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Original Article

Ciprofloxacin, oxacillin, piperacillin and sulfamethoxazole by systemic administration for the control of severe infections: Is dose adjustment required for critical burn patients?

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Aim: To investigate the kinetic disposition of ciprofloxacin, oxacillin, piperacillin, and sulfamethoxazole and evaluate PK/PD target attainment in burn patients. **Methods:** Forty adult burn patients, both genders (76 sets of plasma levels) from the Intensive Care Unit of Plastic Surgery and Burns (ICU) were included in the study. Patients received antimicrobial therapy at the recommended initial dose regimen as part of their medical care. Namely, ciprofloxacin (n = 8 patients/11 sets) and oxacillin (7/10) were prescribed in the early period of treatment; if nosocomial infection was suspected, piperacillin/tazobactam (20/27) was prescribed; sulfamethoxazole (15/28) was also prescribed for the control of documented or suspected infections. Blood sampling was performed during the dosing intervals and drug plasma measurements were performed. Pharmacokinetic data were derived by applying specific software, and drug effectiveness was evaluated based on PK/PD target attainment. **Finding:** Large variability in the pharmacokinetic data was observed for the investigated antimicrobial agents. For sulfamethoxazole, significant differences were not detected among patients with renal failure and those with preserved renal function. A PK/PD target greater than 60% was attained when renal function was preserved in patients treated with ciprofloxacin, oxacillin, piperacillin and sulfamethoxazole. **Conclusion:** Unpredictable pharmacokinetics were observed for all of the investigated antimicrobial agents. Based on the PK/PD target attainments, once dose adjustments were not required, the effectiveness of antimicrobial therapy against susceptible common pathogens was guaranteed for burn patients with preserved renal function receiving ciprofloxacin (0.5 mg/L, MIC), oxacillin, piperacillin and sulfamethoxazole for the control of infections.

Keywords: Antimicrobial agents, pharmacokinetics, PK/PD correlation, critical burn patients

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1. Introduction

Infections remain the most frequent cause of morbidity and mortality in critical burn patients. The disruption of the normal skin barrier, immunocompromised state and prolonged hospital stay makes burn patients easier targets for microbial or fungal colonization. Thus, the diagnosis of infection and early administration of antimicrobial therapy against etiological microbial agents are decisive factors for the successful treatment and control of infections in burn patients [1].

Consequently, a significant number of factors have an effect on burn patients, and the area and depth of burn injury, sepsis, degree of hydration, serum protein concentration, age, renal function and period after thermal injury may affect the pharmacokinetics (PK) of drugs, which alter antimicrobial plasma concentrations and affect antimicrobial activity. Variability in PK parameters has been observed, which makes it difficult to establish a standard dosage regimen and highlights the need for dose adjustment [2-5].

Ciprofloxacin, oxacillin, piperacillin and sulfamethoxazole are commonly prescribed to burn patients in intensive care units (ICU); however, few data related to their pharmacokinetic changes and effects on pharmacodynamics have not yet been reported despite the a considerable amount of data related to others antimicrobial agents [6-10]. Thus, antimicrobial plasma monitoring significantly affects the effectiveness of drug therapy, permitting earlier clinical intervention for dose adjustment, especially in critical burn patients. In addition, dose adjustments based on pharmacokinetic and pharmacodynamics (PK/PD) target attainments, in which key factors include the time course of drug plasma levels after dose administration and the minimum inhibitory concentration (MIC), are relevant to guarantee the control of infection [11].

Because few data concerning dose requirements related to PK/PD analysis for burn patients have been reported, the aim of the present study was to investigate plasma drug monitoring in burn patients receiving ciprofloxacin, oxacillin, piperacillin and sulfamethoxazole by applying pharmacokinetics and PK/PD target attainments to determine the required dose adjustment.

2. Materials and Methods

Study Design and Patient Eligibility

The clinical protocol was a prospective, open-label study and was approved by the Ethical Committee (Protocol nº 0069/09) of the Hospital das Clinicas, Medical School, University of Sao Paulo. The study was conducted from May of 2009 to May of 2012, and informed written consent was obtained from all legally designated patient representatives.

Adult patients with severe thermal injuries from the ICU of Plastic Surgery and Burns were eligible for inclusion. Patients with drug intolerance and pregnant patients were excluded. Sepsis diagnosis was based on clinical and laboratorial data according to the consensus conference of the American Burn Association (2007) [12].

