

# Pharmacokinetics of Ampicillin/Sulbactam in Critically Ill Patients with Acute Kidney Injury undergoing Extended Dialysis

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## Summary

**Background and objectives** The fixed antibacterial combination of ampicillin and sulbactam is frequently used for various infections. Intact kidneys eliminate approximately 71% of ampicillin and 78% of sulbactam. Patients on thrice-weekly low-flux hemodialysis exhibit an ampicillin  $t_{1/2}$  of 2.3 hours on and 17.4 hours off dialysis. Despite its frequent use in intensive care units, there are no available dosing recommendations for patients with AKI undergoing renal replacement therapy. The aims of this study were to evaluate the pharmacokinetics of ampicillin/sulbactam in critically ill patients with AKI undergoing extended dialysis (ED) and to establish a dosing recommendation for this treatment method.

**Design, setting, participants, & measurements** Twelve critically ill patients with anuric AKI being treated with ED were enrolled in a prospective, open-label, observational pharmacokinetic study. Pharmacokinetics after a single dose of ampicillin/sulbactam (2 g/1 g) was obtained in 12 patients. Multiple-dose pharmacokinetics after 4 days of twice-daily ampicillin/sulbactam (2 g/1 g) was obtained in three patients.

**Results** The mean dialyzer clearance for ampicillin/sulbactam was  $80.1 \pm 7.7/83.3 \pm 12.1$  ml/min. The  $t_{1/2}$  of ampicillin and sulbactam in patients with AKI undergoing ED were  $2.8 \pm 0.8$  hours and  $3.5 \pm 1.5$  hours, respectively. There was no significant accumulation using a twice-daily dosage of 2 g/1 g ampicillin/sulbactam.

**Conclusions** Our data suggest that in patients treated with ED using a high-flux dialyzer (polysulphone, 1.3 m<sup>2</sup>; blood and dialysate flow, 160 ml/min; treatment time, 480 minutes), a twice-daily dosing schedule of at least 2 g/1 g ampicillin/sulbactam, with one dose given after ED, should be used to avoid underdosing.

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## Introduction

The fixed antibacterial combination of the  $\beta$ -lactam ampicillin and the  $\beta$ -lactamase inhibitor sulbactam was approved by the US Food and Drug Administration in 1986. The use of this combination is recommended by national and international guidelines as first-line therapy for various respiratory and skin infections (1). In 2003, a survey in 130 hospitals in the United States involving 1,795,504 patients revealed that the ampicillin group of antibiotics seems to be the most commonly prescribed (2). In individuals with normal renal function, 71% of ampicillin (349.4 Da) and 78% of sulbactam (233.2 Da) are excreted unchanged in the urine with an elimination  $t_{1/2}$  of 1.4 hours for ampicillin and 1.7 hours for sulbactam (3). In patients with stage 5 CKD (*i.e.*, GFR <15 ml/min per 1.73 m<sup>2</sup>), the terminal elimination  $t_{1/2}$  of both substances increases to 17 and 15 hours, respectively. Although ampicillin/sulbactam is frequently used in patients on dialysis, the world literature consists of pharmacokinetic (PK) data on only four chronic hemodialysis patients (3). Many characteristics of dialysis have changed over the

last 23 years since the publication by Blum *et al.* (3), such as the use of high-flux dialysis membranes with larger surface area and prolonged dialysis hours. Moreover, in intensive care units (ICUs), extended dialysis (ED), a hybrid of continuous and intermittent renal replacement therapy (RRT), is increasingly used throughout the world (4–7). ED removes various antibiotics more efficiently compared with standard intermittent hemodialysis (IHD) three times a week or continuous RRT (8–13), as very recently reviewed by Bogard *et al.* (14). A single report from a patient with AKI suggests that higher doses of ampicillin/sulbactam might also be necessary for critically ill patients treated with ED compared with intermittent hemodialysis (IHD) in the outpatient setting (15). To enhance the quality of PK information available to clinicians, as recently requested by a Kidney Disease Improving Global Outcomes working group (16), we determined single-dose and multiple-dose PK of ampicillin/sulbactam in critically ill patients with stage 3 AKI, according to the Acute Kidney Injury Network (AKIN) classification, undergoing ED.

