

Meropenem therapy against MDR-GNB by pharmacodynamics based on pharmacokinetic changes during acute kidney injury in critically ill septic major burns

Abstract

Introduction: Septic shock is a preventable event caused by potentially fatal organ dysfunction due to a dysregulated host response to infection. Thus, the clinical outcome in most high-risk cases is death in ICU patients with nosocomial bacterial infections, most often associated with renal failure, receiving therapy with hydrophilic antibiotics against Gram-negative or Gram-positive bacteria to combat the development of multidrug resistance. Furthermore, mortality due to the high incidence of Gram-negative bacterial (GNB) infections in ICU patients has not improved over the past 20 years against nosocomial pathogens, which typically present positive cultures by the end of the first week up to second week of ICU admission. Consequently, increased mortality has been linked to the lack of therapeutic serum monitoring of hydrophilic antibiotics in patients at the bedside in ICUs with failure of therapy. Therefore, dosing regimen should be individualized based on renal function by applying the recommended biomarkers.

Subject: Aim of the study was to investigate ICU patients with severe burns during the septic shock undergoing meropenem individualized therapy to investigate if changes on pharmacokinetics (PK) occurs in a renal function dependence with impact on pharmacodynamics (PD), once target attainment against meropenem susceptible strains up to MIC ≤ 2 mg/L Gram-negative nosocomial pathogens must be reached for guaranteed coverage.

Methods: Inclusion of patients in the clinical protocol was related to ICU major burn patients, adults, both genders, total burned surface area $<40\%$ or $>40\%$, SAPS $3 < 57$ or even >57 . Nosocomial infections were confirmed by clinical signs of suspicious sepsis, with new cultures collected after cure of the first septic shock caused by Gram-positive bacterial or community Gram negative isolates that occurred up to 48 hours of ICU admission of major burn patients. Only two blood samples (2-4 ml each) were required for TDM of meropenem serum measurements, performed twice weekly in real time. Coverage was provided by PK/PD tools including drug serum levels, pharmacokinetics and minimum inhibitory concentration (MIC) data.

Results: Meropenem therapeutic target $100\% \Delta T > MIC$ was attained against susceptible strains up to MIC 2 mg/L for 18/24 patients with renal function augmented by vasopressors during the systemic inflammatory response syndrome, while 1g q6h was required to the rest of them (6/24) to guarantee coverage. In addition, an acute kidney injury occurred during septic shock, and daily dose must be reduced to 1g q24h to guarantee safety and effectiveness. Finally, continuous renal replacement therapy (CRRT) during the acute kidney injury (creatinine clearance lower than 20 ml/min); consequently, dose adjustment (1g q12h) was required to guarantee coverage. During CRRT preserved renal function was restorage, and negative cultures occurred.

Conclusion: Pharmacodynamics based on pharmacokinetic changes in ICU patient/bedside offers an essential tool for combating microbial resistance against nosocomial pathogens, based on drug serum levels and cultures data for individualized therapy done in real time. This strategy was applied to ensure individualized for dosing improved outcomes in 83% of patients, which contributed to combating the selection of nosocomial MDR- GNB.

Keywords: meropenem TDM individualized therapy ICU septic major burns, pharmacodynamics based on PK-changes in renal function dependence, PK/PD approach done in real time

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David de Souza Gomez,¹ Mauro Jorge Santos,² Thais Vieira de Camargo,² Karina Brandt Vianna,² Aline Sandre Gomides Abad,¹ Gabriela Aparecida Ferreira,¹ Thiago Câmara de Oliveira,¹ Maria Severina dos Santos,³ Nilo José Coelho Duarte,³ Paschoalina Romano,³ Persio de Almeida Rezende Ebner,³ Nairo Massakaku Sumita,³ Débora Cristina Sanches Pinto,¹ Edvaldo Vieira de Campos,¹ Elson Mendes da Silva Junior,¹ João Manoel da Silva Jr,¹ Sílvia R C J Santos²

¹Plastic Surgery-Burn Division, Surgery Department of Medical School, University of Sao Paulo/SP, Brazil

²Clinical Pharmacokinetics Center, University of Sao Paulo-Sao Paulo/SP, Brazil

³Central Laboratory Division and Medical Investigation Laboratory (LIM 03) – Medical School, University of Sao Paulo (HCFMUSP), Brazil

Correspondence: Sílvia R C J Santos, Clinical Pharmacokinetics Center, University of Sao Paulo - Sao Paulo/SP, Brazil, Tel 55 11 95357- 8930

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Abbreviations: AKI, acute kidney injury; AUC^{ss}, area under the curve at the steady state serum levels (C^{ss}) at the time dose interval (t: t); BAL, bronchoalveolar lavage (BAL) fluid; BSI, blood stream infection; CLSI, clinical & laboratory standard institute, database USA; c-RP, c-reactive protein; CRRT, continuous renal replacement therapy;

