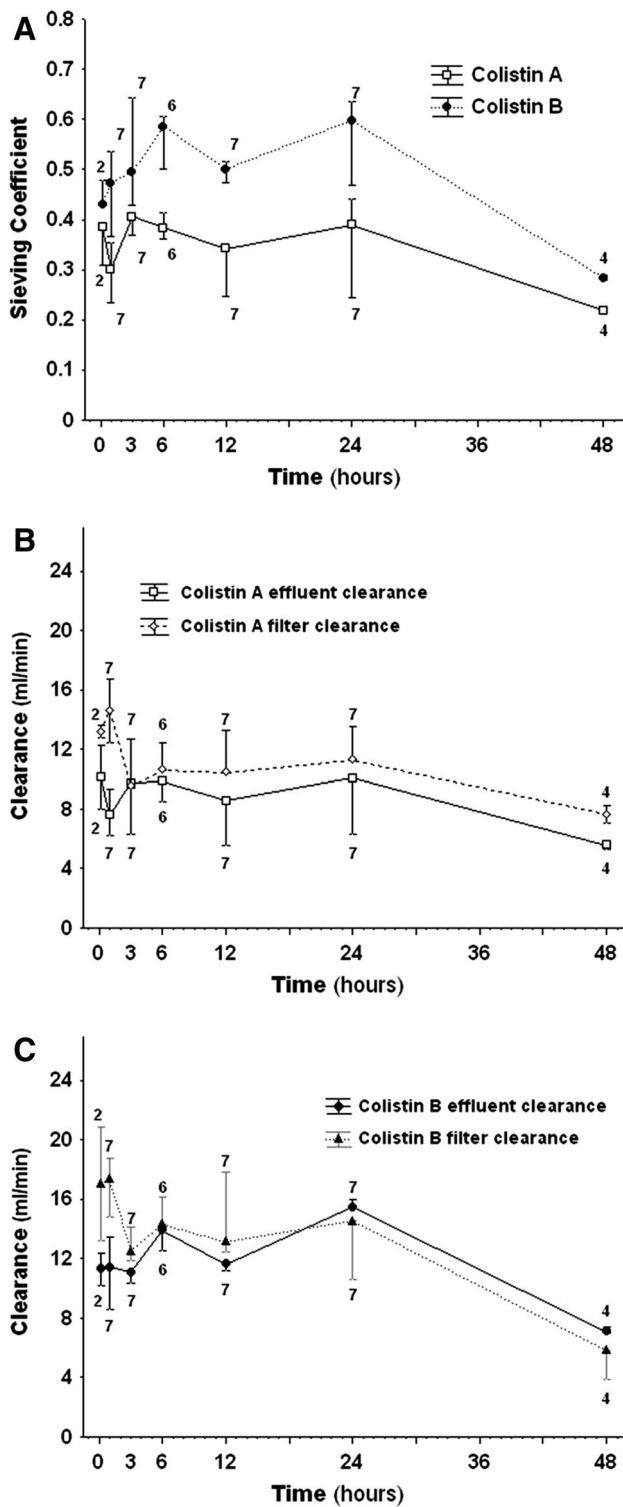


Fig. 1 Colistin A and B removal on CVVHDF. **a** (upper panel) Shows SC_{cvvhdf} of colistin A and B. **b** (middle panel) and **c** (lower panel) Show effluent (Clear_{eff}) and filter clearances (Clear_{filter}) for colistin A and B, respectively. Data are given as median (interquartiles). Numbers of box plots with whiskers indicate the individual data points. CVVHDF continuous venovenous hemodiafiltration, SC sieving coefficient

Colistin handling in the patient undergoing hemoperfusion

In the initial part of the 2-h hemoperfusion session, the postcartridge concentrations for colistin A and B were about 30 % lower than those measured before the cartridge (Fig. 4, panel a). Clearance for both colistin A and B showed similar patterns, declining to a minimal level of 2–3 ml/min at the end of the 2-h session (Fig. 4, panel b).