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## Materials and Methods

Adult ICU patients with AKIN stage 3 AKI being treated with ED and having a clinical indication for the administration of ampicillin/sulbactam were studied after receiving the first dose of the drug. Patients were included in this study after informed consent was obtained from the patient or the patient's legal representative. Ampicillin/sulbactam (2 g/1 g) was infused intravenously in 12 patients over a period of 30 minutes using an infusion pump. ED was performed using the Genius batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany) with a polysulfone high-flux dialyzer (F60S; surface area, 1.3 m<sup>2</sup>) (Fresenius Medical Care) as described previously (12). The technical details of the system are explained elsewhere (17). In brief, sterile bicarbonate dialysate is filled into a 75- or 90-L tank and is then circulated in a closed loop circuit. During dialysis, fresh dialysate is taken from the top of the tank, whereas the spent dialysate flows back to the bottom (17). Thus, complete collection of spent dialysate in the same tank after the dialysis session permits estimation of the total removed amount of a substance, assuming that adsorption of the substance to the dialyzer system is negligible. The average dialysis time during the study was 442±77 minutes and mean blood and counter current dialysate flow was 162±6 ml/min, resulting in a mean urea reduction ratio of 50.1%±2.7%. ED was started approximately 3 hours after the end of the ampicillin/sulbactam infusion. Vascular access in all patients was achieved by a double-lumen catheter inserted either into the internal jugular or the femoral vein. In three patients, multiple-dose PK was obtained on day 4 of treatment using a twice-daily dosage of ampicillin/sulbactam (2 g/1 g). The study protocol was approved by the Hannover Medical School Ethics Committee (Project 4841).

## Sampling and Analysis

EDTA plasma samples (5 ml) were collected via an arterial catheter before intravenous ampicillin/sulbactam 1, 2, and 3 hours after the start of infusion as well as at the start of the ED session. Sampling continued at 0.25, 0.5, 1, 2, 4, and 7 hours after beginning ED as well as 0.25, 1, and 2 hours after the ED session. Samples were centrifuged at 1300×g for 10 minutes at 4°C. Plasma was separated and stored at -80°C until analysis. Additional blood samples were drawn before and after the dialyzer (*i.e.*, from the afferent "artery" and efferent "venous" dialyzer blood tubing 15 minutes after the start of ED to calculate the dialyzer clearance). For the collection of the predialyzer and postdialyzer samples, ultrafiltration was stopped. Furthermore, in seven patients we took samples from the total spent dialysate after it was mixed by air insufflations as well as from the total collected ultrafiltrate, as described previously (12).

## Chemical Assays

Stabilization of ampicillin/sulbactam in plasma was achieved by addition of 100 mM 2-(*N*-morpholino)ethanesulfonic acid buffer (pH 6.5) 1/1 (v/v). Calibrators ranged from 0.1 to 100 mg/L for ampicillin and 0.05 to 50 mg/L for sulbactam, respectively. After addition of amoxicillin as internal standard plasma/2-(*N*-morpholino)ethanesulfonic

acid samples were treated with methanol (80% final concentration) for protein precipitation. Samples were immediately vortexed (20 seconds) and centrifuged for 10 minutes at 20,800×g at 4°C. Four hundred microliters of supernatant was concentrated to dryness using nitrogen gas stream. Dried samples were re-suspended in 150 μl H<sub>2</sub>O. After centrifugation for 3 minutes (20,800×g, 4°C), 100 μl of supernatant was transferred for liquid chromatography-mass spectrometry (LC-MS) analysis. Samples were kept accurately at 4°C using a temperature-controlled autosampler.

