

Individualized therapy based on Meropenem serum levels - MIC data against *non-Enterobacteriaceae* resistance in ICU septic major burns

Abstract

Introduction: The incidence of nosocomial infections in the ICU and mortality in critically ill septic patients have not improved over the past 15 years against Gram-negative strains with incidence after 72 hours of hospital admission. It has been widely reported that increased mortality in the ICU is associated with the lack of serum antibiotic monitoring that is necessary for dose adjustment; particularly in acute kidney injury (AKI) and during continuous Veno-venous hemodialysis filtration (CVVHDF) in those patients.

Subject: The study aims to investigate patients with severe septic burns during second or third septic shock undergoing individualized Meropenem therapy regarding changes in pharmacokinetics (PK) that impact pharmacodynamics (PD) based mainly on coverage against susceptible Gram-negative nosocomial pathogens.

Methods: Twenty-nine patients included in the protocol were distributed in three groups. Meropenem was chosen to ensure coverage against *non-Enterobacteriaceae* as *Pseudomonas aeruginosa*, which occurs from the second septic shock in ICU patients with severe burns, and even for coverage against *Enterobacteriaceae* nosocomial strains. Two blood samples were required for each TDM set and PK study; another blood sampling was done for biomarkers monitoring. One compartment open model was chosen for PK-study; pharmacokinetics of meropenem were based on blood sampling and drug serum measurements by HPLC. Target recommended against *non-Enterobacteriaceae* & *Enterobacteriaceae* of 100% $\Delta T > MIC$ was based on pharmacokinetic changes that could impact pharmacodynamics of isolated strains by cultures monitoring, and by MIC data (CSLI). Non-parametric tests were applied, and the significance of $p < 0.05$ was considered.

Results: Meropenem target recommended was attained against susceptible strains up to MIC 2 mg/L and dose adjustments required were based on renal function reduced in 24/29 patients of G1-G2 with acute kidney injury (AKI) and followed by continuous Veno-venous hemodialysis filtration (CVVHDF) installed. Coverage against *non-Enterobacteriaceae* and *Enterobacteriaceae* occurred up to MIC 2 mg/L susceptible strains, and it was extended up to MIC 4 mg/L for 24 patients of G1-G2. Inflammatory biomarkers (SIRS), such as c-RP and N/L ratio were investigated. A significant difference was demonstrated between 24/29 survivors (83%) and 5/29 non-survivors (17%), who died within 10 to 12 days of Meropenem therapy, related to the (N/L) ratio predicting mortality.

Conclusion: Therapy of septic shock with Meropenem was effective against Gram-negative nosocomial pathogens considering PK/PD analysis done weekly based on TDM, cultures monitoring, and N/L ratio as a predictive biomarker of mortality.

Keywords: Meropenem individualized therapy, ICU septic major burns, pharmacokinetic changes dependent on renal function, PK/PD analysis in a real time, target reached-based 100% $\Delta T > MIC$

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Abbreviations: AKI, acute kidney injury; c-RP, c-reactive Protein; CSLI, clinical standard laboratory institute, database USA; CVVHDF, continuous Veno-venous hemodialysis filtration; GSA, global sepsis alliance; HPLC, high performance liquid chromatography (LC-UV); IBW, ideal body weight; ICU, intensive care unit; IL-6, interleukine-6; MDR, multidrug resistance; MIC, minimum inhibitory concentration; MV, mechanical ventilation; N/L R, neutrophils to lymphocytes ratio; PAHO, Pan American health organization; PCT, procalcitonin; PD, pharmacodynamics; PK, 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; UTI, urinary tract infection; WHO, world health organization

Introduction

The incidence of nosocomial infections in the ICU and mortality of critically ill septic patients have not improved over the past 15 years against Gram-negative strains that generally occur after 72 hours of hospital admission. Clinical outcome in most high-risk cases is death of patients with nosocomial bacterial infections receiving therapy with antibiotics mainly against *non-Enterobacteriaceae* strains that occurs at the late stage of ICU admission.¹⁻³ It has been widely reported that increase in ICU mortality is associated with the lack of serum antibiotic monitoring required for dose adjustment, particularly in acute kidney injury (AKI), and during the continuous Veno-venous hemodialysis filtration (CVVHDF) installed.⁴⁻⁸ Therefore, an immediate change in this scenario is necessary related to the continuous monitoring of antibiotic serum levels in these ICU patients in intensive care through

hemodynamic, respiratory, renal and infectious surveillance. It was demonstrated that 80% of patients cannot reach the therapeutic target against susceptible strains of Gram-negative nosocomial bacteria. Then, this problem reinforces that monitoring of serum levels and cultures are essential to evaluate pharmacokinetic changes that can impact the coverage of the antibiotic chosen based on PK/PD tools.⁹ Therefore, in the last 20 years another therapeutic strategies have been investigated for the most prescribed antibiotics against nosocomial pathogens, related to the dosage regimen, duration of drug infusion and cultures monitoring based on support of hospital costs of those patients to better investigate mortality in ICU.⁶⁻¹¹ Then, pharmacodynamics based on pharmacokinetics changes is an essential tool in combating antimicrobial resistance against nosocomial pathogens by ATB serum levels, cultures and inflammatory biomarkers routinely in ICU critically ill septic patients to guide accurately the individualization of therapy.¹²

Objective

The aim of the study was to investigate, through an open clinical protocol, patients with severe septic burns during the second or at the third septic shock undergoing Meropenem individualized therapy to evaluate changes on pharmacokinetics (PK) in a renal function dependence that could impact the pharmacodynamics (PD) based on target attained with coverage against susceptible Gram-negative nosocomial pathogens.