Discussion

Blood extracorporeal treatments by CVVHDF, CPFA-HF and hemoperfusion all efficiently remove a significant amount of active forms of colistin, the highest clearance values being observed with plasma sorbent technology.

So far, only a few reports based on a limited number of patients have addressed the issue of colistin clearance due to extracorporeal treatments [9–16]. Some information was related to hemodiafiltration and intermittent hemodialysis, and most data were collected upon treatments with polyacrylonitrile membrane [9, 11, 15]. In addition, the reported pharmacokinetics data were not homogeneous, and led to contradictory dosage adjustments to ensure optimal concentrations of active colistin [9–14]. As a matter of fact, presence of residual renal function, dialysis dose, differences in RRT techniques, including the use of filter membrane with different adsorption capacity, might offer a partial explanation for the discrepancies observed in the effluent or filter clearance [9, 13, 15]. As shown in Table 2, the delivered dialysis dose in both groups CVVHDF and CPFA-HF roughly reached (500 ml/kg/day), that is the currently suggested target of dialysis adequacy [23]. To date, no data are available for patients undergoing sorbent technology treatments, such as plasma adsorption or hemoperfusion, and also in the present case findings on colistin extracorporeal clearance obtained from CVVHDF with polysulfone membrane exceed the ones so far reported. This new high-permeability membrane allows improved clearance of middle-size molecules without an increase in albumin loss [28]. At the moment, clearance data for this dialyzer are available for small and some middle-size molecules only, because of the novelty of this type of membrane.

In CVVHDF, the extracorporeal clearance of colistin depends on its elimination through the large exchange area (1.8 mq) of high-flux polysulfone membrane. Polysulfone material is characterized by an anionic surface without significant protein absorption properties, and freely permeable to substances with molecular weight up to 30 kDa [29]. A higher SC for colistin B than for colistin A was