CVVHDF, continuous veno-venous hemodialysis filtration; $[t_{(1/2)}]_b$, elimination half-life or biological half-life; HAP, Hospital-acquire pneumonia; GNB, gram-negative bacteria; GPB, Gram-positive bacteria; GSA, global sepsis alliance; ICU, intensive care unit; MDR, Multidrug Resistance; MDR-GNB, multidrug resistance-gram-negative

bacteria; MIC, minimum inhibitory concentration; MRP4, multidrug resistance protein 4 (MRP4) ATP-binding cassette (ABC) transporter; MV, mechanical ventilation; N/L R, neutrophils to lymphocytes Ratio; OAT₁, organic anion transporter 1; OAT₃, organic anion transporter 3; PAHO/WHO, Pan American Health Organization/World Health Organization; PD, pharmacodynamics; PK, pharmacokinetics; PK/PD, pharmacodynamics based on pharmacokinetics; PNM, pneumonia unrelated to mechanical ventilation; PTA, probability of target attainment; RFA, renal function augmented; RFP, renal function preserved; SAPS3, simplified acute physiology score 3; SIRS, systemic inflammatory response syndrome; TBSA, total burn surface area; TDM, therapeutic drug monitoring; [CL_r], total body clearance; UTI, urinary tract infection; [Vd^{ss}], volume of distribution at steady state levels or apparent volume of distribution; WI, wound infection; WHO, World Health Organization

Introduction

Septic shock is a preventable event caused by potentially fatal organ dysfunction due to a dysregulated host response to infection. Thus, the clinical outcome in most high-risk cases is death of patients admitted to the ICU with nosocomial bacterial infections associated with acute kidney injury and comorbidities treated with hydrophilic antibiotics against Gram-negative bacteria to combat multidrug resistance. Therefore, an immediate change in this scenario is necessary through continuous clinical monitoring of patients in intensive care, through hemodynamic, respiratory, renal, and infectious surveillance.¹⁻³ Furthermore, mortality due to the high incidence of Gram-negative bacterial (GNB) infections in ICU patients has not improved over the past 20 years against nosocomial pathogens, which typically present GNB with positive cultures by the end of the first up to second week of ICU admission.⁴⁻⁶

It was demonstrated that 80-90% of patients did not reach the therapeutic target against susceptible strains of Gram-negative nosocomial bacteria, increased mortality has been expected related to the lack of therapeutic serum monitoring of hydrophilic antibiotics in ICU patients/bedside with unsuccessful therapy related to dose regimen based on renal function augmented or reduced as during the acute kidney injury (AKI). Drug monitoring implemented with antibiotic stewardship program was recommended for the control of nosocomial infections based on serum levels of beta-lactam and carbapenem agents and cultures of isolates in ICU septic patients.^{7,8} It is important also to highlight exigence's based on support of hospital costs that must be carried out linked to individual patient care and clinical outcome to better investigate high ICU mortality.⁸⁻¹³ Therapeutic strategies have been investigated for the most prescribed antibiotics against nosocomial pathogens, related to dosage regimens, infusion duration, and frequent culture monitoring.¹⁰⁻¹⁴

Thus, antibiotic resistance and underexposure in ICU burn or non-burn patients, over the past 30 years represent another challenge to be faced and solved. Therapeutic drug and culture monitoring patient bedside, based on individualized medical prescription, is always necessary and represents a significant challenge to overcome, since these patients exhibit rapid changes in serum creatinine due to high instability of renal function during systemic inflammatory response.

Objective

The aim of the study was to investigate, through an open clinical prospective protocol of study, critically ill ICU patients with severe burns during the septic shock undergoing meropenem individualized therapy to investigate if changes on pharmacokinetics (PK) occur in a renal function dependence with impact on pharmacodynamics (PD), once target attainment against meropenem susceptible MIC<2mg/L

Gram-negative nosocomial pathogens must be reached for guaranteed coverage.

Methods

Study design, Ethics, Patient eligibility: The study was conducted at a tertiary public hospital, HC FMUSP, School of Medicine of the University of Sao Paulo, SP, Brazil. The clinical protocol involved an open and prospective study. The ethical approval records CAAE 07525118.3.0000.0068-v.3, Brazilian Platform, were obtained with approval from the Ethics Committee of the Hospital das Clinicas, University of Sao Paulo. There was no declaration of conflict of interest from any of the authors. The study was conducted from January 2018 to April 2019, with informed written consent obtained from all legally designated representatives of the patients. Therapy of patients with meropenem intolerance was non-eligible, while meropenem therapy of patients without intolerance was eligible.

Meropenem, a carbapenem agent, was chosen for coverage guaranteed against nosocomial Enterobacteriaceae, and non-Enterobacteriaceae, which, in our experience, occurs between 10 - 14 days of ICU admission of major burns. The selection of patients was related to critically ill ICU burn patients (n=24) adults, >18 to 80 years, both genders (17M/7F), TBSA <40% or >40%, SAPS 3<57 or even >57. Adult major burns admitted to the Intensive Care Unit (ICU) with severe burn injury may be diagnosed with suspected septic shock by nosocomial bacteria between 10 and 14 days of ICU admission. Patients with sepsis suspicious of nosocomial infection were confirmed by new cultures collection before meropenem therapy started. Cultures were collected in those patients to investigate blood stream infections (BSI), urinary tract infections (UTI), wound lavage fluid (WI) and pulmonary infections by sample collection of bronchoalveolar lavage BAL/fluid. Demographic, clinical characteristics of patients and laboratorial data at admission were included, Table 1.