Patients presented initially preserved renal function and subsequently received intravenous ciprofloxacin, oxacillin, piperacillin and sulfamethoxazole as part of their medical care, in accordance with the following institutional guidelines: a) until the third day of hospitalization, patients with a suspected or confirmed diagnosis of infection received ciprofloxacin (400 mg, 12/12 h) and/or oxacillin (2 g, 4 qh) until laboratory data were obtained (culture and susceptibility testing results); b) patients with nosocomial suspected infections of gram negative agents received piperacillin/tazobactam (4.5 g, 8 qh); c) patients with a documented or suspected diagnosis of

Stenotrophomonas maltophilia or *Burkholderia cepacia*received sulfamethoxazole (80 mg/kg, daily). Ciprofloxacin, oxacillin, piperacillin and sulfamethoxazole were infused over 0.5 to 1 hours, based on dose regimen guidelines. If end stage renal dysfunction was observed, an empirical dose adjustment of sulfamethoxazole (20 mg/Kg, daily) was performed.

Decisions regarding the initial antimicrobial therapy and subsequent changes in dose regimens were made by the clinical team and were based on perceived clinical indications and laboratory data including pharmacokinetics and PK/PD target attainments. The TBSA (total burn surface area) was estimated by applying the Lund-Browder method [13]. Creatinine clearance was estimated by Cockcroft and Gault's method [14], and all of the patients showed initially preserved renal function.

Sample Collection for Pharmacokinetic Analysis

Blood samples (at least five samples) were obtained from each patient at the steady state level through a central catheter into sodium EDTA tubes (2 mL each) and was strategically planned based on the dosing interval. Collected blood samples were centrifuged immediately after collection at 1800 g, and the plasma was transferred to labeled vials and stored (-20^{o}C) until the drug plasma assays were performed, which was achieved by applying a recently reported bioanalytical method, as outlined below.

Bioanalytical Method

Simultaneous analysis of plasma for antimicrobials (ciprofloxacin, oxacillin, piperacillin and sulfamethoxazole) by high performance liquid chromatography (HPLC) requires as internal standard (IS) ketoconazole (100 μg/mL). Plasma samples (200 μL) were added to acetonitrile (600 μL), vortexed for 20 seconds and centrifuged (8000 g, 5^{o}C). Purified plasma extract was concentrated to residue in a water bath and dissolved in 200 μL of an 8:2 v/v mixture of water: acetonitrile and 10 μL was injected into the HPLC. Chromatographic analysis was performed on a LC10 Class VP (Shimadzu, Japan) using a Shimpack™ CLC-CN column (150 x 6.0 mm, 5 μm, Shimadzu). The mobile phase consisted of 0.01 M phosphate buffer and acetonitrile (68:32, pH 4.0, v/v) at a flow rate of 0.5 mL/min. A UV detector was set at 280 nm (0-9.5 min) for ciprofloxacin and was changed to 210 nm (9.5-35.0 min) for oxacillin, piperacillin, sulfamethoxazole, and IS measurements. The peaks of interest eluted at 8.6 min (ciprofloxacin), 10.4 min (piperacillin), 13.6 min (oxacillin), 15.9 min (sulfamethoxazole) and 28.0 min (IS). Endogenous compounds eluted up to 7.5 min of each chromatographic run, and a total run time of 35 minutes was required. The linear range of the assay was 0.2-20.0 μg/mL for ciprofloxacin, 1.0-100μg/mL for oxacillin and piperacillin, and 0.8-100 μg/mL for sulfamethoxazole. Internal controls with high, medium and low concentrations included 15, 8 and 0.4 μg/mL of ciprofloxacin, 75, 40 and 2 μg/mL of oxacillin and piperacillin, and 80, 40 and 4 μg/mL of sulfamethoxazole, respectively. In-process quality control samples showed a mean inter-day imprecision and accuracy (expressed as the systematic error) of 1.83-4.67%/3.31-9.36% for ciprofloxacin, 6.73-8.16%/3.01-14.01% for oxacillin, 1.74-5.99%/3.86-7.57% for piperacillin, and 0.93-3.39%/4.25-9.39% for sulfamethoxazole. Additionally, good drug plasma stability was demonstrated after three consecutive freezing-thawing cycles.