Methods

Study design, Ethics, Patient eligibility: The study was conducted at a public tertiary hospital, HC FMUSP, School of Medicine of University of São Paulo, SP, Brazil. The clinical protocol involved a prospective and open study. The ethical approval records CAAE 07525118.3.0000.0068-v.4, Brazilian Platform, were obtained with approval from the Ethics Committee of the Hospital das Clínicas of the University of São Paulo, School of Medicine. There was no declaration of conflict of interest from any of the authors. The study was conducted from January 2019 to April 2020, 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. It is important to highlight that Meropenem was chosen to ensure coverage mainly against nosocomial strains *non-Enterobacteriaceae*, and even against *Enterobacteriaceae*, which, in our experience occurs from the second septic shock in ICU patients with severe burns. The selection of patients in the clinical protocol was related to major burn patients, adults (18 to 80 years), both genders (18M/11F), TBSA <40% or >40%, SAPS 3<57 or even >57, nosocomial infections confirmed by sepsis suspicious, and new cultures were collected after the cure of the first septic shock that occurred for each burned patient included in the study protocol.

Meropenem therapy for dose adjustment in septic major burns: Adult patients admitted to the Intensive Care Unit (ICU), with severe thermal injury and a diagnosis of sepsis at the second or at the third septic shock, were treated with Meropenem by 3 hrs.-extended pump infusion, at the recommended dose regimen renal function dependent, based on the ideal body weight (IBW). Twenty-nine patients included in the protocol were distributed in three groups based on renal clearance, as follows:

- 1) Group 1 (n=8): Eight patients included in G1 presented initially renal function preserved (RFP-Set 1: 3g daily) followed by an acute kidney injury (AKI-Set 2: 1g daily), and continuous Veno-venous hemodialysis filtration (CVVHDF-Set 3: 2g daily)

requirements. The cure of infection was based on the desired outcome that occurs by negative cultures with cure of infections and return to renal function preserved at the end of therapy (RFP-Set 4: 3g daily).

- 2) Group 2 (n=16): Sixteen patients included in G2 presented initially an acute kidney injury (AKI-Set 1:1g daily), following by the continuous Veno-venous hemodialysis filtration (CVVHDF-Set 2: 2g daily) requirements. The cure of infection was based on the desired outcome that occurs by negative cultures with return to renal function preserved (RFP-Set 3: 3g daily) at the end of Meropenem therapy.

- 3) Group 3 (n=5) Five patients included in G3 presented initially high vasopressors requirements (PAM> 65 mm Hg) during the systemic inflammatory response syndrome (SIRS), that contributed to renal function augmented (RFA-Set 1: 3g daily). The cure of infection was based on the desired outcome that occurs by negative cultures with return to renal function preserved and dose maintained (RFP-Set 2: 3g daily).

Demographic, clinical characteristics of ICU patients and laboratorial data at admission were included, Table 1. Meropenem serum levels at the steady state were monitored in real time by TDM in sets of all groups after dose adjustment or even dose maintained. Meropenem therapy was prescribed at the earlier stage of septic shock considering dose regimen recommended to burn patients in a dependence of renal function, that could be preserved (RFP), augmented (RFA) by vasopressor requirements or yet, acute kidney injury (AKI) as a function of high inflammatory response, followed by continuous Veno-venous hemodialysis filtration (CVVHDF).

Table 1 Burn septic patients at admission in ICU, median (IQR). Demographic, clinical and laboratorial data

Demographic data	n=29
Gender (M/F)	(18M/11F)
Age (yrs)	43 (38-57) 18/80
Ideal body weight (kg) max/min values	70 (60-71) 43/80
Body surface area (m2) max/min values	1.88 (1.80-1.95) 1.35/2.77
Body mass index (kg/m2) max/min values	25 (24-28) 19/55
Clinical data	n=29
SAPS3	56 (45-62) 29/72
TBSA (%)	37(18-46) 9/72
Thermal/electrical injury	28/1
Inhalation injury	27
Mechanical ventilation	27
Accident with fire (alcohol or petrol)	21
Attempted self-extinction	7
Crime	1
Vasopressor requirements/SIRS	15
Laboratorial biomarkers	n=29
Scr (mg/dL) min/max values	3.03 (2.60-3.40)
C- reactive protein (mg/L)	282 (156-358)
Neutrophils/Lymphocytes ratio (N/L ratio)	8.94 (5.88-13.37)

Abbreviations: SAPS3, simplified acute physiology score III; Scr, serum creatinine; CLcr, creatinine clearance; IQR, quartiles (25-75); min/max, minimum/maximum values; SIRS, systemic inflammatory response syndrome; ICU, intensive care unit

