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Timeline of Burn Infections and Neutrophil-to-Lymphocyte Ratio–Guided Management of Burn Sepsis During Glycopeptide, Beta-Lactams, and Fluoroquinolone Therapy in ICU

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

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

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

[3]Central Laboratory Division & Medical Investigation Laboratory (LIM 03), Medical School, University of Sao Paulo/SP, Brazil)

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[*]**Corresponding author:** Silvia R C J Santos, Clinical Pharmacokinetics Center, University of Sao Paulo–Sao Paulo/SP, Brazil

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ABSTRACT

Introduction: Infection is the most common complication and a leading cause of death among patients with burn injuries, who are particularly vulnerable to infection and burn-related sepsis. In critically ill patients with extensive burns, antibiotic pharmacokinetics may be substantially altered by changes in renal function, including augmented renal clearance (ARC), acute kidney injury (AKI), and the need for continuous renal replacement therapy (CRRT). Considering Gram-negative nosocomial infections, antibiotic (ATB) de-escalation is routinely used to limit the emergence of resistance during prolonged ICU stay requirements in those patients. Accordingly, microbiological cultures and therapeutic drug monitoring are essential for optimizing serum antibiotic concentrations, achieving PK/PD targets, and eradicating susceptible pathogens.

Objective: To guide antibiotic selection for Gram-positive and Gram-negative nosocomial infections using serum levels, MIC data, and PK/PD principles; assess four hospital-recommended antibiotics' pharmacokinetics changes; and evaluate daily NLR monitoring to predict and prevent ICU mortality.

Methods:

Initial assessment and management: At Burn Center ICU admission, medical histories and injury details were recorded for 48 patients. Initial care included resuscitation, wound debridement, and management of respiratory and renal complications.

Diagnosis and monitoring: Septic shock was assessed using early microbiological testing and serial inflammatory biomarkers. Blood and site-specific cultures were collected before antibiotics. Doses were adjusted using cultures, twice-weekly therapeutic drug monitoring, pharmacodynamic targets, and renal function–related pharmacokinetic changes. NLR and serum C-reactive protein (CRP) were measured daily.

Antibiotic therapy: Empirical therapy for hospital-acquired infection combined vancomycin (Gram-positive coverage) and piperacillin/tazobactam (PTZ; Gram-negative coverage). PTZ resistance led to replacement with meropenem after three weeks, continued for five weeks. On day 59, meropenem-resistant *P. aeruginosa* led to a 10-day ciprofloxacin course.

Results

Initial deterioration and microbiological findings: On ICU-day 3, deterioration prompted cultures and broad-spectrum vancomycin plus piperacillin/tazobactam (PTZ). Cultures identified vancomycin-susceptible *Staphylococcus epidermidis* and meropenem-susceptible *Proteus mirabilis*, prompting meropenem therapy.

Treatment adjustment and recurrent septic shock: PTZ was stopped; meropenem and vancomycin continued. Sodium colistinemethate was added in some patients for resistant *Acinetobacter baumannii*. Hospital-recommended regimens were adjusted for renal function using therapeutic drug monitoring and MIC data. Recurrent septic shock in week 4 yielded meropenem-susceptible *Proteus mirabilis* and *Klebsiella pneumoniae*; therapy remained unchanged. **Subsequent infection and clinical outcome:** On day 58 (week 6), ciprofloxacin-susceptible *Pseudomonas aeruginosa* resistant to meropenem or amikacin was isolated. Ciprofloxacin began on ICU-day 59; cultures turned negative after a median of 67 days (range, 58–84). Forty-six patients were discharged from the ICU within 90 days and from hospital five days later.

Conclusion

Therapeutic approach: Antibiotic selection was guided by the identified infections and antimicrobial susceptibility profiles.

Dose optimization: Doses were individualized using therapeutic drug monitoring, MIC data, and PK/PD target attainment. Accounting for pharmacokinetic changes helped maintain therapeutic antibiotic exposure and supported treatment decisions.

Biomarker relevance: Daily NLR monitoring showed greater utility than C-reactive protein for clinical decision-making and may serve as an early indicator of mortality risk in the ICU.

HIGHLIGHTS

- Burn infections timeline & burn sepsis
- Antibiotics serum monitoring and MIC data guaranteed therapy individualized
- PK/PD coverage occurred according to PK-changes renal dependent
- Inflammatory biomarker NLR in decision making guided therapy.

