Research Article
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Vancomycin and meropenem serum monitoring for target attainment by PK/PD approach as an effective tool in the battle against nosocomial pathogens in septic pediatric burn patients

Abstract

Introduction: Optimizing antimicrobial prescription for severe infections is a challenge in Intensive Care Units for critically ill patients to improve clinical outcome. Aim of the study was to evaluate drug effectiveness in septic pediatric burn patients undergoing combined therapy with vancomycin and meropenem.

Methods: Pediatric septic burn patients receiving vancomycin and meropenem combined therapy were included (7F/10M). Characteristics of patient's population, expressed by minimum/maximum values were: 3.1/11.2 yrs; 12/44 kg; 11/75% TBSA; SCr: 0.15/0.47 mg/dL; 10/36 days in ICU, 21/45 days hospitalization for 15 patients. Drug serum measurements were done by liquid chromatography. Pharmacokinetic changes were investigated. Pharmacokinetic-pharmacodynamics (PK/PD) target recommended for vancomycin is $AUC^{ss}_{0\text{-}24}$/MIC>400; while the PK/PD meropenem target considered is 100%*f*ΔT>MIC.

Results: Target attainment (PTA) MIC 1 mg/L gram-positive strains was reached in 48% with vancomycin Set 1 empiric dose 40-60mg/kg daily 1hr- intermittent infusion (10-15mg/kg q6h); then, optimization of drug therapy was done Set 2 by dose adjustment patient bedside up to 102 mg/kg/day with cure for all patients. Meropenem effectiveness was reached against gram-negative susceptible strains up to MIC 2 mg/L and coverage was extended up to MIC 4 mg/L against strains of intermediate susceptibility due to the extended 3hrs-infusion. Then, meropenem coverage was guaranteed for all patients up to MIC 4 mg/L by recommended dose for ICU pediatric septic patients (40mg/kg q8h) after the extended infusion, to avoid mutant's selection of *Klebsiella pneumoniae* or *Pseudomonas aeruginosa,* intermediate susceptibility.

Conclusion: A combined therapy with vancomycin - meropenem improves the effectiveness against infections in burn pediatric patients. Vancomycin dose adjustments must be done in real time by PK/PD approach based on serum levels permitting an earlier intervention of ICU Medical Team to reach the desired clinical outcome against nosocomial infections in septic pediatric burn patients and contributes also to avoid the bacterial resistance.

Keywords: vancomycin-meropenem combined therapy, ICU septic pediatric burns, PK/PD approach, target attainment, clinical and microbiological cure, desired outcome

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Introduction

Burn-related injuries are the main causes of morbidity and mortality in pediatrics and burning are one of the three main causes of injury-related to death as a consequence of the disruption of the normal skin barrier, immunocompromised status, and prolonged hospitalization. Burns make patients easy targets for microbial colonization and infections are responsible for poorer prognosis in these patients.[1] Then, appropriate antimicrobial therapy has proved to be quite important for the treatment of critically ill patients with suspicious or clinical and laboratorial documented sepsis. Long-term outcome of children surviving massive burns related to the major advances in treatment of burn injuries in the last 35 years have made it possible to save the lives of children with massive burns.[2] Then, appropriate antimicrobial therapy has proved to be quite important for the treatment of critically ill patients with blood stream, severe infections, and clinical suspicious or laboratorial documented sepsis. Over the last 50 years, vancomycin has remained the drug of choice for the treatment of nosocomial Gram-positive infections, including methicillin-resistant *Staphylococcus spp*, MRSA or MRSE.[3] Therefore, vancomycin plasma monitoring is quite important to improve the outcome and, consequently, to avoid multi-resistant bacterial infections in pediatric critically ill patients.[4] Considering vancomycin for control of nosocomial infections caused by MRSA/MRSE, the empirical pediatric dosage regimen for patients without renal dysfunction is 40–60 mg/kg/day, and the trough concentration at the steady-state was a former guide for subsequent dosage adjustment. However, data indicate that dose requirements higher than 2g daily are recommended to adults to attain the 10–15 mg/mL target trough concentrations.[5,6] Recently, data reported in pediatric burn patients with normal renal function recommend 90 mg/kg as a loading dose, since the biological half-life is shorter than would be expected as a consequence of the reduction of volume of distribution at the steady state and plasma clearance decreased or even increased in the hypermetabolic phase after thermal accident that occur in pediatric burn patients in comparison to burn adults.[7] Current recommended dosing of vancomycin for pediatric

patients with invasive methicillin-resistant *Staphylococcus aureus* MRSA infection at the lowest recommended dose resulted in sub-therapeutical blood levels; therefore, bacterium resistance appears, and a poor outcome is expected.[8] Few studies were found concerning the empiric vancomycin dosage recommendations in burn patients related to the target attainment recommended to critically ill patients; consequently, vancomycin dose adjustment based on the predictive index estimated by pharmacokinetic-pharmacodynamics (PK/PD) analysis must improve the clinical outcome in burn adult patients and also in pediatrics even after massive burns.[6,7,9] Recently, a blood stream infection mortality risk score was available as an excellent tool to predict the prognosis of patients with gram-negative based on acute severity of illness, the primary source of infection and major host comorbidities. Since over half million individuals developed gram-negative blood stream infections annually in the USA, and 75,000 deaths occurred; then, appropriate empirical antimicrobial therapy is critical to improve the outcome, and the ability to predict the prognosis of patients with gram-negative blood stream infections have a significant impact on the morbidity and mortality of critically ill patients.[10] Consequently, vancomycin plus a carbapenem agent seems to be a rational association for patients in sepsis caused by gram-positive and also gram-negative/resistant strains to beta-lactams as piperacillin-tazobactam, ampicyllin-sulbactam or even to cephalosporins third/forty generations. Then, meropenem is recommended for pediatrics, based on its reduced neurotoxicity by comparison with imipenem, to be prescribed to patients with blood stream infections caused by beta-lactamase producer's gram-negative pathogen susceptible.