Complete medical history, physical examination was obtained for each enrolled patient; laboratory data, and microbiology of isolated strains were documented in blood cultures, bronchoalveolar lavage, wound/bone, and urinary tract. Susceptibility testing was done

to obtain the minimum inhibitory concentration for Meropenem against each pathogen isolated according to the Clinical Standard Laboratory Institute (CSLI database). Meropenem coverage was based on the recommended pharmacokinetics-pharmacodynamics target $100\%/ \Delta T > MIC$.¹³ Renal function based on creatinine clearance was estimated by serum creatinine levels applying Cockcroft-Gault equation measured by the COBAS Analyzer 8000 series; inflammatory biomarkers such as c-RP in serum were performed on the COBAS Analyzer 8000 series (Roche, trademark), 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 were sent to the ICU via the network. Additionally, drug serum levels were determined by high performance liquid chromatography/ultraviolet detection (LC-UV), Shimadzu series LC-10, with automatized injection of purified extracts from serum samples done in the Clinical Pharmacokinetics Center, by a bioanalytical method detailed previously.¹⁴

Meropenem therapy in septic burn patients: blood sampling for TDM & PK study, PK/PD approach: Twenty-nine septic major burns received a chosen therapy with Meropenem, at regimen recommended in hospital according to renal function. Meropenem was administered systemically by pump 3hrs.-extended infusion. Patients with acute kidney injury (AKI), a dose regimen was adjusted to 0.5g q12h, or yet 1g q12h for septic patients undergoing continuous Veno-venous hemodialysis filtration (CVVHDF).

Blood sampling for TDM & PK study at the steady state levels equivalent, five biological half-lives: Blood volume of 3-4 mL each, at the 3rd hr. of started infusion was collected (sample 1), and a second one, 1hr. before the next infusion (sample 2) for Meropenem serum levels purposes to estimate the coverage by the percentage of target attainment (PTA), and for PK-change purposes. Meropenem serum levels were obtained by a validated bioanalytical chromatographic method previously reported.¹⁴

Conventional pharmacokinetics calculation: PK was based on the one-compartment open model after 3hrs.-extended infusion, via calibrated pump to estimate the PK-parameters as biological half-life [$t_{(1/2)\beta}$], total body clearance [CL_T], and volume of distribution at the steady state [Vd^{ss}]. Pharmacokinetics (PK) modeling was applied to investigate if the coverage attained by PK/PD approach is impacted on a renal function-dependence, as it frequently occurs in those ICU septic major burn patients.

PK/PD Analysis: Meropenem effectiveness was evaluated by applying the PK/PD tools to estimate the coverage of the carbapenem agent, that was based on the following parameters: minimum inhibitory concentration (MIC data, expressed by mg/L) from CSLI database related to Gram-negative strains isolated from the monitoring cultures, and the required kinetic parameters as follows: trough equivalent to the free Meropenem concentration (C_{trough}^{ss} ; mg/L), elimination rate constant (kel: hr⁻¹), time interval between consecutive doses (τ : hrs) based on one compartment PK-model. Meropenem target attainment was based on equation $\%f\Delta T > MIC$, that means the percentage time dose interval ($\% \Delta T$) required to maintain the minimum the free (f) drug serum levels (C_{trough}^{ss}) before the next infusion. Meropenem target recommended is equivalent $100\%/ \Delta T > MIC$, against Gram-negative strains susceptible strains (MIC: 0.25- 2.0 mg/L). 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_{trough}^{ss}) must be maintained higher than MIC data against each pathogen isolated.¹³

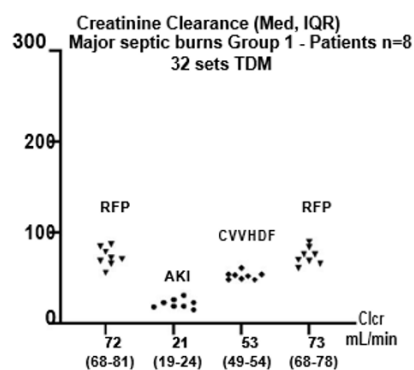
Statistical analysis

Individual and population data: The actual statistics of this study conducted on 29 major burn patients included, at the second or at the third septic shock treated with Meropenem that occurred between 12-14 days of the cure of the first septic shock caused by nosocomial Gram-negative strains of ICU admission. Software's were as follows: OFFICE 365, version 2208 (Excel); GraphPad Prism version 10.1.1. Non-parametric tests (Mann Whitney) for unpaired and paired data were applied to data obtained from the investigated patients; significance of $p < 0.05$ was considered.

