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Pharmacokinetics of linezolid in critically ill patients on continuous renal replacement therapy: Influence of residual renal function on PK/PD target attainment

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ABSTRACT

Purpose: To assess the pharmacokinetics of linezolid in septic patients undergoing continuous renal replacement therapy (CRRT) and investigate whether residual renal function affects the probability of attaining the pharmacokinetic/pharmacodynamic (PK/PD) target.
Material and methods: Prospective study conducted in three Spanish hospitals. Linezolid concentrations were measured in plasma and effluent samples and pharmacokinetic parameters were calculated. The probability of target attainment (PTA) and the cumulative fraction of response (CFR) were calculated considering AUC_{24}/MIC>80 and $\%T_{>MIC}$ > 85% as the PK/PD indexes related to efficacy.
Results: In anuric patients (CrCl<10 mL/min), the contribution of extracorporeal Cl to total Cl was higher (47% vs 16%) than in patients with residual renal function (CrCl≥10 mL/min). For an MIC of 2 mg/L, AUC_{24}/MIC>80 was achieved in >85% of the anuric patients, but in <15% of the patients with residual renal function.
Conclusions: The standard dose (600 mg q12h) ensures a moderately high probability of treatment success in anuric patients when the infection is due to microorganisms with MIC≤2 mg/L; although higher doses increase the probability of treatment success, the safety is compromised. In patients with residual renal function, the standard dose is insufficient, but 900 mg q8h provide higher probability of treatment success without compromising the safety.

1. Introduction

Linezolid is an oxazolidinone antibiotic with activity against various Gram-positive organisms [1,2]. Clinical practice guidelines recommend linezolid as an alternative to vancomycin in critically ill patients with severe infections caused by multi-resistant Gram-positive bacteria [3-5].

In critically ill patients, pathophysiological changes may alter pharmacokinetics (PK). Regarding antimicrobials, five main factors may cause alterations in PK: increased volume of distribution (Vd), altered protein binding, impaired renal clearance, augmented renal clearance, and hepatic dysfunction [6]. Moreover, in intensive care units (ICUs), half of patients develop acute kidney injury and many require continuous renal replacement therapy (CRRT) [7]. This therapy maintains fluid and electrolyte balance by removing fluid and solutes; however, it also removes valuable substances, including antibiotics, which complicates the optimization of dosing regimens and put patients at risk of developing dialytrauma, defined as the set of possible and non-desired complications associated with the use of CRRT [8]. That is, the pharmacokinetics of antibiotics in critically ill patients receiving CRRT may be altered as consequence of both sepsis and CRRT itself.

Data about the pharmacokinetic profile of linezolid during CRRT are scarce. For this reason, the primary objective of this study was to characterize the pharmacokinetics of linezolid after administration of the standard dose (600 mg q12 h) to septic patients undergoing CRRT as an empirical treatment. The secondary objective was to determine

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whether it is possible to reach the pharmacokinetic/pharmacodynamic (PK/PD) target associated with efficacy with the standard dose, considering the residual renal function of the patient.

2. Materials and methods

2.1. Patients and study design

A prospective study was conducted in three Spanish university hospitals: University Hospital Araba (Vitoria-Gasteiz), Doce de Octubre Hospital (Madrid), and University Hospital Juan XXIII (Tarragona). The protocol was approved by the Basque Clinical Research Ethics Committee (EPA2014025) and the Spanish Agency of Medicinal Products and Medical Devices (FJM-LIN-2012-01). All patients or legal representatives were informed about the study and written informed consent was obtained.

Critically ill septic adults became candidates for the study when an attending physician prescribed linezolid as the empirical treatment. Patients were eligible for inclusion if they were i) admitted in the ICU with sepsis and undergoing CRRT, ii) had an infection probably caused by a multi-resistant Gram-positive microorganism and subsequent treatment with linezolid, and iii) gave informed consent, and iv) it was possible to obtain plasma and ultrafiltrate samples from the extracorporeal circuit. The exclusion criteria were age < 18 years, pregnancy, hypersensitivity to linezolid or any of the excipients, and being on any medicinal product which inhibits monoamine oxidase A or B.

We included 21 patients and, for each, the following information was collected: demographic data (sex, age), severity score (APACHE II), initial reason for ICU admission (medical, surgical), medical history, clinical parameters, type of infection and anti-infective therapy, and renal replacement therapy characteristics. The patients were grouped by renal function: group I included patients with severe renal dysfunction, defined as creatinine clearance (CrCl) <10 mL/min; and group II included patients with CrCl between 10 and 30 mL/min (CrCl ≥10 mL/min). CrCl was measured using urine collected over 10 h. Table 1 summarises demographic, anthropometric and illness severity data.