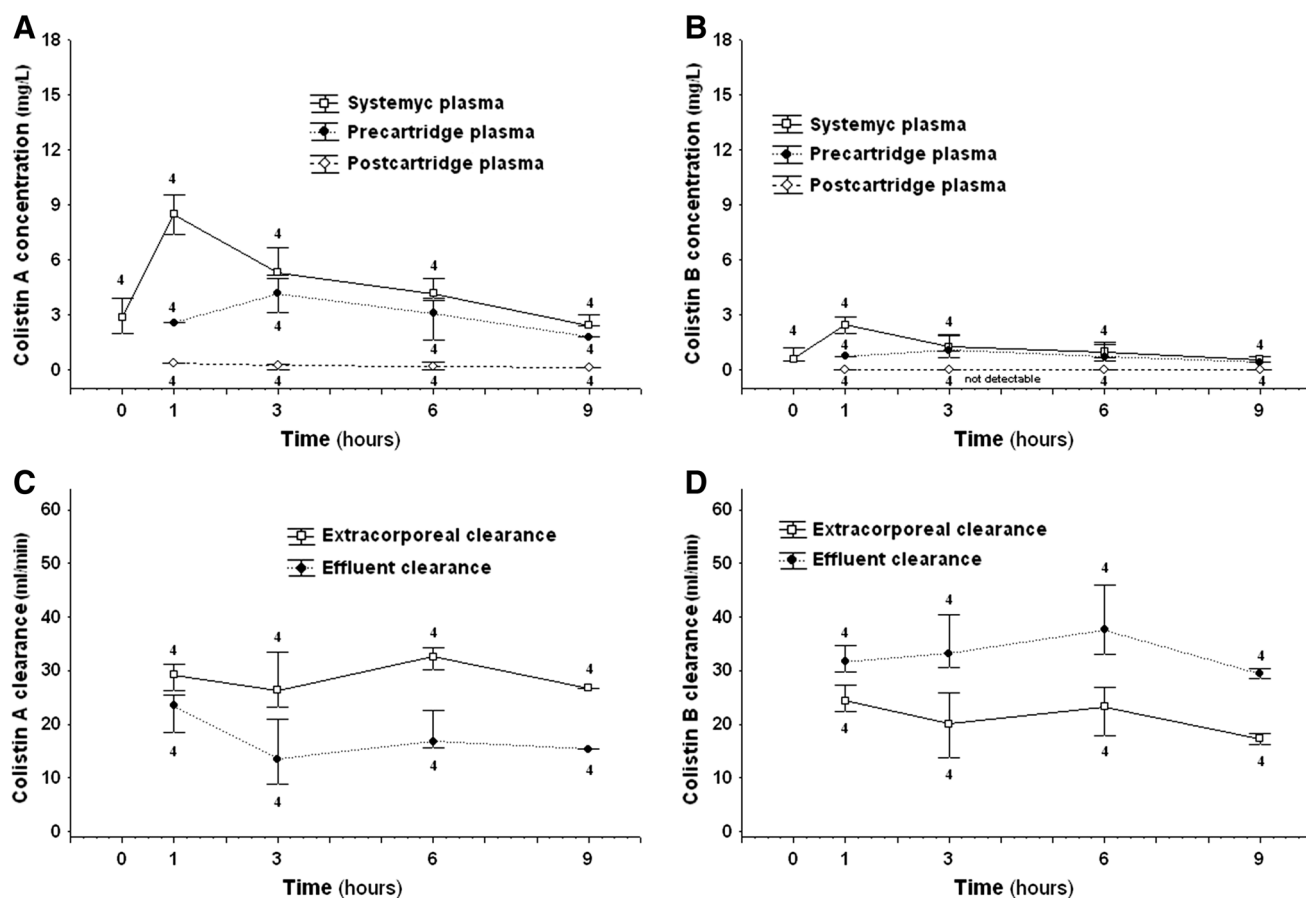


Fig. 2 Colistin A and colistin B concentrations and clearances throughout 9-h CPFA-HF treated patients (n 4 sessions). **a** and **b** Show concentrations of colistin A (upper left panel) and colistin B (upper right panel) in systemic, pre-cartridge and post-cartridge plasmas. **c** and **d** Show extracorporeal and effluent clearances of colistin A (lower left panel) and colistin B (lower right panel).

confirmed [21], as colistin A is likely to be more extensively bound to albumin than colistin B due to its longer fatty acid residue [4]. As expected, the extent of Clear_effl and Clear_filter (the latter representing the sum of effluent and adsorption clearance) in the patients treated with CVVHDF were substantially the same (Fig. 1b, c), as the polysulfone membrane has small and transient adsorption capacity [29].

In four patients (2 with severe burns and 2 with polytrauma) affected by AKI and refractory septic shock, a CPFA-HF treatment was applied [17, 18, 24]. By measuring the clearance of colistin for hemofilter and sorbent cartridge separately, we found that the plasma colistin A and B present in the pre-cartridge (after the plasmafilter) were fully adsorbed by the cartridge, leaving negligible concentrations in the post-cartridge sampling site, as shown in Fig. 2a, b. Interestingly, the concentrations of colistin determined in the pre-cartridge plasma were proportional to those present in the systemic plasma, and comparatively