Pharmacokinetic Analysis

Plasma concentration–time data were analyzed using non-compartmental analysis and PK Solutions 2.0 software (Summit, USA), and parameters at the steady state were obtained for the maximum ($C^{ss}max$) and minimum ($C^{ss}min$) drug plasma concentration. The estimated parameters included the terminal elimination rate constant (kel), biological half-life ($t1/2_{\beta}$), area under the plasma concentration-time dosing interval curve (τ) ($AUC^{ss}\tau$), plasma clearance (CL_T) and apparent volume of distribution (Vd^{ss}).

Pharmacokinetic/Pharmacodynamic (PK/PD) Target attainment

PK/PD target attainments (target) were established according to each antimicrobial

characteristic as described below and were expressed as the percentage of desired target sets achieved. PK/PD analysis was performed to evaluate the effective attained concentration range.

For ciprofloxacin, when the ratio between the area under the plasma concentration *versus* time curve and the minimum inhibitory concentration was greater than 125 (AUC^{ss}_{0-24}/MIC> 125), drug efficacy was predicted [15]. For β-lactam derivatives such as oxacillin and piperacillin, the PK/PD data indicated that the best parameter was the percentage of the time dosing interval in which the drug plasma concentration remained above the minimum inhibitory concentration (%*f*T>MIC). Data equivalent to 50% were required for antimicrobial activity against *Staphylococcus aureus*, while 70% was required for other strains [16]. For sulfamethoxazole, AUC^{ss}_{0-24}/MIC values greater than 25 were considered to guarantee antimicrobial effectiveness [17].

Concerning potential common pathogens, the MIC values selected for PK/PD target attainments were obtained based on antimicrobial susceptibility data in the EUCAST/European Committee Antimicrobial Susceptibility Testing database. The MIC for sulfamethoxazole was 38 mg/L for susceptible microbials [*18*]. Patients' antimicrobial effectiveness was estimated according to the percentage of target attainment.

Statistics

Demographic and pharmacokinetic data were analyzed with GraphPadPrisma, Version 5.0 (GraphPad Software, Inc., Chicago, IL) software. Data related to the daily dose and pharmacokinetic parameters (biological half-life, plasma clearance and apparent volume of distribution) were analyzed by the Shapiro-Wilk normality test.

For sulfamethoxazole, dose and kinetic data were compared by applying Wilcoxon's matched pair signed rank test. The level of statistical significance for all of the tests was defined as a p-value less than 0.05.

Results

Forty adult burn patients with preserved renal function or renal dysfunction at the hypermetabolic stage (48 h after thermal injury and resuscitation) were included in the present study. As part of their treatment, patients investigated during the clinical follow-up period in the ICU received antimicrobials alone or in association, as described in Table I. In addition, five patients (9 sets) presented renal dysfunction during sulfamethoxazole therapy.

TABLE I

Demographic data, expressed as the mean and standard deviation, are presented in Table II. A high percentage of inhalation injuries by thermal accident were registered and thermal injuries were predominant compared to electrical accidents. Pharmacokinetic parameters (median/quartile) for antimicrobial agents are also described in Table II. In addition, only data concerning sulfamethoxazole were distributed in two groups of sets, according to the patient's renal function (preserved or renal impairment). Statistical significant differences were not observed (p>0.05) between groups.

TABLE II

PK/PD data were plotted against the MIC values (Table II) of the investigated antimicrobial agents, considering the predictive index for drug efficacy, as expressed for ciprofloxacin (AUC^{ss}_{0-24}/MIC>125), oxacillin (50-70%*f*T>MIC), piperacillin (50-70%*f*T>MIC) and sulfamethoxazole (AUC^{ss}_{0-24}/MIC>25 for NRF and RF), and the percentages of PK/PD target attainment were determined.

Discussion

To reduce morbidity and mortality in critically ill patients with severe infections, source control

Table I. Patients' individual characteristics in different periods of follow up in the ICU

