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Combating bacterial resistance to Meropenem by infusion strategy applied to septic burn patients with vasopressor requirements or acute kidney injury to achieve the target

Abstract

Introduction: Faced with the growing challenge to the use of antimicrobials for the adequate and effective therapy of nosocomial infections, international health agencies have reinforced that combating bacterial resistance and preventing the development of multidrug-resistant (MDR) strains are urgent, since a significant increase based on minimum inhibitory concentration (MIC) for therapeutic agents were reported by the committee of hospitals infection. Meropenem, a carbapenem agent, is widely prescribed for therapy of septic shock caused by susceptible Gram-negative bacteria. In general, the prolonged 3-hrs-infusion has been widely applied in these patients over the past 10 years providing coverage only against susceptible Gram-negative pathogens (MIC 2 mg/L), extended also to intermediate susceptible strains up to MIC 4 mg/L, according to Clinical Laboratory Standard Institute (CLSI database). However, new strategies have been recommended to combat the development of resistance to pathogens isolated from cultures to increase the coverage of this carbapenem agent up to MIC 8 mg/L, to avoid mutant selection with death in ICU.

Subject: Clinical protocol was carried out to investigate the efficacy & safety of meropenem at the dose regimen recommended 1g q8h by prolonged infusion, based on serum levels and on cultures monitoring of isolates. Aim of protocol was to assess pharmacodynamics (PD) based on changes of pharmacokinetics (PK), which could affect the coverage of meropenem in septic burns patients with increased or decreased renal function. Pharmacokinetic-pharmacodynamics (PK/PD) tools were applied to investigate efficacy & safety.

Methods-clinical protocol: Forty-eight major septic burn patients with high variability on renal function in ICU were included. Cultures were collected before meropenem therapy starts; all of them had nosocomial infection caused by Gram-negative pathogens isolated. Patients undergoing meropenem therapy at the initial stage of septic shock from day-0 to day-8 (D0-D8) and at the late stage of septic shock from day 8 to day 14 (D-8 to D-14) were investigated according to dose requirements based on creatinine clearance, drug serum levels (TDM), and coverage up to MIC 8 mg/L, dose dependent on renal function.

Results: Coverage occurred for all patients of both groups after the extended infusion against susceptible Gram-negative strains up to MIC 2 mg/L (minimum inhibitory concentration), and up to MIC 4 mg/L, strains of intermediate susceptibility, according to Clinical Laboratory Standards Institute (CLSI, database) of our hospital. It was demonstrated in patients with renal function augmented by vasopressors, the superiority on coverage by trice that occurred in 24/27 patients (89%) after 4 hrs.-infusion at TDM3 against strains MIC 8 mg/L by comparison with coverage registered in 12/39 patients (30%) after 3 hrs.-infusion at TDM2. On the other hand, meropenem dose regimen must be adjusted to 1g q24h in patients with AKI to guarantee effectiveness & safety in those patients. In addition, after continuous venovenous haemodialysis-filtration (CVVHDF) installed in those patients, meropenem PK/PD target was attained up to MIC 8 mg/L in patients with the empirical dose regimen recommended of 1g q8h, 3hrs.-infusion.

Conclusion: Precision medicine guarantees meropenem serum levels combined with cultures monitoring; consequently, must be applied routinely to guarantee coverage against Gram-negative nosocomial pathogens susceptible including strains of intermediate susceptibility (MIC 4-8 mg/L) to avoid mutant selection. Therefore, effective, and safe antimicrobial therapy for patients in septic shock, combined with a continuous monitoring of inflammatory biomarkers, should guide clinical management to ensure cure with early ICU discharge.

Keywords: PK/PD approach in septic burns, meropenem coverage related to duration of infusion, individualized therapy in acute kidney injury, continuous dialysis

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Silvia R C J Santos,[1,2] Thais Vieira de Camargo,[1] Karina Brandt Vianna,[1] Leonard de Vinci Kanda Kupa,[1] Beatriz Aparecida Passos Bismara Paranhos,[1] Mauricio Yonamine,[1] Valentina Porta,[1] Aline Sandre Gomides Abad,[2] Gabriela Aparecida Ferreira,[2] Thiago de Oliveira Câmara,[2] Débora C Sanches Pinto,[2] Edvaldo Vieira de Campos,[2] João Manoel da Silva Junior,[2] David de Souza Gomez[2]