Keywords:

1. Antibiotics prescribed to ICU septic burn patients
2. Vancomycin, Piperacillin/tazobactam, Meropenem, Ciprofloxacin
3. Therapeutic serum monitoring and MIC data
4. Pharmacokinetic changes in renal dependence
5. Pharmacodynamics based on Pharmacokinetics for target attainment

ABREVIATIONS

AKI Acute kidney injury; ARC Augmented Renal Clearance; ARDS acute respiratory distress syndrome; BAL Bronchoalveolar lavage (BAL) fluid; BSI Blood stream infection; CLSI Clinical & Laboratory Standard Institute database USA; c-RP c-Reactive Protein; CRRT Continuous Renal Replacement Therapy; [CL_T] Total body clearance; [$t_{(1/2\beta}$] Elimination half-life/biological half-life; [Vd^{ss}] Volume of distribution at the steady state; GNB Gram negative bacteria; GPB Gram-positive bacteria; ICU Intensive care unit; MDRB Multidrug resistance bacteria; MIC Minimum Inhibitory Concentration; MV Mechanical ventilation; NLR Neutrophils to Lymphocytes Ratio; PK Pharmacokinetics; PK/PD Pharmacodynamics based on Pharmacokinetics; PRF Preserved Renal Function; PTA Probability of Target Attainment; SAPS3 Simplified Acute Physiology Score 3; SIRS Systemic Inflammatory Response Syndrome; SOFA score Sequential Organ Failure Assessment score, known as the sepsis-related organ failure; TBSA Total Burn Surface Area; TDM Therapeutic Drug Monitoring.

INTRODUCTION

ICU nosocomial infections and mortality among critically ill septic patients have not improved over the past 15 years. Gram-negative infections generally emerge after 72 hours of hospitalization, and late infections caused mainly by non-Enterobacteriaceae often prove fatal in high-risk patients despite antibiotic therapy. Increased mortality has been associated with inadequate serum antibiotic monitoring for dose adjustment, particularly during acute kidney injury and continuous venovenous hemodiafiltration installed (CVVHDF). Continuous monitoring addition of antibiotic levels, alongside hemodynamic, respiratory, renal, and infectious surveillance, is therefore needed. Reports that 80% of critically ill septic patients fail to achieve therapeutic targets against susceptible Gram-negative nosocomial bacteria highlight the importance of serum monitoring and cultures to assess pharmacokinetic changes and guide PK/PD-based antibiotic coverage. Over the past 20 years, strategies involving dosing regimens, infusion duration, and culture monitoring have been investigated for commonly prescribed antibiotics, with hospital cost support, to better understand ICU mortality.[1-5]

Infection is the most frequent complication and leading cause of death among burn patients, as post-burn physiological changes increase susceptibility to infection and burn wound sepsis. Accurate diagnosis and management require physical examination and assessment of wound pathology. In patients with major burns, prolonged ICU stays, ongoing critical illness, repeated surgeries, and persistent infection risk weaken the immune response. Recurrent infections and multiple organ dysfunction often require extended intensive care, while immunosuppression increases susceptibility to opportunistic fungal and yeast infections, prolonging

hospitalization and complicating recovery. Burn sepsis management includes local wound dressings, prompt surgical excision, and systemic anti-infective therapy.[6,7]

Thus, integrating pharmacodynamics with pharmacokinetic changes, serum antibiotic levels, cultures, and routine inflammatory biomarker monitoring will be essential to individualize therapy and combat nosocomial antimicrobial resistance in critically ill septic ICU patients.

STUDY SUBJECT

Therapeutic Drug Monitoring (TDM) and culture data: The study evaluated antibiotic serum levels using therapeutic drug monitoring (TDM) and culture data to assess whether target attainment was achieved against Gram-positive and Gram-negative nosocomial bacteria isolated from cultures.

Clinical course and antibiotic therapy initiation: After ICU admission and stabilization, antibiotics were initiated for signs of sepsis associated with systemic inflammatory response syndrome (SIRS), vasopressor use, and augmented renal clearance (ARC). Their pharmacodynamic effects were evaluated in relation to pharmacokinetic changes in patients with extensive burns, acute kidney injury (AKI), and continuous renal replacement therapy (CRRT). **Guiding therapy with inflammatory biomarkers:** To guide antibiotic therapy, the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (c-RP) were monitored and compared to predict ICU mortality, providing insight into treatment response and prognosis.

