

# Pharmacokinetics and total elimination of meropenem and vancomycin in intensive care unit patients undergoing extended daily dialysis\*

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**Objective:** Extended daily dialysis (EDD) combines the advantage of both intermittent hemodialysis and continuous renal replacement therapy: excellent detoxification accompanied by cardiovascular tolerability. The aim of this study was to evaluate pharmacokinetics of meropenem and vancomycin in critically ill patients with renal failure undergoing EDD.

**Design:** Prospective clinical study.

**Setting:** Surgical intensive care unit in a tertiary care center.

**Patients:** We studied intensive care patients with anuric acute renal failure being treated with EDD and receiving meropenem (n = 10) or vancomycin (n = 10) therapy.

**Interventions:** The antibiotics were administered 6 hrs (1.0 g meropenem) or 12 hrs (1.0 g vancomycin) before EDD was started in order to study the pharmacokinetics before and during EDD. In addition to the application of different methods to calculate pharmacokinetic parameters, the total dialysate concentration of both drugs was measured.

**Results:** Based on the amount of the drug recovered from the

collected spent dialysate, the fraction of drug removed by one dialysis treatment was 18% for meropenem and 26% for vancomycin. Dosing regimens for intermittent hemodialysis and continuous renal replacement therapy cannot be used for critically ill patients treated with EDD.

**Conclusion:** Our data suggest that patients treated with EDD by means of a high-flux dialyzer (polysulphone; surface area, 1.3 m<sup>2</sup>; blood and dialysate flow, 160 mL/min; EDD time, 480 mins) and current dosing regimens run the risk of being significantly underdosed, which may have detrimental effects on critically ill patients with life-threatening infections. The exact dose has to be tailored according to weight and severity of illness as well as the current minimal inhibitory concentration against the incriminated bacteria. Whenever possible, therapeutic drug monitoring should be performed. (*Crit Care Med* 2006; 34:51–56)

**KEY WORDS:** pharmacokinetics; vancomycin; meropenem; extended dialysis

Although there is no international consensus, the current literature suggests that the survival of critically ill patients with acute renal failure (ARF) can be improved by increasing the dose of renal replacement therapy, whether by intermittent hemodialysis (IHD) or continuous renal replacement therapy (CRRT) (1, 2). Recently, the advantages of these two classic modalities of renal replacement therapy in the intensive

care unit (ICU) have been successfully combined in a new hybrid technique named extended daily dialysis (EDD) (3–5). Results of a randomized controlled study as well as a recently published 2-year single-center experience showed that EDD provides excellent detoxification, accompanied by cardiovascular tolerability, even in severely ill patients in the ICU (3, 6). EDD for 12 hrs per day eliminated as much creatinine and urea as 24 hrs of continuous venovenous hemofiltration, with an average substitution rate of 3.2 L/hr (3). Despite the increasing use of EDD in the ICU throughout Europe and the United States (7), no published data are available on the effect of this highly efficient renal replacement therapy on the elimination of frequently used drugs in critically ill patients with renal failure. Moreover, the existing dosing and pharmacokinetic data for patients undergoing either IHD or CRRT may not be applicable to patients treated with EDD, because duration, filters

used, and blood flow are quite different from the two aforementioned techniques.

Because ARF in the ICU is frequently part of a multiple-organ-dysfunction syndrome encountered in patients with sepsis, the present study was undertaken to evaluate pharmacokinetics of meropenem and vancomycin in critically ill patients with ARF who were treated with EDD. For meropenem, a carbapenem  $\beta$ -lactam antibiotic with a wide therapeutic spectrum against Gram-positive and Gram-negative bacteria such as  $\beta$ -lactamase-producers and *Pseudomonas aeruginosa*, drug serum concentration monitoring is not routinely available. The glycopeptide vancomycin is used for the treatment of severe infections with pathogens such as *Staphylococcus* and *Streptococcus* species. Because of the narrow therapeutic range of vancomycin, large variation in volume of distribution and clearance, and the need to rapidly achieve and maintain a target range,

**\*See also p. 240.**

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Table 1. Clinical characteristics of the meropenem recipients