Table 1 Characteristics of critically ill major burn patients after ICU admission Demographic, Clinical and Laboratorial data. Med (IQR)

Demographic data	Patients (n=24)
Gender (M/F), n (ratio)	(17/7)
Age (yrs)	47 (39-57)
Body weight (kg)	75 (70-78)
Ideal body weight (kg)	75 (64-80)
Heights (cm)	174 (170-180)
Body surface area (m ²)	1.91 (1.82-1.95)
Body mass index (kg/m ²)	24 (23-25)
Admission data	
SAPS3	55 (52-67)
TBSA (%)	39 (28-59)
Thermal/electrical injury, n ratio (%)	23/1 (96/4%)
Inhalation injury, n (%)	20 (83%)
Mechanical ventilation, n (%)	22 (92%)
Vasopressors, n (%)	12 (50%)
Accident, n (%)	19 (79%)
Suicide attempt, n (%)	4 (17%)
Crime, n (%)	1 (4%)
Laboratorial data (CLSI)	
Leucocytes (*10 ³ cells/mm ³)	20.66 (14.28-31.22)
Neutrophils (*10 ³ cells/mm ³)	16.02 (11.45-26.59)
Lymphocytes (*10 ³ cells/mm ³)	1.65 (0.82-3.15)
Serum creatinine (mg/dL), min/max value	1.55 (0.77-3.06) 0.56/4.99
Creatinine clearance (mL/min), min/max value	61 (20-174) 14/256

Table I Continued.....

C- reactive protein (mg/L)	295 (189-386)
Neutrophils/Lymphocytes ratio (N/L ratio)	8.19 (5.99-14.35)

Abbreviations: Med (IQR): median, quartiles (25-75); SAPS3: Simplified Acute Physiology Score III; TBSA: total burn surface area; NLR: neutrophils to lymphocytes ratio; **CLSI:** Clinical & Laboratory Standard Institute.

Statistics: GraphPad Prism, v.9.1.4, Medians IQR.

Complete medical history, physical examination was obtained for each enrolled patient; laboratory data, and microbiology of isolated strains documented in blood cultures, bronchoalveolar lavage, wound, and urinary tract were considered. Susceptibility testing was done to obtain the minimum inhibitory concentration for meropenem against pathogens isolated according to the Clinical Laboratory Standard Institute (CLSI database). Meropenem coverage was based on the recommended pharmacokinetics-pharmacodynamics target $100\%f\Delta T > MIC$.⁸ Renal function based on creatinine clearance was estimated by creatinine serum levels applying Cockcroft-Gault equation measured by the COBAS Analyzer 8000 series; inflammatory biomarker such as c-RP serum levels were performed on the COBAS Analyzer 8000 series (c-RP) (Roche, trademark), and neutrophil-to-lymphocyte ratio (N/LR) in blood count was measured using a Hematological Analyzer (SYSMEX brand). All results of the tests carried out in the hospital's Central Laboratory, including data from the cultures that were sent via the network. Additionally, drug serum levels were determined by high performance liquid chromatography/ultraviolet detection (LC-UV, Shimadzu series 10, with automatized injection of serum samples as purified extracts) in the Clinical Pharmacokinetics Center, after development and revalidation of bioanalytical method detailed previously.¹⁴

Meropenem therapy, blood sampling for TDM, PK study, PK/PD approach: Twenty-four septic major burns received therapy with meropenem, and all of them contributed to each subgroup sequentially at regimen recommended in hospital according to renal function. Meropenem was administered systemically by pump 3hrs.-extended infusion, at the protocol recommended for major burns at dose regimen prescribed 1g q8h for patients with renal function preserved or augmented by vasopressors requirements to attain the target against Gram-negative susceptible strains up to MIC 2 mg/L. Patients with acute kidney injury (AKI), dose regimen prescribed was 1g q24h, or yet 1g q12h for patients undergoing continuous replacement renal therapy (CRRT) by veno-venous hemodialysis filtration (CVVHDF) prescribed by Nephrology Service.

It is important to highlight that meropenem was chosen for treatment of ICU septic burn patients against nosocomial infections caused by Gram-negative pathogens, *Enterobacteriaceae* as *Klebsiella pneumoniae* and non-*Enterobacteriaceae* like *Pseudomonas spp.*, and other free-living Gram-negative bacillus like *Burkholderia cepaciae* or *Stenotrophomonas maltophilia*, that frequently were found in hospitals settings, that in general can occur also in ICU patients with long term hospital staying.

Blood sampling done in strategic time for TDM & PK study: Two blood samples at the steady state levels of meropenem were collected per TDM twice a week, volumes of 2-4 mL each into vacuum tubes. Then, at the 3rd hr. of started meropenem infusion, blood sample was collected (sample 1), and a second one, 1hr. before the next infusion (sample 2) for meropenem serum levels purposes., to investigate if PK-changes may occur in a dependence of renal function with impact on coverage. Meropenem serum levels were obtained by a validated bioanalytical chromatographic method previously reported.¹⁴ TDM data included meropenem serum levels at the peak (C^{ss}_{peak}) and at

the trough serum levels predicted (C^{ss}_{trough}), once drug serum level at the trough was predicted based on one compartment open model monoexponentially decay and pharmacokinetic parameters estimated by Pk Solution software-Summit Research Services, were: elimination rate constant, elimination half-life or biological half-life, total body clearance and volume of distribution at steady state.