METHODS

Study design, Ethics, Patient eligibility: Study was conducted at a public tertiary hospital, HC FMUSP, School of Medicine of University of Sao Paulo, SP, Brazil. The clinical protocol involved a prospective and open study. The ethical approval records were obtained with approval Brazilian Platform /Ethics Committee of the Hospital das Clinicas of the University of Sao Paulo, School of Medicine, Sao Paulo, SP, Brazil. There was no declaration of conflict of interest from any of the authors. The study was conducted from January 2018 to April 2020, with informed written consent obtained from all legally designated representatives of the patients. Therapy of patients with ciprofloxacin, meropenem, piperacillin/tazobactam or vancomycin intolerance was non-eligible.[7]

ICU admission to the burn center of hospital: Medical history, comorbidities, injury details, and ICU admission were recorded. Resuscitation and surgical debridement were performed, with attention to respiratory and renal complications. Septic shock was diagnosed early by microbiological investigation and inflammatory biomarkers. Broad-spectrum therapy began after clinical decline on ICU-day 3, following cultures of blood, urine, and bronchoalveolar lavage (BAL) fluid. Vancomycin for suspected Gram-positive and piperacillin/tazobactam recommended for Gram-negative infections in our hospital were prescribed. Doses were adjusted weekly by culture data and twice a week by serum monitoring. NLR and c-RP were compared by daily measurements to assess ICU mortality risk.

Medical history – Comorbidities - ICU admission and injury details: Forty-eight major burn patients, both genders were admitted to a tertiary public hospital and transferred to the ICU of the Burn Center – Plastic Surgery, University of Sao Paulo, Sao Paulo/SP, Brazil. Demographic data was 38 M/10 F; age 42 (36-51) years; weight 77 (72-80) kg; height 171 (161-175) cm; BMI 24 (23-26) kg/m^2, median (IQR). Patients with thermal or

electrical injuries occurred in 46/2 (96/4%), after accidents in 42 (88%) patients, suicide attempts in 4 (8%) or crime in 2 (4%). On admission, most had hypovolemic/distributive shock and moderate acute respiratory distress syndrome (ARDS) requiring mechanical ventilation, with inhalation injury in 40/48 (83%), and acute renal failure with vasopressor requirements in 36 (75%). SAPS*3 score was 55 (52-65) with mortality risk (35-69%), SOFA score 8-9, and TBSA%
37 (25-49).

Table 1 -Characteristics of critically ill major burn patients at ICU admission. Med (IQR)

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Demographic data	**Patients (n=48)**
Gender (M/F), n (ratio)	M: 38/F:10
Age (yrs)	42 (36-51)
Body weight (kg)	77 (72-80)
Ideal body weight (kg)	75 (65-81)
Heights (cm)	171 (161-175)
Body surface area (m^2)	1.88 (1.80-1.92)
Body mass index (kg/m^2)	24 (23-26)
Admission data	
SAPS3	55 (52-65)
TBSA (%)	37 (25-49)
Thermal/electrical injury, n ratio (%)	46/2 (96/4%)
Inhalation injury, n (%)	40/48 (83%)
Mechanical ventilation, n (%)	38/48 (79%)
Vasopressors, n (%)	36 (75%)
Accident, n (%)	42 (88%)
Suicide attempt, n (%)	4 (8%)
Crime, n (%)	2 (4%)
Laboratorial data (CLSI database)	
Leucocytes 14-34 ($*10^3$ cells/mm^3)	21.56 (13.88-33.67)
Neutrophils13-25 ($*10^3$ cells/mm^3)	17.01 (12.56-24.51)
Lymphocytes 0.85-3.59 ($*10^3$ cells/mm^3)	1.67 (0.85-3.59)
Serum creatinine 0.67-3.98 (mg/dL)	1.59 (0.67-3.98)
Creatinine clearance 18-144 (mL/min)	66 (18-144)
C- reactive protein 68-128 (mg/L)	95 (68-128)
Neutrophils/Lymphocytes ratio (N/L ratio)	8.55 (6.16-12.42)
Abbreviations: Med (IQR): median, quartiles (25-75); SAPS3: Simplified Acute Physiology Score III; SIRS: systemic inflammatory response syndrome; TBSA: total burn surface area; N/L ratio: neutrophils to lymphocytes ratio; CLSI: Clinical & Laboratory Standard Institute**. Statistics:** GraphPad Prism, GraphPad Prism, version 10.0, Medians (IQR).	

Immediate medical management - Resuscitation & surgical debridement: ICU patients presented with severe burns requiring rapid intervention. Cardiopulmonary resuscitation stabilized vital signs, and surgical debridement removed dead tissue to lower infection risk and support healing.

Airway, respiratory, and renal complications: Due to ongoing hypoperfusion, patients required intubation and mechanical ventilation. Hypovolemic-distributive shock led to ARDS and acute kidney injury (creatinine clearance
<25 mL/min) with vasopressors requirements or CRRT for fluid and electrolyte management. On ICU-day 3,

septic shock was suspected, blood and site-specific cultures were collected before initiating antibiotics recommended against nosocomial strains: vancomycin against Gram-positive (*Streptococcus spp*, *Staphylococcus spp*) and piperacillin-tazobactam to combat Gram-negative bacteria (*Enterobacteriaceae*). Broad-spectrum testing was guided daily by c-RP and NLR, supporting the SIRS diagnosis typical in severe burn infections. Cultures were processed by the hospital's Central Laboratories/Microbiology using the CLSI database.