[1]Clinical Pharmacokinetics Center, University of Sao Paulo–Sao Paulo/SP, Brazil

[2]Plastic Surgery and Burns Division, Department of Surgery of Medical School, University of Sao Paulo/SP, Brazil

Correspondence: Silvia R C J Santos. Clinical Pharmacokinetics Center. University of Sao Paulo -Sao Paulo/SP. Brazil, Tel 55 11 95357- 8930, Email pharthe@usp.br

Co-Correspondence: David de Souza Gomez. Plastic Surgery and Burns Division. Department of Surgery of Medical School. University of Sao Paulo – Sao Paulo/SP. Brazil, Tel 55 11 9 83530011, Email davgome@usp.br

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Abbreviations: AKI, acute kidney injury; CLSI, clinical laboratory standards institute; CVVHD-F, continuous venovenous haemodialysis-filtration; FDA, food and drug administration; GSA, global sepsis alliance; ICU, intensive care unit; MDR, multidrug resistance; MIC, minimum inhibitory concentration; MV, mechanical ventilation; PAHO, pan American health organization; PD, pharmacodynamics; PK, pharmacokinetics; PK/PD, pharmacokinetics/pharmacodynamics; PTA, probability of target attainment; SAPS3, simplified acute physiology score 3; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SSC, surviving sepsis campaign; SIRS, systemic inflammatory response syndrome; TBSA, total burn surface area; TDM, therapeutic drug monitoring; WHO, World Health Organization

Introduction

Septic shock is potentially fatal organ dysfunction caused by a dysregulated host response to infection. Clinical outcome in most high-risk cases is the mortality of patients including in elderly or

pediatric with nosocomial bacterial infections associated with viral infections as influenza, and most recently SARS-CoV-2 related to One Global Health Treat: Sepsis, Pandemics. Antimicrobial Resistance largely discussed recently. I was included the recommendation of Pan American Health Organization PAHO/World Health Organization WHO, related to an "Epidemiological Alert Emergence", that occurred by an increase of new combinations of carbapenemases in Enterobacterales reported in Latin America and the Caribbean, Brasilia, D.F., Brazil, 2021.[1] More recently, at the last event of Global Sepsis Alliance 2023[2] it was discussed, in view of the growing challenge to the prescription of antimicrobials for adequate treatment and effective control of bacterial infectious conditions during COVID-19 pandemic. In addition, recommendations of the Brazilian National Health Surveillance Agency (2023), International Guidelines for Management of Sepsis and Septic Shock and World Health Organization (2023) have reinforced that combating bacterial resistance, and the prevention of the development of multidrug-resistant strains (MDR) is urgent.[1-6] It is well known that at the last twenty-five years, it was reported a significant increase in the minimum inhibitory concentration (MIC), in a monitoring program of antimicrobial therapy for several infections based on serum levels of beta-lactams in ICU septic patients. Information reinforces that antimicrobial serum levels monitoring is essential to assess pharmacokinetics changes that occurs during the septic shock with impact on coverage of the prescribed antimicrobial agent expressed through target attainment reached by pharmacokinetic-pharmacodynamics (PK/PD) approach. Therefore, new therapeutic strategies have been proposed for the most prescribed antimicrobial agents including meropenem related to the dose regimen and the duration of infusion.[7,8]

Some prospective controlled studies including therapeutic drug monitoring (TDM) were considered to compare drug efficacy based on serum levels of several antimicrobial agents usually prescribed in the therapy of septic shock. Considering that therapeutic meropenem serum monitoring after 3 hrs.-extended infusion will be a strategy that ensures an adequate serum level against intermediate susceptible strains with coverage guaranteed up to MIC 4 mg/L. In fact, it is mainly related to K. pneumoniae and P. aeruginosa in major septic burns with renal function preserved or augmented by vasopressors.[9,10] In addition, to allowing the evaluation of antimicrobial effectiveness considering the dose regimen prescribed to septic ICU patients, drug serum levels are a laboratory strategy of great value in the individualization of therapy in a real time, guaranteeing the expected clinical outcome, and to combat the development of bacterial resistance, also reducing the duration of antimicrobial therapy, and consequently hospital costs.[5,11] Impact of the introduction of real-time therapeutic drug monitoring on empirical doses of carbapenems in septic burn patients was reported to adequate empirical antibiotic dose selection for these patients, once is difficult due to extreme variability in drug pharmacokinetics. Therapeutic drug monitoring (TDM) by liquid chromatography may aid antibiotic prescription and implementation of initial empirical antimicrobial dosage recommendations. In several studies it was evaluated how gradual TDM introduction altered empirical dosages of carbapenem agents as meropenem largely prescribed to treat infections caused by nosocomial pathogens in critically ill major burn patients of the ICU Burn Center of hospital.[9] However, this should be done in large tertiary hospitals with a great number of ICUs to care for a huge number of septic ICU patients treated daily for nosocomial infections purposes.[12] Clinical management for critically ill patients in intensive care has been guided by cultures, through the isolation of the agent, and susceptibility test of the pathogen to the antimicrobial, supported also by ICU routine of serum biomarkers of the systemic inflammatory response syndrome (SRIS). Then, selective techniques as liquid chromatography must be chosen as laboratory strategy in hospitals of high complexity to facilitate therapeutic drug serum monitoring done in a real time for ICU critically ill septic patients with nosocomial infections.[13]

