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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. 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 used 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 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 against MIC 2 mg/L strains in 71% (15/21) patients in Set 2. Vancomycin effectiveness occurs by clinical and microbiological cure of infections. Meropenem (40 mg/kg q8h, 3-hour infusion) showed age-dependent pharmacokinetic differences but achieved rapid clinical cure in all Gram-negative infections. 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%fΔT>MIC, time dose interval that free drug levels higher than 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; 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

Septic shock is potentially fatal organ dysfunction caused by a dysregulated response to infection.[1] In high-risk pediatric patients, nosocomial bacterial infections, often linked to influenza or SARS-CoV2, increase mortality. The Surviving Sepsis Campaign, Global Sepsis Alliance, and World Health Organization stress the need for effective antimicrobial therapy and prevention of multidrug-resistant bacteria.[1–5]

Recent studies have shown increasing minimum inhibitory concentrations (MICs). In ICU patients treated with beta-lactams, nearly 80% did not reach therapeutic targets for susceptible Gram-positive strains managed with vancomycin or Gram-negative bacteria managed with meropenem. These data support serum drug-level monitoring to identify pharmacokinetic changes, guide PK/PD-based dose adjustment, and support extended meropenem infusion strategies.[6–11]

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.[7] However, these agents are still not routinely monitored in many ICUs.[8,9] 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 sub therapeutic levels increase the risk of treatment failure.[10,12]

Objective

This study assessed combined vancomycin–meropenem therapy in pediatric patients with major burns, preserved or augmented renal clearance, and vasopressor support. 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), a marker associated with mortality risk, was also used 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 burns, clinical/laboratorial data, dose regimens PK-data, PK/PD coverage, Clinical Outcome, 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
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
SAPS3 >57	55(52-60)	57(55-61)	NS

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Table 1 Continued...

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 ICU Admission (CLSI database)	**Group 1**	**Group 2**	**P**
Reference: Leucocyte values: 4.5-13 (*1000 cells/ mm3)	13.10(7.49-16.98)	17.1(14.22-19.21)	NS
Reference: Neutrophil values: 1.5-8.5 (*1000 cells/ mm3)	10.99(8.56-14.34)	13.4(10.6-15.7)	NS
Reference: Lymphocyte values:1.7-6.5(*1000 cells/ mm3)	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
Reference: c-Reactive protein: (lower than 5mg/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 at Therapeutic Drug monitoring	**Group 1**	**Group 2**	**P**
Neutrophils/Lymphocytes ratio (N/L ratio) TDM1	9.02 (6.92-10.75)	8.92 (4.75-12.85)	NS
Neutrophils/Lymphocytes ratio (N/L ratio) TDM2	7.69 (6.38-10.83)	7.56 (6.13-8.08)	NS
c-Reactive protein TDM1	141(88-147)	139(95-155)	NS
c-Reactive protein TDM2	168(122-199)	188(151-223)	NS
Creatinine clearance (ml/min) TDM1	170(153-182)	175(169-195)	NS
Creatinine clearance (ml/min) TDM2	141(123-162)	134(120-164)	NS
Vancomycin dose regimen 1hr.-infusion	**Group 1**	**Group 2**	**P**
Empirical dose regimen IBW normalized (mg/kg q6h)	10-15	10-15	NS
Adjusted dose regimen IBW normalized (mg/kg q6h)	20-38	20-40	NS
PK- parameters – Vancomycin [Reference values]	**Group 1**	**Group 2**	**P**
$t_{(1/2)\beta}$: [Reference healthy volunteers: 3.7-5.3 hrs]	2.9(2.6-3.4)	3.0(2.6-3.3)	NS
Vd^{ss}: [Reference healthy volunteers: 0.45-0.65 L/kg]	0.49(0.40-0.60)	0.44(0.36-0.54)	NS
CLT: [Reference healthy volunteers: 1.2-1.7 mL/min*kg]	1.70(1.53-1.94)	1.90(1.59-2.28)	NS
Vancomycin PK/PD target attained against GPB	**Group 1**	**Group 2**	**P**
Coverage MIC 0.5 mg/L (empirical dose vs adjusted) 21/21(100%)	11/11 vs 11/11	10/10 vs 10/10	NS
Coverage MIC 1.0 mg/L (empirical dose vs adjusted) 13/21 (62%)	5/11 vs 11/11	8/10 vs 10/10	p<0.05
Coverage MIC 2.0 mg/L (empirical dose vs adjusted) 15/21 (71%)	0/11 vs 7/11	0/10 vs 8/10	p<0.05
Meropenem dose regimen 3hrs. Infusion [RFP/ARC]	**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 3hrs. infusion	Group 1	Group 2	P
$t_{(1/2)\beta}$: [Reference healthy volunteers: 3.7-5.3 hrs]	2.0(1.9-2.4)	2.5(2.2-2.6)	NS
Vd^{ss}: [Reference healthy volunteers 0.13-0.15 L/kg]	1.05 (0.95-1.25)	0.88 (0.82-0.95)	NS
CLT: [Ref. healthy volunteers 0.17-0.19 mL/min*kg]	0.99(0.85-1.08).	1.2 (0.99-1.77)	NS
Meropenem PK/PD target attained GNB	**Group 1**	**Group 2**	**P**
Coverage MIC 2.0 mg/L susceptible 21/21 (100%)	11/11	10/10	NS
Coverage MIC 4.0 mg/L intermediate susceptible 21/21 (100%)	11/11	10/10	NS
Coverage MIC 8.0 mg/L intermediate susceptible 11/21 (52%)	6/11 (55%)	5/10 (50%)	NS
Clinical outcome	**Group 1**	**Group 2**	**P**
ICU period (days)	28(18-45)	36(29-60)	NS
Hospitalization (total days)	34(26-56)	45(42-63)	NS
Survivals	11/11	10/10	NS