Biomarkers monitoring in hospital: Leukocyte, neutrophil, and lymphocyte counts were obtained using a SYSMEX hematology analyzer, and the neutrophil-to-lymphocyte ratio (NLR) was calculated from the blood count. Serum creatinine and C-reactive protein (c-RP) were measured using the COBAS 8000 series analyzer. Creatinine clearance was estimated from serum creatinine using the Cockcroft–Gault equation. All results from the hospital's Central Laboratory, including biochemical and culture results, were transmitted electronically to the ICUs each day. **Blood sampling for therapeutic drug monitoring:** Once steady state was reached, two blood samples were collected within each dosing interval, accounting for renal function and pharmacokinetic changes. Each sample contained 2–3 mL: the first was collected 4 hours after the antibiotic infusion began, and the second 1 hour before the next dose. MIC data for Gram-positive and Gram-negative isolates were also needed to evaluate PK/PD target attainment.

Therapeutic drug monitoring and individualized dosing: Serum concentrations of the four study antibiotics were measured twice weekly in 48 patients with major burns during almost 3 months using bioanalytical chromatographic methods developed and validated at the Clinical Pharmacokinetics Center, University of Sao Paulo, Sao Paulo, SP.[8–10] Cultures were collected from ICU patients with major burns and data was obtained weekly. Antibiotic doses were individualized according to each patient's renal function–dependent pharmacokinetics and the time needed to reach steady state after the loading dose, with the aim of improving effectiveness and reducing toxicity. **Antibiotic dose individualization based on renal function–related pharmacokinetic changes:** Noncompartmental analysis was based on blood collection of samples related to each antibiotic set: one collected 4 hours after the infusion began and the other 1 hour before the next infusion. Serum levels of four antibiotics were used to predict peak and trough concentrations and to estimate the elimination half-life ($t_{(1/2\beta)}$, h), based on elimination rate constant (kel, h^{-1}), total body clearance (CL_T, L/h), and apparent volume of distribution at steady state (Vd^{ss}, L).

DATA ANALYSIS

Data management and statistical software: Data were managed using Microsoft Excel for Office 365, version 2208, and analyzed using GraphPad Prism, version 10.0 (GraphPad Software Corporation, San Diego, CA, USA).

Statistical analysis and reporting: Results were expressed as medians and quartiles. Comparisons were performed using the Mann–Whitney (GraphPad Prism software, version 10.0), and p values below 0.05 were considered statistically significant.

RESULTS

Antibiotic management of infection and septic shock

ICU patients with burns and sepsis initially received vancomycin plus piperacillin/tazobactam, the hospital's recommended regimen for nosocomial infections. Daily doses were individualized according to ideal body weight (IBW) and renal function to attain therapeutic targets until cultures became negative.

Table 2 – ICU Septic burn patients undergoing antimicrobial therapy during septic shock

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ATB therapy – TDM twice a week	**Dose regimen recommended**	**Daily dose adjusted (mg/kg)**
Therapeutic ATB Serum Monitoring	**According to renal function**	**According to renal function**
• Vancomycin (IBW/dose normalize) **Loading dose 1g (1hr-infusion)** **Prescription: 7-10 days** up to negative cultures	1g q6h 1hr-infusion 1g q12h 1hr-infusion 1g q24h 1hr-infusion 1g q12h 1hr-infusion	57 mg/kg (ARC) 29 mg/kg (RFP) 14 mg/kg (AKI) 29 mg/kg (CRRT)
PK/PD target AUC^{ss}_{24}/MIC> 400-600	**Duration**: 33 days [D3-D36]	**PTA up to MIC 2mg/L**
• PTZ (IBW/dose normalize) **Loading dose 4.5g (4hrs-infusion)** **Prescription: 7-10 days** up to negative cultures	4.5g q6h 4hrs-infusion 4.5g q8h 3hrs-infusion 4.5g q24h 3hrs-infusion 4.5g q12h 3hrs-infusion	257 mg/kg (ARC) 193 mg/kg (RFP) 64 mg/kg (AKI) 129 mg/kg (CRRT)
PK/PD target 100%fΔT>MIC	**Duration**: 20 days [D3-D23]	**PTA up to MIC 16g/L**
• Meropenem (IBW/dose normalize) **Loading dose 1g (4hrs-infusion)** **Prescription: 7-10 days** up to negative cultures	1g q8h 4hrs-infusion 1g q8h 3hrs-infusion 1g q24h 3hrs-infusion 1g q12h 3hrs-infusion	42 mg/kg daily (ARC) 42 mg/kg daily (RFP) 14mg/kg daily (AKI) 28 mg/kg daily (CRRT)
PK/PD target 100%fΔT>MIC	**Duration**: 34 days [D24-D58]	**PTA up to MIC 2mg/L**
• Ciprofloxacin (IBW/dose normalize) **Loading dose 400mg (1hr-infusion)** **Prescription: 7-10 days** up to negative cultures	400mg q12h 1hr-infusion 400mg q12h 1hr-infusion 400mg q24h 1hr-infusion 400mg q24h 1hr-infusion	11.4 mg/kg daily (ARC) 11.4 mg/kg daily (RFP) 5.7 mg/kg daily (AKI-NA) 11.4 mg/kg daily (CRRT-NA)
PK/PD target AUC^{ss}_{24}/>125	**Duration**: 10 days [D59-D69]	**PTA up to MIC 4mg/L**
Abbreviations: IBW: ideal body weight; CLSI: Clinical Laboratory Standard Institute; TDM: therapeutic drug monitoring; PK/PD: pharmacokinetic-pharmacodynamic approach; PTA: Percent of target attainment; PTZ: piperacillin/tazobactam; ICU: Intensive care unit; NA: Not applied; ARC: augmented renal clearance; RFP: renal function preserved; AKI: acute renal injury; CRRT: continuous renal replacement therapy.		