Considering the treatment of nosocomial infections caused by gram-negative strains susceptible to meropenem, the empirical pediatric dosage regimen for a patient with normal renal function usually starts with 40mg/kg tid.[11] Drug effectiveness of the carbapenem agent against isolated strains is based on the fraction of the time dose interval that the free drug serum levels at the steady-state is maintained above the minimum inhibitory concentration (MIC 90) of colonies in blood cultures. Then, the bactericidal free drug levels in the patient (host) must be attained above the MIC at the time dose interval to guarantee meropenem effectiveness. Consequently, the predictive index for meropenem effectiveness (100%fΔT>MIC) recommended by Abdul-Aziz (2015) will be a guide based on serum levels after extended 3hr-infusion.[12] However, few data reported in burns indicate that dose requirements to attain the therapeutic target in pediatrics differs those recommended to adults. Therefore, optimizing antimicrobial prescription is required to improve clinical outcome from severe infections and to reduce the development of antimicrobial resistance, once it is well known that the pharmacokinetics is altered in critically ill patients, including burns. Additionally, it was reported in those patients, that in general, drug kinetic disposition changes in a different way in adults compared to pediatric patients, and also, few evidence are available on population dosing and dose adjustment requirements in burns.[7,13] It is well known that the thermal injury affects negatively the pharmacokinetics of antimicrobial agents, making it difficult to establish dose-regimen guidelines in critically ill pediatric burns. Then, drug serum monitoring and PK/PD approach must be applied, since the predictive index of drug effectiveness must be estimated to guide the physician concerning effectiveness during the antimicrobial therapy.[14]

Subject: The aim of the present study was to evaluate if the PK/PD target was attained at the empirical vancomycin–meropenem dose regimens in a combined therapy for septic burn pediatric patients in the Intensive Care Burn Unit by applying the PK/PD approach based on serum levels for the treatment septic shock caused by nosocomial pathogens.

Methods

Study design, patient eligibility and the antimicrobial therapy

The clinical protocol was a prospective, open-label study. Ethical approval register CAAE 07525118.3.0000.0068 was obtained by 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 2018 to December 2019, and informed written consent was obtained from all legally designated patient representatives. Pediatric patients from the Intensive Care Burn Unit higher than 2 years up to 11 years old, presenting severe thermal injury and a sepsis diagnosis by the "American Burn Association consensus conference to define sepsis and infection in burns" in clinical evaluation and laboratorial data were eligible for inclusion.[15] On the other hand, patients with vancomycin or meropenem intolerance or renal impairment 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 meropenem combined therapy were prescribed at dose regimen recommended for pediatric patients with renal function preserved. Patients received the antimicrobials prescribed as empiric daily dose and the initial dose regimen was given 10–15 mg/kg q6h, equivalent to 40-60 mg/kg daily, by one hour pump infusion for vancomycin. In addition, meropenem were administered systemically by pump 3 hrs.-infusion at the dose regimen 40 mg/kg q8h, according to the institutional protocol. Complete medical histories, physical examinations were obtained for each enrolled patient; laboratory data included strains documented in blood cultures and susceptibility testing done to obtain the minimum inhibitory concentration (MIC 90) for each antimicrobial agent against the pathogen isolated. Individual demographic and clinical characteristics at admission in the Intensive Care Burn Unit (ICBU) are shown in Table 1. Creatinine clearance was estimated by Schwartz's method, population laboratory data are shown in Table 1.[16]

Blood sampling

A set of blood samples was obtained by collection via a venous catheter at a steady-state level. Serial blood samples (2 mL/each) were collected at the 3nd, 5th, 6th of drug administration, for dosing regimen every 8 hours. Three blood samples (2ml/each) were drawn from each patient from a venous catheter into BD Gel vacuum tubes. Blood samples collected from each patient' set were centrifuged at 2800 g for 20 minutes; then, transferred to labeled polyethylene vials and analyzed on the same day, or yet stored at -35ºC in a freezer until drug assay.

Analytical procedure for serum drug measurements

Drugs in blood samples were analyzed after purification procedure by the precipitation of serum proteins with acetonitrile for vancomycin and meropenem. Then, purified extracts of vancomycin and meropenem were analyzed by a liquid chromatograph LC10A, Shimadzu Corporation (Kyoto, Japan) as reported previously by Lopez *et al*. for vancomycin and by Santos *et al.* for meropenem.[13,17] Only 0.2 mL of each sample was required for drug serum measurements, replicates n=2, using high performance liquid chromatography/ ultraviolet detection (HPLC–UV) according to the simple and accurate bioanalytical methods with adequate linearity and sensitivity. The coefficient of determination (r2>0.99) for the drug assay over the

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standard curve concentrations based on eight serum calibrators (C1-C8: 0.2–100 mg/L) plus the zero (C0) were acceptable; additionally internal quality controls were included. Calibration daily curve was accepted on the basis on the systematic error lower than 15% for the quality internal controls (high, medium and low drug serum concentrations); then, drug serum levels in patients' samples were determined on the basis of the accepted daily curve using the internal standard method.

