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Combating bacterial resistance in ICU-pediatric burns under vasopressor support with vancomycin–meropenem, guided by PK/PD and neutrophil-to-lymphocyte ratio

Abstract

Background—Study objective: Meropenem and vancomycin are widely used to treat hospital-acquired Gram negative and Gram-positive infections in septic patients with systemic inflammatory response. In pediatric ICU patients with major burns, pharmacokinetic changes may reduce antimicrobial exposure and compromise outcomes, making serum antibiotic levels and culture monitoring essential, especially when early dose adjustment is needed. This study evaluated combined vancomycin-meropenem therapy in pediatric major burns with preserved or augmented renal clearance under vasopressor support. Treatment was adjusted in real time using culture results and serum drug monitoring to reach PK/PD targets for efficacy and safety during the first ICU episode of septic shock. The neutrophil-to-lymphocyte ratio (N/L-ratio), associated with mortality risk, was also used as a selected biomarker of systemic inflammatory response syndrome in septic pediatric burn patients.

Methods: Twenty-one pediatric septic burn patients (2–13 years; 12M/9F) treated with vancomycin meropenem were evaluated after empiric dosing normalized to ideal body weight. Then, patients were stratified by age in Group 1 (2-7 yrs) and Group 2 (8-13yrs). Vancomycin was initially administered in Set 1 at 40–60 mg/kg/day by 1-hour infusion and, when necessary, adjusted in Set 2 to achieve an AUC^{ss}_{0-24}/MIC target of >400–600. Meropenem (40 mg/kg q8h, 3-hour infusion) targeted 100%*f*ΔT>MIC. Drug Serum concentrations were routinely measured at predefined time points, pharmacokinetics was assessed using a one-compartment model, and the daily neutrophil-to-lymphocyte ratio (N/L-ratio) was applied to monitor systemic inflammation and ICU mortality risk. Drug effectiveness was assessed using antibiotic-specific PK/PD targets, negative culture results, and the microbiological profile of the isolated pathogens. The neutrophil-to-lymphocyte ratio (N/L-ratio) was also used as a supporting biomarker associated with ICU mortality risk in critically ill septic patients.

Results: Septic pediatric major burn patients 21 (12M/9F) with renal function preserved or augmented were distributed by age: 2-7 yrs. (Group 1, n=11), 8-13 yrs. (Group 2, n=10). Target was attained by vancomycin up to MIC 1 mg/L against Gram-positive strains only in 62% (13/21) patients receiving an empiric dose regimen (1015mg/kg q6h, 1hr infusion (Set 1). Individualized therapy was prescribed; then, the coverage was extended up to MIC 2 mg/L strains in 71% (15/21) patients in Set 2 to avoid MDRB. Vancomycin effectiveness occurs by clinical and microbiological cure of infection. Meropenem (40 mg/kg q8h, 3-hour infusion) showed age-dependent pharmacokinetic differences but achieved cure of infections caused by Gram-negative bacteria isolated. It eradicated susceptible strains up to MIC 2 mg/L, extended coverage to MIC 4 mg/L in all patients, and covered MIC 8 mg/L occurred in 55% of Group 1 (6/11) and 50% of Group 2 (5/10), helping prevent multidrug resistance bacterial, MDRB.

Conclusion: Pediatric septic burn patients receiving combined vancomycin–meropenem therapy for nosocomial infections requires frequent culture and serum drug-level monitoring to ensure PK/PD target attainment and eradication of Gram-positive and Gram-negative bacteria. No relevant between-group difference was observed in vancomycin pharmacokinetic changes, despite a twofold reduction in half-life associated with vasopressor use. In contrast, age-independent meropenem pharmacokinetic differences affected antimicrobial coverage across groups. Individualized antimicrobial coverage supported clinical and microbiological cures. The neutrophil-to-lymphocyte ratio (N/L-ratio) provided real-time assessment of systemic inflammation and helped guide decision-making in pediatric patients at the ICU Burn Center.