Patient	Sex	Age in yrs	Height in cm	Weight in kg	BMI	Clinical Condition
1	M	60	172	50	16.9	Lung transplantation due to pulmonary fibrosis
2	M	62	175	80	26.1	Ulcerative colitis, sepsis
3	F	53	170	70	24.2	Sepsis
4	M	48	175	60	19.6	Lung transplantation due to lung fibrosis
5	F	36	165	104	38.2	Acute myelocytic leukemia
6	M	49	189	80	22.4	Osteomyelofibrosis, sepsis
7	F	53	165	80	29.4	Pneumonia, heart and lung transplantation
8	F	50	170	73	25.5	Multiple organ failure
9	M	65	175	90	29.4	Pneumonia
10	M	67	175	80	26.1	Sepsis

BMI, body mass index.

therapeutic drug monitoring is routinely used.

## PATIENTS AND METHODS

**Patients and Study Protocol.** The Hannover Medical School Ethics Committee approved the study protocol. Adult intensive care patients with anuric ARF being treated with EDD and receiving meropenem (n = 10) or vancomycin (n = 10) were enrolled. The choice of the antibiotic for each patient was made on clinical grounds. Patients were enrolled in the study after informed consent had been obtained from the patient or the patient's legal representative. Meropenem was administered to ten patients in a 1-g dose as an intravenous infusion over a period of 30 mins, 6 hrs before EDD was started. Vancomycin (1.0 g) was infused in ten patients over a period of 60 mins, 12 hrs before EDD was started. This approach was chosen to study the pharmacokinetics of each drug before and during dialysis in the same patient whilst avoiding interday variability.

EDD was performed in all patients with a batch dialysis system (GENIUS, Fresenius Medical Care, Bad Homburg, Germany) with a polysulphone high-flux dialyzer (F60S [surface area, 1.3 m<sup>2</sup>], Fresenius Medical Care), as described previously (8, 9). The technical details of the system are explained in detail elsewhere (10). In brief, sterile bicarbonate dialysate is filled into the 75-L tank and is thereafter circulated in a closed-loop circuit. During dialysis, fresh dialysate is taken from the top of the tank while the spent dialysate flows back to the bottom. Thus, complete collection of spent dialysate in the same tank after the dialysis session permits measurement of the total amount removed of any substance. The average (mean ± sd) dialysis time during the study was 480 ± 6 mins, and mean blood and countercurrent dialysate flow was 160 ± 3 mL/min.

Blood samples were drawn from the radial or femoral artery line in all patients before administration of vancomycin; at 0.5, 1, 2, 4, 6, 8, and 12 hrs after administration of vancomycin; before dialysis; during EDD at time points 2, 4, and 6 hrs; at the end of EDD; and

at 0.5, 1, 3, and 8 hrs after EDD. For meropenem recipients, blood samples were drawn from the arterial line before administration of the drug; at 0.5, 1, 2, 4, and 6 hrs after its administration; before EDD; during EDD, at time points 2, 4, and 6 hrs; at the end of EDD; and at 0.5, 1, 3, and 8 hrs after EDD. Additional blood samples were drawn pre- and post-dialyzer in order to calculate the dialyzer clearance from the arteriovenous concentration difference and blood flow. Total drug removal was assessed by measuring drug concentration in the spent dialysate, because the GENIUS system permits easy access to the entire amount of substances that have been removed during a dialysis session (10).

**Chemical Assays.** After protein removal by methanol, concentrations of meropenem were determined with high-performance liquid chromatography (Merck Supersphere 100 RP 18, 250 × 4; Merck, Whitehouse Station, NJ) and ultraviolet detection at 298 nm by a method previously described (11). The mobile phase consists of 5% acetonitril and 95% of a 0.1% ammonium formate solution. Vancomycin was measured in a monoclonal fluorescence polarization immunoassay (Abbott Laboratories, Abbott Park, IL).

**Pharmacokinetic Calculations.** Pharmacokinetic parameters of meropenem and vancomycin before and during EDD were estimated by noncompartmental methods with assumed steady-state conditions. The half-life during EDD (T<sub>1/2, on</sub>) and before/after EDD (T<sub>1/2, off</sub>) were estimated from the concentration decline before and during EDD. The drug clearance without EDD was calculated as CL<sub>off</sub> = D/AUC<sub>off</sub> (dose/area under the curve). In the case of a first dose, the AUC<sub>off</sub> was calculated as the AUC from the infusion until the beginning of EDD plus extrapolated from the beginning of EDD to infinity with use of T<sub>1/2, off</sub>. In the case of steady-state conditions after multiple doses, the AUC<sub>off</sub> was extrapolated to the end of the individually applied dosage interval disregarding EDD. The apparent volume of distribution (V<sub>d</sub>) was estimated as V<sub>d</sub> = CL<sub>off</sub> · T<sub>1/2, off</sub>/ln (2), with the assumption that the time-averaged concentration of solute over the period approximates that logarithmic mean.