2.2. Continuous renal replacement therapy

CRRT was performed in venovenous haemodiafiltration (CVVHDF) or venovenous haemodialysis (CVVHD) modes, with replacement fluid delivered post-filter. Fluid therapy was prescribed according to clinical status. Anticoagulation was performed, if necessary, with unfractionated heparin. The filters had polysulphone membranes (Aquamax HF12; Fresenius, Germany) or AN69 membranes (Nephral ST 400, Hospal, Bologna, Italy), with surface areas of 1.8 and 1.65 m^2, respectively. Table 1 summarises the characteristics of CRRT sessions undergone by each patient.

2.3. Linezolid administration, sampling procedure and analytical methods

A 600-mg dose of linezolid was administered every 12 h by intravenous infusion over 30 min, in accordance with the summary of product characteristics. Samples were collected at steady-state. Pre-filter predilution blood samples were obtained pre-dose and over the following 12 h (8 samples per patient) and they were centrifuged to obtain plasma. At the same time points, effluent samples were taken directly from the dialysate-ultrafiltrate device. Plasma and effluent samples were immediately frozen at −80 °C until analysis.

Concentrations of linezolid were quantified by high performance liquid chromatography with ultraviolet detection. The analytical technique was previously validated following the FDA [9] and EMA [10] guidelines. Linezolid drug substance for standards and quality control was kindly provided by Pfizer.

2.4. Pharmacokinetic analysis

Plasma and effluent concentrations of linezolid were plotted against time, and individual pharmacokinetic parameters were determined with Phoenix® WinNonlin® (version 6.4, Pharsight Corporation) using one-compartment model. The sieving coefficient (Sc), defined as the fraction of drug eliminated across the membrane, was calculated as $Sc = AUC_{ef}/AUC_p$, where AUC_{ef} and AUC_p are the areas under the concentration versus time curve for the effluent and the plasma, respectively. Extracorporeal clearance (Cl_{EC}) was estimated as the sieving coefficient times the effluent plus dialysate flow rates (Q_{CRRT}). The percentage of total clearance (Cl) contributed by Cl_{EC} (Cl_{EC} %) was considered significant when higher than 25% [11].

2.5. Pharmacokinetic/pharmacodynamic analysis (PK/PD)

As linezolid is an antimicrobial agent with a long duration and time-dependent activity, the area under the plasma concentration-time curve at steady state over 24 h divided by the MIC (AUC_{24}/MIC) and the time that the plasma concentration exceeds the MIC ($\%T_{>MIC}$) were used as PK/PD indices [12,13]. We selected AUC_{24}/MIC>80 [14] and $\%T_{>MIC}$ > 85 [15] as targets to calculate the probability of treatment success, expressed as the probability of target attainment (PTA) over a range of doubling MICs between 0.25 mg/L and 8 mg/L, [16] and as the cumulative fraction of response (CFR). The CFR makes it possible to estimate the proportion of the population achieving a certain PK/PD value, given PK parameters and the MIC distribution of the target microorganisms [17]. The profile of susceptibility (MIC distribution) of *Enterococcus faecium*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, and coagulase-negative staphylococci (CoNS) was obtained from the University Hospital Araba database (only the first isolate per patient, patients admitted in the ICU at this hospital from January 2013 to December 2015). Laboratory data from the microbiology departments were managed with Whonet [18].

Monte Carlo simulations were conducted using Oracle® Crystal Ball Fusion Edition (V 11.1.1.1.00, Oracle USA Inc., Redwood City, CA). In order to estimate the PTA and CFR uncertainty, we performed 1000 simulation sets of 1000 subjects, and from the 1000 PTA curves at each MIC and CFR curves, we calculated the 2.5th and 97.5th percentiles [19]. A log-normal distribution of the pharmacokinetic parameters was selected.

PTA and CFR were calculated for the standard dose (600 mg q12h) and for higher doses: 600 mg q8h, 900 mg q8h, and 900 mg q12h. The dosing regimens were considered optimal if the PTA or CFR were ≥ 90% whereas a CFR or PTA values between 80% and 90% were associated with moderate probabilities of success [20-22].

For the estimation of the potential toxicity, the probability that C_{min} reaches a value higher than 10 mg/L was estimated also by using Monte Carlo simulation.

2.6. Statistical analysis

Statistical analysis was performed with IBM® SPSS® Statistics for Windows, Version 21 (IBM) to compare the physiopathological and pharmacokinetic parameters of linezolid between patients in the two groups. The normality of the data distribution was assessed with the Shapiro Wilk test and the homogeneity of variance with the Levene test. The data were compared with Student's *t*-test, and differences were considered significant at $p < .05$.