Table 1 Demographic characteristics of pediatric burn patients investigated clinical and laboratorial data-PK/PD approach –outcome

Demographic data	Medians (quartiles)	Min/Max values
Gender	10M/7F	NAP
Age (yrs)	4.9 (3.3-5.9)	3.1/11.2
Body weight (kg)	18 (14-23)	12/44
Height (cm)	109 (102-112)	95/156
Body surface area (m^2)	0.74 (0.61-0.88)	0.58/1.39
Body mass index (kg/m^2)	15.1 (14.4-15.5)	11.5/25.3
Admission data		
TBSA %	30(18-38)	11/75
Inhalation injury	12/17	NAP
Thermal burn	17/17	NAP
Mechanical ventilation	12/17	NAP
Vasopressors	12/17	NAP
Biomarkers at admission		
C- reactive protein	109 (39-176)	29/196
Biomarkers at TDM		
C- reactive protein (mg/L)	141 (128-176)	90/196
Leucocytes (*1000 cells/mm^2)	15.85 (12.66-22.68)	7.61/26.25
Serum creatinine mg/dL	0.31 (0.22-0.37)	0.15/0.47
Creatinine clearance	214 (172-273)	138/381
PK/PD approach-coverage	**Vancomycin**	**Meropenem**
Coverage (emperical regimen)	MIC 1 mg/L 8/17	MIC 4 mg/L 17/17
Coverage (adjusted regimen)	MIC 1 mg/L 17/17	
Coverage (adjusted regimen)	MIC 2 mg/L 10/17	
Microbiological cure	During the clinical course of combined therapy	
Negative cultures	Up to 10 days	
Clinical outcome		
ICU period (days)	18-25 days	
Hospitalization (total days)	23-45 days	
Survivals	15/17	
Nonsurvivals	2/17	

Abbreviations: TDM, therapeutic drug monitoring; NAP, not applied; min/max, minimum/maximum values in the population investigated

Pharmacokinetic analysis

Drug serum concentrations–time data were analyzed by the traditional approach based on one compartment model, through a Noncompartmental PK Data Analysis, PK Solutions 2.0 (Summit, Montrose, CO, USA).

PK/PD approach

PK parameters are related to the in vivo parameter, while PD data is related to the minimum inhibitory concentration (MIC) by antimicrobial susceptibility testing done for each pathogen in the Microbiology Laboratory after strains isolation; MIC 90 is the minimum inhibitory concentration to kill 90% of pathogen colonies according to the American data base of Clinical Laboratory Standard Institute[18] applied in our hospital. The index of antimicrobial effectiveness is time and concentration dependence and is estimated based on vancomycin serum concentration over time. Thus, the predictive index of vancomycin effectiveness is expressed by $AUC^{ss}_{0\text{-}24}$/MIC ratio > 400; once ratio values above 400 up to 600 were recommended for PK/PD target attainment.[6,7,28] In addition, since the meropenem effectiveness is time dependent for the carbapenem agent investigated in this clinical study protocol, the predictive index of drug effectiveness is estimated on the basis of the trough level, the rate constant (kel), the time dose interval and MIC data. Thus, drug effectiveness expressed by the PK/PD approach for target attainment was estimated by the percentage of the time dose interval that the free meropenem serum levels is maintained above the MIC, 100%fΔT>MIC strain.[10,14,19]

Data analysis

Statistical data analysis was carried out using the Statistical Package for Social Sciences 13.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism Version 10.0 (GraphPad Software Corporation, San Diego, CA, USA); p-Values lower than 0.05 were considered significant. Quantitative variables were described using central tendency and dispersion measures. The statistical model used for the evaluation of each variable was chosen based on the distribution pattern of each variable.

Results and discussion

Antimicrobial combined therapy of vancomycin Meropenem was considered the best choice for the combat of nosocomial pathogens in critically ill septic patients. Initially, Empirical doses recommended were administered systemically by pump infusion; significant dose adjustment requirements for target attainment were

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necessary for vancomycin against MIC >1 mg/L susceptible strains; while for meropenem dose regimen 40mg/kg q8h administered by 3hrs-extended infusion, PK/PD target was reached for MIC<2mg/L susceptible gram-negative strains, and the coverage was guaranteed up to CIM 4 mg/L for patients investigated.

Vancomycin dosing adjustment is required for drug effectiveness – Microbiology of isolates

Based on drug requirements for target attainment, vancomycin daily dose was stratified for pediatric burn patients investigated; data related to the empiric dose against adjusted dose were compared, once it was shown the proportionality between dosing increases and trough levels obtained. Considering the trough target recommended (10-20mg/L), when the empiric vancomycin daily dose recommended in our Institution (40-60mg/kg) was administered. In the present study, the initial daily dose recommended for children 50 (44-52) mg/kg was not enough to achieve the PK/PD target in 50% of burn patients investigated; consequently, dose required to reach the therapeutic target was significantly increased to 102 (83-114) mg/kg medians (IQ25-75) $p < 0.001$, for target attainment illustrated in Figure 1.

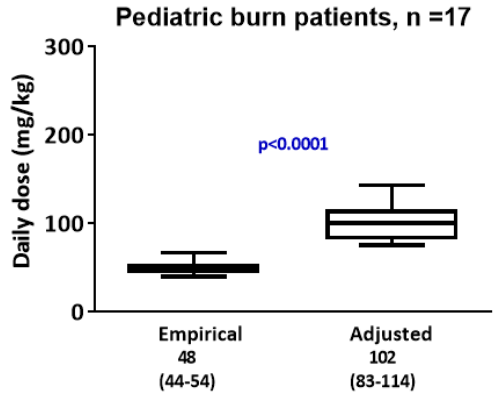

Figure 1a Vancomycin therapy in critically pediatrics, Empirical versus adjusted daily dose.