Clinical pharmacokinetic parameters estimated: Pharmacokinetic (PK) modeling was applied to investigate whether the coverage achieved by the PK/PD approach is impacted by changes on renal function, and how to prevent the rapid change in glomerular filtration rate that occurs in ICU acute septic patients during renal failure to avoid death. PK parameters estimated were based on the one-compartment open model followed by 3hrs.-extended infusion of meropenem at the steady state levels, via calibrated pump as follows: elimination rate constant [kel: 1/hr], biological half-life [$t_{(1/2)\beta}$: hrs.], total body clearance [CL_T : L/h]; volume of distribution at the steady state [Vd^{ss} : L], where, Vd^{ss} : L was based on CL_T/kel ratio.

Pharmacodynamics based on Pharmacokinetics: Meropenem effectiveness was evaluated by pharmacodynamics based on pharmacokinetic changes by applying PK/PD tools to estimate the coverage of the carbapenem agent based on parameters: trough equivalent to the minimum drug serum concentration (C^{ss}_{trough} : mg/L), elimination rate constant (kel: 1/hrs.), time interval between consecutive doses (τ : hrs.), and PD parameter including the minimum inhibitory concentration (MIC data, mg/L) related to strains isolated from the monitoring cultures recommended, CSLI database. Meropenem percent of target attainment was based on predictive index $\%f\Delta T > MIC$, that means the percentage of time dose interval (%T) required to maintain the minimum of free (f) meropenem serum levels at the trough level (C^{ss}_{trough}) before the next infusion. Then, meropenem target tested by our group and today strongly recommended against Gram-negative strains coverage is equivalent to $100\%f\Delta T > MIC$. It means that meropenem coverage after dose regimen will depend on time interval between two consecutive doses (τ) that the free minimum serum concentration (C^{ss}_{trough}) must be maintained higher than MIC data against each pathogen isolated.¹³

Information to the ICU/ clinicians in turn - Laboratory exam report: In turn ICU/clinicians received in real time all data related to each patient of the study, in a Laboratory Exam Report [Pt #ID- hospital number] sent by the network daily that includes information related to coverage based on target attained for dose adjustment based on TDM/PK/PD:

- I. PK/PD data including dose regimen prescribed, target attainment by meropenem coverage attained, related to MIC data of each Gram-negative bacteria isolated from cultures of a patient.
- II. Additional comments related to PK parameters of a patient: elimination half-life (hrs.); total body clearance (L/hr.); volume of distribution at steady state (L) by comparison: Patient data versus Reference data related to Meropenem in healthy volunteers.
- III. Important additional information's were added in the Laboratory Exam Report concerning patient's daily creatinine clearance, c-RP & N/L ratio done daily in hospital's Central Laboratory, same day of meropenem blood sampling for TDM and coverage based on PK/PD tools.

Statistical analysis

Individual and population data: Statistical data from this study was conducted on 24 severely burned patients with nosocomial Gram-negative strains isolated from cultures in general collected after 10 and

14 days of ICU admission. Software's applied were as follows: OFFICE 365, version 2208 (Excel); GraphPAD InStat- GraphPad Prism version 9.1.4 (2023). Non-parametric tests (Mann Whitney) for unpaired and paired data tested were applied to data obtained from the investigated patients. The significance of $p < 0.05$ was considered.

Results

PK study: Twenty-four major burn patients included in the protocol, and all of them contributed to each subgroup sequentially. Therapy with

meropenem by 3 hrs.-extended pump infusion, at the recommended dose regimen was based on renal function dependence according to creatinine clearance as follows: Subgroup 1-RFA (CLcr 120 -150 mL/min); Subgroup 2-AKI (CLcr < 20 mL/min); Subgroup 3- CRRT/CVVHDF (CLcr 50--80 mL/min); Subgroup 4-RFP (CLcr > 60-90 mL/min). In this study, meropenem PK parameters according to renal function dependence were compared as described in Table 2.

Table 2 Pharmacokinetics of Meropenem after 3hrs-extended infusion, Med (IQR). Renal function subgroups: PK changes in a dependence on renal function (n=24 patients)

PK-one compartment open model	PK-parameters RFA	PK-parameters AKI	Statistics P
$t_{(1/2)\beta}$ (hrs)	1.5 (1.4-1.6)	5.2 (4.3-5.9)	0.0002
CL_T (L/h)	9.7 (9.1-10.3)	3.0 (2.4-4.1)	0.0002
Vd^{ss} (L)	21.4 (19.2-23.0)	26.8 (13.0-35.0)	0.6426
	AKI	CVVHDF	
$t_{(1/2)\beta}$ (hrs)	5.2 (4.3-5.9)	3.9 (3.6-4.2)	0.1958
CL_T (L/h)	3.0 (2.4-4.1)	5.5 (4.8-6.1)	0.0016
Vd^{ss} (L)	26.8 (13.0-35.0)	30.5 (27.2-37.0)	0.3256
	CVVHDF	RFP	
$t_{(1/2)\beta}$ (hrs)	3.9 (3.6-4.2)	2.2 (1.9-2.6)	0.0002
CL_T (L/h)	5.5 (4.8-6.1)	7.8 (7.5-9.2)	0.0002
Vd^{ss} (L)	30.5 (27.2-37.0)	22.4 (17.7-28.6)	0.3178

Comments related PK change that impacts coverage: Cure of infection occurred up to negative cultures. Adjustment of dose regimen was done by TDM twice a week for efficacy/safety based on target attainment.

Half-life [$t_{(1/2)\beta}$ (hrs.)] was reduced by vasopressor requirements (RFA) during SIRS in 50% of patients and it was prolonged with a high variability during AKI. Reduction on half-life remained statistically unchanged between subgroups AKI versus CVVHDF. Finally, significant reduction of elimination half-life occurred in RFP.