LC-MS was realized by direct coupling the LC column (Nucleodur Pyramid 3μ, 50×3.0 mm, used in combination with an C<sub>18</sub> column SecurityGuard) to an MS system (LC-MSD SL, Agilent 1100) equipped with electrospray ion source allowing adequate selective and sensitive detection in single ion mode. An aliquot of 5 μl of supernatant of each prepared sample was injected and analyzed under isocratic conditions (90% eluent A = H<sub>2</sub>O, 2 mM NH<sub>4</sub>Oac, 0.1% acetic acid, pH 3.8 and 10% eluent B = methanol) with a constant total flow rate of 400 μl/min for 12 minutes at 40°C column temperature. MS detection in negative single ion mode (capillary voltage, -4000 V; exit voltage, 100 V; temperature, 350°C; gas supply, 100 psi; nebulizer gas, 35 psi; drying gas, 10 L min<sup>-1</sup>) enables detection of ampicillin (t<sub>R</sub>=6.3 minutes, *m/z* 348.2), sulbactam (t<sub>R</sub>=2.2 minutes, *m/z* 232.2), and amoxicillin (t<sub>R</sub>=1.3 minutes, *m/z* 364.2) deprotonated molecular ions.

Three quality controls (2.5 mg/L, 10 mg/L, and 50 mg/L for ampicillin, and 1.25 mg/L, 5.0 mg/L, and 25 mg/L for sulbactam, respectively) were included during the assay validation for determination of intraday and interday variation coefficients (*n*=5). The mean variation coefficient for precision was 8.3% and the mean accuracy was 107%. All relative SDs for accuracy and precision were <10%.

## PK Calculations

Noncompartmental PK analyses for the data were performed using WinNonlin software program (WinNonlin, version 3.1; Pharsight Corporation, Mountain View, CA). The maximum concentration in plasma (C<sub>max</sub>) and time to reach C<sub>max</sub> (T<sub>max</sub>) after drug administration were obtained directly by visual examination of concentration-time data.

The area under the plasma concentration-time curve from time 0 to infinity (AUC<sub>0-∞</sub>) was calculated by the log-linear trapezoidal rule until the time of last quantifiable plasma concentration and then extrapolated to infinity by using the quotient of the last measurable concentration (C<sub>last</sub>) to the terminal phase rate constant (β). The terminal elimination rate constant (β) was estimated from the slope of terminal exponential phase of the logarithmic plasma concentration-time profile using at least three data points. The elimination half-life (t<sub>1/2β</sub>) was determined as 0.693/β. Overall drug clearance (CL<sub>tot</sub>; *i.e.*, residual drug elimination capacity by the body and drug elimination by ED) was determined as dose/AUC<sub>0-∞</sub>. The apparent volume of distribution during the terminal phase (V<sub>z</sub>) was calculated as dose/(AUC<sub>0-∞</sub>β). For all variables, arithmetic mean values, SD, median, and minimum and maximum values were calculated, with the exception of T<sub>max</sub>, for which median and minimum-maximum ranges are given. The dialyzer

clearance ( $CL_{dial}$ ) was calculated based on plasma perfusion rate and extraction ratio  $(C_a - C_v)/C_a$ , using the equation  $CL_{dial} = Q_e \cdot (C_a - C_v)/C_a$ , where  $Q_e$  is the effective plasma perfusion rate of the dialyzer (dialyzer blood flow rate  $\times [1 - \text{hematocrit}]$ ) and  $C_a$  and  $C_v$  are arterial and venous dialyzer plasma drug concentrations, respectively. A multiple-dose PK was obtained in three patients who received ampicillin/sulbactam over a period of 4 days, at a dosage of 2 g/1 g every 12 hours, using the same timed blood draw regimen as on day 1 of treatment. In these patients, overall drug clearance was calculated as  $\text{dose}/AUC_{0-12}$ .

