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Antimicrobial therapy in severe septic ICU major burn patients to combat bacterial resistance by pharmacokinetic-pharmacodymamics of vancomycin, meropenem, and piperacillin, cultures, and inflammatory biomarkers

Abstract

Introduction: In view of the growing challenge to the use of antimicrobials for the adequate and effective therapy of hospital infections, international health agencies have reinforced that it is urgent to combat bacterial resistance in preventing the development of multidrug-resistant (MDR) strains. There has been a significant increase in the minimum inhibitory concentration (MIC) for most available and prescribed therapeutic agents against hospital pathogens based on reports of this occurrence by hospital infection control committees. Currently, vancomycin, meropenem and piperacillin-tazobactam are widely prescribed in the therapy of septic shock of critically ill ICU patients caused by susceptible Gram-positive and Gram-negative bacteria. Therefore, combating the development of resistance is a relevant first-line topic to ensure the maintenance of these antibiotics in the therapeutic arsenal, especially in tertiary public hospitals with high demand for care for this population of critically ill septic patients admitted to Intensive Care Units. Then, the therapy of vancomycin combined with piperacillin-tazobactam or with meropenem are largely prescribed to critically ill patients in ICUs including major septic burn patients. Consequently, an early implementation strategy for antimicrobial therapy for septic shock done by pharmacokinetics-pharmacodynamic (PK/PD) approach based on serum levels of antibiotics (ATBs), and cultures monitoring become fundamental in ensuring the desired clinical outcome attained by an early microbiological cure, and obviously with a reduction in the hospitalization period in the ICU of patients by reducing deaths and mainly save lives.

Subject: Aim of the study was investigate by an open label clinical protocol carried out in twenty-seven major burns at the first septic shock in ICU to evaluate pharmacodynamics based on pharmacokinetics, that could affect the coverage of vancomycin, 1-hr. intermittent infusion against Gram-positive strains, and meropenem or piperacillin-tazobactam by 3-hrs.-extended infusion, against Gram-negative pathogens.

Methods: Criteria considered was based on the PICO strategy: *Patient, Intervention, Comparison, and Outcome.* The primary endpoint was the pharmacodynamics based on microbiology of the isolate strains obtained from cultures, and the antimicrobial coverage of each patient considering the percentage of them that achieving the recommended therapeutic target (100% *f*ΔT>MIC) attained by piperacillin-tazobactam or by meropenem. In addition, coverage of each patient by vancomycin was based on recommended target ($AUC^{ss}_{0\text{-}24}$/MIC>600). The primary outcome was to evaluate two combined therapies prescribed to patients, considering vancomycin-piperacillin, or vancomycin-meropenem, done by extended infusion against Gram-negative strains. Antimicrobial efficacy was measured by pharmacokinetic-pharmacodynamics (PK/PD) tools based on drug serum levels. As a secondary outcome, ICU 30 days death of patients undergoing intensive care was considered, during the systemic inflammatory response syndrome (SIRS) that was monitored by inflammatory biomarkers hospital routine as c-reactive protein (CRP), neutrophils to lymphocyte's ratio (NLR), and interleukin-6 (IL6).

Results: Coverage strategy was based on the prediction index ($AUC^{ss}_{0\text{-}24}$/MIC, ratio) of vancomycin effectiveness related to target $AUC^{ss}_{0\text{-}24}$/MIC>600. In addition, coverage strategy related to piperacillin-tazobactam or to meropenem was the prediction index (%*f*ΔT>MIC) of drug effectiveness based on target 100%*f*ΔT>MIC for both agents. Different changes occurred in the coverage of these ATBs related to renal function of patients. It is important to highlight that ATBs coverage were monitored at the early phase of septic shock in patients with high variability of renal dysfunction, and with vasopressor requirements. It was shown that the combined IL6_NLR monitoring was a good predictor of ICU death of septic major burn patients.

Conclusion: Combined monitoring of inflammatory biomarkers in septic burns was very useful to predict mortality in severely ill septic patients. PK/PD approach done once a week based on ATBs serum levels, and microbiology of cultures should be implemented in the routine of tertiary hospitals to guarantee the individualized therapy of antimicrobial coverage, that contributes for combating the mutant´s selection, and preventing consequently the development of bacterial resistance.

Keywords: combined antimicrobial therapy in ICU major septic burns, pharmacokinetics-pharmacodynamics approach based in serum levels, microbiology of cultures, combined NLR_IL6 biomarkers monitoring, coverage dependent of systemic inflammatory response

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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; IAI, intra-abdominal infection; ICBU, intensive care burn unit; ICU, intensive care unit; IL6, interleukin-6; MDR, multidrug resistance; MIC, minimum inhibitory concentration; MRP4, multidrug resistance-associated protein 4; MV, mechanical ventilation; NLR, neutrophils to lymphocytes ratio; OAT1, OAT1-organic anion transporter 1; OAT3, OAT3-organic anion transporter 3; PD, pharmacodynamics; PK, pharmacokinetics; PNM, pneumonia; 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; UTI, urinary tract infection; WHO, World Health Organization