3. Results

We enrolled 21 septic patients (37 to 79 years old) with different degrees of renal function in this study. Of these, 13 were included in group I (CrCl <10 mL/min) and the other 8 in group II (CrCl ≥10 mL/min). The source of infection was pulmonary in 8 cases, abdominal in 6,

Table 1
Characteristics of patients in Group I (CrCl <10 mL/min) and in Group II (CrCl ≥10 mL/min).

Group I (CrCl < 10 mL/min)																	
ID	Infection	AP II	Gender	Age (y)	Weight (Kg)	BMI (Kg/m^2)	Cr (mg/dL)	CrCl (mL/min)	Urea (mg/dL)	Alb (g/dL)	TP g/dL)	BR (mg/dL)	CRRT	Membrane	$CRRT_Q$ (mL/h)	Q_s (mL/min)	Q_{uf} (mL/h)	Q_d (mL/h)
1	Respiratory	18	W	78	65	26.0	1.0	0	107	2.0	6.0	1.2	CVVHDF	AN69	3150	200	1650	1500
2	Respiratory	28	W	37	90	33.1	0.9	6	59	2.4	4.5	0.8	CVVHDF	AN69	3250	140	1750	1500
3	Neurological	18	W	78	60	22.0	0.6	0	120	2.0	5.0	0.1	CVVHD	AN69	1600	180	100	1500
4	Respiratory	26	M	63	75	26.0	0.6	0	25	2.1	5.8	0.8	CVVHD	AN69	2150	150	150	2000
5	Respiratory	19	M	76	70	25.2	1.0	0	68	2.4	5.5	0.6	CVVHDF	AN69	2900	140	1400	1500
6	Abdominal	17	W	49	68	25.0	0.7	0	NA	1.7	3.1	0.3	CVVHDF	PS	3000	180	1500	1500
7	Biliary	18	M	69	74	25.9	1.4	0	86	1.9	2.7	1.3	CVVHDF	PS	3300	NA	1800	1500
8	Respiratory	17	M	64	87	NA	2.1	0	85	2.5	NA	2.1	CVVHDF	PS	3050	220	1550	1500
9	Neurological	21	W	51	55	24.4	2.6	5	68	1.9	3.8	0.3	CVVHDF	PS	3000	NA	1500	1500
10	Abdominal	34	M	72	80	32.0	1.1	9	106	2.6	4.6	0.7	CVVHDF	PS	3250	220	1750	1500
11	Abdominal	23	M	75	74	26.0	1.3	0	61	2.0	5.0	0.8	CVVHDF	PS	3000	180	1500	1500
12	Biliary	22	W	69	80	26.1	2.4	0	128	2.2	7.3	2.6	CVVHDF	PS	3000	NA	1500	1500
13	Abdominal	NA	M	67	95	23.1	1.0	0	68	1.8	5.1	1.5	CVVHDF	PS	2100	180	1100	1000
	Mean	**21.8**		**65**	**75**	**26.2**	**1.3**	**1.5**	**81.8**	**2.1**	**4.9**	**1.0**			**2827**	**179**	**1327**	**1500**
	SD	**5.3**		**13**	**12**	**3.2**	**0.7**	**3.0**	**29.5**	**0.3**	**1.3**	**0.7**			**529**	**29**	**563**	**204**

Group I (CrCl ≥ 10 mL/min)																		
ID	Infection	AP II	Gender	Age (y)	Weight (Kg)	BMI (Kg/m^2)	Cr (mg/dL)	CrCl (mL/min)	Urea (mg/dL)	Alb (g/dL)	TP g/dL)	BR (mg/dL)	CRRT	Membrane	$CRRT_Q$ (mL/h)	Q_s (mL/min)	Q_{uf} (mL/h)	Q_d (mL/h)
14	Respiratory	NA	M	74	70	25.7	1.2	28.1	58	2.6	5.3	0.5	CVVHDF	AN69	2600	180	1100	1500
15	Abdominal	25	M	58	95	31.0	1.2	25.0	96	2.6	5.2	1.0	CVVHDF	AN69	2200	180	1200	1000
16	Abdominal	NA	M	71	70	27.3	0.8	27.9	61	2.1	6.0	0.7	CVVHD	AN69	1050	280	50	1000
17	Respiratory	25	M	41	70	24.2	1.9	30.0	117	2.6	5.7	0.4	CVVHD	AN69	1050	180	50	1000
18	Other	16	W	68	90	33.1	1.0	23.3	175	2.0	5.2	0.4	CVVHDF	AN69	3200	180	1200	2000
19	Respiratory	24	M	73	90	29.4	1.4	14.3	86	2.5	5.0	0.6	CVVHDF	PS	3150	200	1650	1500
20	Other	24	M	79	75	24.5	1.5	17.0	104	3.1	NA	1.7	CVVHDF	PS	3000	240	1500	1500
21	Other	29	M	65	65	24.5	1.4	21.0	77	3.6	6.5	0.4	CVVHDF	PS	3000	NA	1500	1500
	Mean	**23.8**		**66**	**78**	**27.5**	**1.3**	**23.3**	**96.8**	**2.6**	**5.6**	**0.7**			**2406**	**206**	**1031**	**1375**
	SD	**4.3**		**12**	**12**	**3.4**	**0.3**	**5.6**	**37.6**	**0.5**	**0.5**	**0.4**			**898**	**40**	**634**	**354**
	***p* value**	**NS**		**NS**	**NS**	**NS**	**NS**	**<0.001**	**NS**	**0.01**	**NS**	**NS**			**NS**	**NS**	**NS**	**NS**