Allocation	Sets	Age	Gender	Weight	TBSA	CL_{cr}	Injury	Antimicrobial
	(no.)	(yrs)		(kg)	(%)	(mL/min)	(T,I,E)	Agent (1-4)
#1	4	43	M	102	18	85.9	E	3, 4
#2	1	41	M	58	10.5	91.6	T	3
#3	2	53	M	70	28.5	97.2	E	3
#4	1	45	M	85	58	128.9	T, I	3
#5	4	22	M	70	75	98.1	T	4
#6	1	62	M	70	29.5	126.4	E	3
#7	1	26	F	50	39	230.1	T	1, 2
#8	5	35	F	60	52.5	128.2	T, I	3, 4
#9	2	36	M	70	8	40.4	T	4
#10	1	26	M	70	62	106.6	T, I	3
#11	4	32	F	70	28	135.2	T, I	1, 2
#12	2	32	M	70	33.5	73.9	E	4
#13	2	90	M	64	8.5	41.2	T	4
#14	2	18	F	52	20.3	117.3	T	4
#15	2	55	M	70	35	40.1	T, I	4
#16	1	19	M	65	23	235.2	E	1
#17	1	22	M	70	49	106.6	T, I	3
#18	2	31	M	75	18	114.7	T, I	3
#19	2	29	F	65	45	250.5	T, I	4
#20	1	60	M	80	23	112	T	3
#21	1	18	M	70	23	163.6	E	3
#22	1	29	M	70	52	112.4	T, I	3
#23	1	50	F	65	30	86.4	T	4
#24	2	27	F	65	75	57.3	T, I	4
#25	1	44	F	80	15	177.1	T	1, 2
#26	1	18	M	75	13	195	T	1, 2
#27	1	62	M	45	17.5	66.8	T	3
#28	1	45	M	90	42	155.1	T	3
#29	2	27	F	60	74	173.2	T,I	2, 4
#30	1	26	F	60	26.5	96.1	T, I	3
#31	1	20	M	90	70	111.2	T, I	1
#32	2	71	M	60	9	108.5	T	1, 2, 3
#33	1	54	M	80	65.5	64.6	T	3
#34	1	41	M	80	58.8	91.7	T, I	4
#35	2	36	M	70	36	202.2	T, I	1, 2, 4
#36	2	40	M	80	20	231.5	T, I	3
#37	1	36	F	65	47.5	60	T, I	4
#38	1	64	M	80	14.5	82.5	T, I	3
#39	1	47	M	75	30	130.9	T, I	3
#40	2	38	M	70	4	147	E	3

Abbreviations - ICU: Intensive Care Unit; F: Female; M: Male; TBSA: total burn surface area; CL_{cr}: creatinine clearance; Injury - T: thermal; I: inhalation; E: electrical; Antimicrobials - 1: ciprofloxacin; 2: oxacillin; 3: piperacillin; 4: sulfamethoxazole

of the pathogen and early and appropriate antimicrobial therapy remain the most important interventions that the clinician can implement. Therefore, an appropriate

antimicrobial dosing regimen is key for the eradication of infection-causing bacteria and an important factor in the emergence and proliferation of antibiotic-resistant strains. Within this context, drug plasma monitoring coupled with drug effectiveness prediction tools by PK/PD target attainments are key issues to ensure adequate drug therapy. An adequate bioanalytical method must also be developed to ensure the safe use of these tools and to implement interventions in a timely manner [23].

The pharmacokinetics of several drugs has been studied in burn patients, including antimicrobial agents, and wide variability within and among patients has been reported. Thus, the unpredictability of the pharmacokinetics of antimicrobial agents in burn patients must be highlighted [4,5,9,19,20].

Pharmacokinetic data obtained in the present study for ciprofloxacin were in accordance with the data reported for burn patients by Garrelts (1996) and was in agreement with data related to the plasma clearance and volume of distribution in critically ill patients without burns [9,21,22].

Regarding the attainment of effective drug plasma concentrations for the recommended dose of ciprofloxacin (800 mg/daily), data from the present study was based on PK/PD target attainments and $AUC^{ss}_{0\text{-}24}$/MIC>125. For ciprofloxacin, 73% target attainment was guaranteed for 0.5 mg/L (MIC) versus the inefficacy for strains with the same reported MIC values [9,22]. Based on the data obtained in the present study, dose adjustments were not required for strains with a MIC of 0.5 mg/L. However, as suggested by van Zanten*et al*., the daily dose of ciprofloxacin (800 mg) should be increased to 1200 mg to achieve the desired target [22]. In contrast, target attainment was 64% for a MIC of 1.0 and 36% for a MIC of 2.0 mg/L.