Introduction

Septic shock is a preventable and potentially fatal organ dysfunction caused by a dysregulated host response to infection.[1] Clinical outcome in most high-risk cases is the death of patients with nosocomial bacterial infections associated with various comorbidities, including viral infections, most recently SARS-CoV-2.[2] About 50 million cases diagnosed annually worldwide, at least 11 million patients die being mostly concentrated in underdeveloped countries. Results of a large international prospective trial show that 70% of ICU patients receive antibiotics.[3] However, incidence of infections and associated mortality in the ICU have not improved over the last 30 years.[4] This indicates that it may be possible to improve care for septic patients and clinical outcomes in ICU. In addition, considering renal clearance in those patients, the association between increased mortality rate and antimicrobials dose adjustment in intensive care unit patients with renal impairment is reported, or even augmented renal clearance is another common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy.[5-10]

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, Surviving Sepsis Campaign in the International Guidelines for Management of Sepsis and Septic Shock (2021), Global Sepsis Alliance (2020) and World Health Organization (2023) have reinforced that combating bacterial resistance, and the prevention of the development of multidrug-resistant strains (MDR) is urgent.[2-4]

Thus, this population requires an immediate change in the behavior of the clinical team and continuous monitoring of these patients undergoing intensive care through continuous hemodynamic, respiratory, renal, and infectious surveillance. Additional recommendations were published regarding the application of the pack of anticipated emergency clinical procedures for the 1st hour replacing the 12-hour period recommended previously for septic ICU patients, including the collection of cultures before starting antibiotics. In a monitoring program of antimicrobial therapy for several infections based on serum levels of beta-lactams in patients admitted to the ICU, it was reported that 73% of patients did not reach the therapeutic target against susceptible strains of gram-negative bacteria. This fact reinforces that monitoring serum levels is essential to assess changes in pharmacokinetics that impact the coverage of the prescribed antimicrobial agent, expressed through the PK/PD approach. Therefore, new therapeutic strategies have been proposed for the most prescribed beta-lactam agents related to the dose regimen and duration of infusion for meropenem and for piperacillin-tazobactam.[5-8]

In addition, to allowing the evaluation of effectiveness of the dose regimen prescribed to septic ICU patients, vancomycin, meropenem and piperacillin 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 combating the development of bacterial resistance, also reducing the duration of antimicrobial therapy, and consequently hospital costs. It is noteworthy that, so far, serum levels of these agents are not routinely monitored in hospitals for these critically ill patients admitted to ICUs.[9-11] Therefore, research involving pharmacoeconomic studies must be carried out linked to patient care in the ICU and clinical outcome to better investigate mortality in ICUs. A planned implementation of cost-effective monitoring of serum antimicrobial levels, carried out in the central laboratory of tertiary hospitals, will allow dose adjustment in real time, saving lives and reducing patient mortality in the ICU.[12]

Objective

Subject of study was to investigate antimicrobial effectiveness of a combined therapy of vancomycin-piperacillin/tazobactam or vancomycin-meropenem in adult major burns with renal function preserved or augmented by vasopressors requirements, renal insufficiency, or even patients undergoing continuous veno-venous hemodialysis filtration (CVVHDF) done in a real time by pharmacokinetic-pharmacodynamics (PK/PD) approach based on drug serum measurements (TDM). Impact of inflammatory biomarkers C-RP, NLR and IL6 monitoring during the therapy of septic shock on coverage done by PK/PD approach and cultures monitoring.

Methods

Study design, patient eligibility, antibiotic therapy, laboratorial data monitoring

The clinical protocol was a prospective, open-label study. Ethical approval register CAAE 07525118.3.0000.0068, Brazilian Platform was obtained followed by approval 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. The study was conducted from July 2019 to December 2021,and informed written consent was obtained from all legally designatedpatient representatives. Adult patients from the Intensive Care Burn Unit, presenting severe thermal injury and a sepsis diagnosis as reported Greenhalgh et al. in the "American Burn Association consensus conference to define sepsis and infection in burns" in clinical evaluation and laboratorial data were eligible for inclusion.[13]

On the other hand, patients with vancomycin, meropenem or piperacillin/tazobactam intolerance were excluded. The study was based on the recommended antimicrobial treatment to suspected or documented Gram-positive and Gram-negative nosocomial infections of hospital. Thus, vancomycin-piperacillin/tazobactam or vancomycin-meropenem combined therapy were prescribed at dose regimen recommended for patients with renal function preserved, augmented by vasopressors required at the earlier stage of septic shock, acute renal injury (AKI) or yet undergoing continuous veno-venous hemodialysis filtration procedure (CVVHDF). Septic major burn patients 27 (16M/11F) at the earlier stage of the first septic shock were included to investigate antimicrobial effectiveness of combined therapy guided by cultures, and PK/PD approach based on drug serum levels. Adult patients were allocated in two groups based on antimicrobial combined therapy with Vancomycin-Piperacillin/

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Tazobactam (Group 1, n=19) and Vancomycin-Meropenem (Group 2, n=8). It is important to highlight that antimicrobial prescription of combined initial therapy with Vancomycin - Meropenem is reserved as the first choice, instead of piperacillin-tazobactam, just in high critically ill septic patients as recommended by the infection committee of hospital. Then, meropenem was prescribed for eight patients, that were allocated in Group 2.