Alb: albumin; AP II: Apache II; BMI: body mass index; BR: bilirubin; Cr: creatinine; CrCl: creatinine clearance; CRRT: continuous renal replacement therapy; NA: not available; NS: non-significant; Q_d: dialysis flow; Q_s: blood flow; Q_{uf}: ultrafiltrate flow; SD: standard deviation; TP: Total proteins.

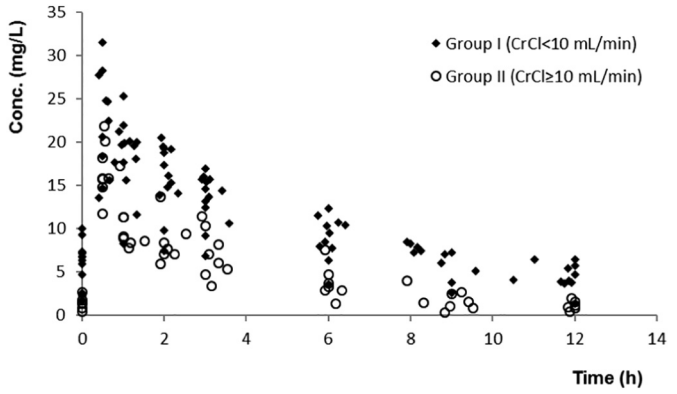

Fig. 1. Linezolid plasma concentration vs time in patients grouped by residual renal function. Diamonds: group I (CrCl <10 mL/min), circles: group II (CrCl ≥10 mL/min).

neurological in 2, and biliary in 2, with other sources in the other 3 cases. Most of the patients received CVVHDF, only 4 receiving CVVHD, 2 in group I and 2 in group II (Table 1). Differences between groups were only significant for CrCl and albumin. No adverse effects attributable to linezolid treatment were reported.

Overall, 168 plasma samples from the 21 patients were analysed. Fig. 1 displays the concentration levels of linezolid over time in all the patients included in the study. Linezolid concentration ranged from 11.5 to 31.5 mg/L at the end of the infusion from 0.4 to 7.4 mg/L at the end of the dosing interval (12 h after infusion). In general, plasma concentrations of linezolid were higher in the samples from group I than those from group II.

Table 2 lists the pharmacokinetic parameters of linezolid in all patients. No significant difference was found in Sc between groups (0.8 and 0.9). Although Vd was lower in the anuric patients, the difference was not significant (36.5 vs 39.3 L). Significant differences were detected between groups in $t_{1/2}$, Cl, AUC_{24}, Cl_{EC} (%), C_{max} and C_{min}. In group I, $t_{1/2}$ was significantly higher than in group II (5.1 vs 2.1 h), and Cl was significantly lower (5.3 vs 12.6 L/h); consequently, AUC_{24}, C_{max} and C_{min} were significantly higher. The contribution of Cl_{EC} to Cl was significantly higher in group I patients (47.0% vs 16.6%). A correlation (r^2) was observed between AUC_{24} and C_{min} (0.89). For an MIC of 2 mg/L, AUC_{24}/MIC>80 was achieved in 85% of the anuric patients, but only in 12% of the patients with residual renal function.

Table 3 presents the PTA values for AUC_{24}/MIC>80 and $\%T_{>MIC}$ > 85% in the simulated population for all dose levels studied. In patients with severe renal dysfunction (group I), the standard dose provided a PTA > 80% for microorganisms with MIC≤2 mg/L, and based on $\%T_{>MIC}$, 600 q8h and 900 q12 h cover also the MIC of 4 mg/L. In patients with residual renal function (group II), for the MIC of 1 mg/L we found that both 600 mg q8h and 900 mg q8h yielded PTAs>80%. Additionally, 900 mg q8h provided a PTA > 85% for an MIC of 2 mg/L based on AUC_{24}/MIC.