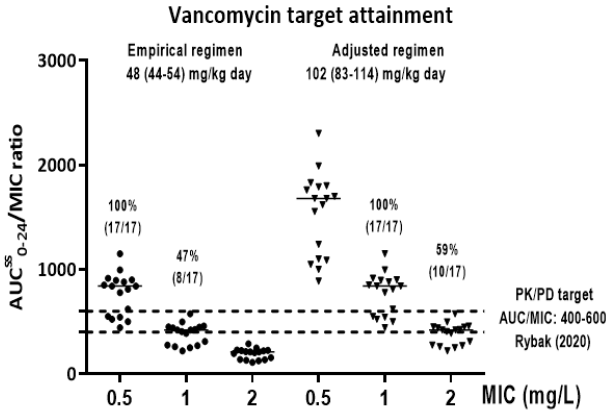

Figure 1b Vancomycin therapy in critically ill pediatrics Empirical versus adjusted daily dose.

Alternatively, for non-burn pediatric patients, vancomycin daily dose of 60.6 mg/kg resulted coverage lower than 60%.[19] In addition, Eiland et al. recommended to pediatric critically ill patients daily doses of 70-85 mg/kg to maintain the PK/PD target in 85% of patients during the antimicrobial therapy with vancomycin.[20] On the other hand, it was recommended by Gomez et al, a loading dose of 90 mg/kg at the first day of therapy for septic pediatric burns to achieve the steady state faster than the conventional empiric dose (40-60 mg/kg/day), permitting an earlier clinical intervention by dose adjustment if necessary for severe nosocomial infection control in those patients.[7] It is well known that data from the susceptibility testing done after the confirmation of strain will be available later than required by the physicians; therefore, drug plasma monitoring for pharmacokinetic study and PK/PD analysis in a real time will be quite useful and can guide them for an earlier medical intervention to guarantee the control of septic shock by PK/PD analysis. Consequently, adequate antimicrobial therapy including the optimal dosage based on drug plasma monitoring contributes significantly to a desired outcome and obviously to reduce the risk of bacterial resistance in patients with life-threatening infections, such as those that occur in critically ill, including burn patients and pre-term infants.[7,21] Increases on daily dose to reach adequate serum levels have been documented in adult burn and non-burn patients. It was reported previously that vancomycin dosing 2g daily must be prescribed to adult critically ill patients with creatinine clearance lower than 60 mL/min; while for patients with augmented renal function, corresponding doses must be increased to 3 g daily for aged higher than 65 years or to 3-4 g a day for young adult patients, serum creatinine 1mg/dL. This fact could be justified by volume of distribution at the steady state decreased (13 L) in these patients by comparison to data in healthy volunteers (30 - 42 L).[6,9,22]

It is well known that concerning kinetic disposition of vancomycin in adult healthy volunteers described by Boeckh *et al* (1998), it was shown in pediatric burns with normal renal function, a reduction of biological half-life (2.7 hrs.) by comparison with data reported healthy volunteers 3.7-5.3 hrs.[14] It is important to highlight that the total body clearance remained unchanged since several factors could alter this PK-parameter in patients investigated, even with normal renal function in all of them; consequently the total body clearance remains unchanged 1.57 (1.32-1.95) ml/min/kg in our patients by comparison with data of healthy volunteers (1.21-1.70 mL/min/kg). Thus, vancomycin pharmacokinetic data obtained in the present study (17 patients, 34 sets) are according to the results reported for critically ill pediatric patients, burns and non-burns, once a high PK-variability occurs in those patients' para comparison with healthy volunteers.[7,23,24]

Many causes of intra-patient variability (hemodynamic status, fluid administration, surgery and inflammatory processes) may influence PK changes during a patient's stay in the ICU, making it difficult to reach and maintain the desired target, while interpatient PK variability also occurs. Differences between patients related to changes on PK-data could justify the minimum/maximum dose adjustment requirements for vancomycin effectiveness. At the present time, vancomycin remains the drug of choice for the treatment of invasive MRSA infections; however, an increased MIC, even within the susceptible range, is a risk factor for vancomycin treatment failure in critically ill adult or pediatric patients.[3,5,7,8,25,26] Additionally, it was justified by Onishi et al that the vancomycin kinetics disposition are different in adults and children due to differences in body size, fluid compartments and urinary excretion.[25] Therefore, changes on vancomycin pharmacokinetics of vancomycin in pediatric burns varied greatly from the pharmacokinetics previously reported in septic adult burn patients, since the shorter half-life and lower trough resulted from volume of distribution reduced in these patients.[9,22,23,25,26,28] In contrast, pharmacokinetics of vancomycin in adult critically ill patients, burns compared to non-burns, has been described by Garrels & Peterie. PK changes in burns were related to an increased volume of distribution and drug plasma clearance; while the biological half-life was related to alterations in those both PK parameters.[22] Revilla (2010) reported in adult ICU patients' increases on the volume

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distribution of vancomycin higher than serum creatinine data (greater than 1mg/dL); therefore, age and creatinine clearance were identified as the main covariates explaining the pharmacokinetic variability in plasma clearance in critically ill adult ICU patients.[6]

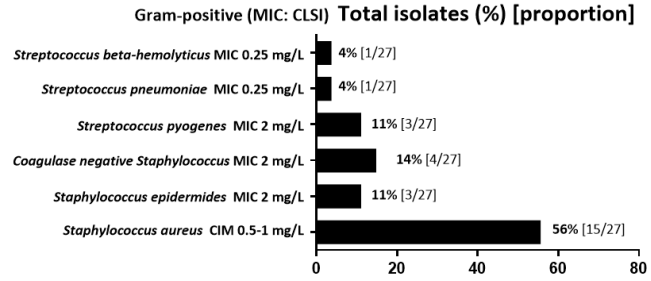

Figure 2 Vancomycin therapy in critically ill pediatrics Microbiology of gram-positive isolates.