Table 3 – Microbiology of Isolates from Cultures

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Coverage -PK/PD Target attained	**Microbiology (166 isolates)**	**MIC data**
Vancomycin [AUC^{ss}_{24}/MIC>400-600]	***Gram positive bacteria (81 isolates)***	**(CLSI)**
Therapy: D3-D36 (duration up to 33 days) Coverage up to MIC 2 mg/L (susceptible strains)	*Streptococcus spp (n=12)* *Staphylococcus aureus (n=34)* *Staphylococcus epidermidis (n=35)*	0.25-0.5 mg/L 0.5-1 mg/L 1-2 mg/L
Piperacillin [100%fΔT>MIC]	***Enterobacterales (18 isolates)***	**MIC**
Therapy: D3-D23 (duration up to 20 days) Coverage up to MIC 16 mg/L (susceptible strains)	*Escherichia coli (n=5)* *Enterobacter cloacae (n=4)* *Haemophylus influenzae (n=2)* *Proteus mirabilis (n=2)* *Klebsiella pneumoniae (n=4)* *Proteus mirabilis/R (n=1)*	4 mg/L 0.5 mg/L 8 mg/L 2 mg/L 4 mg/L >16 mg/L
Meropenem [100%fΔT>MIC]	***Non-Enterobacterales (48 isolates)***	**MIC**

Therapy: D24-D58 (duration up to 34 days) Coverage up to MIC 2 mg/L (susceptible strains) Coverage extended up to MIC 4-8 mg/L (Intermediate susceptibility)	*Klebsiella pneumoniae (n=18)* *Klebsiella pneumoniae (n=4)* *Pseudomonas aeruginosa (n=10)* *Pseudomonas aeruginosa (n=8)* *Pseudomonas aeruginosa (n=4)* *Stenotrophomonas maltophilia (n=2)* *Burkholderia cepacia complex (n=2)*	0.25-0.5 mg/L 1 mg/L 0.5 mg/L 1 mg/L 2 mg/L 2 mg/L 2 mg/L
Ciprofloxacin [AUC^{ss}_{24}/MIC> 125]	***Non-Enterobacterales (n=6 isolates)***	**MIC**
Therapy: D59-D69 (duration up to 10 days) Coverage up to MIC 2 mg/L (susceptible strains)	*Pseudomonas aeruginosa (n=5)* *Pseudomonas aeruginosa (n=1)*	0.5-1 mg/L 2 mg/L
Ciprofloxacin [AUC^{ss}_{24}/MIC> 125]	***Gram positive bacteria (n=13 isolates)***	**MIC**
Therapy: D59-D69 (duration up to 10 days) Coverage up to MIC 2mg/L (susceptible strains)	*Staphylococcus aureus (n=5)* *Staphylococcus epidermidis (n=6)* *Staphylococcus epidermidis (n=2)*	0.5-1 mg/L 1 mg/L 2 mg/L

Abbreviations: CLSI: Clinical Laboratory Standard Institute; MIC: minimum inhibitory concentration; GPB: Gram positive bacteria; GNB: Gram negative bacteria; ICU: Intensive care unit; IS: intermediate susceptibility; PTZ: Piperacillin/Tazobactam; R: resistant.

