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Combating bacterial resistance to antimicrobials in severe septic ICU patients: importance of meropenem, piperacillin serum monitoring as a dose adjustment and duration of infusion strategies

Abstract

Introduction: In view of the growing challenge to the use of antimicrobials for adequate and effective therapy of nosocomial infections, international health agencies have reinforced that combating bacterial resistance and preventing the development of multidrug-resistant (MDR) strains are urgent, since hospital infection control committees have reported a significant increase in the minimum inhibitory concentration (MIC) for therapeutic agents against nosocomial pathogens. Meropenem and piperacillin-tazobactam are largely prescribed in the therapy of septic shock caused by susceptible Gram-negative bacteria. Usually the 0.5 hr.-intermittent infusion that was widely used at the last 30 years in these patients, providing coverage only against susceptible Gram-negative pathogens up to MIC 2 mg/L according to Clinical Standard Laboratory Institute (CSLI database). New strategies have been recommended to combat the development of resistance to pathogens isolated from cultures to increase the coverage of these antimicrobials.

Subject: A systematic review was carried out to evaluate pharmacodynamics based on pharmacokinetics that could affect the coverage of beta-lactams agents (meropenem or piperacillin-tazobactam) after intermittent or extended infusion in septic patients with preserved or augmented renal clearance by applying pharmacokinetic-pharmacodynamics (PK/PD) tools.

Methods: Criteria considered was based on the PICO strategy: *Patient, Intervention, Comparison, and Outcome.* Several prospective controlled clinical studies were considered in this review, mostly published in the last decade, including clinical protocols conducted in septic patients with preserved or augmented renal clearance. The primary endpoint was the pharmacodynamics based on microbiology of the isolates obtained from cultures, and antimicrobial coverage considering drug infusion and the percentage of patients achieving the therapeutic target (100% *f*ΔT>MIC) recommended. The primary outcome was to compare the intermittent infusion (0.5 hr.) with extended (2 to 4 hrs.) infusion related to antimicrobial efficacy done by the pharmacokinetic-pharmacodynamics (PK/PD) tools based on drug serum levels. It was considered also the impact of pharmacokinetic changes that may affect the coverage of beta-lactams in ICU septic patients on the isolated gram-negative strains. As a secondary outcome, the change in pharmacokinetics as a function of the duration of drug infusion reported in septic patients, also considering its comparison with the reference data reported in healthy volunteers.

Results: In the review of studies, the coverage strategy was based on the prediction index (%*f*ΔT>MIC) of drug effectiveness. Superiority of the 3hrs.-extended infusion by comparison with the 0.5hr.-intermittent infusion was evidenced in the most part of studies which had an increase on drug effectiveness in critically ill patients for both antimicrobials. It was demonstrated that different changes might occur in the pharmacokinetics of these beta-lactams as a function of the duration of drug infusion. It is important to highlight that PK-data selected from clinical studies occurred mainly in the early phase of septic shock in those critically ill patients with preserved renal function and receiving vasopressors.

Conclusion: Drug serum levels of these beta-lactams should be implemented in the routine of tertiary hospitals always associated with the PK/PD approach to know the antimicrobial coverage. Therefore, the clinical and microbiological cures by eradicating soon the susceptible pathogens will contribute to the reduction of deaths, combating the mutant´s selection, and preventing consequently the development of bacterial resistance.

Keywords: septic patients, meropenem, piperacillin-tazobactam, pharmacokinetics-pharmacodynamics approach, coverage dependent of drug infusion

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Abbreviations: ANVISA, National health surveillance agency; CSLI, clinical standard laboratory institute, database USA; ER, emergency room; FDA, food and drug administration, GSA, global sepsis alliance; IAI, intra-abdominal infection; ICU, intensive care unit; LAIS, Latin American Institute of Sepsis; MDR, multidrug resistance; MIC, minimum inhibitory concentration; MRP4, multidrug resistance-associated protein 4; MV, mechanical ventilation; OAT1, organic anion transporter 1; OAT3, organic anion transporter 3; PD, pharmacodynamics; PK, pharmacokinetics; PNM, pneumonia; PTA, probability of target attainment; RIUI, regular inpatient units – infirmary; SAPS3, simplified acute physiology score 3; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, sequential organ failure assessment; SSC, surviving sepsis campaign; SIRS, systemic inflammatory response syndrome; TBSA, total burn surface area; TDM, therapeutic drug monitoring; UTI, urinary tract infection; WHO, world health organization