Extracorporeal clearances are obtained by the sum of cartridge and effluent clearance (n 4 sessions). Data are given as median (interquartiles). Numbers of box plots with whiskers indicate the individual data points. CPFA-HF coupled-plasma filtration adsorption-HF

higher for colistin B, probably because of its lower binding to proteins [4]. Thus, the measured cartridge clearance (roughly 15–20 ml/min) added to the effluent clearance of the hemofilter, produces for the 9 h of treatment a total extracorporeal clearance as extensive as 34 and 43 ml/min for colistin A and B, respectively. These extracorporeal clearance values should be added to the endogenous clearance of both colistin and its prodrug CMS, which are in turn affected by renal failure [11]. Even if the decreased renal function implies that a larger fraction of the CMS dose (mainly eliminated by the kidneys) is converted to colistin, renal clearance of colistin represents only a minimal fraction (about 4 %) of its extrarenal clearance of 48.7 ml/min [30]. The CPFA-HF extracorporeal colistin clearance of 40 ml/min for 9 h is close to that recently reported in a patient on extended dialysis by Strunk et al. [31], demonstrating no accumulation of drug after 9 days of treatment. In effect, in our burn patient on CPFA-HF, after 16–17 days of treatment colistin peaked at 20 mg/l.

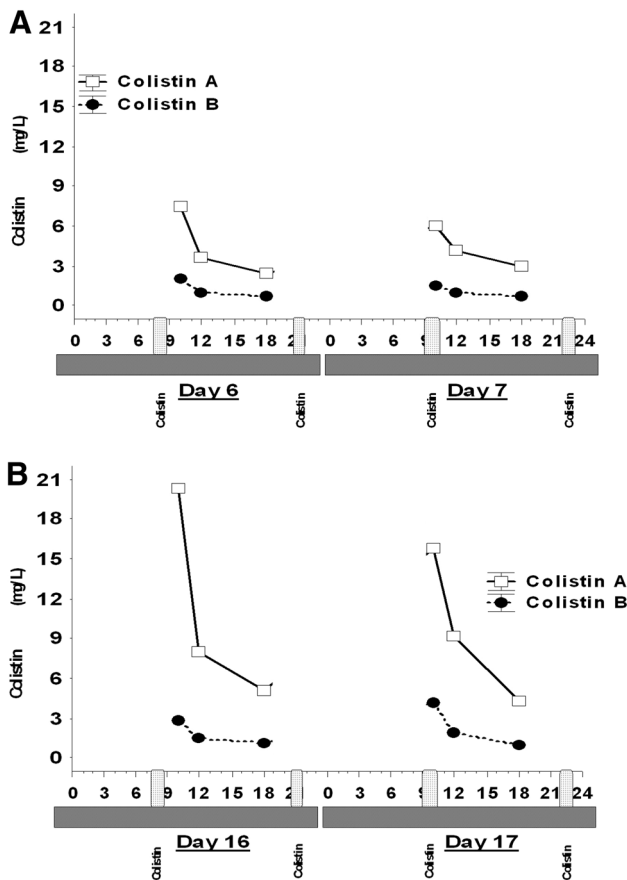


Fig. 3 Colistin A and colistin B systemic colistin concentration in a burned patient during CPFA-HF treatment. **a** Shows the colistin systemic levels on day 6–7 of colistin therapy, whereas panel **b** after 16 and 17 days of colistin administration. CPFA-HF coupled-plasma filtration adsorption-HF

On the other hand, the patient responded well to this antibiotic therapy, and he survived with a complete recovery of renal function.

Since both SC and clearance depend on many dialytic parameters, such as blood flow, ultrafiltrate flow, albumin fraction sampling time, and patency of circuit (which is also affected by the type of anticoagulant), a separate evaluation of the effect of the anticoagulant used is very difficult. The same applies to the relationship between SC and blood flow (see Fig. 5), which are substantially uncorrelated during CVVHDF (Fig. 5, panel a, b) and CPFA-HF (Fig. 5, panel c, d) over the operative conditions of blood flow variations (100 vs. 135 ml/min, see Table 2).