Total body clearance [CL_T (L/h)] was increased by vasopressors in RFA, reduced during AKI, with increases during CVVHDF. At the end of meropenem therapy high increases occurred in the parameter during RFP.

Volume of distribution [Vd^{ss} (L)]: any changes occurred in the parameter by comparison of four patients' subgroups that received vasopressors at RFA, during AKI or CVVHDF, and in patients with preserved renal function (PRF).

Abbreviations: Med (IQR): median, quartiles (25-75); RFA: renal function augmented; AKI: acute kidney injury; CVVHDF: continuous veno-venous hemodialysis filtration; IQR: quartiles (25-75); RFP: renal function preserved; $t_{(1/2)\beta}$ (hrs.): elimination half-life; CL_T (L/h): total body clearance; Vd^{ss} (L): volume of distribution at steady-state; TDM: therapeutic drug monitoring. PK/PD: pharmacokinetics-pharmacodynamics; ICU: Intensive care unit.

Statistics: GraphPad Prism, v.9.1.4, Mann Whitney. Significance: $p < 0.05$.

Equations to estimate PK parameters

$kel = (\ln C_1 - \ln C_2) / (T_2 - T_1)$	[h ⁻¹]	C_1, C_2 (mg/L): meropenem levels at blood sampling
$t_{(1/2)\beta} = (0.693 / kel)$	[hrs.]	T_1, T_2 (hrs.): meropenem times at blood sampling Elimination half-life is the period to reduce by 50% meropenem serum levels
$Vd^{ss} = CL_T / kel$	[L]	Volume of distribution at the steady state measures the distribution of from blood (central compartment) transferred to the tissue fluids in peripheral compartment
$CL_T: L/h = D\tau / AUC^{ss\tau}$	[L/h]	Total body clearance is the elimination of meropenem from the body

Equation to estimate the total body clearance based on $AUC^{ss\tau}$

Where, $D\tau$ (mg) was estimated by dose administered at time interval considered (τ , hrs.), and the area under the curve ($AUC^{ss\tau}$: mg²hr/L) integrated by meropenem serum levels during the time dose interval.

Meropenem coverage by PK/PD approach - Microbiology of Isolates Gram-negative bacteria Meropenem coverage was impacted by PK changes based on renal function dependence that affected parameters: elimination half-life and total body clearance. Consequently, adjustment of dose regimen was done twice a week if

required by therapeutic serum monitoring for efficacy/safety. Cures of infection occurred based on negative cultures. It is important to highlight that meropenem therapeutic target $100\% f\Delta T > MIC$ was attained against susceptible strains up to MIC 2 mg/L for all subgroups, Table 3. Microbiology of isolates is presented in Table 4.

Table 3 Septic major burn patients undergoing Meropenem therapy by 3hrs-extended infusion, Med (IQR)

Meropenem therapy	Dose regimen	Dose regimen	P
Subgroups: 1: RFA; 2: AKI; 3: CVVHDF; 4: RFP	Based on renal function	Based on renal function	Subgroup
RFA, n=18/6 versus AKI, n=24	1g q8h/1g q6h (RFA)	1g q24h (AKI)	[(1) versus (2)]
Daily dose/IBW normalized (mg/kg)	57.8 (49.9-62.0)	17.5 (15.4-19.6)	0.0002
AKI versus CVVHDF, n=24	1g q24h (AKI)	1g q12h (CVVHDF)	[(2) versus (3)]
Daily dose/IBW normalized (mg/kg)	17.5 (15.4-19.6)	34.9 (30.7-39.2)	0.0002
CVVHDF versus RFP n=24	1g q12h (CVVHDF)	1g q8h (RFP)	[(3) versus (4)]
Daily dose/IBW normalized (mg/kg)	34.9 (30.7-39.2)	52.3 (46.1-58.8)	0.0016
PK/PD Target attainment	100%fΔT>MIC	100%fΔT>MIC	**GNB
Meropenem coverage	Up to 2mg/L	Extended up to 4mg/L	MIC 4mg/L
Subgroups	Susceptible strains isolated	Intermediate susceptibility	Strains isolated
1-RFA: 1g q8h/1g q6h n=18/6 (3-4g daily)	MIC 0.25-2 mg/L	MIC>2 up to 4 mg/L	None
2-AKI: 1g q24h (1g daily)	MIC 0.25-2 mg/L	MIC>2 up to 4 mg/L	None
3-CVVHDF: 1g q12h (2g daily)	MIC 0.25-2 mg/L	MIC>2 up to 4 mg/L	None
4-RFP: 1g q8h (3g daily)	MIC 0.25-2 mg/L	MIC>2 up to 4 mg/L	None
Laboratorial data at meropenem therapy during septic shock (n=24 patients)			
Laboratorial Data (CLSI database)	Meropenem start of therapy	Meropenem end of therapy	P
Serum creatinine (mg/dL)	1.98 (1.47-3.30)	0.91 (0.65-1.51)	0.0002
Creatinine clearance (mL/min)	55 (18-178)	78 (68-116)	0.6542
C-reactive protein (mg/L)	336 (156-359)	147 (138-182)	0.5491
Leucocytes (*10 ³ cells/mm ³)	15.88 (13.53-28.86)	13.07 (11.36-15.55)	0.8472
Neutrophils (*10 ³ cells/mm ³)	13.15 (9.55-20.89)	8.89 (7.64-10.71)	0.1582
Lymphocytes (*10 ³ cells/mm ³)	1.65 (0.95-3.06)	1.80 (0.95-2.78)	0.917
Inflammatory biomarkers	Meropenem start of therapy	Meropenem end of therapy	P
c-Reactive protein (mg/L) in Survivors n=20 (83%)	337 (232-344)	35 (24-38)	0.0002
c-Reactive protein (mg/L) in non-Survivors n=4 (17%)	325 (294-396)	261 (244-309)	0.4765
NLR in Survivor n=20/24 (83%)	7.61 (4.88-13.00)	0.43 (0.27-1.02)	<0.0001
NLR in non-Survivor n=4/24 (17%)	6.81 (4.63-9.49)	14.6 (8.3-16.2)	0.6764
Clinical outcome	30 days ICU mortality	Hospital (days)	P
Survivors, n=20 patients (days)	31 (16-55)	44 (29-75)	0.6854
non-Survivors, n=4 patients (days)	26 (21-28)	26 (21-28)	1