In the present study, vancomycin target attainment against gram-positive strains related to dosing stratification done for pediatric burns was based on the area under the serum concentration over time (AUC^{ss}_{0-24}) and the MIC 90 ratio. A ratio higher than 400 is related to target attainment, assuming 1 mg/L MIC or less.[5,7,28] Despite the fact that the trough-based on dose adjustment data described in other studies, the results from the present study have revealed the need of dosing increases from 48 to 102 mg/kg daily to reach the therapeutic target by PK/PD approach, since the predictive index of vancomycin effectiveness AUC^{ss}_{0-24}/MIC ratio was above 400 in 100% of the sets for pathogens with 0.5 mg/L MIC, but the PTA decreases at 1 mg/L MIC strains to 47% (7/17) of pediatrics investigated and unfortunately, patients weren't protected against *Staphylococcus epidermidis* and *Coagulase negative Staphylococcus* MIC 2 mg/L. After dose adjustment, the PK/PD target was attained against MIC 1mg/L strains for all patients (17/17) and the coverage was increased up to MIC 2 mg/L strains in 10/17 (59%) pediatric burns. Consequently, a desired outcome related to clinical cure by eradication of nosocomial pathogens isolated occurred for all of them.

PK/PD approach indicate that the daily dose must be increased almost by twice for target achievement and strains with MIC values higher than 1 mg/L. These results are according to data reported previously by Gomez et al for pediatric burn patients. In contrast, considering pediatric patients (burns compared to non-burns), in whom vancomycin daily dose increases in a different manner as reported by Frymoyer et al, by 66% against 100% necessary to pediatric burns described by Gomez et al.[7,8] Optimizing vancomycin doses according to PK/PD principles showed in the present study, the potential to maximize the drug efficacy against MIC strains higher than 1 mg/L. Recommended trough range (10–20 mg/L) was proposed to guarantee PK/PD target achievement AUC^{ss}_{0-24}/MIC ratio higher than 400 and to increase the probability of the clinical cure of MRSA.[5,7,28] However, the efficacy and safety of the recommended target trough concentration and the PK/PD parameter have not been evaluated by any randomized or interventional studies.[5] More recently, a prospective multicenter trial to investigate the effectiveness and safety was conducted; and it was reported by authors that vancomycin trough concentrations above 15 mg/L with a threefold increased risk of nephrotoxicity.[29] Otherwise, it was suggested in the last consensus by Rybak *et al* that the AUC^{ss}_{0-24}/MIC > 400 up to 600 instead vancomycin trough levels range must be considered for patients with complicated infections like bloodstream infection, endocarditis, osteomyelitis, meningitis and hospital-acquired pneumonia caused by *S. aureus*.[28] While, higher troughs are usually associated with daily dose and highest AUCs; a more deep discussion related to this problem is necessary, since a single vancomycin plasma concentration like the trough does not directly reflect the AUC estimated by drug plasma concentration over time; once the trough is highly dependent on the dosing interval, i.e., daily doses with longer time dosing resulted in lower troughs. Therefore, dose adjustments based solely on trough values may be clinically misleading depending on the MIC data for strain documented, and vancomycin effectiveness depends on drug plasma concentrations over time dosing higher than the MIC 90. Thus, it is essential to highlight the importance of vancomycin exposure related to the dose regimen, the area under the curve and the MIC concerned to the strain's microbiological profile, especially for MRSA, to provide the clinical team with a safe and reliable dose adjustment tool.[7,8] Finally, the current empiric daily dose of approximately 40–60 mg/kg recommended to hospitalized children is inadequate for achieving target trough levels and desirable AUCs in pediatric burns, and an increase in daily doses of 80–100 mg/kg are needed to achieve the desired targets in terms of drug effectiveness/safety and for achieving pharmacodynamic goals.

Meropenem dose regimen 40mg/kg q8h by 3hrs-extended infusion and PK/PD approach

Meropenem dosing and its pharmacokinetics in critically ill patients are the broad-spectrum β-lactam antimicrobials that have been largely prescribed for the therapy of infections caused by gram-negative strains that occur in critically ill patients after higher surgeries, in burns and also in nonburn patients. Those critically ill patients with serious infections frequently have an altered volume of distribution for these antimicrobials.[12,13, 19,27,31,32,33] Therefore, the clinical significance for the dosing of these agents, such as current dosage guidelines for meropenem (1g q8h) are derived from pharmacokinetics studies in healthy volunteers.[32] Many studies suggested that at steady-state, PK-data related to increases on the volume of distribution and its biological half-life for meropenem could impact the coverage of gram-negative strains mainly at the earlier period of septic shock.[34-37] Additionally, it was shown that the meropenem total body clearance increased in pediatric burns since similar values were obtained by comparison to data from healthy volunteers (2.7-4.3 mL/min*kg). Watanabe et al., which no changes on PK-parameters were obtained in adult patients with severe respiratory infection. It is important to observe that high variability on PK of carbapenems was registered for patients in the investigations described by both authors.[14,19]

Dose regimen recommended for antimicrobial therapy with meropenem in ICU adults was 1g q8h, or 40 mg/kg q8h for pediatric septic patients administered by 0.5hr-inttermitent infusion. More recently, it was investigated a comparison of intermittent 0.5hr-infusion with the extended 3hr-infusion of meropenem.[34,35] Considering MIC >2 mg/L (MIC 4-8 mg/L strains) drug intermittent infusion was replaced more recently by meropenem extended infusion.[34] Then, the present study was conducted in pediatric burns undergoing therapy of septic shock with meropenem 40mg/kg q8h by 3hrs-extended infusion based on available MIC data against MIC 2 mg/L susceptible strains. PK-parameters are dose independent at therapeutic dose recommended for adults and children. The present study that was conducted in pediatric burn patients compares dosing, serum concentrations and drug effectiveness by PK/PD approach, illustrated in figure 3.