As there is no standard approach, we applied five methods to estimate drug removal by hemodialysis. First, the dialysis clearance was calculated from the area under the curve during EDD (AUC<sub>EDD</sub>) and the drug concentration (C<sub>dial</sub>) and amount of dialysate (V<sub>dial</sub>) as CL<sub>dial</sub> = C<sub>dial</sub> · V<sub>dial</sub>/AUC<sub>EDD</sub>. Second, the dialysis clearance (CL<sub>dial</sub>) was estimated from concentrations before (C<sub>in</sub>) and directly after (C<sub>out</sub>) the dialysis membrane as CL<sub>dial</sub> = (F<sub>in</sub> · C<sub>in</sub> - F<sub>out</sub> · C<sub>out</sub>)/C<sub>in</sub>, where the plasma flow in (F<sub>in</sub>) and out (F<sub>out</sub>) of the dialyzer was estimated with use of the blood flow, hematocrit, and ultrafiltration rate. Third, the fraction of drug removed by one EDD was calculated as fract<sub>dial</sub> = 1 - exp(-CL<sub>dial</sub> · T<sub>EDD</sub>/V<sub>d</sub>), where T<sub>EDD</sub> is the time on EDD. Fourth, the removed fraction was derived from the half-life on and off EDD as fract<sub>dial</sub> = (1 - exp[-ln(2) · T<sub>EDD</sub>/T<sub>1/2, off</sub>]) · (T<sub>1/2, off</sub> - T<sub>1/2, on</sub>)/T<sub>1/2, off</sub>. Fifth, the removed fraction was estimated on the basis of the area under the curves as fract<sub>dial</sub> = (AUC<sub>withoutEDD</sub> - AUC<sub>withEDD</sub>)/AUC<sub>withoutEDD</sub>, as described previously (12). All pharmacokinetic calculations were performed with the help of software (WinNonlin Professional 4.0.1, Pharsight, Mountain View, CA) and Excel 2000 (Microsoft, Redmond, WA).

## RESULTS

We treated ten patients with each antibiotic substance studied. The patient demographic and clinical information is given in Table 1 and Table 2. There were no adverse effects attributable to the use of meropenem and vancomycin in our patients. Average plasma concentration-time data for meropenem and vancomycin are shown in Figure 1 and Figure 2. Based on the ten pharmacokinetic profiles obtained for each substance, pharmacokinetic parameters as well as the total amount of the drug removed during EDD were calculated. These data are summarized in Table 3 (meropenem) and Table 4 (vancomycin) and compared with the results reported for IHD and CRRT in the literature (Table 3).

Table 2. Characteristics of the vancomycin recipients

Patient	Sex	Age in yrs	Height in cm	Weight in kg	BMI	Clinical Condition
1	M	40	170	130	45.0	Sepsis after lung transplantation
2	F	74	160	60	23.4	Sepsis, ARDS
3	F	51	158	50	20.0	Esophagus carcinoma, hepatic encephalopathy
4	M	66	180	84	25.9	Sepsis, pancreas adenoma
5	M	35	180	118	36.4	Alcohol abuse, sepsis, ARDS
6	M	49	189	80	22.4	Osteomyelofibrosis, sepsis
7	F	53	165	80	29.4	Pneumonia after heart/lung transplantation
8	F	50	170	73	25.5	Multiple organ failure, cardiopulmonary arrest
9	M	65	175	90	29.4	Pneumonia
10	M	67	175	80	26.1	Pancreatitis, sepsis

BMI, body mass index; ARDS, acute respiratory dysfunction syndrome.