In the last twenty years, despite the lack of research concerning oxacillin pharmacokinetics and PK/PD target attainments, researchers have suggested that a continuous infusion of β-lactams would provide better bactericidal activity based on their short half lives [23,24]. Surprisingly, in the present study, the biological half-life of oxacillin was prolonged in burn patients compared to data reported by Kampf in 1983 for non-burn patients [23]. Thus, the results obtained in the present study were attributed to an increase in the biological half-life and volume of distribution, which does not change the drug plasma clearance in critically ill burn patients with preserved renal function. These changes support target attainment by PK/PD target attainments (50%fT to 70%fT >MIC) for strains with MICs ranging from 0.5 to 2 mg/L, corresponding to drug effectiveness ratesof100% (0.5mg/L MIC) and greater than 70% (1 – 2mg/L MIC). Consequently, oxacillin dose adjustments were not required after the drug was administered via short infusion every 4 hours.

Concerning piperacillin, several studies have shown that a continuous infusion is required in hospitalized patients [24-26]. However, pharmacokinetic data obtained in the present study were in accordance with those previously reported by Shikuma *et al.* and Bourget *et al* .for burn patients [10,27]. In addition, increases in the apparent volume of distribution of piperacillin were obtained more often in burn patients than in non-burned, critically ill patients with sepsis, as reported by Roberts *et al.* [25]. Finally, the data obtained in the present study indicated that dose adjustments for piperacillin were required for burn patients. Dose adjustments were performed once for strains with MICs of 2 –16 mg/L, and PK/PD target attainments greater than 80% were attained against the recommended index of 50%fT>MIC. Considering 70%fT>MIC, the percentage of target attainment was less than 80% and was equal to 59% in the follow-up periods for strains with MICs of 16 mg/L.

Table no 2: Demographic data, Pharmacokinetics and PK/PD target attainment

	Ciprofloxacin	**Oxacillin**	**Piperacillin**	**Sulfamethoxazole**
Patients (N)	Aug-40	Jul-40	20/40	15/40
Sets of plasma levels (N)	Nov-76	Oct-76	27/76	28/76
Age, yrs (mean ± SD)	33.5±16.7	36.6±16.1	42.9 ± 14.9	38.6± 16.7
Weight, kg (mean ± SD)	70.0 ±11.4	66.4±9.5	71.2± 12.8	68.5± 10.8
TBSA,%	29.1	30.6	29.4	41.4
(mean/ CI95%)	(16.3-41.9)	(15.2-45.9)	(22.0-36.8)	(30.3-52.5)
Thermal accident N/total (%)	7/8 (87%)	7/7 (100%)	15/20 (75%)	13/15 (87%)
Inhalation injury N/total (%)	3/7 (43%)	3/7 (43%)	10/15 (67%)	08/13 (62%)
Electrical accident no/total (%)	1/8 (13%)	NAP	5/20 (25%)	02/15 (13%)
Renal Failure no/total (%)	NAP	NAP	NAP	5/15 (33%)

Pharmacokinetics

PK Parameters and	**Ciprofloxacin**	**Oxacillin**	**Piperacillin**	**Sulfamethoxazole**	
Daily dose	(n=11 sets)	(n=10 sets)	(n=27 sets)	NRF	RF
				(n=19 sets)	(n=09 sets)
$t1/2_b$	6.1	1.6	2.6	8.9	15
(h)	(3.0-10.7)	(0.6-7.5)	(1.5-4.9)	(5.8-14.0)	(7.1-32.0)
CL_T	1.3	5.13	3.33	0.5	0.4
(mL/min.kg)	(0.40-6.50)	(2.48-8.55)	(2.08-5.19)	(0.34-0.61)	(0.23-0.50)
Vd^{ss}	0.9	1.16	0.68	0.41	0.43
(L/kg)	(0.21-2.23)	(0.19-5.00)	(0.38-1.27)	(0.16-0.72)	(0.12-0.99)
Daily dose	9.8	120.6	172	70.1	34.6
(mg/kg)	(7.8-11.7)	(87.2-154.0)	(156.1-187.9)	(58.2-82.0)	(16.1-53.1)

Pharmacokinetic-Pharmacodynamic Correlation -PK/PD target attainment (%)

PK/PD parameter	**AUC^{SS}_{0-24}/ MIC>125**		**50%*f*T>MIC**		**70%*f*T>MIC**		**50%*f*T>MIC**		**70%*f*T>MIC**		**AUC^{SS}_{0-24}/MIC>25**		**AUC^{SS}_{0-24}/MIC>25**	
	MIC	**TA%**	**MIC**	**TA%**	**MIC**	**TA%**	**MIC**	**TA%**	**MIC**	**TA%**	**MIC**	**TA%**	**MIC**	**TA%**
	0.5	73	**0.5**	100	**0.5**	100	**2**	100	**2**	100	**38**	79	**38**	67
	1	64	**1**	100	**1**	80	**8**	100	**8**	80	**76**	56	**76**	33
	2	36	**2**	90	**2**	70	**16**	90	**16**	70				

Statistics: Wilcoxon matched pair signed rank test. Data expressed as median (Quartiles 25-75%) for kinetic data and as mean (CI95%): confidence interval 95% for daily dose.