Empirical dose regimen for vancomycin, body weight normalized, was given 1g q12h by one hour pump infusion for serum monitoring in Set 1 (TDM-1); dose adjustment was done in Set 2 (TDM-2), if required to individualize therapy to achieve clinical desired outcome. In addition, piperacillin-tazobactam was given 4.5g q6h and meropenem was given 1g q8h; both were administered systemically by pump 3 hrs.-infusion at the dose regimen recommended, according to the institutional protocol. Complete medical histories, physical examinations were obtained for each enrolled patient; laboratory data included biomarkers monitoring, and microbiology of isolated strains documented in blood cultures, bronchoalveolar lavage, wound/bone, and urinary tract. Susceptibility testing was done to obtain the minimum inhibitory concentration for each antimicrobial agent against each pathogen isolated (CLSI data base).

Demographic and clinical characteristics of patients at admission, and during drug serum monitoring in the Intensive Care Burn Unit (ICBU) are detailed. 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 and IL6 in serum were performed on the COBAS Analyzer 8000 series (C-RP) or COBAS E411 series for IL-6 (Roche, trademark), Neutrophil-to-lymphocyte ratio (blood count) was measured using a Hematological Analyzer (SYSMEX brand). All results of the tests carried out in the hospital's Central Laboratory, including cultures were sent to the ICUs via the network. Antibiotics serum measurements were done by liquid chromatography/ultraviolet detection (LC-UV, Shimadzu series10, with automatized serum samples extracts injection) of our laboratory at the Clinical Pharmacokinetics Center, as detailed previously.[17,18,20,25,27,28] It is important to highlight that antimicrobial agents were prescribed, and cultures were collected before the therapy with antibiotics start.

Vancomycin therapy in septic burn patients and blood sampling for TDM, PK/PD

It was investigated vancomycin effectiveness with an empirical dose recommended, and if requires dose adjustment must be done soon to achieve the pharmacokinetics-pharmacodynamics target recommended by Rybak *et al*, in the last consensus $AUC^{ss}_{0\text{-}24}$/MIC>400-600 in major burn patients.[14] Then, major burn patients were included in the protocol of study. Patients were allocated based on antimicrobial combined therapy recommended in hospital, and they received vancomycin, empirical dose regimen recommended by 1hr.-infusion at TDM-1. Dose adjustment, if required to achieve effectiveness against Gram-positive isolated from cultures, was done at TDM-2. Vancomycin coverage obtained in TDM-1 was compared with results obtained in TDM-2, after individualization of therapy. Twenty-seven patients included in the study received vancomycin dose regimen recommended in hospital, according to renal function of patient considered. Only at the steady state level reach, blood was sampling for TDM at the 3rd hr. of the infusion started, and one hour before the next infusion for drug serum levels. Drug effectiveness was evaluated by pharmacokinetic-pharmacodynamic approach, based on PK/PD target $AUC^{ss}_{0\text{-}24}$/MIC>400 recommended; microbiology of Gram-positive isolates from cultures was monitored.

Piperacillin/Tazobactam or Meropenem therapy, blood sampling for TDM, PK/PD

Septic adult patients, n=27 of both genders (16M/11F) were distributed in two groups according to antimicrobial therapy chosen: Group 1, n=19 Vancomycin-Piperacillin/Tazobactam (10M/9F); Group 2, n=8 Vancomycin-Meropenem (6M/2F). In addition, septic burn patients received the dose regimen recommended in hospital according to renal function, and Piperacillin/tazobactam or Meropenem was administered by 3 hrs.-infusion to attain the target (100%*f*ΔT>MIC), MIC: minimum inhibitory concentration reported previously by Abdul-Aziz et al. for beta lactam agents largely prescribed for ICU septic patients.[10] Piperacillin-tazobactam is the first choice recommended in our hospital against Gram-negative pathogens in nosocomial infections, and it was prescribed to ICU septic burn patients. Then, it was given 4.5g q6h, piperacillin-tazobactam, administered systemically by pump 3 hrs.-infusion at the dose regimen recommended, according to the institutional protocol described for 19 patients with renal function preserved, or 4.5g q8-12h for patients with renal failure or CVVHDF, dose dependent based on renal dysfunction. Meropenem initial therapy as the first choice, instead of piperacillin-tazobactam, is reserved for very seriously septic patients, high ICU death risk, with also high values of inflammatory biomarkers at the beginning of antimicrobial therapy. Meropenem was given 1g q8h by pump 3 hrs.-infusion at the dose regimen recommended, according to the institutional protocol described for patients with renal function preserved, or 4.5g q8-12h for patients with AKI or CVVHDF. Blood was sampling at the 3rd hr. (end of extended infusion) and one hour before the next infusion for piperacillin or meropenem for drug serum levels done by liquid chromatography. One compartment open model was chosen to investigate pharmacokinetic parameters for PK/PD therapeutic targets purposes, and noncompartmental data analysis was applied. Drug effectiveness was evaluated by PK/PD approach based on target 100%*f*ΔT>MIC and serum levels, guided also by the microbiology of Gram-negative isolates from cultures.