**Results**

Data from 12 critically ill patients (seven men and five women, aged 19–83 years) treated with ampicillin/sulbactam and undergoing ED for AKIN stage 3 AKI were analyzed. Patient demographics, laboratory data, and disease

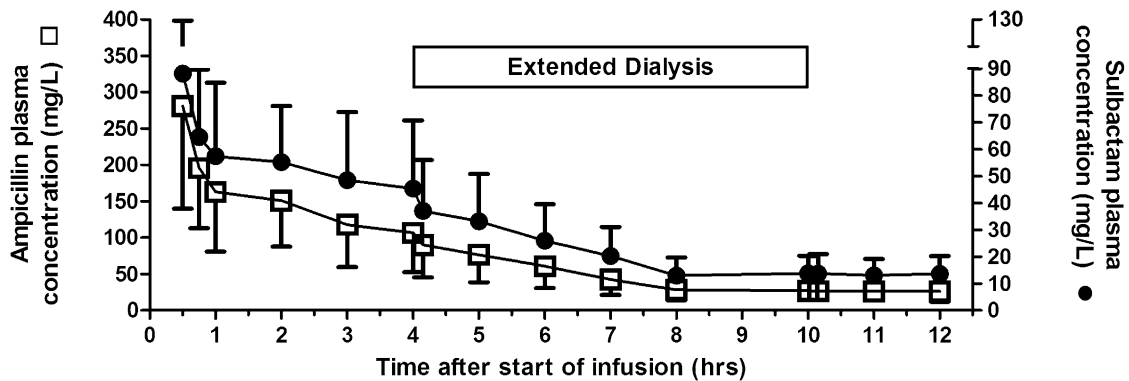
severity score within the 24-hour study period are reported in Table 1.

Average plasma concentration–time data for ampicillin/sulbactam are shown in Figure 1. The dialyzer clearance for ampicillin and sulbactam was  $80.1 \pm 7.7$  and  $83.3 \pm 12.1$  ml/min, respectively, as shown in Figure 2. Tables 2 and 3 summarize all PK data and compare them with literature data for IHD in an outpatient’s setting as well as with normal controls without renal impairment. Average plasma concentration–time data for ampicillin/sulbactam on day 1 and day 3 of treatment (*i.e.*, multiple-dose PK data) are shown in Figure 3. The median (interquartile range) recovery of the substances in the collected spent dialysate and ultrafiltrate of seven patients was 1739 mg (range, 1605–2520) for ampicillin and 930 mg (range, 615–1020) for sulbactam, respectively. On the basis of these data, 87% of ampicillin and 93% of sulbactam had been removed by a single ED session. The combination

**Table 1. Clinical data of critically ill patients treated with a single dose of ampicillin/sulbactam and undergoing extended dialysis**

Sex	Age (yr)	Clinical Condition	Weight (kg)	Height (cm)	APACHE II Score	SOFA Score	Protein (g/L)	UF Volume (ml)
M	69	GI bleeding	71	176	25	8	46	2400
M	59	Liver transplant	86	180	24	12	49	3150
F	62	Pancreatitis	65	160	15	6	41	2380
M	70	Sepsis	140	180	38	19	44	70
F	83	VRP	70	165	21	11	48	840
F	49	HRS	70	165	28	14	52	600
F	61	Liver cirrhosis	86	168	22	12	54	2000
F	33	HIV/GN	50	165	21	10	36	2010
M	57	Kaposi sarcoma	66	178	23	11	39	120
M	56	Sepsis	85	182	33	18	53	140
M	19	Liver transplant	66	178	22	13	55	410
M	49	Sepsis	70	173	15	5	55	870

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; UF, ultrafiltration; GI, gastrointestinal; VRP, valve replacement; HRS, hepatorenal syndrome.



**Figure 1. | Mean plasma concentrations of ampicillin/sulbactam in plasma of critically ill patients with AKI undergoing extended dialysis (duration depicted by box size) after a single intravenous dose of 2.0 g/1.0 g ampicillin/sulbactam. Infusion period was 30 minutes. Extended dialysis started about 3 hours after the end of the ampicillin/sulbactam infusion. Values are arithmetic means  $\pm$  SEM,  $n=12$ .**

therapy of ampicillin/sulbactam was well tolerated in all patients.