Introduction

Septic shock is a preventable and potentially fatal organ dysfunction caused by a dysregulated host response to infection.[1] The clinical outcome in most high-risk cases is the death of patients with

nosocomial bacterial infections associated with various comorbidities, including viral infections, most recently SARS-CoV-2.[2]

About 50 million cases diagnosed annually worldwide, at least 11 million patients die being mostly concentrated in underdeveloped countries. Results of a large international prospective trial show that 70% of ICU patients receive antibiotics.[3] However, both the incidence of infections and associated mortality in the ICU have not improved over the last 30 years.[4] This indicates that improvements in clinical out-comes of ICU patients might be possible. In addition, considering renal clearance in those patients, the association between increased mortality rate and antimicrobials dose adjustment in intensive care unit patients with renal impairment is reported, or even augmented renal clearance is another common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy.[5-7]

In Latin America, including Brazil, a prevalence study carried out in 2015 conducted in 230 ICUs pointed out that 30% of the beds are occupied by patients with septic shock; it is estimated, based on these data, that the death rate is 50%. These findings indicate that the severity of nosocomial infection results in a high social and economic cost for the Latin America countries.[8] According to the latest annual report by the Latin American Institute of Sepsis (LAIS 2019),[9] the evolution of the infectious clinical condition in a patient with septic shock has increased exponentially in the Latin America between 2005 and 2019, especially for the elderly population with pneumonia as the primary site of infection.[9]

In view of the growing challenge to the prescription of antimicrobials for adequate treatment and effective control of bacterial infectious conditions during COVID-19 pandemic, Surviving Sepsis Campaign in the International Guidelines for Management of Sepsis and Septic Shock (2021), Global Sepsis Alliance (2020) and World Health Organization (2023) have reinforced that combating bacterial resistance, and the prevention of the development of multidrug-resistant strains (MDR) is urgent.[2,10,11]

It is well known that at the last 15 years, the professionals responsible for the control of hospital infection have reported a significant increase in the minimum inhibitory concentration (MIC), independently of microbial database considered. Historically in the first international consensus hold in Belgium (2016), the Surviving Sepsis Campaign group published that the prescription of antibiotics at the early stage of septic shock is essential to guarantee the maintenance of life in critically ill patients with severe infections in the ICU. Thus, this population requires an immediate change in the behavior of the clinical team and continuous monitoring of these patients undergoing intensive care through continuous hemodynamic, respiratory, renal, and infectious surveillance.[12] More recently, additional recommendations were published regarding the application of the pack of anticipated emergency clinical procedures for the 1st hour replacing the 12-hour period recommended previously for septic ICU patients, including the collection of cultures before starting antibiotics.[13]

Then, the treatment of critically ill patients with serious infections caused by susceptible Gram-negative bacteria generally follows the manufacturer's recommendation in the package insert a beta-lactam agent commonly used for the through short infusion of 0.5 hr.; it is noteworthy that the dose regimen prescribed of these agents varies according to the renal function of each patient. In addition, the 0.5 hr.-intermittent infusion of beta-lactam agents was widely used at the last 30 years for severe and high-risk patients with septic shock caused by susceptible nosocomial pathogens, providing coverage against susceptible Gram-negative pathogens up to MIC 2 mg/L. This fact is a consequence of the changes that occurs in the pharmacokinetics of hydrophilic beta-lactam agents after systemic administration and restricted hospital use, resulting in serum levels lower than those required in the adequate treatment of the infection. In a monitoring program of antimicrobial therapy for several infections based on serum levels of beta-lactams in patients admitted to the ICU, it was reported that 73% of patients did not reach the therapeutic target against susceptible strains of gram-negative bacteria. This fact reinforces that monitoring serum levels is essential to assess changes in pharmacokinetics that impact the coverage of the prescribed antimicrobial agent, expressed through the PK/PD approach. Therefore, new therapeutic strategies have been proposed for the most prescribed beta-lactam agents related to the dose regimen and duration of infusion for meropenem and for piperacillin-tazobactam.[14]