Statistical analysis

Individual and population data statistics: The actual statistic of this study conducted on 27 major burn patients at the first septic shock after ICU admission was done on the basis of the use of software's as follows: OFFICE 365, version 2208 (Excel); GraphPAD Instat - GraphPad Prism versions 9.1.14 and 10. Parametric and non-parametric tests (Mann Whitney and Wilcoxon, for unpaired and paired data tested) were applied to data obtained from the investigated patients, and a significance of $p<0.05$ was considered.

Results and discussion

Demographic, clinical, and laboratorial data at admission-discharge/death

Demographic and admission data were presented in table 1, and no significant differences were found between the groups considering the demographic data, including the parameters recorded at the admission of patients into the ICU such as SAPS3 and TBSA. It was considered that 3/8 patients/Group-2 presented electrical injuries, while the remainder (5/8)/ Group-2 mostly presented thermal injury in a large extend against 16/19 patients- Group-1. This fact justifies the combined therapy that was chosen with Vancomycin-Meropenem since a greater risk of death occurred in those patients/Group-2 compared to Group-1 patients. Furthermore, a significant difference related to inflammatory biomarkers (C-RP, NLR and IL-6) at admission was recorded only for surviving patients when comparing ICU admission with discharge.

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Table 1 Burn septic patients undergoing ICU antimicrobial therapy, median (IQR) demographic, clinical - laboratorial data-inflammatory biomarkers (C-RP, NLR, IL6), outcome

	Vancomycin-Piperacillin	**Vancomycin-Meropenem**	
Demographic data	**Group 1 n=19**	**Group 2 n=8**	**P**
Gender (16M/11F)	10M/9F	6M/2F	0.2763*
Age (yrs)	45 (39-55)	47 (41-66)	0.8856
Body weight (kg)	70 (66-74)	75 (74-80)	0.1985
Ideal body weight (kg)	65 (51-70)	70 (66-73)	0.223
Heights (cm)	167 (160-170)	170 (169-179)	0.1342
Body surface area (m2)	1.79 (1.71-1.86)	1.91 (1.83-1.96)	0.1424
Body mass index (kg/m2)	25 (24-28)	25 (24-26)	0.8247
Admission data	**Group 1 n=19**	**Group 2 n=8**	**P**
SAPS3	45 (38-59)	52 (42-64)	0.3559
TBSA (%)	18(10-33)	31(25-40)	0.0628
Thermal /electrical injury	16	3	<0.0001*
Inhalation injury	10	8	0.0285*
Mechanical ventilation	10	8	0.0285*
Vasopressors	10	8	0.0285*
Accident	14	6	0.0256*
Crime	3	4	1.0000*
Laboratorial data (CSLI)	**ICU Admission**	**ICU Discharge/Death**	**P**
Leucocytes (*10^3 cells/mm^3) n=27	20.38 (14.70-23.35)	11.47 (7.30-27.13)	0.1149
Neutrophils (*10^3 cells/mm^3) n=27	14.98 (11.65-19.77)	8.31 (4.90-23.78)	0.0746
Lymphocytes (*10^3 cells/mm^3) n=27	1.76 (1.01-2.57)	1.72 (1.21-2.95)	0.6461
Serum creatinine (mg/dL) n=27, min/max value	1.02 (0.72-1.78) 0.43/4.39	1.55 (0.74-2.93) 0.51/5.25	0.2998
CLcr (mL/min) n=27, min/max value	80 (43-110) 19/147	53 (30-103) 15/195	0.2229
C- reactive protein (mg/L), survivors n=15	276 (201-352)	13 (10-17)	<0.0001
C- reactive protein (mg/L), non-survivors n=12	408 (202-454)	340 (248-282)	0.2844
NLR, survivors n=15	8.89 (6.01-14.25)	2.97 (2.32-4.51)	0.0004
NLR, non-survivors n=12	8.33 (5.65-12.50)	11.64 (9.57-16.45)	0.1432
IL6 (pg/mL), survivors n=15	125 (82-162)	48 (35-87)	0.0005
IL6 (pg/mL) , non-survivors n=12	2783 (2291-3748)	2583(2032-2877)	0.4428
Inflammatory biomarkers	**ICU - TDM 1**	**ICU - TDM2**	**P**
C- reactive protein (mg/L), survivors	224 (131-331)	107 (18-187)	0.0128
C- reactive protein (mg/L), non-survivors	425 (394-496)	281 (251-318)	0.0006
NLR, survivors	9.84 (5.77-16.46)	5.00 (2.96-8.97)	0.0497
NLR, non-survivors	11.02 (8.85-13.79)	7.82 (4.49-15.59)	0.3282
IL6 (pg/mL), survivors	150 (87-246)	78 (35-111)	0.0038
IL6 (pg/mL), non-survivors	2854 (2500-3748)	2233 (1498-2591)	0.0281
Clinical outcome Med (IQR) min/max values	**ICU-30 days**	**Hospital (days)**	**P**
Survivor patients (days), med (IQR) min/max	31 (16-55) 8/89	34 (29-58) 15/113	0.2981
LOS, survivors (days), med (IQR) min/max	34(29-58) 8/89	38 (31-65) 15/113	0.1395
ICU 30 days non-survivors, n=8 (days)	17 (13-21)	17 (13-21)	1.0000
LOS, non-survivors 8 *versus* 4 deaths (days)	17 (13-21)	61 (54-66)	0.004
LOS, non-survivors 8 *versus* 12 deaths (days)	17 (13-21)	23 (15-43)	0.2327
Death/Hospital Discharge	**ICU (%)**	**Hospital (%)**	**P**
Death patients (%)	8 (30%)	12 (44%)	0.2203*
Discharge patient's (%)	19 (70%)	15 (56%)	0.4672*