Table 4 - Pharmacokinetic-changes based on renal function preserved/RFP - Med (IQR)

Table 4 - Pharmacokinetic-changes based on renal function preserved/RFP - Med (IQR)

Vancomycin	**AKI**	**CRRT**	**ARC**	***RFP****
$t_{(1/2)\beta}$ ***(hrs.)***	15(11-25) *	10(8-12) *	3(2-4) *	8(6-10)
CL_T (L/hr)	1.2(0.8-1.6) *	1.8(1.2-2.3)	5.5(3.9-5.8) *	2.1(1.8-2.6)
Vd^{ss} (L)	26(12.7-57.7)	26(14-40)	23(11-34)	24(16-38)
Significance (P)	**p<0.05**	**p<0.05**	**p<0.05**	***Reference****
Piperacillin	**AKI**	**CRRT**	**ARC**	***RFP****
$t_{(1/2)\beta}$ ***(hrs.)***	6.0(4.0-8.0) *	4.0(2.5-6.0) *	1.5(1.0-2.4) *	**2.5(2.0-3.2)**
CL_T (L/hr)	1.3(1.0-1.5) *	6.5(3.4-6.8) *	16(13-18) *	**11(10-12)**
Vd^{ss} (L)	11(5.8-17.3) *	38(12-59)	35(19-62)	**40(29-55)**
Significance (P)	**p<0.05**	**p<0.05**	**p<0.05**	***Reference****
Meropenem	**AKI**	**CRRT**	**ARC**	***RFP****
$t_{(1/2)\beta}$ ***(hrs.)***	5.5(4.5-6.1) *	3.8(3.2-4.8) *	1.5(1.1-2.2) *	**2.5(2.0-3.2)**
CL_T (L/hr)	2.3(1.9-3.8) *	5.1(3.8-5.5) *	8.8(8.1-9.9)	**7.8(7.5-9.2)**
Vd^{ss} (L)	18(12-33)	28(18-38)	19(13-31)	**29(19-47)**
Significance (P)	**p<0.05**	**p<0.05**	**p<0.05**	***Reference****
Ciprofloxacin	**AKI**	**CRRT**	**ARC**	***RFP****
$t_{(1/2)\beta}$ ***(hrs.)***	NA	NA	2.5(2.1-3.5) *	**4.1(3.8-4.5)**
CL_T (L/hr)	NA	NA	33(28- 44) *	**21(18-25)**
Vd^{ss} (L)	NA	NA	119 (85-222)	**124(99-162)**
Significance (P)	-	-	**p<0.05**	***Reference****

Abbreviations: NA: Not Applied; MIC: minimum inhibitory concentration; GPB: gram-positive bacterial; GNB: gram-negative bacterial; PK/PD: pharmacodynamics based on pharmacokinetics; ICU: Intensive care unit; ARC: augmented renal clearance; RFP: renal function preserved (reference data subgroup); AKI: acute renal injury; CRRT: continuous renal replacement therapy; $t_{(1/2)\beta}$: biological half-life; CL_T: total body clearance; Vd^{ss}: volume of distribution at the steady state. **Statistics:** GraphPad Prism, GraphPad Prism, version 10.0, Medians (IQR).

Vancomycin Therapy: Vancomycin doses were adjusted to renal function to attain therapeutic targets until cultures became negative: 1 g q6h (57 mg/kg/day) in patients requiring vasopressors with augmented renal clearance (ARC); 1 g q12h (29 mg/kg/day) with preserved renal function (RFP) or acute kidney injury treated with continuous renal replacement therapy (CRRT); and 1 g q24h (14 mg/kg/day) for safety in acute kidney injury (AKI) before CRRT installed, **Table 2**.

Treatment continued for up to 33 days, from ICU-day 3 to day 36. Changes in vancomycin pharmacokinetics affected coverage of susceptible Gram-positive bacteria (MIC, 0.25–2 mg/L); **Table 3**. Doses were adjusted for

efficacy and safety during AKI, CRRT, and ARC, using preserved renal function (RFP) as the reference, **Table 4**.

- Biological half-life was prolonged more markedly in AKI than during CRRT and decreased substantially in ARC associated with vasopressor use.
- Total body clearance decreased more in AKI than during CRRT, whereas vasopressor use increased clearance in ARC.
- Volume of distribution remained unchanged relative to RFP across AKI, CRRT, and ARC, regardless of renal function.