Keywords: pediatric septic burns, combined vancomycin–meropenem therapy, PK/PD-guided serum monitoring, culture-guided antimicrobial therapy, neutrophil-to-lymphocyte ratio, clinical decision-making

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Abbreviations: ARC, augmented renal clearance; AUC^{ss}_{0-24}, area under the curve; AUC^{ss}_{0-24}/MIC>400, area under the curve: MIC ratio higher than 400 up to 600 (Vancomycin target recommended); 100%*f*ΔT>MIC, time dose interval that free drug levels higher than

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MIC (meropenem target recommended); CSLI, clinical standard laboratory institute, database USA; GNB, gram-negative bacteria; GPB, gram-positive bacteria; GSA, global sepsis alliance; IBW, ideal body weight; ICU, intensive care unit; MDRB, multidrug resistance bacterial; MIC, minimum inhibitory concentration; MV, mechanical ventilation; N/L-ratio, neutrophils/lymphocytes-ratio; PD, pharmacodynamics; PICU, pediatric intensive care unit; PK, pharmacokinetics; PK/PD, pharmacokinetics/pharmacodynamics; PNM, pneumonia; PRF, Preserved renal clearance; PTA, probability of target attainment; SAPS*3, simplified acute physiology score III; ARC, augmented renal clearance; PRF, preserved renal clearance; 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

Burns are a major global burden to public health concerns, and the World Health Organization (WHO) estimates that burn injuries cause approximately 180,000 deaths each year in the African, South-East Asia and in Latin America & Caribe. Most burn deaths happen in low- and middle-income countries; children and women are at the highest risk and particularly vulnerable to burn injuries. Children under five were the most impacted by disability-adjusted life years (DALYs), which rank as the fifth most common cause of non-fatal childhood injury.[1] Furthermore, another global public health concern is septic shock, a life-threatening organ dysfunction caused by a dysregulated response to an infection. In high-risk patients, healthcare-associated bacterial infections contribute to increased mortality in ICUs. In this context, Surviving Sepsis Campaign, Global Sepsis Alliance, and World Health Organization emphasize the need for effective antimicrobial therapy and the prevention of multidrug-resistant bacteria.[2–5]

A series of studies has demonstrated an increase in the minimum inhibitory concentrations (MICs) of antibiotics used against nosocomial infections in septic ICU patients treated with glycopeptides and beta-lactams. It was observed that 80% of these patients failed to achieve therapeutic targets when treated with vancomycin (against susceptible Gram-positive strains) or meropenem (against Gram-negative bacteria). These data highlight the need to monitor serum levels of these drugs to identify pharmacokinetic alterations, guide dose adjustments based on pharmacokinetic/pharmacodynamic (PK/PD) parameters and implement prolonged meropenem infusion strategies to ensure therapeutic coverage.[6–12]

Prospective controlled studies using therapeutic drug monitoring (TDM) have compared antimicrobial efficacy based on serum levels in septic shock therapy. For meropenem, 3-hour extended infusion with serum monitoring can support coverage of intermediate-susceptibility strains up to MIC 4 mg/L, including *K. pneumoniae* and *P. aeruginosa*, in major septic burns requiring vasopressors. For vancomycin, serum levels help evaluate effectiveness, individualize dosing in real time, improve clinical outcomes, reduce bacterial resistance, shorten therapy, and lower hospital costs. However, these agents are still not routinely monitored in many ICUs.[7–9] Combining cultures, susceptibility testing, SIRS biomarkers, and serum-level–based PK/PD assessment can guide antimicrobial therapy. Adequate serum exposure supports microbiological cure and clinical recovery, whereas subtherapeutic levels increase the risk of treatment failure.[10,12]

Objective

This study assessed combined vancomycin–meropenem therapy in pediatric patients with major burns with preserved or augmented renal clearance as a function of vasopressor support during septic shock. Real-time treatment guidance used culture results and serum drug monitoring to achieve PK/PD targets for efficacy and safety during the first septic shock episode caused by nosocomial pathogens. The neutrophil-to-lymphocyte ratio (N/L-ratio) associated with ICU mortality risk was applied as a selected biomarker of systemic inflammatory response syndrome to support therapeutic decision-making in septic pediatric burn patients.