Objective

Aim of protocol was to assess pharmacodynamics based on pharmacokinetics, which could affect the coverage of meropenem in septic burns patients with increased, or even decreased renal function by applying pharmacokinetic-pharmacodynamic (PK/PD) tools to investigate the efficacy & safety of this carbapenem agent against Gram-negative nosocomial pathogens. Pharmacokinetic-pharmacodynamics approach-based on serum levels, and the minimum inhibitory concentration (MIC) of each pathogen isolated was applied to investigate if the therapeutic target of 100%fΔT>MIC recommended for meropenem was reached. Then, the prediction index of antimicrobial effectiveness (%fΔT>MIC) was the key to evaluate the meropenem coverage. Pharmacodynamics was based on monitoring cultures of fluids as blood, urine, wound lavage, and bronchoalveolar lavage secretion. Focus of infections investigated in burn patients occurred in skin, wound and bone obtained by intraoperative biopsy.

Methods

Study design, patient eligibility, meropenem therapy for target attainment

The clinical protocol was a prospective, open-label study. Ethical approval registers CAAE 07525118.3.0000.0068, Brazilian Platform was obtained followed by approvals of the Ethical Committee of Hospital of Clinics, Medical School of University of Sao Paulo; no conflicts of interest to declare were obtained from all authors. This study was conducted from December 2018 to March 2020, informed written consent was obtained from all legally designated patient representatives. The study protocol was carried out to investigate the efficacy and safety of meropenem at the dose regimen recommended by prolonged infusion, based on serum levels, and on cultures of isolates. Forty-eight ICU major burn patients of both genders and with high variability on renal function were included; all of them have infections caused by Gram-negative nosocomial pathogens. PK/PD approach was based on meropenem serum levels and monitoring of nosocomial pathogens isolated from their cultures.

Blood sampling for meropenem serum monitoring – Bioanalytical method

Blood was sampling from patients in ICU by the nurses of clinical staff, 48 hrs. after the meropenem therapy started (D0) for therapeutic drug monitoring. Two blood samples were collected; the first one at the end of meropenem extended infusion, and the second blood sample, one hour before the next infusion.

Bioanalytical method for meropenem serum levels was detailed as follows. To each 200 µL of serum sample, 25 µL (50 mg/mL) of cefepime (internal standard, US Pharmacopeia) was added to an Eppendorf tube followed by 600 µL of acetonitrile and centrifuged 8,000 rpm (5ºC) for 15 min. Supernatant was evaporated to dryness in a water bath (45ºC) under a stream of nitrogen. A volume of 600 µL of 10% of acetonitrile in water was added to dissolve the residue, and 5 µL of serum extracts were injected into a Shimpack ODS column (150 mm x 6 mm ID, 5 micron) Shimadzu, Japan. Elution of peaks was done by an isocratic system with a mobile phase of a mixture of acetate buffer 0.01 M, pH 5.0 and acetonitrile (9:1, v/v)