Piperacillin/tazobactam Therapy: Doses were tailored to achieve therapeutic targets: 4.5 g q6h (257 mg/kg/day) in patients requiring vasopressors with ARC; 4.5 g q8h (193 mg/kg/day) with RFP; 4.5 g q12h (129 mg/kg/day) during CRRT; and 4.5 g q24h (64 mg/kg/day) for safety in AKI before CRRT installed, **Table 2**. Treatment lasted 20 days (ICU days 3–23). On day 23, several *Enterobacteriaceae* isolates were resistant to piperacillin/tazobactam but susceptible to meropenem, **Table 3**. Antibiotic de-escalation is routinely used to limit resistance during prolonged ICU stays. Piperacillin/tazobactam was therefore discontinued on day 23 and replaced with meropenem on day 24. Vancomycin continued through day 36 for Gram-positive coverage, and meropenem through day 58 for Gram-negative coverage, including *Enterobacteriaceae* and *non-Enterobacteriaceae*, GNB.

Pharmacokinetic changes in piperacillin affected coverage against susceptible *Enterobacteriaceae* (Gram-negative bacteria) with MICs up to 16 mg/L. Doses were adjusted for efficacy and safety during AKI, CRRT, and ARC, using preserved renal function (RFP) as the reference, **Table 4**.

- Biological half-life was prolonged more in AKI than during CRRT and decreased markedly in ARC associated with vasopressor use.
- Total body clearance decreased substantially more in AKI than during CRRT, whereas vasopressors increased clearance in ARC.
- Volume of distribution decreased in AKI, remaining unchanged during CRRT and ARC because of high interpatient variability due to differences on vasopressor requirements in those burn patients.

Meropenem Therapy: Meropenem doses were tailored to attain therapeutic targets and negative cultures. The regimen was 1 g q8h (42 mg/kg/day), infused over 4 hours in patients requiring vasopressors with augmented renal clearance (ARC), or over 3 hours with preserved renal function (RFP). Patients with acute kidney injury (AKI), with or without continuous renal replacement therapy (CRRT), received 1 g q24h (14 mg/kg/day) over 3 hours for safety and effectiveness. Treatment lasted 34 days (ICU days 24–58), **Table 2**. On day 58, cultures identified *P. aeruginosa* (non-*Enterobacteriaceae*; MIC >16 mg/L) resistant to meropenem or amikacin but susceptible to ciprofloxacin. Meropenem was discontinued that day and replaced with ciprofloxacin, **Table 3.**

Pharmacokinetic changes in meropenem affected coverage against susceptible Gram-negative strains with MICs up to 2 mg/L, with coverage extending to strains of intermediate susceptibility with MICs of 4–8 mg/L. Dose adjustments were required for safety during AKI, CRRT, and ARC, using preserved renal function (RFP) as reference, **Table 4**.

- Biological half-life was prolonged more in AKI than during CRRT installed and decreased markedly in ARC associated with vasopressor use.
- Total body clearance decreased more in AKI than during CRRT installed, whereas vasopressors increased in ARC.
- Volume of distribution remained unchanged across AKI, CRRT, and ARC because of high interpatient variability.

Ciprofloxacin Therapy: Ciprofloxacin 400 mg q12h (11.4 mg/kg/day), infused over 1 hour, was given to attain therapeutic targets in patients with preserved renal function (RFP) and those requiring vasopressors with augmented renal clearance (ARC) associated with acute kidney injury (AKI) during the last ICU episode of septic shock **(Table 2)**. Cultures became negative within 10 days of therapy in ICU. Treatment targeted ciprofloxacin-susceptible *Pseudomonas aeruginosa* (non-*Enterobacteriaceae* Gram-negative bacteria; MIC, 0.5–2 mg/L) and Gram-positive *Staphylococcus* spp. (MIC, 1–2 mg/L), **Table 3.**

Pharmacokinetic changes of ciprofloxacin were observed during the final phase of ICU therapy for multidrug-resistant bacteria resistant (MDRB) to vancomycin and meropenem. Vasopressor support was needed for only a few days, while these patients did not require management for AKI or CRRT, **Table 4.**

- Vasopressors shortened biological half-life during ARC, affecting total body clearance, 33 (28–44) L/h).
- Volume of distribution during ARC was comparable to the RFP reference data because of high interpatient variability.

In patients with ARC, ciprofloxacin achieved coverage against susceptible Gram-negative and Gram-positive strains with MICs up to 2 mg/L (Table 3). The 400 mg q12h regimen, infused over 1 hour, was therefore maintained because total body clearance remained unchanged during treatment, ensuring coverage against the isolated Gram-positive and *non-Enterobacteriaceae*, Gram-negative bacteria.

Inflammatory biomarkers and ICU mortality risk assessment

- Antimicrobial therapy ended on ICU Day 77. Median treatment duration was 67 days (IQR, 58–84).
- ICU discharge was assessed over a 90-day period, and hospital discharge five days later.

Survival at 30 and 90 days in ICU: Thirty days after ICU admission, 46 of 48 patients were alive. The two patients who died had burns covering more than 65% of total body surface area (TBSA); both deaths occurred during the third week after admission. Consequently, at ICU 90 days, 46 patients remained alive.