Methods

Study design, patient eligibility, and the vancomycin-meropenem combined therapy:

The clinical protocol was a prospective, open-label study. Ethical approval register Brazilian Platform was obtained by approval of the Ethical Committee of Hospital of Clinics, Medical School of University of Sao Paulo, Sao Paulo/SP, Brazil. No conflicts of interest to declare were obtained from all authors. The study was conducted from May 2017 to April 2020 after written informed consent from legally designated representatives. Eligible patients were 2–13 years old, admitted to the Intensive Care Burn Unit with severe thermal injury and sepsis diagnosed according to American Burn Association criteria for burn sepsis and infection.[13] Patients with intolerance to vancomycin or meropenem, or with renal impairment, were excluded. The study recommended antimicrobial treatment for suspected or documented Gram-positive and Gram-negative nosocomial infections in a tertiary public hospital.

Diagnosis of sepsis and early microbiological investigation of septic shock: On ICU Day 3, suspected septic shock prompted blood and site-specific cultures before starting antibiotics for nosocomial Gram-positive (*Streptococcus spp.*, *Staphylococcus spp.*) and Gram-negative (*Enterobacteriaceae*) strains. Daily N/L-ratio monitoring supported SIRS diagnosis in severe burn infection. Cultures were processed by the hospital Microbiology Laboratory. Twenty-one pediatric major burn patients (12M/9F) with preserved or augmented renal function and vasopressor support were included to assess culture-guided vancomycin–meropenem therapy using serum-level/MIC PK/PD tools. Patients were grouped by age: 2–7 years (Group 1, n=11, 6M/5F) and 8–13 years (Group 2, n=10, 6M/4F). Vancomycin was infused over 1 hour in Set 1 and adjusted in Set 2 when needed; meropenem was given by 3-hour infusion according to the ICU Burn Center protocol. Medical history, physical examination, cultures, susceptibility tests, and MIC values were recorded. Admission characteristics are shown in Table 1; creatinine clearance was estimated by Schwartz's method.[14]

Table 1 Demographic characteristics of Pediatric Septic Burns, clinical/laboratory data at Admission and during Therapeutic Drug Monitoring - ARC. Med (IQR).

Demographic, Clinical & Laboratorial data	Group 1(2-7yrs n=11)	Group 2 (8-13yrs n=10)	P
Gender (12M/11F)	6M/5F	6M/4F	NS
Age (yrs)	4(2-6)	10(9-12)	p<0.05

Citation: Santos SRCJ, Pires FR, Santos MJ, et al. Combating bacterial resistance in ICU-pediatric burns under vasopressor support with vancomycin–meropenem, guided by PK/PD and neutrophil-to-lymphocyte ratio. *Pharm Pharmacol Int J.* 2026;14(4):102–108. DOI: 10.15406/ppij.2026.14.00501

Table 1 Continued...