Dose regimen individualized for target attainment - 100%fΔT>MIC (Meropenem coverage against GNB)

Abbreviations: Med (IQR): median, quartiles (25-75); AKI: acute kidney injury; ATB: antibiotic; CLSI: Clinical & Laboratory Standard Institute; CVVHDF: continuous veno-venous hemodialysis filtration; GNB: Gram-negative bacteria; **GNB: Gram-negative bacteria of intermediate susceptibility; IBW: ideal body weight; ICU: Intensive care unit; MIC: minimum inhibitory concentration; NLR: neutrophil/lymphocyte ratio; PK/PD: pharmacokinetics/pharmacodynamics; RFA: renal function augmented; RFP: renal function preserved; TDM: therapeutic drug monitoring. **Statistics:** GraphPad Prism, v.9.1.4, Mann Whitney. Significance: p<0.05.

Table 4 Septic major burn patients undergoing Meropenem combined therapy Microbiology of Isolated Strains (CLSI database)

Microbiology of isolates - Meropenem	GNB -Susceptible isolates	GNB - Coverage	Coverage extended
Enterobacteriaceae susceptible, n=36 (90%)	MIC 0.25-2 mg/L n (%)	Up to MIC 2 mg/L	MIC >2-4 mg/L
<i>Enterobacter cloacae</i> (MIC 0.5-1 mg/L)	2 (5%)	2/2 (100%)	2/2 (100%)
<i>Haemophilus influenza</i> (MIC 0.25 mg/L)	6 (15%)	6/6 (100%)	6/6 (100%)
<i>Klebsiella pneumoniae</i> (MIC 0.25- 1 mg/L)	6 (15%)	6/6 (100%)	6/6 (100%)
<i>Morganella morganii</i> (MIC 0.25 mg/L)	5 (12.5%)	5/5 (100%)	5/5 (100%)
<i>Proteus mirabilis</i> (MIC 0.25 mg/L)	7 (17.5%)	7/7 (100%)	7/7 (100%)
<i>Providentia stuartii</i> (MIC 0.25 mg/L)	5 (12.5%)	5/5 (100%)	5/5 (100%)
<i>Serratia marcescens</i> (MIC 1mg/L)	5 (12.5%)	5/5 (100%)	5/5 (100%)
Enterobacteriaceae (total of 36 isolates from cultures)	36 (90%)	All isolates	None
Non- Enterobacteriaceae susceptible, n=4 (10%)	Isolates GNB n (%)	Up to MIC 2 mg/L	MIC >2-4 mg/L
<i>Pseudomonas aeruginosa</i>	3 (7.5%)	3/3 (100%)	3/3 (100%)
<i>Burkholderia cepaceae</i>	1 (2.5%)	1/1 (100%)	1/1 (100%)
Non-Enterobacteriaceae (total of 4 isolates/cultures)	4 (10%)	All	None
Microbiology of isolates in a combined therapy with meropenem			
Vancomycin susceptible Gram-positive, n=27 (79%)	GPB isolates, n (%)	MIC (mg/L)	Up to 1mg/L

Table 4 Continued.....

<i>Staphylococcus aureus</i>	8 (24%)	0.5-1.0	Susceptible
<i>Staphylococcus epidermidis</i>	15 (44%)	1	Susceptible
<i>Enterococcus faecalis</i>	4 (12%)	0.5-1.0	Susceptible
Polymyxin B susceptible, n=3 (9%)	GNB-MDR isolates, n (%)	MIC (mg/L)	Up to 2mg/L
<i>Acinetobacter baumannii</i> complex	3 (9%)	0.5-2.0	Susceptible
Fluconazole susceptible <i>Candida spp.</i>, n=4 (12%)	Fungal isolates, n (%)	MIC (mg/L)	Up to 2mg/L
<i>Candida albicans</i>	3 (9%)	0.5-1.0	Susceptible
<i>Candida tropicalis</i>	1 (3%)	2	Susceptible

Abbreviations: CLSI: Clinical & Laboratory Standard Institute; GNB: Gram-negative bacteria; **GNB: Gram-negative bacteria of intermediate susceptibility; GNB MDR: Gram-negative bacteria multidrug resistant; GPB:

Prescription of meropenem dosing regimen via prolonged 3-hour infusion was done on real-time for TDM considering daily renal function, based on creatinine clearance estimated by serum creatinine. Then, pharmacokinetic changes of meropenem affected critical parameters such as half-life and total body clearance, which positively impacted on clinical outcome related to the PK/PD target attained.