Pharmacokinetics of meropenem in pediatric critically ill patients

Although, PK-parameters have been reported in adult healthy subjects, patients without critical illness, and in critically ill patients,

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total body clearance were poorly described for carbapenem agents; 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.

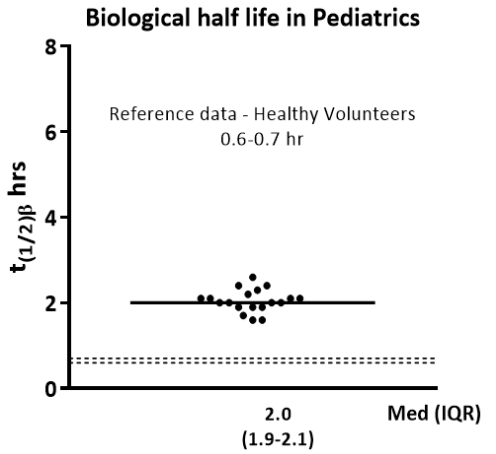

Figure 3a Meropenem 1g q8h extended 3hrs-infusion effectiveness impacted by PK changes.

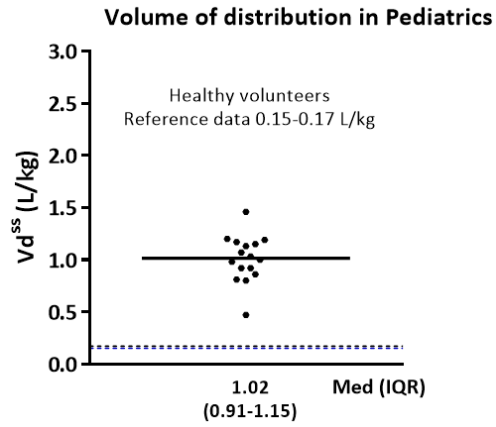

Figure 3b Meropenem 1g q8h extended 3hrs-infusion effectiveness impacted by PK changes.

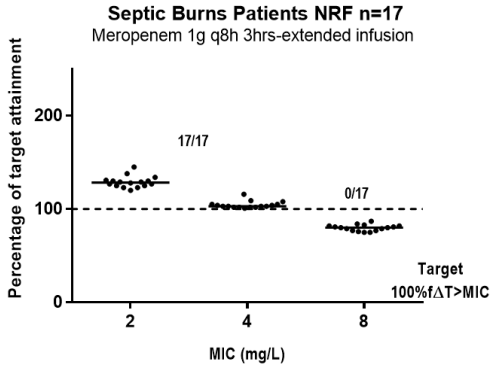

Figure 3c Meropenem 1g q8h extended 3hrs-infusion effectiveness impacted by PK changes.

Meropenem PK in pediatric burns seem to be altered by increases on volume of distribution 1.02 (0.91-1.15) L/kg by five-fold by comparison with healthy volunteers (0.15- 0.17L/kg), while the biological half-life in pediatric burns was 2.0 (1.9-2.1) hrs, medians (quartiles), against 0.7-1.1 hr in healthy volunteers) 2-3 times prolonged in pediatric burns. It was shown increases in total body clearance in pediatrics 6.0 (5.7-6.4) mL/min*kg by comparison with data reported previously in healthy volunteers 2.7-4.3 ml/min*kg.[32] PK-data related to the body clearance suggests that elimination of meropenem is increased by vasopressors, since in 15/17 of patients had creatinine clearance increased during the early stage of septic shock. In addition, the volume of distribution was 5 times increased in pediatric burns after the extended 3hrs-infusion of meropenem with a consequent prolongation of biological half-life by twice after comparison with results reported in healthy volunteers. It is important to highlight that the antimicrobial coverage was positively impacted by these PK-changes.

Related to previous PK investigation in pediatric critically ill patients treated with meropenem few studies were found, while, for imipenem just one study was found.[11,13,14,33,36] Blumer et al investigated in a single dose meropenem in a PK study carried out in hospitalized infants and children. Changes on pharmacokinetics occurred by increases on volume of distribution with a proportional prolongation of biological half-life in these patients.[33] In addition, PK-studies with meropenem at steady state were reported.[11,14,33,36] Du et al, investigated 99 pediatric patients with meningitides, who received the recommended dosing for pediatrics; authors describe an important change in all PK-parameters by the reduction on plasma clearance, increases on volume of distribution and a prolongation of biological half-life in those patients by comparison with data in healthy adults.[11] Therefore, meropenem PK-data obtained in the present study in pediatric burns are according to the results reported previously in pediatrics as infants, children, and teenagers.[11,14,33,36] Thus, it is considered that the pharmacokinetics of meropenem is altered in pediatric burn patients with normal renal function when data were compared with the results reported in healthy adults.[32] In addition, a reduction on total body clearance described in these patients by comparison with data reported in healthy subjects. It is important to highlight that the difference on pharmacokinetics obtained by comparison of carbapenem agents (meropenem and imipenem) in pediatric burns are strictly related to the volume of distribution increased three folds for meropenem against twice for imipenem, while the total body clearance was twice reduced for both agents. Consequently, based on interpatient variability PK-changes for meropenem were higher than registered for imipenem in pediatric burns investigated in hospital.[14]