Ideal body weight (kg)	16(15-18)	40(39-45)	p<0.05
Height (cm)	101(91-109)	128(119-156)	p<0.05
Body surface area (m2)	0.68(0.61-0.91)	1.21(1.15-1.35)	p<0.05
Body mass index (kg/m2)	18.9(18.5-20.8)	23.0(22.3-24.4)	p<0.05
Admission data	**Group 1**	**Group 2**	**P**
TBSA (%)	23(18-39)	31(29-35)	NS
SAPS*3	55(52-60)	57(55-61)	NS
Inhalation injury	10/11	10/10	NS
Thermal burn	11/11	10/10	NS
Mechanical ventilation	10/11	10/10	NS
Vasopressors	10/11	10/10	NS
Biomarkers at Admission (CLSI database)	**Group 1**	**Group 2**	**P**
Leucocyte values: 4.5-13 (*1000 cells/ mm^3)	13.10(7.49-16.98)	17.1(14.22-19.21)	NS
Neutrophil values: 1.5-8.5 (*1000 cells/ mm^3)	10.99(8.56-14.34)	13.4(10.6-15.7)	NS
Lymphocyte values:1.7-6.5(*1000 cells/ mm^3)	1.90(1.86-2.05)	1.5(1.7-1.9)	NS
Neutrophils/Lymphocytes ratio (N/L ratio)	5.78(4.60-7.00)	8.93(6.24-8.26)	NS
c-Reactive protein: (lower than 5 mg/L)	90(41-128)	79(45-125)	NS
Serum creatinine (0.53-0.70 mg/dL)	0.25(0.21-0.31)	0.32(0.23-0.42)	NS
Creatinine clearance (2-13yrs: 100-150 ml/min)	240(167-265)	282(242-296)	NS
Biomarkers during TDM (Sets 1-2)	**Group 1**	**Group 2**	**P**
Neutrophils/Lymphocytes ratio Set 1	9.02 (6.92-10.75)	8.92 (4.75-12.85)	NS
Neutrophils/Lymphocytes ratio Set 2	7.69 (6.38-10.83)	7.56 (6.13-8.08)	NS
c-Reactive protein Set 1	141(88-147)	139(95-155)	NS
c-Reactive protein Set 2	168(122-199)	188(151-223)	NS
Creatinine clearance (ml/min) Set 1-ARC	170(153-182)	175(169-195)	NS
Creatinine clearance (ml/min) Set 2-PRF	141(123-162)	134(120-164)	NS

(USA); ICU, intensive care unit; NS, not significant difference; RFP, renal function preserved; SAPS*3 score, simplified acute physiology score III; TBSA, total body surface area; TDM, therapeutic drug monitoring

Statistics: Results related to pediatric patients investigated were expressed by medians (quartiles) [Med. (IQR 25-75)]; Statistical significance: P<0.05

Vancomycin therapy in pediatric septic burn patients – Target recommended: Vancomycin effectiveness was assessed using the empiric dose regimen, and early dose adjustment when needed to achieve the PK/PD target AUC^{ss}_{0-24}/MIC >400–600 recommended by Rybak et al., including pediatric major burn patients.[15]

Twenty-one patients were allocated by age to receive vancomycin 1-hour infusion, Set 1.

- Group 1: 2–7 years (n=11), 10–15 mg/kg every 6 hours (40–60 mg/kg/day).
- Group 2: 8–13 years (n=10), 10–15 mg/kg every 6 hours (40–60 mg/kg/day).

Vancomycin sampling, analysis, and drug effectiveness: Blood volumes (2.5 mL/sample) were collected 3 and 5 hours after the infusion began, and serum concentrations were measured by liquid chromatography.[16]

Treatment comparison data Set 1 *versus* Set 2: Vancomycin coverage in Set 1 was compared with Set 2 after individualized dose adjustment. Effectiveness was assessed using the PK/PD target AUC^{ss}_{0-24}/MIC >400-600 and Gram-positive culture results. Pharmacokinetics were evaluated using a one-compartment open model and non-compartmental analysis.

Meropenem therapy in pediatric septic burn patients and blood sampling: Twenty-one patients were allocated by age to receive meropenem by 3-hour extended-infusion to attain the target (100%$f\Delta$T>MIC), MIC: minimum inhibitory concentration reported previously by Abdul-Aziz et al., for beta lactam agents largely prescribed in ICU septic patients.[10] Patients allocated by age and dose regimen are described as follows:

- Group 1: 2–7 years (n=11), dose regimen 40mg/kg q8h (120 mg/kg daily).
- Group 2: 8–13 years (n=10), dose regimen 40mg/kg q8h (120 mg/kg daily).