## Discussion

Our study provides the first systematic PK data of ampicillin/sulbactam in critically ill patients with anuric AKI. The PK data obtained in this prospective study in patients undergoing ED show the following: (1) ampicillin/sulbactam is eliminated by ED, (2) current dosing recommendations from patients undergoing IHD (3 g every 24 hours) would cause a significant underdosing of the drug in patients treated with ED, and (3) a dosage of 3 g every 12 hours in patients undergoing ED does not lead to a significant accumulation of the drug.

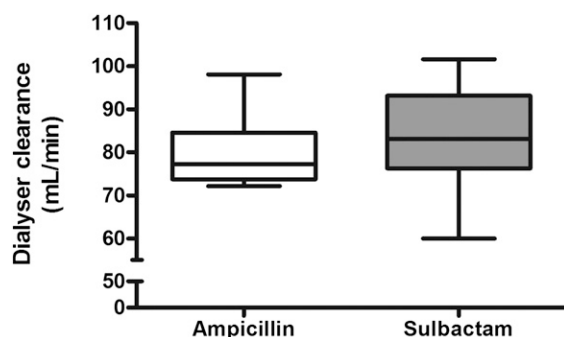
Ampicillin and sulbactam have a similar PK profile. In healthy adult humans are 28% of ampicillin and 38% of sulbactam protein bound. The volume of distribution of ampicillin/sulbactam is  $0.22 \pm 0.04$  and  $0.30 \pm 0.12$  L/kg, respectively. Both drugs have a plasma elimination  $t_{1/2}$  of approximately 1 hour, and >60% is primarily excreted unchanged by the kidneys in both cases. Patients with stage 4 CKD (*i.e.*, an estimated GFR of <30 ml/min per

1.73 m<sup>2</sup>) exhibit mean sulbactam AUC values three times higher and ampicillin AUC values twice those of patients with normal renal function (3).

Ampicillin/sulbactam is removed by hemodialysis. Blum *et al.* (3) found that 35% of the administered ampicillin and 45% of the administered sulbactam dose is eliminated in a 4-hour hemodialysis session using a modified cellulose low-flux dialyzer with a 1.0 m<sup>2</sup> surface (C-DAK model 3500; CD-Medical Inc, Miami Lakes, FL) and a blood flow of 200 ml/min. On the basis of the PK results obtained in four chronic hemodialysis patients, the current recommended dosage for ampicillin (2.0 g) and sulbactam (1.0 g) is every 24 hours. All PK parameters showed a remarkable variation. This is in line with data from healthy volunteers. Foulds *et al.* (18) reported a  $C_{max}$  with a wide variation for ampicillin and sulbactam from 82.1 to 154.3 mg/L and 32.0 to 93.7 mg/L. In our study  $C_{max}$  for ampicillin/sulbactam ranged from 75 to 360 mg/L and 74 to 157 mg/L, which can in our view be explained by the various underlying clinical conditions and comorbidities as well as the difference in the volume of distribution.

The  $t_{1/2}$  of ampicillin/sulbactam in our study was significantly higher than in healthy controls but shorter than in patients with stage 5 CKD (*i.e.*, chronic hemodialysis patients). This is not surprising because the dialyzer extraction ratio was also higher in our study. This is most likely due to differences in the dialyzer surface and material comparing the membrane from the 1980s with a currently used membrane. Because the protein binding of the two drugs is rather low, we do not think that the low serum albumin concentration had a profound influence on the enhanced elimination of ampicillin/sulbactam.

Like other antibiotics with time-dependent kill activity, the main PK/pharmacodynamic parameter for ampicillin/sulbactam is the proportion of time of the dose interval during which the drug concentration exceeds the minimum inhibitory concentration (MIC) ( $T > MIC$ ). For penicillin a  $T > MIC$  of approximately 50% of the dose interval was previously suggested to be effective (18). In our study, however, ampicillin/sulbactam concentrations exceeded MIC<sub>90</sub> values of Enterobacteriaceae, such as *Escherichia coli* or *Klebsiella pneumoniae* (MIC<sub>90</sub>  $\leq 2.0$  mg/L) or *Enterococcus faecalis*



**Figure 2.** | Dialyzer clearance of ampicillin/sulbactam in plasma of critically ill patients with AKI undergoing extended dialysis. Predialyzer and postdialyzer blood samples were drawn 15 minutes after start of treatment with no net ultrafiltration. Data are visualized as box and whisker plots. Horizontal bars indicate median values.