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at a flow rate of 0.8 mL/min. Peaks were monitored by UV detection at 307 nm for this carbapenem agent. Validation study was based on international standards considering the following parameters as linearity, lower limits of quantification and of detection, intra-day/inter days precisions, intra-day/inter days systematic error, stability of standards including the internal standard on the bench during 4 hrs., short samples stability on the bench (6 hrs.), post-process stability of serum extracts in the rack of autosampler rack (24 hrs.), samples long stability storage in an ultralow freezer, cycles freezing/de-freezing stability, and the robustness of chromatographic system. Method was revalidated during this project by liquid chromatography technique that was developed for meropenem serum measurements included a linear response of 0.5 up to 200 mg/L (r^2:0.9998) that was obtained with a lower limit of quantification (LLOQ) of 0.5 mg/L, and a limit of detection 0.25 mg/L. Intraday, and inter days precisions were acceptable at low, medium, and high concentrations based on internal controls, and the relative recovery ranging 94-103% was registered. It was evidenced acceptable stability studies related to standards, serum samples, post-process stability in the autosampler, samples long stability (ultralow freezer), cycles freezing/de-freezing stability and robustness of each chromatographic system was also included.[13]

Meropenem PK/PD target attainment – Therapeutic drug monitoring

Then, the prediction index of antimicrobial effectiveness (%fΔT>MIC) was applied to evaluate the meropenem coverage and target attainment (100%fΔT>MIC) recommended by Abdul-Aziz, et al.,[14] that was based on therapeutic serum monitoring.[14] Pharmacodynamics was based on monitoring of cultures of fluids as blood, urine, wound lavage, and bronchoalveolar lavage secretion. Focus of infections investigated in burn patients occurred in skin, wound and bone obtained by intraoperative biopsy. Burn patients undergoing therapy at the initial stage of septic shock, or at the late stage were distributed on meropenem prescription recommended based on renal function (Table 1).

Table 1 Burn septic patients undergoing Meropenem therapy by extended infusion

Group	Renal function	TDM (N) Dose regimen/duration of infusion
Group 1	Set 1. Preserved renal function (PRF)	TDM1: n=27, 1g q8h /3-hrs.
Group 1	Set 2. Augmented renal function (ARF)	TDM2: n=39, 1g q8h /3-hrs.
Group 1	Set 3. Augmented renal function (ARF)	TDM3: n=27, 1g q8h /4-hrs.
Group 2	Set 1. Acute renal injury, EDR-AKI	TDM1: n=33, 1g q8h /3-hrs.
Group 2	Set 2. Acute renal injury, ADR-AKI	TDM2: n=33, 1g q24h /3-hrs.
Group 2	Set 3. CVVHDF installed, EDR	TDM3: n=27, 1g q8h /3-hrs.

Abbreviations: PRF, preserved renal function; ARF, augmented renal function; EDR, empiric dose regimen; ARD, adjusted dose regimen; TDM, therapeutic drug monitoring

Group 1 – Initial stage of septic shock, burn patients with renal function preserved or augmented by vasopressors were considered.

At the first week of meropenem therapy, majority of ICU burn patients presented systemic inflammatory response syndrome (SIRS) at the earlier stage of the first septic shock, with or without vasopressors requirements.

Meropenem therapy started with the empirical dose regimen 1g q8h by 3hrs.-infusion recommended in hospital was prescribed to 27 burn septic patients with preserved renal function (RFP) at the initial phase of septic shock. After 48 hours of therapy started, blood was sampling at the steady-state level for therapeutic drug monitoring-renal function preserved (TDM1/RFP) done by liquid chromatography described previously.[13] During the systemic inflammatory response syndrome, vasopressors were prescribed to the same 27 patients investigated previously, and for another 12 patients in SIRS included afterwards, totaling 39 patients in septic shock with renal function augmented (RFA) by vasopressors requirements at TDM2. Blood was sampling at the steady-state level for meropenem therapeutic drug monitoring in patients with renal function augmented by vasopressors (TDM2-RFA).

Group 2 – At the late of septic shock, it was included only septic burn patients with renal dysfunction that occurred in general at the second week of meropenem therapy, mainly at the late stage of the first septic shock. Therapeutic drug monitoring (TDM1) included 33 patients that received the empirical dose regimen 1g q8h, 3hrs.-infusion, but all of them developed acute kidney injury (AKI). Then, daily dose was adjusted for effectiveness & safety on TDM2. Finally, it was installed the continuous venovenous haemodialysis-filtration in those patients that received 1g q8h by 3hrs.-infusion. Blood was sampling at the steady state, for therapeutic drug monitoring (TDM3).