Abbreviations: ARC, augmented renal clearance (vasopressors); CLSI, clinical laboratory standard institute (USA); GNB, gram negative bacteria; GPB, gram positive bacteria; IBW, ideal body weight; ICU, intensive care unit; 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; CL_T, total body clearance; PK/PD, pharmacodynamics based on pharmacokinetics; 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: P0.05.

Vancomycin therapy in pediatric septic burn patients and blood sampling: 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*ΔT>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*ΔT>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).[16] 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 were accepted based on quality controls (high, medium low), when internal-controls error were below 10%. Patient concentrations were calculated by the internal standard method.

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

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] Previous burn studies showed age-dependent PK changes affecting early septic shock coverage under vasopressors.[20,21] In Set 1, 62% (13/21) reached MIC 1 mg/L with 10–15 mg/kg q6h; after individualized dosing in Set 2, all reached MIC 1 mg/L and 71% (15/21) reached MIC 2 mg/L, supporting rapid clinical and microbiological cure. Early vasopressor use was mainly associated with a twofold reduction in half-life, whereas clearance and volume of distribution did not differ from reference values reported in healthy volunteers, Table 1.[22]

Meropenem as a function of vasopressors based on TDM, PK-changes and Coverage:

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*ΔT>MIC. All achieved clinical and microbiological cure; Gram-negative isolates were eradicated up to MIC 2 mg/L, with target attainment at MIC 4 mg/L in all patients and MIC 8 mg/L in 55% (11/21), without significant group difference, Table 1. Early vasopressor use may explain the marked increases in clearance (6–7-fold) and volume of distribution (6–8-fold), while half-life increased threefold versus healthy volunteers, Table 1.[23] Earlier burn studies without vasopressors also showed that extended meropenem infusion is affected mainly by increased volume of distribution and prolonged elimination half-life.[6,8–10,24–26]

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, 64 isolates were identified from four infection sites: 31 vancomycin-susceptible Gram-positive bacteria and 33 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.

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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