Abbreviations: SAPS3, simplified acute physiology score III; TBSA, total burn surface area; CLcr, creatinine clearance; NLR, neutrophils to lymphocytes ratio; IL6, interleukin-6; CLSI, clinical laboratory standard institute; TDM, therapeutic drug monitoring; IQR, quartiles (25-75); min/max, minimum/maximum values; NAP, not applied; PK/PD, pharmacokinetic-pharmacodynamic approach; ICU, intensive care unit; MIC, minimum inhibitory concentration; IS, intermediate susceptible strain; LOS, length of stay in hospital; CVVHDF, continuous veno-venous hemodialysis filtration; RFA, renal function augmented; AKI, acute renal injury

Statistics: GraphPad Prism, v.9.1.4, Mann Whitney $p<0.05$, *Fisher test.

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Vancomycin effectiveness based on serum monitoring

Vancomycin therapy was monitored in septic major burn patients 27 (16M/11F) with renal function preserved, augmented by vasopressors, or yet with renal failure, or undergoing continuous veno-venous hemodialysis-filtration; therapeutic target $AUC^{ss}_{0\text{-}24}$/MIC>400 recommended by Rybak et al., at the last consensus, was considered in the study to investigate drug effectiveness by applying PK/PD target based on serum levels in major burn patients included in the protocol.[14]

Considering previous dose adjustment, pharmacokinetic studies done in septic adults and pediatrics patients (burns and non-burns), it is well known that its coverage is impacted by differences in vancomycin pharmacokinetics due to the reduction in biological half-life resulted from an increase in total body clearance, expected mainly at the earlier phase of septic shock by the need of vasopressors. Additionally, PK changes that occurs in pediatric septic patients age dependently affecting vancomycin coverage, even without vasopressor agents.[15-21]

It was demonstrated in table 2, of study that the therapeutic target for vancomycin was achieved at MIC 0.5 mg/L, strains for all patients (27/27) by the vancomycin serum monitoring (TDM-1) with eradication of Gram-positive strains isolated. However, the dose was reduced to 1g every 24 hours in 15/27 patients due to renal failure in TDM-2. On the other hand, the dose of vancomycin was increased to 1g every 8 hours in 12/27 patients due to vasopressor requirements, and Gram-positive coverage against MIC 1 mg/L strains occurred just in 9/27 patients. Thus, vancomycin 1g q6h regimen was prescribed for the rest of them, ensuring coverage for clinical and microbiological cure against MIC 2 mg/L Gram-positive strains isolated from three patients, table 2.

Table 2 Burn septic patients undergoing combined antimicrobial therapy, median (IQR) dose regimen-infusion, Pharmacokinetics, PK/PD approach based on serum levels-dose adjustment required

ATB therapy TDM_PK/PD target	**Empirical dose regimen**	**Dose regimens adjustments**
Meropenem n=8 (IBW dose normalized)	1g q8h 3hrs-infusion	1g q12h (CVVHDF)
Daily dose (mg/kg)	43 (40-50)	1g q12-24h (AKI)
Dose regimen (mg/kg)	14 (13-17)	
Piperacillin-Tazobactam n=19 (IBW dose normalized)	4.5g q6h 3hrs-infusion	4.5g q8h (CVVHDF)
Daily dose (mg/kg)	225 (214-246)	4.5g q8-12h (AKI)
Dose regimen (mg/kg)	62 (51-72)	
Vancomycin n=27 (IBW dose normalized)	1g q12h 1hr-infusion	1g q24h (AKI)
Daily dose (mg/kg)	31 (29-33)	1g q6-8h (RFA)
Dose regimen (mg/kg)	14(13-17)	
Microbiology Cultures (CSLI data base)	**Coverage (%)**	**Dose regimens adjustments**
· Meropenem [PK/PD target 100%fT>MIC]	(n=8 patients)	AKI, CVVHDF
MIC up to 2 mg/L/Susceptible	100% (8/8)	
MIC 4 mg/L/Intermediate susceptibility (none isolate)	100% (8/8)	
MIC 8 mg/L/ Intermediate susceptibility (none isolate)	100% (8/8)	
· Piperacillin [PK/PD target 100%fT>MIC]	(n=19 patients)	AKI, CVVHDF
MIC up to 16 mg/L/Susceptible	100% (19/19)	
· Vancomycin [PK/PD target AUC24/MIC>400]	N=27 patients	Target attainment
MIC up to 0.5 mg/L/Susceptible strains	100% (27/27)	dose decreased/AKI (15/27)
MIC 1 mg/L/ Susceptible strain isolated	100% (9/27)	dose increased/RFA (9/27)
MIC 2 mg/L/Susceptible strain isolated	100% (3/27)	dose increased/RFA (3/27)