Sites of infection occurred on blood stream (59%), nosocomial pneumoniae (21%) unrelated to mechanical ventilation (bronchoalveolar lavage fluid/BAL), wound/bone (15%) and urinary tract (5%). The cure of infections was achieved by meropenem coverage target reached against nosocomial Gram-negative bacteria, susceptible strains with MICs of 0.5 to 2.0 mg/L. In Table 3 were described, meropenem coverage against *Enterobacteriaceae* & non-*Enterobacteriaceae* that was investigated after 40 isolated strains from cultures. A total of 36 (90%) isolates susceptible of *Enterobacteriaceae* were described against 4 (10%) susceptible strains MIC 1.0 - 2.0 mg/L of non-*Enterobacteriaceae* isolated.

It is important to highlight that meropenem combined therapy occurred, as described in Table 4 for vancomycin against susceptible Gram-positive isolates, polymyxin B against *Acinetobacter baumannii* complex GNB- MDR, and fluconazole against susceptible *Candida albicans*, *C. tropicalis*.

Inflammatory biomarkers: Furthermore, inflammatory biomarkers were described in Table 3, it was shown a significant difference only for surviving patients (n = 20/24, 83%), since any difference was obtained in the group of non-survivors (n = 4/24, 17%) related to biomarkers at the beginning of therapy compared to the subsequent period, based on early ICU death that occurred between 21 and 28 days.

Discussion

PK changes based on duration of drug infusion for drug effectiveness and safety: At the beginning of the third millennium, the emergence of new beta-lactams combined with beta-lactamase inhibitors against nosocomial GNB infections made them available for combating MDRB. Afterwards, the inclusion of meropenem, a new carbapenem with reduced neurotoxicity compared to imipenem, was a new milestone in combating nosocomial infections in critically ill ICU patients.

Earlier this century it was reported in ICU/hospitals that meropenem (1g q8h, eq. 3g daily) or piperacillin- tazobactam (4.5g q8h, eq. 13.5g daily) should be administered by intermittent infusion of 0.5h to ICU patients undergoing septic shock therapy without acute kidney injury. Since the duration of infusion is critical, a serial of clinical protocols developed with meropenem, and piperacillin/tazobactam was tested at dose regimens recommended as a function of the duration of drug infusion. Consequently, prolonged by 2hrs, or even 3hrs- infusion versus 0.5hr-intermittent infusion were investigated for both antibiotics of renal elimination with shortest half-lives. It was demonstrated that the

coverage against GNB was increased by trice due to an effective trough level by 3hrs.-prolonged infusion compared with 0.5hr-intermittent short infusion. Consequently, impacting coverage occurred by PK-changes with increases on the volume of distribution and prolongation of biological half-life by trice after 3hrs.-extended infusion, in a linear relationship between them, independently of total body clearance of patients with renal function preserved. It was reported also that PK-changes could impact positively the coverage at the target 100% $fT > MIC$ recommended; then, a reduction of ICU deaths was expected by cure of nosocomial infections caused by GNB.⁸⁻¹⁵

Meropenem therapy is the preferred choice against susceptible GNB causing nosocomial infections and has been widely applied for the past fifteen years. In the present study, it was demonstrated that biological half-life varied proportionally in an inverse ratio with the total body clearance due to changes on pharmacokinetics in a renal function dependence for all patients in the four subgroups considered. In addition, volume of distribution remained unchanged in our study, due to the prolonged infusion of 3 hours as previously demonstrated in studies related to short versus prolonged infusion. Consequently, the efficacy of the carbapenem was positively impacted by the 3-hour infusion, based on pharmacokinetic changes with guaranteed coverage up to MIC 2 mg/L against susceptible strains and an extended coverage achieved against strains of intermediate susceptibility, MIC of 4 mg/L (CLSI database). Data presented in the study bring evidence of meropenem TDM for dose adjustment purposes done by 3-hrs-infusion proved that an earlier eradication of pathogens occurred, with cure of the infection by desired clinical outcome reached 83% (20/24) in major burns. Then, the contribution of meropenem to achieving the desired clinical outcome with cure of infections, had an impact on the reduction of deaths in this ICU of the hospital.

In addition, it is well known that elderly patients in general develop acute kidney injury within hours rapidly due to reduced renal perfusion, with the onset of acute renal failure resulting from the inflammatory response; in these cases, continuous renal replacement therapy using various hemodialysis techniques is necessary. Antimicrobial resistance is quite important for major burns in ICU and should be considered, since two or three surgical interventions, such as debridement followed by grafting, may occur weekly for each burn patient, depending on the extent and depth of the injury, and the ability of each patient during recovery. Subsequently, immunosuppression and systemic inflammatory response syndrome are expected, which contributes to nosocomial bacterial infections caused by Gram-negative bacteria in the immediate postoperative period.