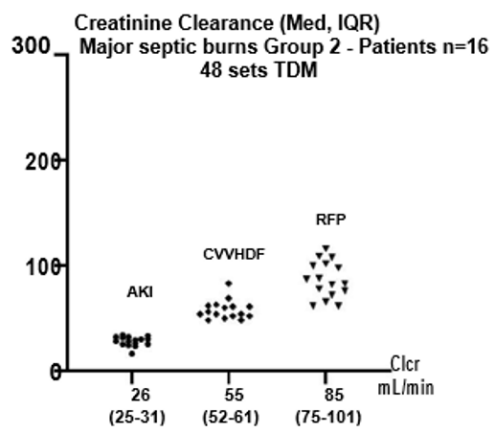
Results

Results of renal function subgroups undergoing Meropenem therapy

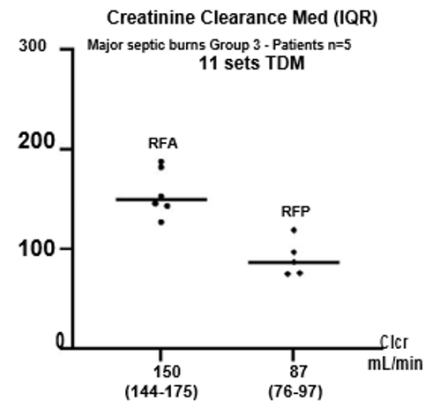
- Group 1 (n=8/32 Sets):** Eight patients included in G1 presented initially renal function preserved (RFP-Set 1: 52.3 mg/kg q8h) followed by an acute kidney injury (AKI-Set 2: 17.5mg/kg q12h), and continuous Veno-venous hemodialysis filtration (CVVHDF-Set 3: 34.9 mg/kg q12h) requirements. The cure of infection occurred up to MIC 2 mg/L susceptible strains based on the desired outcome by negative cultures and return to renal function preserved (RFP-Set 4: 52.3 mg/kg q8h). A total of 32 sets were investigated including these eight patients (G1) of individualization of Meropenem therapy.
- Group 2 (n=16/48 Sets):** Sixteen patients (G2) presented initially an acute kidney injury (AKI-Set 1: 14.3 mg/kg q12h), followed by continuous Veno-venous hemodialysis filtration installed (CVVHDF-Set 2: 27.8 mg/kg q12h). The cure of infection occurred up to MIC 2 mg/L susceptible strains based on the desired outcome by negative cultures and return to renal function preserved (RFP-Set 3: 40.3 mg/kg q8h). A total of 48 sets were investigated including these 16 patients (G2) of individualization of Meropenem therapy.
- Group 3 (n=5/11 Sets):** Five patients included in G3 presented initially vasopressor requirements during the systemic inflammatory response syndrome (SIRS). It was shown renal function augmented (RFA-Set 1: 42.9 mg/kg q8h). The cure of infection occurred just up to MIC 2 mg/L susceptible strains based on the desired outcome by negative cultures and by the return to renal function preserved (RFP-Set 2: 42.9 mg/kg q8h) for all patients. A total of 11 sets were investigated including five patients (G2) of Meropenem dose regime maintained. (Table 2, Figure 1)



G1 - Creatinine clearance in eight septic burns (32 Sets): Renal function preserved (RFP), Acute kidney injury (AKI), continuous Veno-venous hemodialysis filtration (CVVHDF), Renal function preserved (RFP).



G2 - Creatinine clearance in 16 septic burns (48 Sets): Acute kidney injury (AKI), continuous Veno-venous hemodialysis filtration (CVVHDF), Renal function preserved (RFP).



G3 - Creatinine clearance in 5 septic burns (11 Sets): Renal function augmented (RFA), Renal function preserved (RFP).

Figure 1 Changes on pharmacokinetics according to renal function during therapy with Meropenem in ICU septic major burn patients, Medians (IQR).

Table 2 Septic major burn patients undergoing Meropenem therapy by 3hrs-extended infusion, medians (IQR) Dose regimen individualized – Renal function subgroup outcomes - Laboratorial data inflammatory biomarkers and clinical outcome/ICU mortality

Meropenem therapy based on TDM	TDMI	TDM2	Statistics
Dose prescription based on renal function	Dose based on renal function	Individualization (effectiveness-safety)	
G1- Meropenem n=8 Patients/32 sets (RFP versus AKI)	1g q8h (RFP)	0.5g q12h (AKI)	P
IBW dose normalized - Daily dose (mg/kg)	52.3 (46.0-59.0)	17.5 (15.4-19.6)	0.0002
G1- Meropenem n=8/32 sets (AKI versus CVVHDF)	0.5g q12h (AKI)	1g q12h (CVVHDF)	
IBW dose normalized - Daily dose (mg/kg)	17.5 (15.4-19.6)	34.9 (30.7-39.2)	0.0002
G1- Meropenem n=8/32 sets (CVVHDF versus RFP)	1g q12h (CVVHDF)	1g q8h (RFP)	
IBW dose normalized - Daily dose (mg/kg)	34.9 (30.7-39.2)	52.3 (46.1-58.8)	0.0017
G2- Meropenem n=16 patients/48 sets (AKI versus CVVHDF)	0.5g q12h (AKI)	1g q12h (CVVHDF)	
IBW dose normalized - Daily dose (mg/kg)	14.3 (13.1-17.0)	27.8 (25.0-31.0)	0.0018
G2- Meropenem n=16/48 sets (CVVHDF versus RFP)	1g q12h (CVVHDF)	1g q8h (RFP)	
IBW dose normalized - Daily dose (mg/kg)	27.8 (25.0-31.0)	40.3 (36.5-43.5)	0.0021
G3- Meropenem n=5 patients/11 sets (RFA versus RFP)	1g q8h (RFA)	1g q8h (RFP)	
IBW dose normalized - Daily dose (mg/kg)	42.9 (38.8-42.9)	42.9 (37.5-42.8)	0.9999
Laboratorial data TDMI versus TDM2 (CSLI)	TDMI	TDM2	P
Serum creatinine (mg/dL) n=29, min/max value	1.21 (0.91-2.6) 0.55/4.02	1.98 (1.47-3.30) 0.30/4.90	0.7763
Clcr (mL/min) n=29, min/max value	61 (33-83) 15/188	53 (30-103) 15/195	0.8123
c-RP (mg/L) n=29, min/max value	336 (156-359) 113/495	337 (148-382) 112/499	0.9188
Leucocytes (*103 cells/mm3) n=29, min/max value	15.88 (13.53-28.86) 8.14/34.81	15.07(11.36-24.86) 8.31/37.21	0.7427
Neutrophils (*103 cells/mm3) n=29, min/max value	13.15 (9.55-20.89) 4.6/31.5	10.52(7.64-16.71) 3.68/25.17	0.1158
Lymphocytes (*103 cells/mm3) n=29, min/max value	1.65 (0.95-3.06) 0.56/7.66	1.80 (0.95-2.78) 0.30/4.90	0.917
N/L ratio, n=29, min/max value	7.61 (4.88-13.00) 1.42/31.44	0.43 (0.27-1.02) 0.04/1.98	<0.0001
Inflammatory biomarkers Laboratorial data (CSLI)	Survivors n=24 (83%)	Non-survivors n=5 (17%)	P
N/L ratio n=24/29 (83%) versus n=5/29 (17%) min/max	6.81 (4.63-9.49) 1.42/18.35	23.6 (23.3-26.2) 18.5/31.4	<0.0001
c-RP n=24/29 (83%) versus n=5/29 (17%) min/max	337 (148-382) 113/495	239 (210-344) 169/345	0.7481