Pharmacokinetic-pharmacodynamics approach-based on meropenem serum levels, and the minimum inhibitory concentration (MIC) of each pathogen isolated was done to investigate if the therapeutic target of 100%*f*ΔT>MIC recommended was reached. Then, the prediction index of antimicrobial effectiveness (%*f*ΔT>MIC) was applied for meropenem target attainment. Laboratorial data related to inflammatory biomarkers as C-reactive protein and neutrophils to lymphocytes ratio were monitored routinely in the central laboratory of hospital in those ICU patients. Creatinine clearance was estimated by the Cockcroft-Gault equation based on serum creatinine levels measured by the COBAS Analyzer 8000 series; inflammatory biomarkers such as C-RP in serum was performed on the COBAS Analyzer 8000 series (Roche, trademark), Neutrophil-to-lymphocyte ratio (blood count) was measured using a Hematological Analyzer (SYSMEX brand). In addition, meropenem serum measurements was done in our laboratory at the Clinical Pharmacokinetics Center, University of Sao Paulo, SP, Brazil.

Statistical analysis

Individual and population data: The actual statistic of this study conducted on 48 major burn patients at the first septic shock after ICU admission was done based on the use of software's described as follows: OFFICE 365, version 2208 (Excel); GraphPAD Instat-GraphPad Prism version 9.1.14 and version 10. Fisher's exact test, and also Mann Whitney and Wilcoxon tests applied to unpaired and paired data were applied to data obtained from the investigated patients, and a significance of $p<0.05$ was considered.

Results and discussion

Demographic characteristics of 48 burn patients' population included in the study were: 35M/13F, 49 (39-62) yrs., 71 (68-74) kg,

ideal body weight, 1.91 (1.83-1.95) m^2, body surface area, 25 (24-26) kg/m^2, body mass index, expressed by medians (IQR). Admission data of burn patients in ICU of hospital after the accident (45) or crime (3) were: Simplified Acute Physiology Score 3 at ICU admission (SAPS3) 57 (52-68), 35 (25-56) %, total burn surface area, thermal/electrical injury (45/3), inhalation injury occurred in 42 requiring mechanical ventilation in 38/42 patients, and vasopressor requirements in 39/48 patients. Meropenem coverage against Gram-negative strains; creatinine clearance was estimated by Cockcroft-Gault equation considering the ideal body weight and serum creatinine.

At the initial stage of septic shock, burn patients with renal function preserved or augmented by vasopressors were considered (Group 1). Then, at the first week of meropenem therapy, majority of ICU burn patients presented systemic inflammatory response syndrome (SIRS) at the initial stage of the first septic shock, with or without vasopressors requirements and three TDMs were required for drug effectiveness as represented in figure 1A. Meropenem therapy started with the empirical dose regimen 1g q8h by 3hrs.-infusion recommended in hospital was prescribed to 27 burn septic patients with preserved renal function (RFP) at the initial phase of septic shock. After 48 hours of therapy started, blood was sampling at the steady-state level for therapeutic drug monitoring (TDM1/RFP) done in our laboratory by liquid chromatography.[13] Then, meropenem coverage estimated was guaranteed against intermediate susceptible strains up to MIC 4 mg/L for all of them (27/27). It is important to highlight that coverage against MIC 8 mg/L strains dropped to 55% (15/27) of patients as represented in Figure 1A. In addition, during the systemic inflammatory response syndrome, vasopressors were prescribed to the same 27 patients investigated previously, and for another 12 patients in SIRS included, totaling 39 patients in septic shock with renal function augmented (RFA) by vasopressors requirements at TDM2-meropenem. Blood was sampling at the steady-state level for meropenem therapeutic drug monitoring in patients with renal function augmented by vasopressors (TDM2-RFA). Then, antibiotic coverage estimated was guaranteed against intermediate susceptible strains up to MIC 4 mg/L for all of them (39/39), while after 3hrs.-infusion the meropenem coverage against MIC 8 mg/L strains dropped to 30% (12/39) of patients in SIRS receiving vasopressors.

Since the target was attained up to MIC 8 mg/L in only 12 patients, meropenem 4 hrs.- infusion was prescribed for the rest of patients (n=27) to investigate the coverage up to MIC 8 mg/L strains to avoid mutant selection. After 48 hours of dose regimen of 1g q8h by 4hrs.-infusion, blood was sampling again for TDM3 in patients with renal function augmented (RFA) by vasopressors. Consequently, it is important to highlight that the meropenem coverage was increased by trice in 89% (23/27) of patients receiving vasopressors, done by 4 hrs. Infusion instead by 3hrs-infusion (Figure 1A), (Table 2).