Meropenem sampling, analysis, drug effectiveness: Blood volumes (2.5mL/sample) were collected 3 and 7 hours after the infusion began, and serum concentrations were measured by liquid chromatography.[17] Drug effectiveness was evaluated by PK/PD approach based on target 100%$f\Delta$T>MIC and serum levels, guided also by the microbiology of Gram-negative isolates from cultures. One compartment open model

was chosen to investigate pharmacokinetics, and non-compartmental data analysis was applied.

ICU mortality caused by septic shock in pediatric burn patients: Serum levels were routinely measured at predefined times, pharmacokinetics used a one-compartment model, and daily neutrophils/lymphocytes-ratio (N/L-ratio) monitored systemic inflammation for ICU mortality risk.

Effectiveness assessment: Drug effectiveness was assessed using antibiotic-specific PK/PD targets, negative culture results, and the microbiological profile of the isolated pathogens. The neutrophil-to lymphocyte ratio (N/L-ratio) was used as a supportive biomarker to estimate 28-day ICU mortality risk related to nosocomial infection in critically ill septic patients, as reported by Liu et al.[18] More recently, Setiawan et al, identified a high neutrophil-to-lymphocyte ratio (N/L-ratio) on ICU admission days 1, 2, and 3 as a predictor of mortality in patients with major burns.[19]

Biomarkers blood monitoring at Central Laboratory Division of hospital: Biomarker measurements in ICU patients: c-RP and serum creatinine were monitored by the COBAS Analyzer 8000 series, and creatinine clearance was estimated by Schwartz's method.[14] Neutrophil-to-lymphocyte ratio (NLR - blood count) was measured using a Hematological Analyzer (SYSMEX brand). All results of the tests carried out in the hospital's Central Laboratory that were sent to the ICUs via the network, including cultures results.

Statistical analysis

Individual and population data: Analyses included 21 pediatric major burn patients admitted to the ICU with a first septic shock episode and cure within 14–21 days. All received vancomycin, meropenem and achieved cure of nosocomial Gram-positive and Gram-negative infections. Data was analyzed using Office 365 Excel, version 2208, and GraphPad Prism, version 10.1.1. Nonparametric Mann–Whitney tests were applied to unpaired and paired data from the investigated patients, with statistical significance set at $p<0.05$.

Results – discussion

Analytical procedures for serum drug measurements: Vancomycin and meropenem serum levels were measured by HPLC–UV after protein precipitation with acetonitrile, using an LC10A liquid chromatograph (Shimadzu, Kyoto, Japan). Each assay used 0.2 mL of serum in duplicate. Eight-point calibration curves plus zero (0.2–100 mg/L) showed linearity ($r^2>0.99$), and daily curves accepted based on quality controls (high, medium low), when internal-controls error were below 10%. Drug serum levels were calculated by the internal standard method.[16,17]

Vancomycin coverage as a function of vasopressors based on TDM, PK-changes

Twenty-one pediatric septic burn patients with preserved or augmented renal function received vancomycin, with effectiveness assessed by AUC^{ss}_{0-24}/MIC >400–600.[15] Early vasopressor was associated with a twofold reduction in half-life, whereas clearance and volume of distribution did not differ from reference values reported in healthy volunteers. In Set 1, 62% (13/21) of burn patients reached MIC 1 mg/L with the empirical dose regimen recommended (10–15 mg/kg q6h, 1hr- infusion). After individualized therapy in Set 2 (20-40 mg/kg q6h) MIC 1 mg/L was reached for all patients supporting clinical and microbiological cure, while MIC 2 mg/L was extended to 71% (15/21) contributing to avoid bacterial resistance, Table 2. Previous studies in ICU pediatric burns and non-burns showed age-dependent PK-changes affecting early septic shock coverage under vasopressor requirements. The current dose regimen of approximately 10-15 mg/kg q6h, 1hr.-infusion for vancomycin empirical dose recommended to ICU septic pediatric burns with preserved renal function is inadequate for achieving target trough levels and desirable AUCs in those patients.[20–23]

Table 2 Dose regimens, PK-data, PK/PD coverage, Clinical Outcome, Med (IQR).