Abbreviations: CLSI, clinical laboratory standard institute; TDM, therapeutic drug monitoring; IQR, quartiles (25-75); NAP, not applied; IBW, ideal body weight; PK/PD, pharmacokinetic-pharmacodynamic approach; ICU, Intensive care unit; MIC, minimum inhibitory concentration; IS, intermediate susceptible strain; LOS, length of stay in hospital; CVVHDF, continuous veno-venous hemodialysis filtration procedure; RFA, renal function augmented; AKI, acute renal injury

Piperacillin-Tazobactam effectiveness based on piperacillin serum monitoring

Critically ill major burn patients (n=19: 10M/9F) at the earlier phase of the first septic shock received piperacillin/tazobactam as first choice recommended in hospital. Dose regimen 4.5g q6h eq. 18g/daily done by 3 hrs.-infusion were considered. Coverage by piperacillin occurred for all patients with renal function augmented that received the empirical dose regimen (TDM1) up to MIC 16 mg/L for susceptible strains isolates from cultures done at the Microbiology of central laboratory of hospital, based on Clinical Standard Laboratory Institute (CSLI database), table 2. Effectiveness was guaranteed since PK/PD target 100% *f*DT>100 was achieved up to MIC 16 mg/L strains susceptible and extended to MIC 32 mg/L of intermediate susceptibility strains in patients with renal function preserved or undergoing continuous veno-venous hemodialysis-filtration procedure, table 2. Then, it was guaranteed effectiveness/safety of the beta-lactam agent at the dose regimen 4.5g q8h by 3 hrs.-extended infusion in these patients. However, patients with renal failure received 4.5g q12h with coverage guaranteed up to MIC 32 mg/L strains. It is important to highlight that piperacillin dose regimen prescribed to ICU burn patients guaranteed clinical and microbiological cure, despite non-Gram-negative strains MIC 32 mg/L weren't isolated from patients investigated in the protocol. Piperacillin pharmacokinetics studies were previously reported in septic burn or non-burn adult patients, and plasma clearance depends basically on glomerular filtration rate. It is well known that piperacillin/tazobactam coverage after extended 3hrs- infusion or even 4hrs.-infusion compared to 0.5 hr.-intermittent infusion impacted positively by pharmacokinetics alterations, because of

increases on volume of distribution, with proportional prolongation of biological half-life based on increases on serum levels. It is important to highlight that vasopressor requirements at the earlier stage of septic shock must justify the increases that occurred on piperacillin total body clearance higher than meropenem plasma clearance in critically ill septic patients.[22-27]

Meropenem effectiveness based on serum monitoring.

Critically ill eight major burns that received meropenem at the earlier period of the first septic shock were investigated. Meropenem therapy was reserved as the first choice instead of piperacillin-tazobactam for very seriously septic patients, with high values of inflammatory biomarkers. Dose regimen 40mg/kg q8h (120 mg/kg daily) done by 3 hrs.-infusion were considered. Coverage by meropenem occurred for all patients with renal function augmented that received the empirical initial dose regimen; considering MIC data 2 mg/L for susceptible strains isolates from cultures in the Microbiology of central laboratory of hospital, Clinical Standard Laboratory Institute (CSLI database), table 2. Drug effectiveness was guaranteed since PK/PD target 100% *f*DT>100 was attained, and extended to intermediate susceptibility strains, MIC 4-8 mg/L for patients with renal function preserved or undergoing procedure of continuous veno-venous hemodialysis-filtration. Then, it was guaranteed effectiveness-safety of meropenem therapy based on dose regimen 1g q8h by 3 hrs-extended infusion in all patients. However, patients with renal failure received 1g q12h with coverage guaranteed up to MIC 8 mg/L strains that obviously contributes to avoid microbial resistance. It is important to highlight that meropenem dose regimen prescribed to all ICU burn patients guaranteed clinical and microbiological cure, despite any Gram-negative strains MIC 4-8 mg/L weren't isolated from patients investigated in the protocol, table 2.

Meropenem pharmacokinetic and PK/PD studies were previously reported in septic burn or non-burn adult patients, and in pediatrics. It is well known that meropenem coverage after the extended 3hrs or 4hrs-infusions is positively impacted by pharmacokinetics changes, because of major increases on volume of distribution, with proportional prolongation of biological half-life. Additionally, vasopressors requirements at the earlier stage of septic shock must justify the increases that occurred on total body clearance in those critically ill septic patients by increases on glomerular filtration rate. It is important to highlight that during the septic shock, meropenem plasma clearance is reduced by 50% because of decreases that occurs in drug renal tubular secretion.[17,20,21,28-31]