At the late of septic shock, it was included only septic burn patients with renal dysfunction that occurred in general at the second week after meropenem therapy at D9 (Group 2). Therapeutic drug monitoring (TDM1) included 33 patients that received the empirical dose regimen 1g q8h, 3hrs.-infusion, but these patients developed acute kidney injury (AKI). Then, on TDM2, daily dose was reduced for safety to 1g q24h; and meropenem coverage was guaranteed for all patients against strains up to MIC 4 mg/L, while the coverage against strains MIC 8 mg/L occurred in 48% patients (16/33).

Finally, it was installed the continuous venovenous haemodialysis-filtration in 27 patients that received 1g q8h by 3hrs.-infusion. Blood was sampling at the steady state, for therapeutic drug monitoring (TDM3-CVVHD-F). PK/PD approach based on serum levels, and the minimum inhibitory concentration (MIC) of each pathogen isolated was done to evaluate if the target recommended was attained by meropenem for patients up to MIC 4 mg/L (27/27) or even up to MIC 8 mg/L (12/27), as represented in Figure 1B, (Table 2).

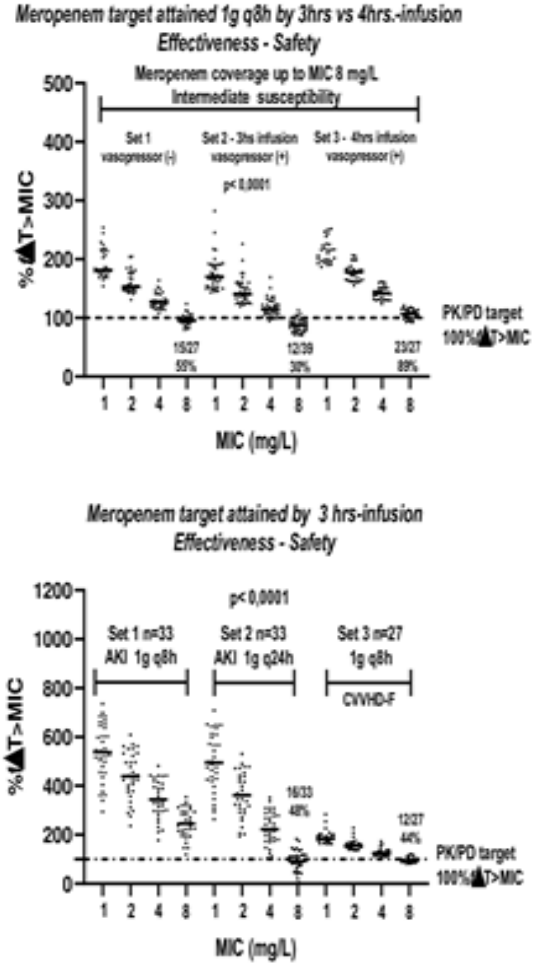

Figure 1

A Top panel: Meropenem 1g q8h 3hrs. *vs* 4hrs.-infusion coverage (8 mg/L).

B Bottom panel: Meropenem target attainment (8mg/L) AKI vs CVVHD-F.

It is important to highlight that at the last decades, pharmacokinetics of meropenem and beta lactam agents as piperacillin/tazobactam was based in serum levels after intermittent 0.5 hr.-infusion, extended 3hrs.-infusions, or even the continuous infusion considered by many authors as described by Abdul-Aziz (2016) to attain therapeutic target of 100%*f*ΔT>MIC for meropenem.[7] Since the inflammatory response syndrome occurs by cytokine storm, mainly at the early stage of septic shock in ICU critically ill patients, periods for blood sampling at the steady state for TDM, PK changes, and PK/PD approach must be considered for drug effectiveness as reported for meropenem in a recent comparison pharmacokinetics study at the initial stage *versu*s late stage of therapy of septic shock in adult burn patients.[15] Serial of data related to PK/PD approach-based on serum levels was reported by many authors considering not only dose size, dose regimen, duration of infusion and renal function dependence, but also whether the protocol was conducted in ICU patients at the early stage, or even at the late stage of septic shock, once significant PK changes that occur impacting meropenem coverage .[8,10,16,17]

Table 2 Burn septic patients undergoing Meropenem therapy by extended infusion, median (IQR) Laboratorial data, Meropenem coverage in ICU at the first septic shock