Concerning adult critically ill patients, Cheatham et al described that any changes occurred in hospitalized patients with normal renal function after another meropenem dose regimen of 0.5g every 6 hours (CLcr >60ml/min). Additionally, patients were allocated in three groups, whom received 0.5 g of meropenem every 6, 8, and 12 hours on the basis on creatinine clearances greater than 60, 40–60, or 10–39 mL/min, respectively. It was shown high variability on data obtained for each group of patients, and changes on PK-parameters were strictly related to the degree of renal impairment for plasma clearances and half-lives.[30] On the other hand, concerning imipenem PK study in critically ill burn patients with normal renal function, Blanchet et al described a revision study that there are conflicting data in the literature regarding the recommended dose and pharmacokinetics of imipenem in burns, once any significant change in pharmacokinetics was found by Boucher et al. in severe burn adult patients.[26] It is important to highlight that a large variability on carbapenems PK-data was registered by many investigators.[14,30,31,33-35,37] Then, it was considered that conflicting data in the literature until now regarding the changes on pharmacokinetics in critically ill adult septic patients,

probably may be due to a blood sampling done in a different stage of therapy during the clinical course of septic shock for PK investigation as discussed recently by Messiano et al.[37]

PK/PD Analysis of Carbapenems in pediatrics

Recommended PK/PD parameter to correlate dosing, PK-data and drug effectiveness for the antimicrobial were based on the time interpose (tid) that drug serum level is maintained above the MIC (%*f*ΔT>MIC); MIC is the in vitro measurement, that is the minimum inhibitory concentration required to kill 90% of culture' colonies for each pathogen isolated. Thus, a new PK/PD target of 100%*f*DT>MIC for meropenem was applied by plotting the predictive index (%*f*ΔT>MIC) against MIC data susceptible strains isolated from cultures, Figure 4.

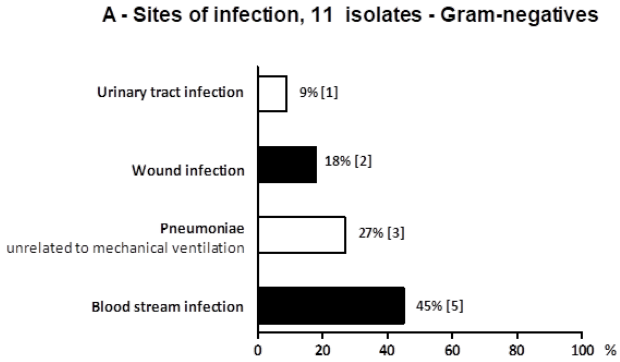

Figure 4a Microbiology of gram-negative isolates.

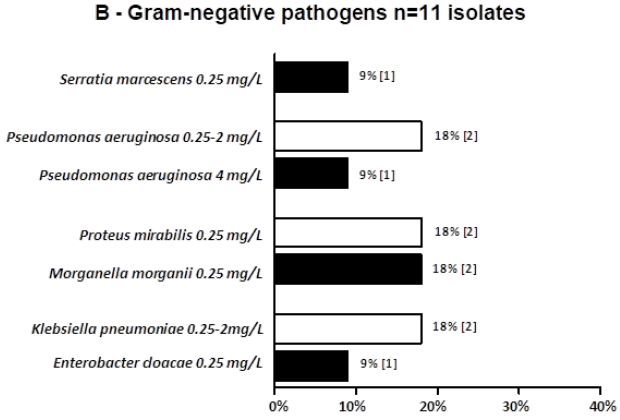

Figure 4b Microbiology of gram-negative isolates.

Final considerations about PK analysis and PK/PD approach in critically ill patients

Pharmacokinetics (PK) is an important tool available to antimicrobial effectiveness by predicting drug exposure and can be associated to pharmacodynamic (PD) goals, since the pathogen susceptibility must always be considered to ensure desired clinical outcome by drug effectiveness against strains isolated from ICU patients. Therefore, the variability on PK and on PD parameters must be careful and individually considered, since the relationship given by the in vivo data and the in vitro data concerned to the pathogen susceptibility could express an important index to predict the antimicrobial effectiveness. PK data are related to the in vivo parameter, while PD data are related to the bactericide minimum inhibitory concentration (MIC 90) obtained by the antimicrobial susceptibility testing done for each pathogen isolated. Therefore, antimicrobial indices for vancomycin effectiveness will depend on drug plasma concentration over time; while the index of drug effectiveness will be time dependent for β-lactams, including carbapenem agents. Thus, the predictive index of vancomycin effectiveness is expressed by $AUC^{ss}_{0\text{-}24}$/MIC ratio >400; once ratio values above 400 up to 600 were recommended by Rybak et al, last consensus for target attainment.[28] While drug effectiveness time dependent occurs for meropenem, and its effectiveness index will be estimated based on trough levels, the elimination rate constant), time dosing and the MIC data of isolate strain. Thus, drug effectiveness time dependent for target attainment will be estimated by the PK/PD approach and defined by the percentage of time dose interval that the free meropenem serum levels is maintained above the MIC, 100%*f*ΔT>MIC strain recommended by Abdul-Aziz et al, must be considered after meropenem extended 3hrs-infusion.[12,34]

Today, it must be considered also that the main problem of the physician during the antimicrobial therapy for cure of severe infections in critically ill ICU patients is related to strain isolated and MIC data available for the clinical team in a short period after blood sampling for cultures. On the other hand, it well known that a week almost is needed to gram-positive strain isolates/susceptibility testing MIC data done in the laboratory of hospital; while takes a longer period, if a nosocomial gram-negative strain was considered. Then, in that case MIC values can be obtained within the typical clinical setting or from surveillance databases as in the Microbiology of the Central laboratory of our hospital.[18] Concerning PK-analysis, it was found in the literature different approaches that can be used. Noncompartmental data analysis, software was applied to individual patients for PK investigation purposes, and in general related to a small number of patients.[7-11,13,14,17,20,21,22,26,30,32-37] In contrast, Monte Carlo Simulation and NONMEM™ software, is applied for population PK analysis based on the nonlinear mixed-effect approach, planned to be applied to patients' population with predictive target attainment.[6,19,23,25] On the other hand, population PK-analysis softwares could present some limitations related to a large number of population-data of patients included; extreme data values based on lower/upper limits for estimated parameters obviously occur, but cannot be extrapolated to all ICU critically ill patients, since changes on PK happen as a consequence of many factors discussed in this chapter related/non-related to each patient, including also the main causes of intra-patient variability (hemodynamic status, fluid administration, surgery and inflammatory processes) may influence PK changes during a patient's stay in the ICU, making it difficult to reach and maintain the desired target; while, interpatient PK-variability also occurs. In the chapter it was discussed changes on vancomycin and carbapenems PK in critically ill patients focusing pediatric burns and differences that occur in children compared to critically ill adult patients or in healthy subjects. Therefore, it is important to highlight that PK can be altered in a different manner in those patients and changes will depend on additional factors including the severity of infection, multi-resistant strains, immunosuppressed status, and co-morbidities related to each individual patient.