Some prospective controlled studies including therapeutic drug monitoring (TDM) were added in this review to compare the recommended 0.5 hr.-intermittent infusion with the extended infusion to assess drug efficacy. Considering that therapeutic drug monitoring after 3 hrs.-extended infusion ensures an adequate drug serum level against intermediate susceptible strains coverage up to MIC 4 mg/L for meropenem, and up to MIC 32mg/L for piperacillin, and contributes to preventing the development of resistance, and in combating the intermediate susceptibility strains primarily related to *K. pneumoniae* and *P. aeruginosa* in major septic burns receiving vasopressors. In addition, to allowing the evaluation of effectiveness of the dose regimen prescribed to septic ICU patients, drug serum levels are a laboratory strategy of great value in the individualization of therapy in a real time, guaranteeing the expected clinical outcome, and to combating the development of bacterial resistance, also reducing the duration of antimicrobial therapy, and consequently hospital costs.[15] It is noteworthy that, so far, serum levels of these agents are not routinely monitored in hospitals for these critically ill patients admitted to ICUs.[16,17]

Clinical management for critically ill patients in intensive care has been guided by cultures through the isolation of the agent followed by determination of the susceptibility of the pathogen to the antimicrobial and supported by the serum biomarkers of Systemic Inflammatory Response Syndrome (SIRS). Then, if these results are combined with antimicrobial serum levels and PK/PD approach, it is possible to have the fundamental data to guide antimicrobial therapy. If serum levels of the prescribed antimicrobial agent are equal to or greater than those required to eradicate the susceptible pathogens, microbiological cure will occur, and the desired clinical outcome will be achieved by appropriately treating the septic shock and healing the patient. On the other hand, for serum levels below the recommended level, therapeutic failure will occur. The fact has been justified by the selection of mutant strains with intermediate susceptibility, development of resistant or even multi-resistant strains, favoring bacterial emergence and death in these cases.[18] Consequently, the application of the PK/PD tools combined with the results of the cultures should guide the clinical team, allowing the change of prescription in real time for the individualization of the antimicrobial therapy for each patient. This new dynamic will enable the guarantee of clinical and microbiological cure by eradicating isolated pathogens with reduced treatment period.[5,19]

Therefore, investigations involving pharmacoeconomic studies must be carried out associated with the ICU patient care, and clinical outcome to prove or not the reduction in ICU mortality, and the need to implement a cost-effective routine for therapeutic monitoring of serum levels for antimicrobials routinely performed by the central laboratory of tertiary hospitals, allowing real-time dose adjustment.

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Subject

A systematic review was carried out to evaluate pharmacodynamics based on pharmacokinetics, that could affect the coverage of beta-lactams agents, meropenem or piperacillin-tazobactam, after intermittent or extended infusion in septic patients with preserved or augmented renal clearance by applying pharmacokinetic-pharmacodynamics tools.

Methods

The criteria considered was according to the PICO strategy: Patient, Intervention, Comparison and Outcome.[20] Several prospective controlled clinical studies considered in this review, mostly published in the last decade, including clinical protocols conducted in septic patients with preserved or augmented renal clearance. The primary endpoint was the pharmacodynamics based on microbiology of the isolates obtained from cultures, and antimicrobials coverage considering the percentage of patients achieving the new therapeutic target (100% *f*ΔT>MIC) recommended. The primary outcome was to compare the intermittent infusion (0.5 hr.) with extended infusion (2 to 4 hrs.) related to antimicrobial efficacy done by the pharmacokinetic-pharmacodynamics tools based on drug serum levels. It was considered also the impact of pharmacokinetic changes that may affect the coverage of beta-lactams in ICU septic patients on the isolated Gram-negative strains. As a secondary outcome, the change in pharmacokinetics as a function of the duration of drug infusion reported in septic patients, also considering its comparison with the reference data reported in healthy volunteers.

Patients: This review included protocols of clinical studies conducted in critically ill major burns and non-burns adult patients with septic shock, and renal function preserved or augmented by vasopressors. Pharmacokinetic data from healthy volunteers' studies were also considered as reference results for comparative purposes.