Laboratorial data (CLSI) n=48	**Group 1**	**Group 2**	**P**
	Initial stage of septic shock	**Late stage of septic shock**	
Leucocytes (*10^3 cells/mm^3)	11.12 (7.45-27.56)	20.22(12.73-24.33)	0.12509
Neutrophils (*10^3 cells/mm^3)	8.66 (4.98-24.86)	14.98 (11.65-19.77)	0.0654
Lymphocytes (*10^3 cells/mm^3)	1.62 (1.11-2.98)	1.66 (1.01-2.64)	0.6614
Clcr (mL/min) TDM1 n=27/48	76 (61-80)	-	NAP
Clcr (mL/min) TDM2 n=39/48	158 (135-189)	-	NAP
Clcr (mL/min) TDM3 n=27/48	138 (117-168)	-	NAP
Clcr (mL/min) TDM1 n=33/48	-	34 (27-37)	NAP
Clcr (mL/min) TDM2 n=33/48	-	32 (22-35)	NAP
Clcr (mL/min) TDM3 n=27/48	-	61 (53-70)	NAP
Inflammatory biomarkers			
NLR, survivors n=45	2.97 (2.32-4.51)	8.89 (6.01-14.25)	0.0005
NLR, non-survivors n=3	11.64 (9.57-16.45)	9.55 (8.78-12.50)	0.3214
C- reactive protein (mg/L), survivors n=45	107 (18-187)	224 (131-331)	0.0187
C- reactive protein (mg/L), non-survivors n=3	281 (251-318)	425 (404-496)	0.0006
Meropenem - regimen-extended infusion	**Coverage up to 4mg/L**	**Coverage up to 8mg/L**	**P**
Group 1 - Normal/Augmented Clcr	**Susceptible strains Intermediate susceptibility**	**Intermediate susceptibility**	
TDM1: 1g q8h 3hrs.-infusion. NRF n=27	100% (27/27)	55% (15/27)	< 0.0001
TDM2: 1g q8h 3hrs.-infusion. RFA n=39	100% (39/39)	30% (12/39)	< 0.0001
TDM3: 1g q8h 4hrs.-infusion. RFA n=27	100% (27/27)	89% (24/27)	0.001
Meropenem - regimen-3hrs.-infusion	**Coverage up to 4mg/L**	**Coverage up to 8mg/L**	
Group 2 - AKI-CVVHD-F	**Susceptible strains Intermediate susceptibility**	**Intermediate susceptibility**	
TDM1: 1g q8h 3hrs.-infusion. AKI n=33	100% (33/33)	100% (33/33)	1
TDM2: 1g q24h 3hrs.-infusion. AKI n=33	100% 33/33	48% (16/33)	< 0.0001
TDM3: 1g q8h 3hrs.-infusion. CVVHD-F n=27	100% 27/27	44% (12/27	< 0.0001

Abbreviations: Clcr, creatinine clearance; NLR, neutrophils to lymphocytes ratio; CLSI, Clinical Laboratory Standard Institute; TDM, therapeutic drug monitoring; IQR, quartiles (25-75); NAP, not applied; ICU, Intensive care unit; MIC, minimum inhibitory concentration; CVVHD-F, continuous venovenous haemodialysis-filtration; NRF, normal renal function; RFA, renal function augmented; AKI, acute renal injury

Statistics: GraphPad Prism, v.9.1.4, Mann Whitney, *Fisher test; Kruskal-Wallis test.

Any information related to the 4-hour infusion of meropenem was not found in the recent literature. On the other hand, the first clinical protocol describing a 4-hour infusion was related to piperacillin/tazobactam, described by Chung et al.,[18] That study was carried out in adult septic patients, with preserved renal function for a target attainment of 90%*f*ΔT>MIC considered by authors. The impact of pharmacokinetic changes in piperacillin coverage following a dose of 4.5g every 8h by prolonged 4hrs-infusion was recorded during septic shock therapy. In addition, authors described a pronounced three-folds increase in the apparent volume of distribution despite, a two-folds prolonged biological half-life. Such kinetic changes ensured coverage for all patients at the target of 90% *f*ΔT>MIC considered against *P. aeruginosa* and *Enterobacteriaceae* isolates up to MIC 16 mg/L. Nonetheless, the wide variability of results concerning the total body clearance of piperacillin occurred either using vasopressors in titrated doses according to the greater or lesser need of each patient related to the results of the Chung study.[18]