Cultures of isolated strains

Therapeutic drug serum monitoring was done by blood sampling in ICU septic burn patients routinely once a week, or twice a week for patients that TDM was required to guarantee drug efficacy-safety, table 2. Clinical cure occurred in a short period by negative cultures for Group 1-patients undergoing combined therapy with vancomycin-piperacillin, and for Group 2-patients receiving vancomycin-meropenem combined therapy. Sites of infection were blood stream (51%), lungs, with pneumoniae (PNM) unrelated to mechanical ventilation (18%), wound/bone (24.4%) and urinary tract (6.6%). Related to microbiology of isolates, it was shown in septic burn patients that majority of pathogens were *Staphylococcus spp* isolated from patients were *Staphylococcus spp (22/25)* followed by *Streptococcus spp (3/25)*. Major prevalence of Gram-positive strains was related to *S. aureus* susceptible (MIC 0.5-1.0 mg/L) followed by *Staphylococcus epidermidis* (MIC 1-2 mg/L). Then, dose adjustment done in a real time was considered to guarantee drug effectiveness. In addition, it was isolated Gram-negative strains, piperacillin susceptible (MIC 0.25-8 mg/L) of *Enterobacteriaceae* including *Klebsiella pneumoniae* (6/27). Also, it was isolated *Pseudomonas aeruginosa* (5/27), *Burkholderia cepacia complex* (3/27), meropenem susceptible (MIC 2 mg/L)*, non-Enterobacteriaceae* strains of lower prevalence in the ICU of Burns of hospital, table 2. Despite of clinical cure for all patients, ICU 30-day death occurred in major burn septic patients with elevate inflammatory response based on combined IL6-NLR biomarkers at the first two weeks of ICU admission.

Inflammatory biomarkers monitoring

Several studies of inflammatory biomarkers have been reported for patients with sepsis or septic shock, and unfortunately it was shown large variability in data reported in most studies from the last 5 years. However, it was found a quite interesting article reported by Shimazui *et al* (2019) based on IL-6 serum levels on ICU admission and subsequent outcomes in septic patients with acute kidney injury, dysfunction of high incidence in critically ill patients. It was discussed by authors that the exacerbated inflammatory response is considered one of the key elements of acute kidney injury (AKI). Interleukin-6 (IL-6) is an inflammatory cytokine that plays important roles in the inflammatory response and may be useful for predicting the clinical outcomes in patients with AKI. Patients allocated were distributed into three groups by admission IL-6 tertiles. Associations between IL-6 on ICU admission and in-hospital 90-day mortality, short-term/long-term renal function were analyzed in a patient population (n = 646) that were based on IL-6 serum levels low (1.5–150.2 pg/mL), middle (152.0–1168 pg/mL), and high (1189-2,346,310 pg/mL) on ICU admission groups. Patients in the high IL-6 group had higher in-hospital 90-day mortality (low vs. middle vs. high, P = 0.0050), lower urine output (low vs. middle vs. high, $p < 0.0001$), and an increased probability of persistent of anuria for ≥12 hrs. (low vs. middle vs. high, $p < 0.0001$) within 72 h after ICU admission. In contrast, the high IL-6 group had a lower incidence of persistent AKI at 90 days after the ICU admission in survivors (low vs. middle vs. high, P=0.013). It was concluded that interleukin-6 serum levels on ICU admission may predict short-term renal function and mortality in acute kidney insufficiency (AKI) patients and were associated with renal recovery in survivors.[32]

More recently, another very interesting data was related to combined biomarkers interleukin-6 and neutrophil-to-lymphocyte ratio (NLR) in predicting 28-day mortality in patients with sepsis was reported by Liu *et al* (2021). Study aimed to evaluate the relationship between the neutrophil-to-lymphocyte ratio (NLR) combined with interleukin-6 (IL6) on admission day and the 28-day mortality of 264 septic patients diagnosed with sepsis. It was reported in the study that the levels of NLR and IL-6 were significantly higher in the deceased patients with sepsis. NLR and IL-6 appeared to be independent predictors of 28-day mortality in septic patients. Moreover, NLR combined with IL-6 could dramatically enhance the prediction value of 28-day mortality (186 survivors/78 non-survivors). Cut-off points considered by authors in the study related to biomarkers considered isolated were NLR= 5.55, and IL6= 100 pg/ml, while for combined biomarkers NLR_IL6, the cut-off points were NLR = 4.937 IL6 = 117.6.[33]

In our pilot study, twenty-seven major burns ICU patients were included, and three inflammatory biomarkers chosen were monitoring. Protocol was designed to investigate inflammatory biomarkers in severely burned ICU patients, considering the first septic shock after ICU admission. Blood samples were collected at admission for serum IL6 measurements and every two days from the beginning

until the end of combined therapy, and a maximum of two weeks was considered. Serum C-RP levels and NLR-based blood counts were performed daily and routinely in ICU patients by the hospital's central laboratory division. Biomarkers expressions were investigated during ATB therapy, and clinical outcome in ICU 30-day mortality was considered by ICU-death (non-survivors) or yet surviving patients, table 1.

In addition, the length of stay in hospital, table 1, was based by ICU death, or by hospital discharge. Inflammatory biomarkers data was described in table 1, as C-RP, IL-6 serum levels and NLR/hemograms after therapeutic antibiotics monitoring at periods: TDM-1 after 48hrs. of starting ATBs, and subsequently at TDM-2 at 9th to 10th of therapy. Frequency of TDM in general was once a week for patients with renal function preserved, or twice a week for patients with renal failure, CVVHDF or renal function augmented by vasopressors to guarantee drug effectiveness and safety for all of them.