Abbreviations: CSLI, clinical standard laboratory institute; RFP, renal function preserved; RFA, renal function augmented; AKI, acute renal injury; CVVHDF, continuous veno-venous hemodialysis filtration; TDM, therapeutic drug monitoring; IQR, quartiles (25-75); IBW, ideal body weight; Clcr, creatinine clearance; N/L ratio, neutrophil/lymphocyte ratio; c-RP, c-reactive protein; ICU, intensive care unit

Statistics: GraphPad Prism, v.10 (2023), Mann Whitney ($p < 0.05$).

Dynamics of N/L ratio as a predictive biomarker of mortality in burns

Inflammatory Biomarkers: Furthermore, among the inflammation biomarkers (SIRS) investigated, it was shown a significant difference related only to neutrophil/lymphocyte ratio (N/L ratio) between 24/29 survivors (83%) versus 5/29 non-survivors (17%) who died within 10 to 12 days of meropenem therapy. Data obtained are justified,

since the desired clinical outcome was achieved in survivors by significant reducing the N/L ratio between TDM2 vs. TDM1, while in non-survivors (17%) who died within 10-12 days (5/29), the ratio remained unchanged during meropenem therapy, culminating in ICU death, Table 2. It is important to highlight that these non-survivors' patients suffered severe burns related to the extent and depth of the burns (TBSA > 55%) of the total burned surface area, which ranged from 58 up to 72% (min./max. values)

Table 3 ICU septic major burn patients undergoing Meropenem therapy by 3hrs-extended infusion, medians (IQR) Renal function subgroups – Meropenem dose adjustment based on PK-changes