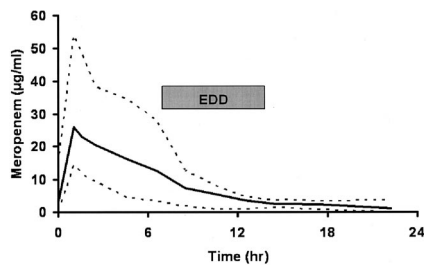


Figure 1. Meropenem plasma concentrations in ten intensive care patients with acute renal failure, before, during, and after extended daily dialysis (EDD) treatment. Concentrations are presented as median (continuous line) and range (broken line).

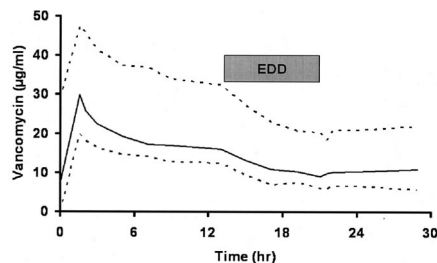


Figure 2. Vancomycin plasma concentrations in ten intensive care patients with acute renal failure, before, during, and after extended daily dialysis (EDD) treatment. Concentrations are presented as median (continuous line) and range (broken line).

## DISCUSSION

The pharmacokinetic data obtained in the present prospective study of critically ill ICU patients with ARF document that both meropenem and vancomycin are significantly eliminated by EDD and that dosing regimens for neither IHD nor CRRT can be used for critically ill septic patients with renal failure being treated with EDD. These patients are usually highly catabolic and often need a larger dose of renal replacement therapy. In-

deed, two recent controlled studies have revealed that increasing the dose of renal replacement therapy increases survival among critically ill patients with renal failure (1, 2). Thus, the progress to renal replacement therapies with higher clearances and their wider application require reassessment of dosing regimens and pharmacokinetic data. We have therefore assessed the pharmacokinetics and elimination of two commonly used antibiotics in septic ICU patients—meropenem and vancomycin—with use of EDD, the renal replacement therapy of choice for septic patients at our facility.

We found that the half-life values of meropenem on and off EDD were similar to those reported for IHD in the literature (13–16) and as reviewed by Thalhammer and Hörl (17). However, the half-life on EDD was shorter than most of those reported for CRRT (17–24). Meropenem half-life off dialysis (8.7 hrs) was shorter than described for anuric patients (13.7 hrs) (17). The volume of distribution in our critically ill patients tended to be higher than that reported previously for critically ill patients (17–24); the latter can be explained in part by fluid overload in these patients. The amount of meropenem removed by EDD was 51%, which is in accordance with IHD data (15). However, in that respect both EDD and IHD were much more effective than CRRT (17–24) (Table 3). Generally, meropenem plasma concentrations did not show a rebound after EDD. The dialysate-based estimates of dialysis clearance and the fraction removed for meropenem were too low in comparison with the dialysis clearance estimated from drug concentrations before and after application of the dialysis membrane. A possible explanation for this observation (already described previously) could be adsorption of meropenem by the dialysis membrane

(25) or instability of meropenem in the dialysate.

Meropenem is renally excreted at levels of about 65% to 80% (26, 27). With progressive renal failure, renal clearance of meropenem decreases and the nonrenal pathway of elimination becomes relatively more important (14). IHD with cuprophane membranes has been shown to effectively remove the drug, necessitating a supplemental, 500-mg dose of meropenem after each dialysis session (13, 15). In ICU patients with ARF undergoing continuous venovenous hemofiltration and continuous venovenous hemodialysis, a meropenem dose of 1.0 g every 12 hrs up to 1.0 g every 8 hrs was necessary in order to maintain appropriate plasma levels (17–24). Our data suggest that EDD—by definition an intermittent mode of renal replacement therapy—eliminates meropenem at least to an extent similar to continuous venovenous hemofiltration. Thus, physicians run the risk of underdosing, and this problem is aggravated by markedly different recommendations concerning dosing, ranging from 500 mg/day in IHD to 1.0 g every 8 hrs in CRRT (17). Because the consequences of underdosing are much more dangerous than the adverse effects of overdosing, a dose of 0.5 to 1.0 g meropenem every 8 hrs is recommended (17). However, the exact dose should be tailored according to weight and severity of illness as well as to the current minimal inhibitory concentration against the incriminated bacteria.