Table 4 shows the distribution of the MICs for *E. faecium*, *E. faecalis*, *S. epidermidis*, *S. aureus* and coagulase-negative staphylococci (CoNS) and the CFR for linezolid against these microorganisms. In group I, by applying both PK/PD indices, the standard dose provided CFR values higher than 80% for E. *faecium*, E. *faecalis* and *S. aureus*. With the higher doses (600 mg q8h and 900 q 12 h), the CFR increased, being >80% for all the microorganisms. In group II, the standard dose provided CFR values around 20% for *Enterococcus* and < 10% for all species of *Staphylococcus*. The increase of the dose (900 mg q12h), the decrease of the dosing interval (600 mg q8h), or both (900 mg q8h) provided higher values, being always >60% with 900 mg q8h.

Table 5 shows the probability that the trough level of linezolid reaches a value >10 mg/L. In patients with residual renal function, the risk is insignificant, and in anuric patients, the risk increases as the dose increases or the dosing interval decreases.

4. Discussion

There is controversy over whether standard dosing with linezolid provides adequate plasma concentrations in critically ill patients. Notably few studies have reported linezolid blood levels in specific subgroups of ICU patients, such as those receiving CRRT [23,24]. In this study, we have investigated the pharmacokinetics of linezolid in critically ill patients on CRRT and have shown the impact of residual renal function on the probability of treatment success.

Most anuric patients (group I) received CVVHDF as CRRT, and the mean value of Cl (5.3 L/h) was similar to that reported previously in patients receiving this mode of therapy using the same kind of membrane as in our patients [14,25,26]. Regarding group II patients, linezolid Cl (12.6 L/h) was comparable to that observed in other studies including critically ill patients with preserved renal function not receiving CRRT [27-29]. Concerning Vd, this was similar in both groups and comparable to that reported previously for critically ill patients [14,24].

Pathophysiological changes in critically ill patients, such as renal dysfunction, may have profound effects on the PK profile of drugs. Although only 35% of linezolid is excreted in urine [30], in our study, renal function had a relevant influence on total clearance. The fraction of linezolid eliminated by the extracorporeal circuit (Sc) was around 80%, similar to the unbound protein fraction [31], and independent of renal function. This value is similar to that reported previously [24,32]. No differences were found in Sc or Cl_{EC} between the two groups. In contrast, we detected a significant difference in the contribution of Cl_{EC} to the total Cl and this was dependent on whether the patient had residual renal function or not (16.6% vs 47.0%). Previous studies with piperacillin/tazobactam [33] and meropenem [34] have also shown that the contribution of Cl_{EC} to the total Cl increases with declining of the renal function. In our study, patients with residual renal function had a Cl two-fold higher than that in anuric patients (12.6 vs 5.3 L/h). Unfortunately, we did not measure linezolid levels in urine to investigate whether other enhanced elimination pathway such as hepatic clearance could also contribute to this difference in the clearance.

Increased elimination of linezolid led to a faster drop in plasma concentrations, and these findings are expected to be relevant for efficacy. Although the serum albumin was significantly different in the two groups of patients, the difference was not relevant (2.1 vs 2.6 g/dL). Linezolid is not extensively bound to serum proteins (<20%), and the albumin levels did not led to a change in Vd between both groups of patients.

The summary of product characteristics recommends a flat dosing regimen of 600 mg twice daily for all adult patients, including those with renal or hepatic dysfunction. However, the high pharmacokinetic variability found for linezolid between the two groups, and even among patients in the same group, raises doubts about whether the levels of drug exposure generally attained put patients at risk of either therapeutic failure due to underexposure or concentration-dependent adverse events. Therefore, we evaluated the appropriateness of the standard dosing regimen (600 mg q12h) and higher dose levels, 900 mg q12h, 600 mg q8h, and 900 mg q8h.

Based on both the AUC_{24}/MIC and the $\%T_{>MIC}$ targets, linezolid, at the standard dose, may be adequate when the infection is due to microorganisms with MIC≤2 or ≤ 0.5 mg/L for anuric patients and for patients with residual renal function, respectively. Since linezolid has a long duration of antimicrobial activity, in anuric patients it is more likely to achieve the target based on $\%T_{>MIC}$ that based on AUC_{24}/MIC (this is the case for MIC of 4 mg/L); on the contrary, in patients with residual renal function, the PTA was higher when applying AUC_{24}/MIC. Taking into account these results and also the risk to achieve concentrations related to toxicity, for anuric patients it is preferable to increase the dose and keep the dose interval (900 mg q12h) to cover the MIC of 4 mg/L. However, if the patient has renal residual function, it is acceptable to increase the dose and decrease the dosing interval (900 mg q8h) to cover higher MIC values than that covered by the standard dose.