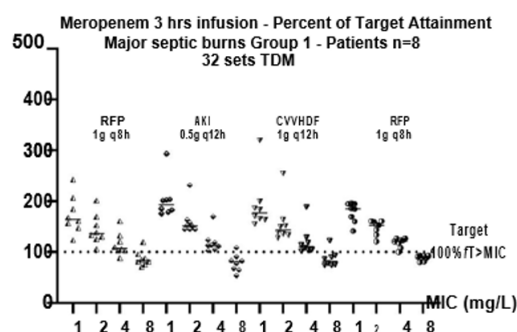
PK-Analysis – One compartment open model G1 (n=8/32 Sets) Meropenem PK changes	PK-parameters RFP	PK-parameters AKI	Statistics P
$t_{(1/2)\beta}$ (hrs)	2.3 (2.0-2.7)	4.8 (4.0-5.5)	0.0002
CLt (L/h)	8.2 (7.6-9.1)	3.0 (2.7-4.1)	0.0002
Vd ^{ss} (L)	29 (25-30)	25 (16-31)	0.6263
	AKI	CVVHDF	
$t_{(1/2)\beta}$ (hrs)	4.8 (4.0-5.5)	3.9 (3.7-4.3)	0.1498
CLt (L/h)	3.0 (2.7-4.1)	5.4 (4.8-5.8)	0.0014
Vd ^{ss} (L)	25 (16-31)	30 (26-33)	0.2345
	CVVHDF	RFP	
$t_{(1/2)\beta}$ (hrs)	3.9 (3.7-4.3)	2.6 (2.1-2.7)	0.0002
CLt (L/h)	5.4 (4.8-5.8)	7.8 (7.5-8.3)	0.0002
Vd ^{ss} (L)	30 (26-33)	29 (24-31)	0.3141
G1 – Comments: PK-changes impacting coverage against susceptible up to MIC 2mg/L and it was extended up to MIC 4 mg/L intermediate susceptibility. Cure of infection occurred by negative cultures after dose adjusted for efficacy or safety			
- Biological half-life (RFP) was prolonged during AKI remaining unchanged during CVVHDF, and significant reduction during PRF. - Total body clearance (RFP) was reduced during AKI, increased during CVVHDF, with significant increases that occurred during PRF. - Volume of distribution (RFP) remained unchanged during AKI, CVVHDF, PRF probably due to reduced patients-G1 (n=8) vs G2 (n=16).			
PK-Analysis – One compartment open model G2 (n=16/48 Sets) Meropenem PK changes on coverage	PK-parameters AKI	PK-parameters CVVHDF	Statistics P
$t_{(1/2)\beta}$ (hrs)	5.3 (4.0-6.1)	3.9 (3.6-4.2)	0.0293
CLt (L/h)	3.5 (2.3-4.4)	5.6 (4.7-6.2)	<0.0001
Vd ^{ss} (L)	29 (13-35)	31 (29-37)	0.2742
	CVVHDF	RFP	
$t_{(1/2)\beta}$ (hrs)	3.9 (3.6-4.2)	2.1 (1.7-2.5)	0.0001
CLt (L/h)	5.6 (4.7-6.2)	8.0 (7.3-8.9)	0.0001
Vd ^{ss} (L) C	31 (29-37)	22 (19-28)	0.0025
G2 – Comments: PK-changes impacting coverage against susceptible up to MIC 2mg/L and it was extended up to MIC 4 mg/L intermediate susceptibility. Cure of infection occurred by negative cultures after dose adjusted for efficacy or safety			
- Biological half-life was prolonged during AKI, but reduced during CVVHDF, with major reduction occurred during PRF. - Total body clearance was reduced during AKI but increased during CVVHDF; during PRF occurred a significant increase of parameter. - Volume of distribution unchanged during AKI versus CVVHDF; reduction on PRF versus CVVHDF as a function of biological half-life reduced by twice in this group of G2-patients.			
PK-Analysis – One compartment open model G3 (n=5/11 Sets) Meropenem PK changes on coverage	PK-parameters RFA	PK-parameters RFP	Statistics P
$t_{(1/2)\beta}$ (hrs)	1.5 (1.4-1.6)	2.5 (2.3-2.5)	0.0152
CLt (L/h)	9.8 (9.1-10.3)	8.3 (7.7-8.6)	0.0758
Vd ^{ss} (L)	21 (19-23)	27 (28-31)	0.1169
G3 – Comments: PK-changes impacting coverage against susceptible strains up to MIC 2mg/L: Cure of infection occurred by negative cultures after dose maintained in Sets 1-2 for efficacy due to vasopressors required in Set 1.			
- Biological half-life was reduced during RFA due to vasopressors requirements during SIRS; but statistically prolonged during RFP. - It was shown that total body clearance unchanged during FRA vs FRP by dose maintained. Data can be justified by reduced patients-G3. - Volume of distribution remained unchanged during FRA compared with PRF, despite the prolongation of half-life that could justify the irrelevant increases on Vd (21/Set1 vs 27/Set2).			

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

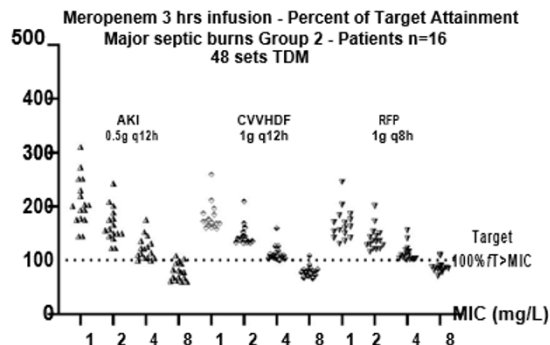
Statistics: GraphPad Prism, v.10 (2023), Mann Whitney (p<0.05).

PK-changes and PK/PD analysis

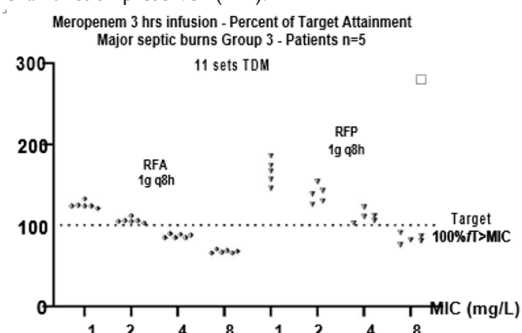
Meropenem coverage impacted by PK-changes: It is important to highlight that Meropenem coverage was impacted by changes in pharmacokinetic parameters, especially related to biological half-life and total body clearance, while the apparent volume of distribution was affected by variability in renal function to a lesser extent. This fact can be explained by the use of Meropenem administration by prolonged 3-hour infusion, as recommended, being responsible for the 3- to 5-fold increase in the apparent volume of distribution, regardless of the renal function of the patient with septic burns in the ICU, as described in Table 3, with added comments regarding the impact of PK changes on antibiotic coverage. It was shown in Figure 2, PK-changes impacting the target attainment, and consequently the Meropenem coverage against Gram-negative nosocomial strains in ICU septic burn patients' subgroups considered.