Daily biomarker monitoring: The neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) were measured daily to guide ICU management and predict mortality associated with clinical deterioration. Both biomarkers provided insight into patients' clinical status and response to treatment.

- CRP decreased from 95 (68–128) mg/L at ICU admission to 23 (15–35) mg/L at discharge.
- NLR decreased from an elevated admission value of 8.55 (6.16–12.42) to 2.54 (1.48–3.74) at discharge, comparable to the CLSI database reference range of 1.67–2.14.

Comparison of inflammatory responses: In our hospital's Burn Center, NLR is established as a faster and more reliable indicator of inflammatory changes during systemic inflammatory response syndrome (SIRS) than CRP. It was shown that a delayed response to the inflammatory state both at ICU admission and at discharge by

CRP after treatment had ended.

DISCUSSION

Bioanalytical chromatographic methods for application in ATB routine of ICU burn patients

Validated and published data related to selective and sensitive LC UV–VIS methods quantify antibiotics in serum and other fluids for therapeutic drug monitoring (TDM) and individualized vancomycin, piperacillin/tazobactam, meropenem, and ciprofloxacin dosing in critically ill adults and pediatrics with major burns and sepsis. With weekly blood sampling and cultures until isolates were undetectable, these measurements supported PK/PD target assessment, dose adjustments for infection resolution and safety, and better understanding of antibiotic pharmacokinetics and pharmacodynamics in this population.[8-10, 11-13]

The public tertiary hospital's 'Infection Committee' recommends vancomycin, a widely used gold-standard glycopeptide, for Gram-positive bacteria (GPB), and initial piperacillin/tazobactam for nosocomial Gram-negative bacteria (GNB), including susceptible *Enterobacteriaceae* (MICs ≤16 mg/L; CLSI database). Meropenem targets piperacillin/tazobactam-resistant *Enterobacteriaceae* and susceptible *P. aeruginosa* (non-*Enterobacteriaceae*), covering MICs 2 mg/L, with extended coverage at 4–8 mg/L attainment. Increased distribution volume, prolonged half-life, and reduced clearance may improve effectiveness and limit multidrug-resistant bacteria (MDRB); 3–4-hour rather than 0.5-hour meropenem infusions may further improve effectiveness. Short-infused meropenem carries greater neurotoxicity concerns, particularly in children with septic burns. Ciprofloxacin, a quinolone active against GNB and GPB, is useful against meropenem-resistant *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* during prolonged ICU treatment of septic burn patients.[14-16,17,18]

Inflammatory biomarkers predict ICU mortality

Silva Jr *et al.* recently investigated C-reactive protein (c-RP), neutrophil-to-lymphocyte ratio (NLR), procalcitonin (PCT), and the pro-inflammatory cytokine interleukin-6 (IL-6) as mortality predictors in ICU patients with major burns and sepsis.[19-21] Liu *et al.* previously confirmed that NLR combined with IL-6 predicts 28-day mortality in non-burn septic patients.[22] Qiu *et al.* linked day-3 postburn NLR to 90-day mortality in burns exceeding 30% TBSA; Setiawan *et al.* also identified high NLR as a mortality predictor in ICU patients with major burns.[23-24] High mortality risk and rapid renal function changes during systemic inflammatory response syndrome (SIRS) require accurate mortality predictors. Antibiotic TDM and renal function–dependent pharmacokinetic assessment guide dosing for efficacy, safety, and toxicity prevention. Protocols initiated in 2018, before the pandemic, compared serum CRP, PCT, and IL-6 individually and combined with daily NLR. After study completion, our tertiary-care public hospital's Burn ICU adopted NLR as a routine early mortality indicator in critically ill patients with extensive burns and septic shock, based on its highly reliable results. NLR was calculated from daily complete blood counts using SYSMEX-derived neutrophil and lymphocyte counts.

CONCLUSION

Therapeutic approach: Antibiotic selection was guided by the identified infections and antimicrobial susceptibility profiles.

Dose optimization: Doses were individualized using therapeutic drug monitoring, MIC data, and PK/PD target

attainment. Accounting for pharmacokinetic changes helped maintain therapeutic antibiotic exposure and supported treatment decisions.

Biomarker relevance: Daily NLR monitoring showed greater utility than C-reactive protein for clinical decision-making and may serve as an early indicator of mortality risk in the ICU.

Limitations:1) The study was an observational nature, single-center design, lack of a comparator arm and the absence of microbiological final confirmation of isolated strains in two non-survivor patients TBSA higher than 60%.

2) Prolonged hospitalization is expected for severe major burns in the ICU of the Reference Burn Center of Tertiary Public Hospital, Sao Paulo, SP.

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