	Ampicillin	ED Patients (n=12)	IHD Patients (n=4)	Healthy Subjects (n=6)
$C_{max}$ (mg/L)		280.9±174.9	—	82.1–154.3 (19)
$T_{max}$ (h)		0.5	0.25	0.25
$AUC_{last}$ (mg·h/L)		847.5±499.5	1654.8±1170.2	158.4±30.1
$t_{1/2}$ (h)		2.8±0.8	2.22±0.92 <sup>a</sup> /17.39±7.94 <sup>b</sup>	1.41±0.65
$V_z$ (L)		13.1±11.1	—	—
$V_z$ (L/kg)		0.16±0.10	0.40±0.10	0.22±0.04
$CL_{tot}$ (ml/min)		61.1±55.2	31.0±21.0 <sup>b</sup>	218.6±52.4
$CL_{dial}$ (ml/min)		80.1±7.7	51.4±2.4	N/A

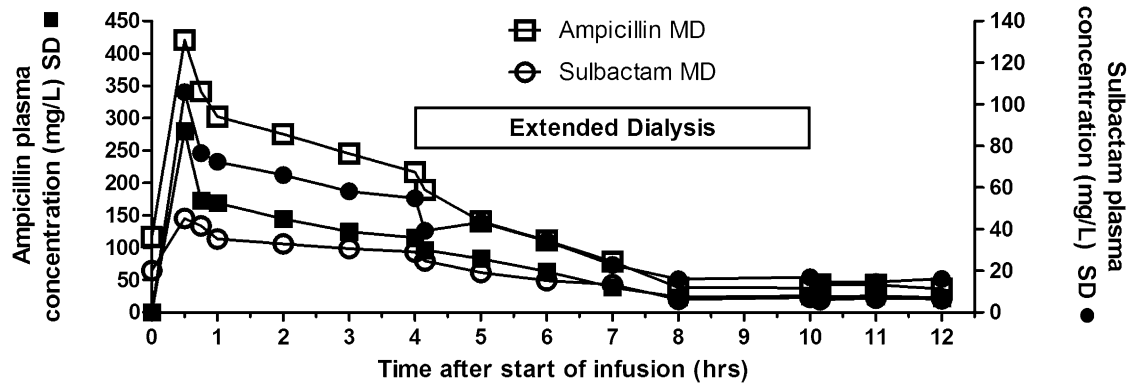
Data of ICU patients receiving ED compared with data by Blum *et al.* (3) on healthy controls and outpatients on intermittent hemodialysis. PK, pharmacokinetic; ED, extended dialysis; IHD, intermittent hemodialysis;  $C_{max}$ , peak plasma concentration;  $T_{max}$ , time of maximal plasma concentration;  $AUC$ , area under the curve;  $V_z$ , volume of distribution;  $CL_{tot}$ , overall drug clearance (*i.e.*, residual drug elimination capacity by the body and drug elimination by ED);  $CL_{dial}$ , dialyzer clearance.

<sup>a</sup>On dialysis.  
<sup>b</sup>Off dialysis.