Equivalent clearance values of 15 ml/min for colistin A and B were observed at the beginning of the two consecutive hemoperfusion sessions carried out in a patient with infection from Klebsiella KPC. However, the short time of application (2 h) likely resulted in a negligible impact of hemoperfusion on the daily total body colistin clearance. Recently some endotoxin adsorbents for extracorporeal

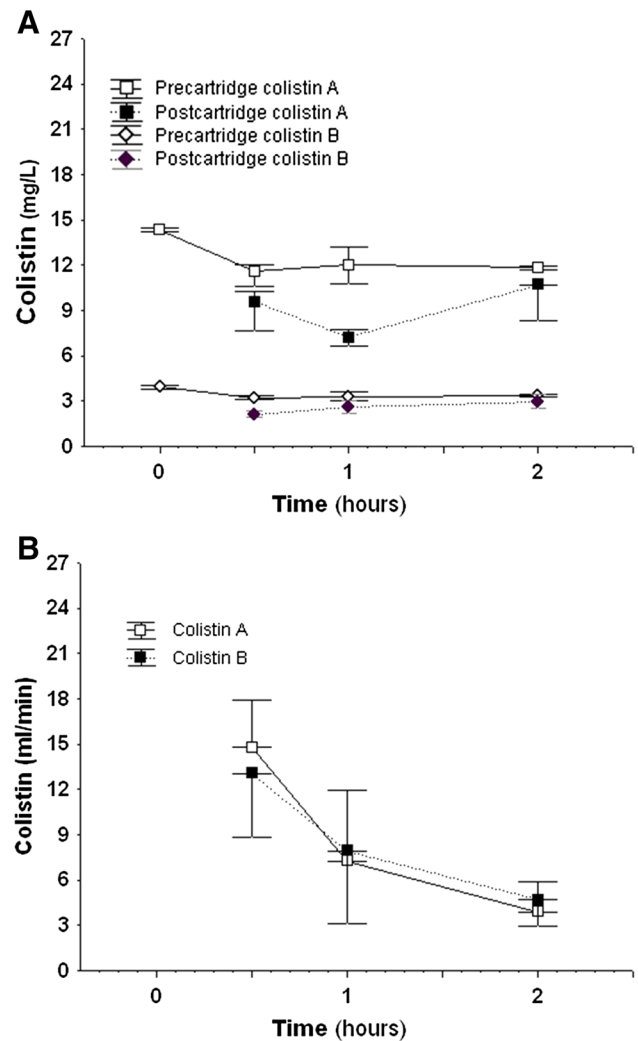


Fig. 4 Colistin A and B concentrations and clearances during hemoperfusion. **a** Shows precartridge and postcartridge plasma concentrations of colistin A and B throughout 2-h hemoperfusion (one patient, 2 consecutive sessions). **b** Shows colistin A and B plasma clearance throughout 2-h hemoperfusion (one patient, 2 consecutive sessions)

blood purification have been compared [32]. Among them, only the polymyxin B-based adsorbents were able to reduce the lipopolysaccharide (LPS) activity. This study [32] showed that during toraymyxin hemoperfusion in vitro (the sorbents used in our clinical setting of hemoperfusion) the reduction in LPS activity was caused by polymyxin B desorption, which inactivated the endotoxins [32]. However, in our clinical settings we found no significant variation in polymyxin B area signal of effluent and circuit blood samples, so we could not confirm this phenomenon (polymyxin B was our internal standard).

In conclusion, we demonstrated that during CPFA-HF and CVVHDF with high-flux polysulfone filter, colistin A and B were efficiently removed. The extent of this removal, quite well predicted by parameters of dialysis efficiency