Abbreviations - NRF: normal renal function; RF: renal failure; t1/2b: half-life; CLT: total body clearance; Vdss: volume of distribution at the steady state; TA: target attainment; MIC: minimum inhibitory concentration; AUCss0-24: daily area under the curve; %*f*T>MIC: time above MIC; NRF: normal renal function; RF: renal failure; NAP: Not applicable

If resistance patterns and other clinical variables are carefully considered, sulfamethoxazole remains a highly useful alternative to expanded-spectrum next-generation agents [23]. Sulfamethoxazole is mainly prescribed in ICU HIV patients with *Pneumocystis jiroveci* pneumonia, *Stenotrophomonasmaltophilia* or *Burkholderiacepacia* infections [17].

Due to the large kinetic variability in the data, significant differences were not observed for sulfamethoxazole when comparing the pharmacokinetic parameters obtained in renal impairment sets versus preserved renal function sets. Consequently, prolonged half-lives in patients with renal impairment were not detected, as previously reported [28,29]. In addition, the total amount of drug eliminated via urinary excretion was low and was approximately 15% of the administered dose. Thus, significant changes in drug clearance were not expected for patients with renal impairment [30, 31].

In contrast, for burn patients with preserved renal function, a similar increase in the volume of distribution and total body clearance was observed. Reduced plasma levels were expected in patients with preserved renal function, as previously reported by Hutabarat*et al.* [31]. Controversial data related to sulfamethoxazole dose regimen based on renal function were previously reported; once, if drug plasma clearance did not change, no decreases on daily dose was required in renal failure [28,29].

Decreases in the daily dose have been recommended for patients with renal dysfunction based on prolonged time-dose intervals [32,33].

Meanwhile, based on the data obtained in the present study, when the dose regimen was adjusted in patients with renal dysfunction by decreasing the daily dose, the target effectiveness was achieved in a lower percentage compared to those with preserved renal function. Thus, for patients with preserved renal function, the initial empirical dose regimen of sulfamethoxazole must be increased to maximize the efficacy, while doses must be carefully decreased for patients with renal dysfunction.

Considering the effectiveness index (AUC/MIC>25) recommended by Cheng *et al.*[17] for sulfamethoxazole and the observed MIC of 38 mg/L, a high percentage of target attainment was obtained in the present study for patients with preserved renal function; however, a lower percentage of target attainment was obtained for burn patients with renal impairment .

Although PK/PD studies are not the only criteria used to determine when therapeutic decisions are necessary, these studies enable clinicians to consider the *in vitro* activity related to the pharmacokinetic profile of a given antimicrobial dosing regimen. Coupled with the knowledge of clinical trial results, resistance mechanisms, local susceptibility patterns and patient characteristics, such information enhances the clinical decision to ensure delivery for optimal care.

Limitations of the study must also be considered, including (i) the use of a calculated creatinine clearance determined by Cockcroft and Gault's method [14] as a renal function measurement instead of a 24 hour creatinine measurement; (ii) assumptions that weight on admission is reflective of the patients' weight throughout their entire stay in the ICU; and (iii) the use of the MIC value from surveillance databases instead of clinical laboratorial data when documented infections did not occur during the dose adjustment time course (iv) total drug plasma measurements.

In conclusion, unpredictable pharmacokinetics was observed for all of the investigated antimicrobials, highlighting the need for therapeutic drug plasma monitoring in burn patients. Regarding the attainment of effective drug plasma concentrations for the recommended dose of ciprofloxacin, 73% target attainment was only guaranteed for a MIC of 0.5 mg/L versus the inefficacy for common pathogens, which was 1-2mg/L (MICs). In

addition, based on these findings, dose adjustments were not required for oxacillin, piperacillin and sulfamethoxazole in burn patients with preserved renal function once effectiveness was attained using the recommended dosing regimens, as evaluated by PK/PD target attainments. Thus, dose adjustment must be carefully considered for sulfamethoxazole in burn patients for renal failure sets.

Conflict of interest: Authors have no conflict of interest to declare

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