In summary, antimicrobial target achievement during the therapy of severe infections caused by nosocomial pathogens, susceptible or resistant to the recommended doses previously established, PK/PD analysis have been performed by applying the traditional noncompartmental PK-data analysis software for PK-parameters estimation for a small number of patients´ population.[7-11,13,14,17,20,21,22,26,30,32-37] In addition, Monte Carlo simulation population software implemented is applied to predict the proportion of patients in different population groups who will achieve the desired PK/PD target, when different pathogens are isolated. Using this kind

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of data for large number of patients, Monte Carlo simulations have been used to predict target achievement in specific patient population, in spite of PK-data obtained in the most part of studies, have been realized in a small number of subjects included in the protocol.[6] Cure of severe infection unfortunately must be reached by the medical team thus for each critically ill ICU patient. Thus, target achievement must be reached to save patients´ lives soon and independently of MIC data available or not for the physician in the hospital. The integrated PK/PD approach permits to consider the variability in PK-data and also on PD goals of the strain, to obtain a desired outcome for a defined population with unpredictable pharmacokinetics like in pediatrics, infants, massive burns and also aged patients' population of critically ill patients, because the variability in the MIC can be obtained from surveillance databases. On the other hand, during the clinical follow-up of an ICU critically ill patient with severe infection, laboratory data, drug plasma monitoring and PK/PD analysis based on MIC value from database considered in each hospital will guide the physician to change or not the dose regimen of an antimicrobial or if another alternative therapy could be chosen, always considering daily ICU patient status during all antimicrobial therapy. Finally, PK/PD approach is a quite specific tool that must be applied carefully in a real time to allow an earlier medical intervention to save lives of ICU critically ill patients.

Drug effectiveness was based on the predictive index recommended for vancomycin ($AUC^{ss}_{0\text{-}24}$/MIC ratio) and for meropenem (%fΔT>MIC).[6,14] Dose adjustment requirements are presented in critically ill pediatric burn patients for the target attainment (PTA) against gram-positive vancomycin susceptible strains MIC>1mg/L. In addition, any dose adjustment was required for meropenem target attainment mainly against gram-negative of intermediate susceptible strains MIC>2mg/L, since meropenem extended 3hr infusion was chosen for all ICUs of our hospital. Differences on PK-data for pediatric and adult burn patients occur, and changes of clinical relevance on PK/PD of antimicrobial is discussed.[14,15,33-37]

Many factors that affect drug pharmacokinetics related to renal function, total burn surface area, drug effectiveness in septic shock, and susceptibility of the nosocomial pathogens were included, always considering the application of the PK/PD tool focusing the improvement on clinical outcome. Finally, PK/PD approach is a powerful tool based on drug serum levels done in a real time that permits the investigation of changes on pharmacokinetics that could impact pharmacodynamics. Consequently, PK/PD approach must be applied routinely any time in ICU patient's bed side to avoid microbial resistance that contributes to increase of death by nosocomial infections caused mainly by gram-positive and gram-negative pathogens.

Conclusion

The current empiric daily dose of approximately 40–60 mg/kg for vancomycin recommended to hospitalized children with normal renal function is inadequate for achieving target trough levels and desirable AUCs in pediatric burns. Thus, an increase on daily doses 80–100 mg/kg are needed to achieve the desired targets in terms of drug effectiveness/safety and for achieving pharmacodynamic goals MIC 2mg/L, strains. Pharmacokinetics of vancomycin was altered in these patients and optimized dosing given every 6 hours was justified by the reduction on volume of distribution and on biological half-life shorter than expected occurs in critically ill pediatric burns.

In addition, it was shown in the same sub-population of pediatric patients, which received meropenem 40mg/kg q8h by extended 3hrs-infusion that changes on PK impacted on target attainment once a prolongation of biological half-life occurs because of increases on volume of distribution. Target attainment in pediatric burns was reached after the empiric dose recommended with cure of infection for all patients. Then, pathogens isolated were eradicated by clinical and also microbiological cure. Then, optimization of therapy was reached by maximization of drug efficacy and minimization of neurotoxicity of this agent or the nephrotoxicity of vancomycin in critically ill pediatric burn ICU patients.

In summary, based on high PK-variability of vancomycin or meropenem in pediatric burn patients, therapeutic drug plasma monitoring (TDM) must be done routinely to investigate changes on PK that can impact drug effectiveness evaluated by PK/PD approach done in a real time to provide relevant data for each individual patient to the physician permitting an earlier clinical intervention and cure of severe infections caused by nosocomial pathogens susceptible or of intermediate susceptibility.

Therefore, this package must be considered an important tool to guarantee adequate dosing during antimicrobial therapy for ICU critically ill pediatric burn patients that contributes significantly to improve the clinical desired outcome and to avoid the development of multi-resistant strains.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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