Vancomycin dose regimen, 1hr.-infusion		**Group 1**	**Group 2**	**P**
Empirical dose IBW normalized (mg/kg q6h)		10-15	10-15	NS
Adjusted dose IBW normalized (mg/kg q6h)		20-38	20-40	NS
PK- parameters – Vancomycin (RFP)		**Group 1 - ARC**	**Group 2 - ARC**	**P**
$t_{(1/2)\beta}$: [Reference: 3.7-5.3 hrs]		2.9(2.6-3.4)	3.0(2.6-3.3)	NS
Vd^{ss}: [Reference: 0.45-0.65 L/kg]		0.49(0.40-0.60)	0.44(0.36-0.54)	NS
CL_T: [Reference: 1.2-1.7 mL/min*kg]		1.70(1.53-1.94)	1.90(1.59-2.28)	NS
PK/PD Coverage Vancomycin (GPB)		**Group 1 (Set 1/Set 2)**	**Group 2 (Set1/Set 2)**	**P**
MIC 0.5 mg/L Susceptible	21/21 (100%)	11/11 vs 11/11	10/10 vs 10/10	NS
MIC 1.0 mg/L Susceptible	13/21 (62%)	5/11 vs 11/11	8/10 vs 10/10	p<0.05
MIC 2.0 mg/L	15/21 (71%)	0/11 vs 7/11	0/10 vs 8/10	p<0.05
Meropenem dose regimen, 3hrs. -infusion		**Group 1**	**Group 2**	**P**
Recommended dose regimen (mg/kg q8h)		38-40	35-42	NS
Dose regimen maintained (mg/kg daily)		114-120	105-126	NS
PK- parameters – Meropenem (RFP)		**Group 1 - ARC**	**Group 2 - ARC**	**P**
$t_{(1/2)\beta}$: [Reference: 3.2-4.2 hrs]		2.0(1.9-2.4)	2.5(2.2-2.6)	NS
Vd^{ss}: [Reference: 0.49-0.83 L/kg]		1.05(0.95-1.25)	0.88(0.82-0.95)	NS
CL_T: [Reference: 1.71- 2.14 mL/min*kg]		0.90(0.85-1.08)	1.20(0.99-1.77)	NS
PK/PD Coverage (GNB)		**Group 1 (Set1/Set 2)**	**Group 2 (Set1/Set 2)**	**P**
MIC 2.0 mg/L Susceptible	21/21 (100%)	11/11	10/10	NS
MIC 4.0 mg/L Intermediate	21/21 (100%)	11/11 (100%)	10/10 (100%)	NS
MIC 8.0 mg/L Intermediate	11/21 (52%)	6/11 (55%)	5/10 (50%)	NS
ICU Clinical outcome - Pediatric Burns		**Group 1**	**Group 2**	**P**

Citation: Santos SRCJ, Pires FR, Santos MJ, et al. Combating bacterial resistance in ICU-pediatric burns under vasopressor support with vancomycin–meropenem, guided by PK/PD and neutrophil-to-lymphocyte ratio. *Pharm Pharmacol Int J.* 2026;14(4):102–108. DOI: 10.15406/ppij.2026.14.00501

Table 2 Continued...

Creatinine clearance (2-13yrs: 100-150 ml/min)		105(97-125)	102(99-129)	NS
Neutrophils/Lymphocytes ratio		3.58 (2.38-3.98)	4.24 (3.13-4.72)	NS
ICU period (days)		28(18-45)	36(29-60)	NS
Hospitalization (total days)		34(26-56)	45(42-63)	NS
Survivals	21/21 (100%)	11/11 (100%)	10/10 (100%)	NS

Abbreviations: ARC, augmented renal clearance (vasopressors); RFP, renal function preserved; CLSI, Clinical Laboratory Standard Institute (USA); GNB, gram negative bacteria; GPB, gram positive bacteria; IBW, ideal body weight; ICU, intensive care unit; IS, intermediate susceptibility; MIC, minimum inhibitory concentration; NS, not significant difference; PK, pharmacokinetics/parameters: ($t_{(1/2)\beta}$, biological half-life; Vd^{ss}, volume of distribution at the steady state; CLT, total body clearance; PK/PD, pharmacodynamics based on pharmacokinetics; TDM, therapeutic drug monitoring.