Vancomycin is effectively cleared by EDD. The discussion of our results concerning vancomycin is limited by the fact that nearly all published data were obtained with a polyclonal fluorescence polarization immunoassay that significantly underestimated the required doses. However, vancomycin clearance off hemodial-

**Table 3.** Pharmacokinetics of meropenem in intensive care patients with acute renal failure undergoing EDD

Meropenem	EDD	IHD (35–38) <sup>a</sup>	CRRT (17–24) <sup>a</sup>
Membrane	Polysulfone, 1.3 m <sup>2</sup>	Cuprophane (13, 14, 16), 0.9–1.2 m <sup>2</sup>	Polyacrylonitrile (18–22, 24)  Polysulfone (23, 25), 0.43–0.9 m <sup>2</sup> (18) 100(19)–200(20)
Q <sub>B</sub> /Q <sub>D</sub> , mL	160/160	198(13)–250(15)/500(13)–600(15)	
T <sub>1/2 off</sub> , hrs	8.7 [4.7–30]	7.0 (13)–10.0 (16)	—
T <sub>1/2 on</sub> , hrs	3.7 [2.1–4.7]	1.4 (15)–2.9 (13)	2.46 (25)–7.5 (23)
V <sub>d</sub> , L/kg	0.72 [0.35–2.78]	0.17 (14)–0.28 (16)	0.28 (19)–0.63 (20)
CL <sub>off</sub> , L/hr	5.01 [2.44–11.15]	—	—
CL <sub>dial</sub> , L/hr	2.3 [0.7–3.7] <sup>b</sup> 5.1 [4.3–5.7] <sup>c</sup>	4.7 (14)–4.9 (16)	1.2 (20)–3.5 (24)
Fract <sub>dial</sub> , %	51 [22–67] <sup>d</sup> 17 [5–48] <sup>e</sup> 18 [5–66] <sup>f</sup>	51 ± 22 (16)	29 (21)–48 (18)

Parameters are half-life off (T<sub>1/2 off</sub>) and on (T<sub>1/2 on</sub>) extended daily dialysis (EDD) treatment, apparent volume of distribution (V<sub>d</sub>), drug clearance off EDD (CL<sub>off</sub>), dialysis clearance (CL<sub>dial</sub>), and fraction of the drug in the body removed by one dialysis treatment (Fract<sub>dial</sub>). Values are given as median [range]. Data were compared to data obtained for intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT) reported in the literature. Q<sub>B</sub>/Q<sub>D</sub>, total body clearance/dialyzer clearance.

<sup>a</sup>Numbers in parentheses are references; <sup>b</sup>estimated from the drug amount recovered in the dialysate; <sup>c</sup>estimated from drug concentrations before and after application of the dialysis membrane; <sup>d</sup>estimated by the classic method; <sup>e</sup>estimated by area under the curve (AUC)—based method; <sup>f</sup>estimated from the drug amount in the dialysate and volume of distribution. Numbers in brackets represent range of data.

**Table 4.** Pharmacokinetics of vancomycin in intensive care patients with acute renal failure undergoing EDD

Vancomycin	EDD (8 hrs)	“EDD” (24 hrs) (34)
Membrane	Polysulfone, 1.3 m <sup>2</sup> , High-Flux	Polysulfone, 1.2 m <sup>2</sup> , Low-Flux
Q <sub>B</sub> /Q <sub>D</sub> , mL	160/160	200/100
T <sub>1/2 off</sub> , hrs	37.3 [14.6–65.9]	(18.8–96)
T <sub>1/2 on</sub> , hrs	11.2 [7.6–19.5]	43.1 ± 21.6 (0.58–1.24)
V <sub>d</sub> , L/kg	0.57 [0.34–2.70]	0.84 ± 0.17
CL <sub>off</sub> , L/hr	1.58 [0.37–2.38]	—
CL <sub>dial</sub> , L/hr	2.1 [1.1–3.0] <sup>a</sup> 3.8 [3.4–5.5] <sup>b</sup>	0.4 ± 0.1 —
Fract <sub>dial</sub> , %	26 [0–46] <sup>c</sup> 23 [7–53] <sup>d</sup> 26 [7–73] <sup>e</sup>	— — —

Parameters are half-life off (T<sub>1/2 off</sub>) and on (T<sub>1/2 on</sub>) extended daily dialysis (EDD) treatment, apparent volume of distribution (V<sub>d</sub>), drug clearance off EDD (CL<sub>off</sub>), dialysis clearance (CL<sub>dial</sub>), and fraction of the drug in the body removed by one dialysis treatment (Fract<sub>dial</sub>). Values are given as median [range]. Q<sub>B</sub>/Q<sub>D</sub>, total body clearance/dialyzer clearance.