Considering septic major burns investigated, it was shown high serum levels of C-RP and of IL6, or elevated Neutrophil to Lymphocyte-Ratio (NLR) at TDM-1, done at the peak of inflammatory response, 48 hrs after ATBs started in a combined therapy by comparison with TDM-2, that occurred in general a week later for all ICU patients. Inflammatory biomarkers were measured at TDM-1 and at TDM-2 in ICU-survivor patients, and data expressed as medians were compared, table 1. It was registered significant differences between data obtained in TDM-1 compared with TDM-2. A rapid decrease occurred in these patients considering serum levels of C-RP and IL6, or reductions on NLR, table 1, registered over time for C-RP (224 *versus* 107 mg/L, p=0.0128), IL6 (150 *versus* 78 pg/mL, p=0.0038), and NLR (9.84 *versus* 5.00, p=0.0497) medians.

On the other hand, inflammatory biomarkers measured at the TDM-1 *versus* TDM-2 were compared for non-survivors, and significant results were pointed out only for C-RP and IL6 serum measurements, table 1. It is important to highlight that high serum levels were registered of C-RP (425 *versus* 281 mg/L, p=0.0006) and IL6 (2854 *versus* 2233 pg/mL, p=0.0281), medians. Considering NLR data obtained in these patients, table 1, as medians were (11.02 *versus* 7.82, p=0.3282), and no statistical differences were found by comparison of data at TDM-1 with TDM-2. Based on NLR data, nonsignificant difference was pointed out between them at TDM-1 *versus* TDM-2, as a function of a reduced ICBU period [17(13-21) 11/26 days; median (quartiles) min/max values], that these patients were kept in ICU. Then, in non-survivors' data were justified as a function of very extremely high inflammatory response based on biomarkers monitored at admission/discharge or death in ICU, TDM-1/TDM-2.

In addition, according to cut-off points for isolated or combined biomarkers NLR_IL6 reported by Liu (2021), the limits considered by authors in that study were related to biomarkers considered isolated NLR= 5.55, and IL6= 100 pg/ml, or for combined biomarkers NLR_IL6, the cut-off points were NLR = 4.937 IL6 = 117.6.[33]

Then, it was shown , table 1, significant results obtained in septic major burn patients investigated in the pilot study, once the cut-off points reported for combined biomarkers in septic major burn patients were at TDM-2 NLR 5.00 (2.96-8.97)_IL6 78 (35-111) pg/mL for survivors, against data NLR 7.82 (4.49-15.59)_IL6 2233 (1498-2591) pg/mL obtained from non-survivors NLR 2.97 (2.32-4.51)_IL6 2233(1498-2591) at the 9th to 10th day of ATB combined therapy. Then, considering data obtained from septic major burn patients, it is possible to justify differences between survivors and non-survivors by applying the combined inflammatory biomarkers NLR_IL6, based on the cut-off points reported previously. It was shown in major burn patients/survivors that data obtained for all inflammatory biomarkers decrease faster than in non-survivor once they are more critically ill patients and of higher risk of death.

During combined therapy, the period to death in the ICU for non-survivors occurred in 17(13-21)11/26 days, table 1. On the other hand, discharge from the ICU occurred in 31(16-55) 8/58 days, and the length of stay of survivors in the hospital was 38 (31-64) 15/113 days. Finally, it was demonstrated in burn survivor patients that data obtained for all inflammatory biomarkers decreased more rapidly than in more seriously ill non-survivor patients due to a higher systemic inflammatory response that occurred in these patients.

Conclusion

a) Vancomycin therapy guided by cultures and serum levels for dose adjustment done in a real time by PK/PD approach permit an earlier clinical intervention to reach the desired outcome with cure in a shortest period. It was shown that the majority of pathogens *Staphylococcus spp* isolated from patients was related to *S. aureus* and *Staphylococcus epidermidis,* then, dose adjustment guaranteed effectiveness.

b) Piperacillin/tazobactam or meropenem therapy in burns was chosen against Gram-negative pathogens in a combined therapy with vancomycin. Clinical and microbiological cure occurred for all patients from both groups in a renal function dependence. Gram-negative susceptible isolates MIC were lower than 16 mg/L in patients receiving vancomycin-piperacillin/tazobactam, while Gram-negative susceptible isolates MIC lower than 2 mg/L were isolated from patients receiving vancomycin-meropenem.

c) Combined antimicrobial therapy against nosocomial pathogens investigated in this pilot study must be considered to combat microbial resistance based on PK/PD and cultures.

d) Inflammatory biomarkers monitoring on combined IL6–NLR is proposed for ICBU septic burn patients to predict the high systemic inflammatory response that occurs always in non-survivor patients.

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. SS 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 IL6 studies. TVC and MJS contributed to the revision of manuscript and of all articles included in the manuscript, and specially at the last revision done of references included in the manuscript. PR and NJCD 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 at the critical revision for important intellectual content. All authors read and approved the final manuscript version.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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