Statistics: Results related to pediatric patients investigated were expressed by medians (quartiles) [Med. (IQR 25-75)]; Statistical significance: $P<0.05$

Thus, an increase on daily doses 20–40 mg/kg q6h done by intermittent 1hr.-infusion are needed to achieve the desired targets AUC^{ss}_{0-24}/MIC >400–600 in terms of drug effectiveness/safety related to pharmacodynamic goals, and to avoid MDR strains. Pharmacokinetics of vancomycin was altered in pediatric burn patients, especially in augmented renal clearance (ARC) by vasopressor requirements. Then, optimized dosing given every 6 hours can justify the biological half-life shorter than expected in ICU septic pediatric burns of both groups of our study.

More recently, subtherapeutic serum levels of vancomycin by 1 or 2 and 3 hrs.-infusion in pediatric septic burn patients were described by Jabar & Mustafa at dose 20 mg/kg q6h. Consequently, it was suggested by authors that vancomycin continuous infusion has been practiced in hospital settings for pediatric patients, once the recommended doses are insufficient to achieve therapeutic concentrations in pediatric patients.[24] In addition, subject of Junker et al, study was to describe the use of vancomycin by continuous infusion in a Free-standing Children´s Hospital, including safety, dosing and whether patients are achieving therapeutic target AUC^{ss}_{0-24}/MIC >400–600. Lower doses of vancomycin were required to reach the target recommended when administered via continuous infusion as compared to intermittent infusion, with an average reduction in total daily dose of approximately 20%. There were no concerns about safety signals with use of continuous infusion vancomycin in this study.[25]

Meropenem coverage as a function of vasopressors based on TDM, PK-changes

Twenty-one pediatric burn patients with septic shock received meropenem 40 mg/kg q8h by 3-hour infusion, stratified as G1 (2–7 years, n=11) and G2 (8–13 years, n=10), targeting 100%$f\Delta T>$MIC. All achieved clinical and microbiological cure; Gram-negative isolates up to MIC 2 mg/L eradicated, with target attainment extended up to MIC 4 mg/L in all patients but reduced to 55% (11/21) at MIC 8 mg/L without significant group difference. Early vasopressor requirement in pediatric septic burn patients justify the twofold increase in volume of distribution and a proportional decrease in biological half-life and in total body clearance of both pediatric groups by comparison with reference adult population, Table 2.

Several study protocols were conducted previously in septic patients admitted to the ICU without vasopressor requirements, it was demonstrated that relevant PK-changes occurred by meropenem 3hrs.-infusion compared with intermittent 0.5hr.-infusion associated with an expressive increase on volume of distribution and a similar prolongation of elimination half-life, leading to reduced meropenem clearance, which accounts for the maintenance of effective serum levels.[6,8–10,26–30]

It is important to highlight that previous study was conducted in ICU pediatric burns (n=17, 10M/7F, 4.9(3.3-5.9 yrs) with preserved renal function (Clcr: 100-130 mL/min, n=5) or augmented renal clearance (Clcr: 172-273 mL/min, n=12) by vasopressor requirements received meropenem 40mg/kg q8h by 3hrs-infusion. PK-changes impacted positively target attainment reached as a function of increases on volume of distribution with prolongation of biological half-life. In addition, total body clearance was poorly described for carbapenem agents, and few PK-data were found in critically ill pediatric patients related to meropenem. A first order kinetic disposition may occur at therapeutic dose regimen for carbapenems in pediatric patients with normal renal function since they are excreted by glomerular filtration and tubular secretion in the urine.[22]

Considering pediatric burn patients G1-G2 population investigated in our study, changes in pharmacokinetics were related to volume of distribution increased by twice proportionally to decreases on biological half-life and total body clearance. Target attainment in pediatric burns was reached by the empiric dose recommended with cure of infection for all patients. Then, optimization of therapy was reached by maximization of drug efficacy and neurotoxicity reduced of this agent in critically ill pediatric burn ICU patients.