Intervention: Systemic administration of recommended dose regimens for meropenem (1g q8h) or piperacillin-tazobactam (4.5g q8h, or 4.5g q6h) was performed by intermittent infusion (0.5 hr.) and by extended infusion (2-4 hrs.). Different dose regimens administered to patients in some clinical protocols of study were also included.

Comparison: Primary and secondary outcomes was based on pharmacokinetics. pharmacokinetic-pharmacodynamic approach; also considering the microbiological coverage of the isolates reported in the clinical protocols. Results from protocols conducted in septic patients undergoing therapy with meropenem or piperacillin-tazobactam receiving intermittent infusion, or extended infusion were compared.

Outcomes: Pharmacodynamics based on microbiology of isolates, and PK/PD approach based on drug serum levels to evaluate the antimicrobial coverage were considered. Pharmacokinetic changes that could impact drug effectiveness were based on the duration of drug infusion related to each beta-lactam agent. The primary outcome was to evaluate pharmacodynamics by comparison of intermittent infusion (0.5 hr.) with extended infusion (2 to 4 hrs.) related to antimicrobial efficacy done by PK/PD tools based on drug serum levels. As a secondary outcome, the change in pharmacokinetics that occurred in septic patients was considered by comparison with the reference results reported in healthy volunteers for each chosen infusion.

Results

Review of Meropenem Studies based on duration of infusion

Pharmacokinetics (PK) from healthy volunteers receiving meropenem were considered a reference data for comparison purposes of pharmacokinetic studies conducted in ICU patients during the clinical course of septic shock, after intermittent infusion, reported by Nilsson-Ehle *et al***,** or after extended infusion by Jaruratanasirikul *& Sriwiriyajan.*[21,22] It is noteworthy that only septic patients under intensive care with preserved or even augmented renal function were considered in this review of meropenem clinical protocols, tables 1-2.

Currently, it is considered the volume of distribution as the best kinetic parameter that pointed out the severity of the systemic inflammatory response syndrome (SIRS) that occurs mainly at the earlier stage of septic shock. In most of the studies considered, regardless of the infusion, the apparent volume of distribution was increased. It is important to highlight that significant increase in the parameter occurred only after the 3hrs-extended infusion compared with the intermittent infusion (0.5 hr.). The biological half-life of meropenem was prolonged during this period resulted of the significant increase in the volume of distribution during SIRS. The greatest prolongation of biological half-life occurred in most studies after extended infusion, remaining unchanged after the intermittent infusion. Therefore, prolongation of the half-life as a function of the proportional increase in the apparent volume of distribution was recorded in the most studies carried out in the early phase of septic shock after extended infusion. Regarding total body clearance in patients with preserved or increased renal function, it should be noted that different results have been reported regardless of the type of infusion. This fact was due to several factors that alter the parameter in patients undergoing intensive therapy for septic shock, such as the use of different doses of one vasopressor, or vasopressor in higher doses, or even vasopressors associated, and the fluid therapy. We must also consider the expression of drug-transporters involved in renal tubular secretion of these hydrophilic beta-lactam agents. In addition, the variability reported for creatinine clearance during the inflammatory cytokine storm as a function up-titration, or down-titration of vasopressors occurs mainly at earlier stage of septic shock.

Meropenem Intermittent Infusion

We will begin the discussion of the results obtained by reviewing the literature to compare protocols conducted in septic patients in the intensive care receiving meropenem through an intermittent infusion of 0.5 hours, table 1. It was included in the review study only prospective protocols conducted in critically ill septic patients with preserved or augmented renal clearance. The alteration or not of the pharmacokinetics registered by the different authors was investigated and compared to the reference data reported by Nilsson-Ehle *et al.* In a study carried out in healthy volunteers after administration of dose regimen of 1g q8h, 0.5 hr intermittent infusion,[21] evidence of changes in pharmacokinetics was related to greater or lesser coverage of meropenem in critically ill patients in intensive care against Gram-negative strains.