Sulbactam	ED Patients (n=12)	IHD Patients (n=4)	Healthy Subjects (n=6)
C <sub>max</sub> (mg/L)	88.1±47.5	—	32.0–93.7 (19)
T <sub>max</sub> (h)	0.5	0.25	0.25
AUC <sub>last</sub> (mg·h/L)	324.1±189.7	432.2±206.3	85.5±23.3
t <sub>1/2</sub> (h)	3.5±1.5	2.27±0.64 <sup>a</sup> /13.36±7.39 <sup>b</sup>	1.73±0.72
V <sub>Z</sub> (L)	22.0±21.8	—	—
V <sub>Z</sub> (L/kg)	0.27±0.23	0.59±0.20	0.30±0.12
CL <sub>tot</sub> (ml/min)	81.0±81.7	45.3±19.5 <sup>b</sup>	216.6±97.2
CL <sub>dial</sub> (ml/min)	83.3±12.1	75.8±27.1	N/A

Data of ICU patients receiving ED compared with data by Blum *et al.* (3) on healthy controls and outpatients on intermittent hemodialysis. PK, pharmacokinetic; ED, extended dialysis; IHD, intermittent hemodialysis; C<sub>max</sub>, peak plasma concentration; T<sub>max</sub>, time of maximal plasma concentration; AUC, area under the curve; V<sub>Z</sub>, volume of distribution; CL<sub>tot</sub>, overall drug clearance (*i.e.*, residual drug elimination capacity by the body and drug elimination by ED); CL<sub>dial</sub>, dialyzer clearance.

<sup>a</sup>On dialysis.  
<sup>b</sup>Off dialysis.



**Figure 3. | Median concentrations of ampicillin/sulbactam in plasma of critically ill patients (n=3) with AKI undergoing extended dialysis (duration depicted by box size) after the first intravenous dose of 2.0 g/1.0 g ampicillin/sulbactam, as well as on day 4 of treatment at a dosing schedule of 2.0 g/1.0 g ampicillin/sulbactam twice daily. Data are presented as median values, n=3. SD, single dose; MD, multiple dose.**

(MIC<sub>90</sub>=2.0 mg/L), only for 8 hours (approximately 30% of the dosing interval for patients on intermittent hemodialysis) after start of infusion.

Despite the large variability of the PK parameter, we recommend administering at least 3 g ampicillin/sulbactam every 12 hours if patients with AKI undergo ED with the above-mentioned specifications. This recommendation is supported by the fact that ED eliminated more than three-quarters of both substances. Moreover, we did not find significant accumulation if patients received ampicillin/sulbactam at a dosage twice daily 2/1 g for up to 4 days. Moreover, Betrosian *et al.* showed that even high doses of ampicillin/sulbactam (18 g/9 g), as well as ultra-high doses (24 g/12 g), are well tolerated (19).

This study has some important limitations. Because the specifics of ED vary between centers, our dosing recommendation holds true only for the specifics of the ED procedure reported here; however, key characteristics (low dialysate and blood flow as well as long treatment hours) are in a rather narrow range worldwide (4), yet an even higher drug clearance is expected when higher flow rates (*e.g.*, blood flow 200 ml/min and dialysate flow 300 ml/

min) are applied. Furthermore, the timing of the start of ED (*i.e.*, 3 hours after the end of the ampicillin/sulbactam infusion) influenced the AUC<sub>0–∞</sub> and ampicillin/sulbactam removal. The earlier the ED with respect to drug administration, the lower the AUC<sub>0–∞</sub>, and the higher the resulting overall drug clearance. Thus, twice-daily dosing of 2/1 g ampicillin/sulbactam would be considered safe and necessary if ED starts within 3 hours after the administration of ampicillin/sulbactam. An ED treatment starting later will have a less marked effect on ampicillin/sulbactam removal. Lastly, the size and the purpose of our trial do not allow us to draw any conclusions regarding the efficacy of ampicillin/sulbactam in patients with AKI undergoing ED. Long-term effects on morbidity, mortality, and ICU length of stay after a change in dosing guidelines must be determined.

In summary, our data suggest that ED, which is by definition an intermittent mode of RRT, eliminates ampicillin/sulbactam effectively and to a larger extent than regular IHD. Thus, dosing ampicillin/sulbactam every 24 hours, as recommended for a regular hemodialysis, would result in a significant underdosing, which could be associated with a substantial risk, especially in septic patients in the ICU.

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### Disclosures

None.

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