Table 2
Pharmacokinetic parameters of linezolid in Group I (CrCl <10 mL/min) and in Group II (CrCl ≥10 mL/min).

Group II (CrCl < 10 mL/min)										
ID	Vd (L)	Vd/Kg (L/Kg)	$t_{1/2}$ (h)	Cl (L/h)	AUC_{24} (mg h/L)	CL_{EC} (L/h)	CL_{EC} (%)	Sc	C_{max} (mg/L)	C_{min} (mg/L)
1	32.9	0.5	5.6	4.1	294	2.4	59	0.8	24.7	6.4
2	47.7	0.5	4.3	7.7	155	3.0	39	0.9	13.6	2.3
3	27.2	0.7	4.5	4.2	286	1.1	24	0.7	27.7	4.7
4	50.7	0.7	3.1	11.4	105	1.7	14	0.8	14.6	1.3
5	28.4	0.4	5.1	3.9	308	2.1	54	0.7	28.2	5.5
6	37.2	0.6	6.5	4.0	304	2.7	70	0.9	22.4	6.4
7	37.0	0.5	5.4	4.8	250	2.5	52	NA	20.6	5.8
8	39.9	0.5	7.2	3.9	311	2.3	60	NA	24.7	7.4
9	37.1	0.7	4.7	5.5	220	2.3	42	NA	17.6	2.6
10	42.9	0.5	6.9	4.3	280	2.5	58	NA	15.6	3.6
11	28.3	0.4	3.8	5.2	233	2.6	51	0.9	25.3	4.1
12	41.0	0.5	5.3	5.4	224	2.7	51	0.9	18.4	3.7
13	24.7	0.3	3.7	4.6	260	1.7	37	0.8	31.5	4.0
Mean	**36.5**	**0.5**	**5.1**	**5.3**	**249**	**2.3**	**47.0**	**0.8**	**21.9**	**4.4**
SD	**8.0**	**0.1**	**1.3**	**2.1**	**62**	**0.5**	**15.5**	**0.1**	**5.7**	**1.8**

Group II (CrCl ≥ 10 mL/min)										
ID	Vd (L)	Vd/Kg (L/Kg)	$t_{1/2}$ (h)	Cl (L/h)	AUC_{24} (mg h/L)	CL_{EC} (L/h)	CL_{EC} (%)	Sc	C_{max} (mg/L)	C_{min} (mg/L)
14	32.3	0.5	3.4	6.6	182	1.8	27	0.7	20.1	1.7
15	25.6	0.3	1.3	13.3	90	1.6	12	0.7	21.8	0.4
16	37.1	0.5	1.4	18.8	64	1.0	5	1.0	15.7	0.0
17	44.2	0.6	3.1	10.0	120	1.1	10	1.0	15.8	1.5
18	50.7	0.6	2.8	12.8	94	2.5	20	0.8	11.7	1.1
19	44.2	0.5	2.3	13.5	89	2.6	23	1.0	14.8	0.9
20	35.3	0.5	1.8	13.7	87	2.3	17	NA	18.1	0.0
21	44.6	0.7	2.6	12.0	100	2.3	19	NA	15.8	3.6
Mean	**39.3**	**0.5**	**2.3**	**12.6**	**103**	**1.9**	**16.6**	**0.9**	**16.7**	**1.2**
SD	**8.1**	**0.1**	**0.8**	**3.5**	**35**	**0.6**	**7.2**	**0.2**	**3.2**	**1.2**
p value	**NS**	**NS**	**<0.001**	**<0.001**	**<0.001**	**NS**	**<0.001**	**NS**	**0.015**	**<0.001**

AUC_{24}: area under the plasma concentration-time curve in a period of 24 h; C_{max}: maximum plasma linezolid concentration; C_{min}: minimum plasma linezolid concentration; Cl: plasma clearance; CL_{EC}: extracorporeal clearance; NA: not available; NS: non-significant; Sc: sieving coefficient; SD: standard deviation; $t_{1/2}$: half-life; Vd: volume of distribution.

Table 3
Probability of target attainment (PTA) for linezolid in simulated patients receiving the standard (600 mg q12h) and higher doses. Numbers in parenthesis indicate the 2.5th and 97.5th percentiles. Group I: CrCl <10 mL/min, group II: CrCl ≥10 mL/min.