G1 - Meropenem coverage in 8 septic burns (32 Sets-TDM) with Renal function preserved (RFP), Acute kidney injury (AKI), continuous veno-venous hemodialysis filtration (CVVHDF), Renal function preserved (RFP).



G2 - Meropenem coverage in 16 septic burns (48 Sets-TDM): Acute kidney injury (AKI), continuous Veno-venous hemodialysis filtration (CVVHDF-TDM), Renal function preserved (RFP).



G3 - Meropenem coverage in 5 septic burns (11 Sets): Renal function augmented (RFA), Renal function preserved (RFP).

Figure 2 Pharmacokinetic-changes according to renal function in ICU septic burns impacting coverage during therapy with Meropenem.

Concerning G1-patients, it was shown that Meropenem PK changes affect significantly the target attained, once coverage occurred just up to MIC 2 mg/L against susceptible strains for 8/8 G1-patients with RFP/Set 1. In addition, coverage was extended up MIC 4 mg/L for AKI patients/Set 2, CVVHDF/Set 3, and RFP/Set 4. Considering the percentage of target attainment in 16 G2-patients, Meropenem coverage occurred up to MIC 4 mg/L in those patients during AKI (Set 1), CVVHDF (Set 2) and RFP (Set 3). It is important to comment on that Meropenem coverage in patients of G1 and G2 occurred against susceptible strains up to MIC 2 mg/L and it was extended up MIC 4 mg/L against strains of intermediate susceptibility, mainly related to non-Enterobacteriaceae considered more aggressive nosocomial strains compared with Enterobacteriaceae of our hospital.

In addition, the percentage of target attainment in five G3-patients, Meropenem coverage occurred only up to MIC 2 mg/L based on significant PK-changes related to vasopressor requirement that occurred (RFA/Set 1) in patients by comparison with RFP/Set 2; once the coverage occurred just up to MIC 2mg/L in Set 1 due to vasopressor requirements, but it was extended up to MIC 4 mg/L in Set 2. Finally, coverage didn't occur against MIC 8 mg/L nosocomial strains of intermediate susceptibility, despite no strain isolated from these cultures in G1, G2, G3 patients.

Obtaining MIC

Cultures according to CSLI for isolated strains during the Meropenem therapy: Meropenem serum monitoring and cultures were routinely done once a week due to changes on renal function in these patient's subgroups requiring a period equivalent five biological half-lives to reach the steady state levels between them. It indicates that TDM was required to guarantee drug efficacy-safety, since the clinical cure occurred in a shorter period by negative cultures for patients undergoing antibiotic therapy. Sites of infection were blood stream (63%), lungs/pneumonia/PNM (17%) unrelated to mechanical ventilation (bronchoalveolar lavage), wound/bone (14%) and urinary tract (6%). Meropenem was chosen for ICU septic burn patients against Gram-negative nosocomial pathogens, especially for the combat of non-Enterobacteriaceae (n=17). It is well known that a metallo-beta-lactamase (MBL)-producing bacteria includes *Pseudomonas aeruginosa*. Isolates of *Burkholderia cepaceae* (3), *Haemophilus influenza*, (4), *Stenotrophomonas maltophilia* (1) occurred in eight burn patients based on immunosuppression and increased inflammatory biomarker (N/L ratio). In addition, it was isolated Gram-negative strains related to Enterobacteriaceae (n=32) meropenem susceptible (MIC 0.25-2.0 mg/L) as *Citrobacter spp* (3), *Enterobacter cloacae* (6), *Escherichia coli* (7), *Klebsiella pneumoniae* (6), *Morganella morganii* (4), *Proteus mirabilis* (4), *Serratia marcescens* (2). Target was attained in septic major burns against Enterobacteriaceae, including six isolates of *K. pneumoniae* MIC $\leq$ 2 mg/L. Finally, coverage was extended up to MIC 4 mg/L, against strains of intermediate susceptibility in 24/29 patients of G1-G2.

Discussion

It has been reported over the past fifteen years that prolonged infusion has a positive impact on pharmacokinetic changes by increasing Meropenem volume of distribution at steady-state level, proportionally to the biological half-life prolonged even considering renal function preserved. These PK changes impact on reduced total body clearance resulting in increased serum levels for Meropenem in major burns of septic patients with preserved renal function (RFP). Then, it is important to highlight that PK-changes at the late stage of septic shock are significantly different from the earlier stage.^{6,8-15} In addition, it is well known that the superiority of coverage after

Meropenem prolonged infusion, during 3hrs-infusion or even 4hrs-infusion occurred. More recently, it was recommended that a continuous infusion must be done in some ICU septic burn patients requiring vasopressors, high doses to attain the PK/PD target attained during the systemic inflammatory response syndrome (SIRS).