In addition, the use of vasopressor high doses, or even the association of two, even three agents in some septic patients included in the protocol of study were reported by De Waele et al.[19] Based on results reported by those authors in reviewed clinical protocols, it becomes relevant to consider that the septic patient with preserved renal function or even receiving vasopressors at the initial stage of shock (SIRS), shows change on the pharmacokinetics parameters given by an extended infusion of 3-hour and 4 hours, impacting positively the coverage.[19] Consequently, drug effectiveness in the most critical period of the infection was guaranteed against Gram-negative isolates. A careful review of studies related to the pharmacokinetics of piperacillin, considering the targets of 90% *f*ΔT>MIC after 4hrs.-infusion, or 100%fΔT>MIC for coverage of this antimicrobial after prolonged infusion, describes the comparison of results obtained in five prospective controlled studies conducted in critically ill patients during septic shock therapy. Pharmacokinetic changes recorded in septic patients in protocol considered in each study were always compared to data reported in healthy volunteers, considering dose regimens to investigate changes that occur in critically ill patients during the period of septic shock.[18,19]

Then, based on data obtained by both authors after an extended infusion of 4-hrs, we can justify the inclusion of this strategy to investigate the kinetic changes that could impact meropenem coverage in ICU burn patients with vasopressors requirements at the initial stage of septic shock during the SIRS.

It is important to highlight that routinely PK/PD was applied for ICU burn septic patients of our hospital by dose regimen 1g q8h 3hrs.-

infusion. Our investigation included meropenem at the initial stage of septic shock, dose regimen 1g q8h by 3hrs.-infusion *versus* 4hrs.-infusion in burn septic patients with augmented renal clearance. It was evidenced the superiority on coverage by trice after 4hrs.-infusion over 3hrs. -infusion described in Table 2, illustrated Figure 1A.

In addition, effectiveness, and mainly safety was investigated in burn patients with renal dysfunction. It was shown in burn patients undergoing empirical dose regimen 1g q8h, 3hrs.-infusion at TDM1 on acute kidney injury (AKI). Then, dose regimen was adjusted to 1g q24h at TDM2, and coverage occurred up to MIC 4 mg/L against intermediate susceptible strains. After the continuous dialysis installed, empirical dose regimen 1g q8h by 3hrs.-infusion was required to guarantee meropenem coverage of susceptible strains up to MIC 2 mg/L and MIC 4 mg/L, against intermediate strains illustrated in Figure 1B.

Finally, coverage occurred for all patients of both groups after the extended infusion against susceptible Gram-negative strains up to MIC 2 mg/L (minimum inhibitory concentration), and up to MIC 4 mg/L, strains of intermediate susceptibility, according to Clinical Laboratory Standards Institute (CLSI, database) considered in the Microbiology of central laboratory of our hospital.

Pharmacodynamics was investigated by isolating pathogens from fluids and secretions (whole blood) collected from septic burn patients considering the total number of isolates from the site of infection. It should be mentioned that in this evaluation the same patient could contribute to the count of infection in more than one site of infection according to microbiological colonization. A total of 54 isolates were stratified into Gram-negative susceptible pathogens-Enterobacterales (29 isolates) including *K. pneumoniae* (10/29) MIC 0.25-2 mg/L, and susceptible non-Enterobacterales (25 isolates) including *B. cepaceae, P. aeruginosa and A. baumannii calcoaceticus complex*. On the other hand, for patients undergoing meropenem therapy, it was isolated five *Burkolderia cepaceae* (5/25), *Pseudomonas aeruginosa* (12/25), meropenem susceptible up to MIC 2 mg/L, and *Acinetobacter baumannii* (8/25) resistant to meropenem (MIC>16 mg/L), but polymyxins susceptible MIC 0.5-2 mg/L. So, for these patients colistin was included in the therapy until negative cultures.

Conclusion

Adequate antimicrobial therapy of major septic burn patients in the ICU ensures coverage of Gram-negative nosocomial pathogens, preventing the selection of mutants by applying the PK/PD approach performed routinely in a real time, based on serum levels of meropenem, and monitoring of isolates from cultures. The choice of sensitive and specific biomarkers such as C-reactive protein, combined with the neutrophil/lymphocyte ratio contributes effectively to the prediction of death in critically ill patients burned in the ICU, since these biomarkers elevated for a prolonged period show worse clinical outcomes. Therefore, effective, and safe antimicrobial therapy for patients in septic shock, as well as continuous monitoring of inflammatory biomarkers, should guide clinical management to ensure cure with early ICU discharge.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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