Group I	AUC_{24}/MIC > 80		$\%T_{>MIC}$ > 85%		
MIC (mg/L)	600 mg q12h	600 mg q8h 900 mg q12h	600 mg q12h	600 mg q8h	900 mg q12h
0.25	100	100	100	100	100
0.50	100	100	99 (98–100)	100	99 (99–100)
1	100 (99–100)	100	96 (95–97)	100 (99–100)	98 (97–99)
2	86(84–89)	98 (98–99)	88 (86–90)	99 (98–99)	94 (92–95)
4	24 (21–27)	64 (61–67)	64 (61–67)	92 (90–94)	80 (78–83)
8	0	0	25 (23–28)	65 (62–68)	48 (45–52)

Group II	AUC_{24}/MIC > 80			$\%T_{>MIC}$ > 85%			
MIC (mg/L)	600 mg q12h	600 mg q8h 900 mg q12h	900 mg q8h	600 mg q12h	600 mg q8h	900 mg q12h	900 mg q8h
0.25	100	100	100	81 (79–83)	99 (98–99)	88 (86–90)	99 (99–100)
0.50	100	100	100	62 (59–65)	95 (94–96)	74 (72–77)	98 (97–99)
1	78 (76–81)	99 (98–99)	100	34 (31–37)	84 (81–86)	51 (48–54)	92 (90–93)
2	4 (3–5)	39 (36–42)	89 (87–90)	9 (8–12)	53 (51–57)	22 (20–25)	74 (70–77)
4	0	0	9 (7–11)	0	14 (12–17)	4 (3–5)	36 (33–39)
8	0	0	0	0	0	0	5 (4–6)

CLSI [35] and EUCAST [36] clinical breakpoints for linezolid are 4 mg/L for *Staphylococcus*, and 2 mg/L for *Streptococcus,* and 2 mg/L (CLSI) and 4 mg/L (EUCAST) for *Enterococcus*. As mentioned above, for an MIC of 2 mg/L, the standard dose seems to be adequate if the patient shows severe renal dysfunction (PTA based on AUC_{24}/MIC: 86%, and based on $\%T_{>MIC}$: 88%), but it is insufficient (PTA based on AUC_{24}/MIC: 4%, and based on $\%T_{>MIC}$: 9%) if the patient has residual renal function. For these patients, 900 mg q8h resulted to be adequate for the MIC of 2 mg/L (PTA based on AUC_{24}/MIC: 89%). For the MIC of 4 mg/L, neither the standard dose nor the highest dose (900 mg q8h) showed to be sufficient to treat the patients with residual renal function. In the case of patients of group I, although 600 mg q8h provided PTA levels in terms of $\%T_{>MIC} \geq 90\%$, the risk of toxicity should be considered (probability that C_{min} reaches 10 mg/L is 40%). These results are in line with the EUCAST PK/PD (non-species related) breakpoint of linezolid, which is 2 mg/L [36]. According to Mouton [37], the use of pharmacokinetic parameters from different populations in Monte Carlo simulations for established dosing regimens results in different breakpoints. When discrepancies in breakpoints are observed, the PK/PD breakpoints are generally lower than those defined by the CLSI or EUCAST [16,38], as seen in the present study. According to our results, the probability of treatment success is lower in critically ill patients with residual renal function. In fact, these patients behave like patients with preserved renal function. Normally, exposure to antimicrobials that are excreted in urine is lower in patients with normal renal function than in patients with renal failure [39], and therefore the probability of reaching the pharmacodynamic target significantly decreases. This means that critically ill patients with residual renal function receiving CRRT are at higher risk of underdosing. In a previous study in critically ill patients with septic shock and CRRT, residual diuresis was also shown to significantly influence meropenem CL [40]. The authors of that work suggested that residual diuresis may be an easy and inexpensive tool to help with titration of the meropenem dose and infusion time in this challenging population.

Linezolid was administered as an empirical treatment, and microbiological analysis found no microorganisms susceptible to linezolid in most of the samples obtained, and therefore direct pharmacodynamic correlation was not possible. Therefore, we used the aforementioned

Table 4
Distribution of MIC of *E. faecium*, *E. faecalis*, *S. epidermidis*, *S. aureus* and coagulase-negative staphylococci (CoNS) in the University Hospital Araba from January 2013 to December 2015 and cumulative fraction of response (CFR) of linezolid for these microorganisms. Numbers in parenthesis indicate the 2.5th and 97.5th percentiles.