Inflammatory biomarkers to predict ICU mortality: It was previously reported by Shimazui et al.,¹⁶ in critically ill non-burn septic patients at ICU admission related to interleukin-6 serum levels and outcome prediction in those septic patients with acute kidney injury.¹⁶ Effects of neutrophil-to-lymphocyte ratio (N/L ratio) combined with interleukin-6 in predicting 28-day mortality in non-burn patients with

sepsis was confirmed by Liu et al.,¹⁷ while, Qiu et al.,¹⁸ described that major burns have a type of trauma with high risk of mortality based on neutrophil-to-lymphocyte ratio measured on the third day postburn associated with 90-day mortality among patients with burns over 30% TBSA.^{17,18} That important knowledge found in critically ICU burn patients was confirmed again by Setiawan et al.,¹⁹ once high neutrophil-lymphocyte ratio could be as a predictor of mortality also in patients major burns.^{18,19}

More recently, inflammatory biomarkers considered as c-Reactive Protein (c-RP), neutrophils/lymphocytes ratio (N/L ratio), procalcitonin (PCT), interleukin 6 (IL-6), another pro-inflammatory cytokine were investigated to predict mortality in ICU septic patients' major burns.^{20–25}

Then, an accurate predictor of mortality indicators is strategically needed in ICU septic major burn patients of high mortality, since it was shown that rapid changes in renal function occur during SIRS. Additional support based on TDM and PK-changes renal function dependently will be important to guide physicians of ICU clinical team related to changes on dosing regimen prescription to guarantee drug efficacy and safety in ICU septic major burns. In previous experience with SIRS inflammatory biomarkers in our ICU for septic major burns, c-reactive protein and the neutrophil-to-lymphocyte ratio were chosen as early indicators of mortality in septic burn and non-burn patients admitted to our hospital's ICUs of the tertiary public hospital in Brazil.

Organic anion transporters during SIRS in critically ill septic major burns: It was described by Zhang J et al.,²⁶ in a review study of the regulation of organic anion transporters involving physiology, pathophysiology, and drug elimination related to drug transference by specific organic anion transporters, drug disposition post-translational modification, and regulation on the organic anion transporter family that are mainly expressed in kidney. These transporters play important roles in the disposition of clinical drugs including antibiotics. Changes in the expression and function of OATs contribute to the intra- and inter-individual variability of the therapeutic efficacy or the toxicity of many antibiotics due to many pathophysiological conditions. Consequently, important changes in organic anion transport (OATs) expression were found in some studies related to OATs and their regulation that can influence the pharmacokinetics of antimicrobial agents, based on increases in pro-inflammatory cytokines regulation of organic anion transporters.^{26–28}

It is well known that an increase on inflammatory cytokines serum levels may cause a reduction of expression of drug renal secretion involving mechanisms that can be expected. Mechanisms involved in antibiotic (ATB) tubular secretion start with influx of molecules of ATB from the bloodstream captured by organic anion transporter (OAT₁/OAT₃) into the cell of basolateral membrane at the proximal renal tubule of nephron. Then, meropenem tubular secretion begins when organic anion transporters (OAT₁/OAT₃) transfer antibiotic molecules from the bloodstream into plasma cell of basolateral membrane of proximal renal tubule. Then, renal tubular secretion is completed by meropenem transferred via MDRP4-transporter responsible for anions secretion in primary urine. It is important to highlight that meropenem tubular secretion occur independently of kidney function capacity of a patient to excrete meropenem by glomerular filtration rate in the urine. Consequently, high risk of nephron and neurotoxicity based on increased serum levels of inflammatory cytokines during SIRS can reduce meropenem secretion with significant impact on reduction of total body clearance and prolonged biological half-life, in ICU patients with acute kidney injury.^{20–25}

Conclusion

Critically ill major burn patients during SIRS must have daily laboratorial support and consequently the clinical team TDM-guided meropenem dosing adjusted for renal function allied to improved microbiological cure and reduced mortality in septic burn patients. Pharmacodynamics based on PK-changes in ICU patient/bedside offers an essential tool for combating microbial resistance, based on serum levels and MIC data for individualized therapy done in a real time. This strategy was applied to ensure individualized therapy, which contributes to combating the selection of nosocomial MDR-GNB.

Limitations

This prospective clinical study was observational, conducted in the ICU of patients with major burns during the treatment of septic shock, with a single-center design. The comparison group was represented by the last subgroup of patients with preserved renal function after infection cure. Microbiological confirmation was absent in four patients who did not survive and died in the ICU between 21 and 28 days. Prolonged hospitalization is expected especially for surviving patients in the ICU due to the extent of total body surface area burned (TBSA) in cases of severe major burns treated at the Burn Center of the tertiary public hospital.

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Authors' contributions

All authors contributed equally to this work based on their specialty. DSG contributed to the study related to ethical approvals at the hospital and the Brazilian Platform for clinical projects, data acquisition, interpretation, and critical review of the manuscript content. SRCJS contributed to the conception and design of the study, acquisition and interpretation of data, statistical analysis and writing of the manuscript with critical review for important intellectual content. DCSP, EDC, EMSJ and JMSJ contributed to clinical data acquisition, interpretation, and critical review of clinical data in the manuscript for important intellectual content. ASGA, GAF, TCO contributed to the critically ill patients care in the ICU, blood collection of viable samples for serum antibiotics measurements, and blood collection for laboratorial data acquisition related to biomarkers. MJS, TVC, KBV contributed to the revision of "detailed information of articles included in the Discussion", and especially at the last revision done related to references included in the manuscript. PR, NJCD and NMS contributed to the critical revision of data for important intellectual new contents. PRA and MSS contributed to the discussion of data related to TDM of ATB, and to the critical revision for important intellectual contents. All authors read and approved the final manuscript version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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