Clinical cure and microbiological outcome: Weekly serum monitoring, when indicated, confirmed treatment efficacy. Combined vancomycin–meropenem therapy produced rapid clinical recovery and negative cultures in all patients. During the first ICU septic shock episode, sixty-four isolates identified from four infection sites: thirty-one vancomycin-susceptible Gram-positive bacteria and thirty-three meropenem-susceptible Gram-negative *Enterobacteriaceae*, distributed by infection site as follows.

Isolates of GPB and GNB (n=64) from G1-G2 ICU pediatric patients at first septic shock:

- **Gram-positive bacteria (n=31):** bloodstream infection, 48.4% (n=15); pneumonia, 12.9% (n=4); wound/bone infection, 32.3% (n=10); and urine, 6.5% (n=2).
- **Gram-negative bacteria (n=33):** bloodstream infection, 48.5% (n=16); pneumonia, 12.1% (n=4); wound/bone infection, 33.3% (n=11); and urine, 6.1% (n=2).

Gram-positive bacteria isolated from ICU pediatric burns: *Streptococcus* accounted for 12.9% (n=4): *S. pneumoniae* (n=1; MIC 0.25 mg/L), *Streptococcus* β-hemolytic (n=2; MIC 0.25 mg/L), and *S. agalactiae* (n=1; MIC 0.5 mg/L). *Staphylococcus spp* represented 87.1% (n=27), mainly *S. epidermidis* (38.7%; n=12; MIC 2 mg/L) and *S. aureus* (48.4%; n=15; MIC 0.5–1.0 mg/L).

Gram-negative bacteria isolated from ICU pediatric burns: *Enterobacteriaceae* totaled 33 isolates, mostly with MIC 0.25 mg/L:

E. coli (n=3; 9.1%), *E. cloacae* (n=7; 21.2%), *H. influenzae* (n=5; 15.2%), and *P. mirabilis* (n=8; 24.2%). *K. pneumoniae* was most frequent (n=10; 30.3%), with MIC 0.25–0.5 mg/L in eight isolates and 2.0 mg/L in two isolates. Consequently, pathogens isolated were eradicated by clinical and microbiological cures.

ICU mortality risk in pediatric burn patients during septic shock: Drug effectiveness assessed antibiotic-specific PK/PD targets was based in frequent serum levels and cultures monitoring. Effects of a potent inflammatory biomarker Neutrophil-to-Lymphocyte ratio was described initially by Liu et al., alone or combined with Interleukin-6 in predicting 28-Day mortality in ICU critically patients with septic shocks during the systemic inflammatory response syndrome.[18] Additionally, it was proposed by Setiawan et al., that high neutrophil-lymphocyte ratio could be a good predictor of mortality in major burns.[19] Consequently, at the last six years, neutrophil-to-lymphocyte ratio (N/L-ratio) was inflammatory biomarker considered a good predictor of mortality with daily monitoring related to ICU-patients that is applied routinely as a supportive biomarker to estimate ICU mortality risk related to nosocomial infection in critically ill septic burn major adult/pediatric patients of the ICU Burn Center in a tertiary public hospital.

Conclusion

Monitoring and target attainment: Frequent culture and serum drug-level monitoring were needed to achieve PK/PD targets and eradicate Gram-positive and Gram-negative bacteria in pediatric septic burn patients treated with vancomycin–meropenem.

Pharmacokinetic findings: Vancomycin showed no relevant between-group PK differences, despite a vasopressor-associated twofold half-life reduction, whereas meropenem PK changes affected coverage across groups.

Clinical relevance: Individualized therapy supported clinical and microbiological cure, while the N/L-ratio enabled real-time assessment of systemic inflammation and ICU decision-making.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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