CFR (%)	% of strains				Group I CrCL < 10 mL/min				
	MIC (mg/L)				AUC_{24}/MIC > 80		$\%T_{>MIC}$ > 85%		
	1	2	4	8	600 mg q12h	600 mg q8h 900 mg q12h	600 mg q12h	600 mg q8h	900 mg q12h
E. faecium	22	78			89 (88–91)	99 (98–99)	92 (90–93)	99 (99–100)	96 (95–97)
E. faecalis	26	72		2	88 (86–90)	97 (96–99)	89 (87–91)	98 (97–99)	94 (93–96)
S. epidermidis		82	3	15	72 (69–75)	84 (82–85)	78 (75–80)	93 (92–95)	87 (85–89)
CoNS		88	3	9	77 (75–80)	89 (87–91)	81 (79–84)	95 (94–97)	89 (88–91)
S. aureus		92	8		81 (79–84)	96 (95–97)	86 (84–88)	98 (97–99)	93 (91–94)

CFR (%)	% of strains				Group II CrCL ≥ 10 mL/min						
	MIC (mg/L)				AUC_{24}/MIC > 80			$\%T_{>MIC}$ > 85%			
	1	2	4	8	600 mg q12h	600 mg q8h 900 mg q12h	900 mg q8h	600 mg q12h	600 mg q8h	900 mg q12h	900 mg q8h
E. faecium	22	78			20 (18–23)	52 (49–55)	91 (89–93)	21 (18–23)	67 (64–70)	36 (33–39)	82 (80–84)
E. faecalis	26	72		2	23 (20–26)	54 (51–57)	90 (88–92)	16 (13–18)	60 (57–63)	29 (27–32)	77 (74–80)
S. epidermidis		82	3	15	3 (2–4)	32 (29–35)	73 (70–76)	8 (6–9)	44 (41–47)	19 (16–21)	62 (59–65)
CoNS		88	3	9	3 (2–5)	34 (32–38)	78 (76–81)	8 (7–10)	48 (45–51)	20 (18–23)	66 (63–69)
S. aureus		92	8		4 (3–5)	36 (33–39)	82 (80–85)	9 (7–10)	50 (47–54)	21 (18–24)	71 (68–73)

Table 5
Probability to reach C_{min} > 10 mg/L. Numbers in parenthesis indicate the 2.5th and 97.5th percentiles.

	600 mg q12h	600 mg q8h	900 mg q12h	900 mg q8h
Group I: CrCl <10 mL/min	10 (8–12)	40 (37–43)	25 (23–28)	n.e.
Group II: CrCl ≥10 mL/min	0	0	0	0

n.e.: not evaluated.

hospital database to calculate the CFR values. If the standard dose of linezolid is administered to anuric patients, moderate to high probabilities of treatment success are achieved for *E. faecium*, *E. faecalis*, and *S. aureus*. For *S. epidermidis* and CoNS, the probability of treatment success is lower although close to 80%. Nevertheless, as indicated in Table 4, at the current dose, this antimicrobial agent is not a good option if the patient has residual renal function and receives CRRT, and hence, other options to optimize therapy should be considered. Increasing the dose and decreasing the dosing interval (900 mg q8h) notably increases the CFR values. Taking into account that linezolid is a time-dependent antibiotic, and although this strategy has not been evaluated in the present study, continuous infusion may be a useful strategy to optimize therapy, as it has been previously proposed [41].

Finally, C_{min} values >10 mg/L have shown to be associated with drug-related toxicity [42,43]. None of our patients had linezolid concentrations above 10 mg/L and no adverse effects related to linezolid concentrations, such as platelet reduction, were detected. For linezolid, the AUC_{24} and C_{min} correlate with efficacy and toxicity. The good linear relationship between these parameters in our study (r^2 0.89), as described elsewhere [23], confirms the utility of C_{min} for monitoring linezolid in clinical practice.

The results we have obtained are conditioned by the selected CrCL cut-off (10 mL/min), and a different cut-off value could give different results. We selected this value because in a previous study, we demonstrated that when the glomerular filtration rate is ≤10 mL/min, the probability that the patient recovers the renal function that would allow interrupting the CRRT is very low (sensitivity of 98% and negative predictive value of 94%) [44]. In any case, dosing linezolid taking into account the ClCr and monitoring serum levels become very important in critically patients undergoing CRRT to ensure proper concentrations, as suggested by several authors [15,45].

In conclusion, this study confirms the greater contribution of Cl_{EC} to total Cl of linezolid in anuric (CrCl <10 mL/min) critically ill patients receiving CRRT in comparison to patients with residual renal function (CrCl ≥10 mL/min). The standard dose (600 mg q12h) provides a moderately high probability of treatment success in patients with severe renal dysfunction when the infection is due to microorganisms with MIC ≤2 mg/L. Although higher dose levels (600 mg q8h or 900 q12h) improve the probability of reaching the pharmacodynamic target, it may compromise the safety of the patients. In contrast, in the presence of residual renal function, the standard dose may be insufficient. For this population of patients, 900 mg q8h provides a much higher probability of treatment success without compromising the safety. Continuous infusion should be investigated to decrease the risk of under exposure to linezolid in this ICU subpopulation.

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Conflict of interest

None declared.

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