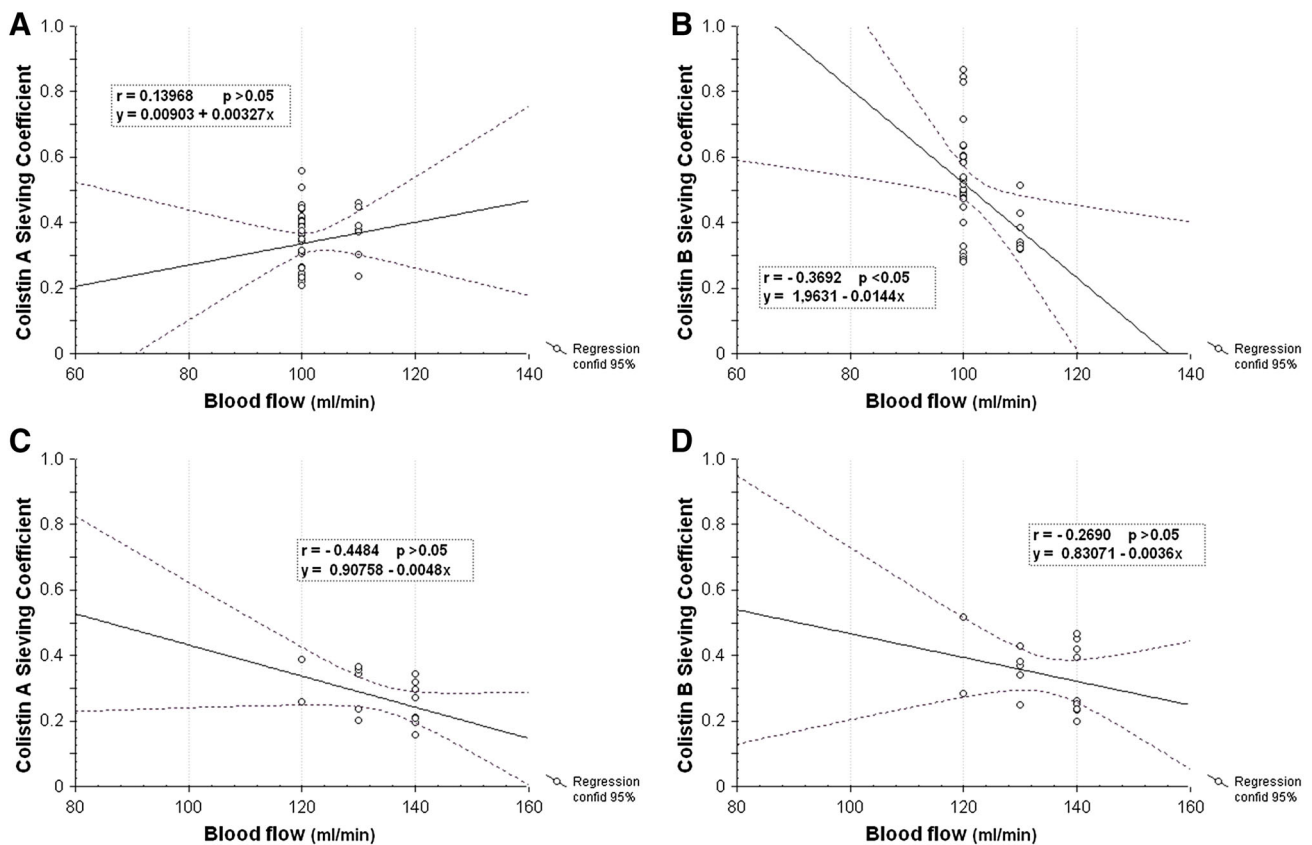


Fig. 5 Correlation between blood flow rate and colistin A and B sieving coefficient. **a** and **b** Show correlations during CVVHDF for colistin A and B, respectively (n 40 points). **c** and **d** Show correlations during CPFA-HF for colistin A and B, respectively (n 16 points). CVVHDF continuous venovenous hemodiafiltration, CPFA-HF coupled-plasma filtration adsorption-HF

(volume of effluent, volume of plasmafiltrate) and by free fraction of drug, can counterbalance or overcome the increased bioavailability of colistin due to renal failure. These data suggest that patients on CVVHDF and, even more, patients on CPFA-HF should receive an unreduced CMS dosage, although, with long-term administration, determination of colistin plasma levels is recommended on account of the risk of drug accumulation.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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