This strategy ensures higher Meropenem serum levels, and lower neurotoxicity compared with Imipenem. In addition, guaranteed coverage against Gram-negative strains was obtained by comparison of 3hrs.-extended infusion with 0.5hr-intermittent infusion done since 2008. Consequently, Meropenem effectiveness was impacted by changes on pharmacokinetics with coverage guaranteed up to MIC 2 mg/L against susceptible strains, reaching also coverage against strains of intermediate susceptibility MIC 4 mg/L according to CSLI database. It is important to highlight that vasopressor requirements at the earlier stage of septic shock or during SIRS justify the increases by twice that occurred on Meropenem total body clearance in ICU major burned patients, with reduction of serum levels at the steady state. Furthermore, studies on the pharmacokinetics of Meropenem were reported previously in adult patients with septic burns.

In those studies, it was shown that the Meropenem elimination must be more complex than occurs with Piperacillin/Tazobactam based just in a dependence on the renal glomerular filtration rate, estimated by creatinine clearance. The strategy of prolonged Meropenem infusion in patients with septic burns requiring vasopressors or with acute kidney injury to achieve the goal has been previously investigated to effectively combat bacterial resistance with guaranteed coverage and safety.

In addition, inflammatory biomarkers as neutrophil-lymphocyte ratio (N/L ratio), Interleukin 6 (IL-6), Procalcitonin (PCT), c-Reactive protein (c-RP) were investigated in ICU septic burns or non-burned patients.¹⁶⁻²⁰ Serum levels of interleukin-6 in critically ill patients with acute kidney injury were initially described by Shimazui et al., in an observational study on ICU admission, and subsequent outcomes. It was investigated by authors that serum levels of IL-6 in ICU septic non burned patients may predict short-term renal function and mortality in AKI patients, also associated with renal recovery in survivors (Chiba, Japan).¹⁶ Another isolated biomarker was described by Qiu et al., related to neutrophil-lymphocyte ratio on the third day postburn that was associated with 90-day mortality among patients with burns over 30% of TBSA in two Chinese Burn Centers.¹⁷ It was also described by Setiawan et al., that neutrophil-lymphocyte ratio can be a good predictor of mortality in major burn patients in ICU of a hospital in Bali, Indonesia; once a high N/L ratio reflects an increased inflammatory response without adequate immune function.¹⁸

It is important to highlight that it was investigated by Liu et al., the effects of neutrophil-lymphocyte ratio combined with interleukin-6 in predicting 28-day mortality in septic patients. It was considered by authors that the N/L ratio and IL-6 appeared to be independent predictors of mortality. On the other hand, the N/L ratio combined with IL-6 can greatly increase the predictive value of 28-day mortality.¹⁹ More recently, Silva Junior et al., investigated that antimicrobial therapy of ICU patients with septic burns with beta-lactam or carbapenem agents should be guided by serum antimicrobial levels, cultures, and biomarkers monitoring including N/L ratio, IL-6, PCT and c-RP. It was demonstrated by authors that interleukin-6 combined with the neutrophil-lymphocyte ratio is a good predictor of death despite of high hospital costs for septic burns long-term in ICU. On the other hand, the high costs of measuring serum IL-6 or PCT as routine inflammation biomarkers in severely burned ICU patients were considered.

Then, the neutrophil-to-lymphocyte ratio (N/L) was chosen as predictive biomarker for inflammation monitoring in ICU major burn patients based on daily blood counts performed at the hospital's Central Laboratory by a hematology analyzer. Data obtained from the network for each patient was required to estimate N/L ratio, the biomarker chosen, to predict mortality in these ICU burn patients.²⁰ Then, the individualization of Meropenem therapy was required for septic major burns, due to the increase in interleukins during the systemic inflammatory response syndrome. A reduction in dosing regimen 0.5g q12h occurred for patients of G1 and G2 during AKI was based on TDM, MIC data of isolated Gram-negative strains and N/L ratio. Clinical and microbiological cures occurred for patients investigated at dose regimen prescribed in a renal function dependence based on PK-changes.

Therapeutic Meropenem serum levels at the steady state were monitored in real time by TDM in the 91Sets of 29 patients by dose adjustment (G1-G2), or dose maintained in G3-patients investigated. Pharmacodynamics based on pharmacokinetics related to the therapeutic target attained or not was considered as frequently occurs in those ICU septic major burn patients. It is important to highlight that death occurred in five major burn patients (17%) due to the high percentage of total burned surface area (58-72%) against 83% of survivors including 24/29 patients investigated.

Conclusion

Serum Meropenem levels measured in real time by pharmacodynamics of strains isolated from cultures were based on pharmacokinetic changes that have become essential tools for dose adjustment in ICU septic burns. The approach demonstrates that individualization of antimicrobial therapy is the only path to be chosen to achieve the goal of eradicating nosocomial pathogens, while also combating MDR strains to avoid death in critically ill ICU patients. Then, the contribution of Meropenem to achieving the desired clinical outcome of cure, had an impact on the reduction of deaths in this ICU of Burns of the 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. 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 ICBU, blood collection of viable samples for serum antibiotics measurements, and blood collection for laboratorial data acquisition related to biomarkers. KBV, MJS and TVC contributed to the revision of detailed information of articles included in the Discussion, especially at the last revision of references. 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.

Limitations

The study was an observational nature, single-centre design, lack of a comparator arm and the absence of microbiological confirmation in five non-survivor patients. 2) Prolonged hospitalization is expected for severe major burns in the ICU of the Reference Burn Center, 8th floor of hospital.

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