<sup>a</sup>Estimated from the drug amount recovered in the dialysate; <sup>b</sup>estimated from drug concentrations before and after application of the dialysis membrane; <sup>c</sup>estimated by the classic method; <sup>d</sup>estimated by area under the curve (AUC)—based method; <sup>e</sup>estimated from the drug amount in the dialysate and volume of distribution.

ysis was higher than the reported values (28). Consequently, the half-life off hemodialysis was somewhat shorter than such values reported previously for IHD and CRRT (29–31). However, clearance half-life in these studies varied by more than 100%. Our estimate of vancomycin volume of distribution was similar to that

reported previously for healthy and anuric subjects. Vancomycin concentrations showed a rebound of about 10% after EDD.

The dialysis clearance of vancomycin was in the range of previously reported values, and we estimated the amount of drug removed by one EDD to be between

8% and 26% (in addition to the amount removed by endogenous clearance). Given our study design, we cannot exclude the possibility that vancomycin distribution was not complete at the initiation of EDD. Consequently, the estimated half-life without hemodialysis might be shorter than values observed on subsequent days. The half-life after EDD could not be estimated in the case of vancomycin, owing to the prolonged rebound phase and the clinical need to administer the next dose. Thus, therapeutic drug monitoring is still necessary, and a lower dose may be observed in subsequent days.

Because of the average elimination half-life of 7.5 days in anephric patients and the low dialytic clearance of low-flux membranes, a dosing interval of 1.0 g vancomycin per week had been considered adequate. However, the use of high-flux membranes significantly increases removal of vancomycin. We found that EDD with a 1.3-m<sup>2</sup> high-flux polysulfone dialyzer eliminates a considerable amount of vancomycin, yielding inappropriately low plasma vancomycin concentrations within a period of 30 hrs after administration of 1.0 g vancomycin. This is consistent with data from a previous study of five patients who were studied with an older polyclonal fluorescence polarization immunoassay. In that study, after a 10-hr session of slow hemodialysis with a high-flux dialyzer, the serum vancomycin concentration decreased from 44.2 to 10.0 mg/L, and 30.10% of the dose was eliminated (32). Our data implicate that a different dosing regimen is necessary to achieve the target trough concentrations of 10 µg/mL. Even higher doses are necessary to achieve the increasingly used (although not evidence-based) target trough concentrations of 15–20 µg/mL. The two-phase post-initial distribution is in line with previous data (33) and argues for delaying the determination of vancomycin levels until 12 hrs after the initial dose. In contrast to findings with classic intermittent modes of hemodialysis, the rebound after EDD is smaller, making determination of trough levels at any time after the end of treatment possible. Although we performed EDD for only 8 hrs, we observed a better removal of vancomycin than previously reported for a 24-hr slow, low-efficiency dialysis (34). However in that study, which has several limitations, a low-flux dialyzer was used.

Taken together, our data suggest that for patients treated with EDD, after an

**U**se of extended daily dialysis mandates adjustment of current dosing regimens to avoid the risk of significant underdosing, which may have detrimental effects on critically ill patients with life-threatening infections.

initial standard dose (20–25 mg/kg), therapeutic drug monitoring should be performed to guide further dosing.

In summary, we provide data that meropenem and vancomycin, two antibiotics commonly administered to ICU patients, are significantly eliminated by EDD treatment (with high-flux dialyzer [polysulphone], 1.3 m<sup>2</sup>; blood and dialysate flow, 160 mL/min; EDD time, 480 mins). These data may not be applicable to low-flux EDD. Aiming for an increased dialysis dose that might increase survival among these patients (1, 2) while adhering to outdated drug-dosing recommendations based on old data that were obtained with rather ineffective (in today's view) means of renal replacement therapy may lead to the underdosing of important drugs such as antibiotics. As a result, this may have detrimental effects on critically ill patients with life-threatening infections. Whenever possible, therapeutic drug monitoring should be performed. Further dosing recommendations for ICU patients with renal failure treated with effective modes of renal replacement therapy should be developed to avoid excess mortality due to underdosing of life-saving medication.

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