Only two studies conducted on septic patients treated with meropenem, 1g q8h by intermittent infusion of 0.5 hr., were found based on the new recommended PK/PD target 100% *f*ΔT>MIC.[23,24] In the more recent study done in a public tertiary hospital, Sao

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Paulo, Brazil, it was included 12/25 major burn patients receiving vasopressors at the earlier stage of septic shock, treated with meropenem 1g q8h by 0.5 hr.-intermittent infusion. Antimicrobial-susceptible Gram-negative bacteria were isolated with emphasis on *K. pneumoniae, Enterobacter cloacae, Pseudomonas aeruginosa, Acinetobacter spp* from sites of bloodstream infection, pneumonia unrelated to mechanical ventilation, wound, bone and abdominal infections. Meropenem coverage occurred for all patients against isolated pathogens up to MIC 2mg/L, reducing coverage to 3/12 patients for MIC 4mg/L isolates for the target 100% *f*ΔT>MIC considered.[23] In addition, another study was conducted by Gonçalves-Pereira *et al* in 15 septic patients admitted to the ICU of a hospital in Lisbon, Portugal. Patients received the same dose regimen 1g q8h, and 0.5hr.-intermittent infusion of meropenem in the treatment of bloodstream, lung, central nervous system, skin/soft tissue infections, and complicated infection after intra-abdominal surgery. The target of 100% *f*ΔT>MIC, considered by these authors, was reached for 14/15 patients up to MIC 2 mg/L, reducing to 9/15 patients against MIC 4mg/L strains.[24] Changes that occurred in pharmacokinetics at the earlier stage of septic shock were similar in major burns and surgical patients related to biological half-life increased by twice, as result of decreases on total body clearance, consequence of reduction expression of renal drug biotransporters for hydrophilic beta-lactams agents during SIRS.[23-26]

On the other hand, Silva Jr *et al*. included a population of 20 major septic burn patients, with 10/20 patients receiving the dose regimen 1g q8h by intermittent infusion of 0.5 h. Similar changes occurred in pharmacokinetics at the earlier stage of septic shock were like discussed for major burns and surgical patients reported.[23,24] It was considered the target of 60% *f*ΔT>MIC, that was higher than the previous one 40% *f*ΔT>MIC recommended initially for carbapenems.[27,28] It was reported coverage up to MIC 2 mg/L against pathogens. *P. aeruginosa* MIC 4mg/L of intermediate susceptibility was isolated just from one patient. The microbiological study revealed positive cultures also for several Gram-positive isolates, with a high prevalence of susceptible Staphylococcus spp., while *P. aeruginosa* MIC 2 mg/L was the most prevalent Gram-negative pathogen in infections registered in the ICU septic major burns. It is important to highlight that clinical cure occurred for patients investigated on the dose regimen administered by 0.5 hr.-intermittent infusion by PK/PD target 60% *f*ΔT>MIC instead 100% *f*ΔT>MIC considered by Kupa *et al* and Gonçalves-Pereira *et al,* both based on serum drug levels.[21,23,24,27]

On the other hand, results of meropenem coverage reported by authors from previous studies done between 2002-2013 were based on the former target 40% *f*ΔT>MIC recommended by Ikawa *at al.* for carbapenem agents.[28-32] Consequently, a target lower than the new one recommended (100% *f*ΔT>MIC) to measure the effectiveness of meropenem through the PK/PD approach were applied in these studies. In addition, it was reported by Adnan *et al.*, a protocol study including five critically ill patients receiving a dose of 1g q8h, 0.5hr.-infusion against pathogens isolated from wound infection sites, surgical drain, and urinary catheter after surgical procedures. In this study, target of 40% *f*ΔT>MIC was achieved for all patients up to MIC 2 mg/L, in the coverage of Enterobacteriaceae and *P. aeruginosa*.[29] Cheatham *et al* investigated 20 patients with pneumonia, osteomyelitis, necrotizing pancreatitis, and peritonitis, that received another dose regimen 0.5g q6h. eq. 2g/day; and only 8/20 septic patients with preserved renal function received meropenem. In this protocol, the target was also 40% *f*ΔT> MIC, and coverage occurred for all patients (8/8) against isolates up to MIC 2 mg/L, dropping to 7/8 patients for pathogens (MIC 4mg/L). It was reported in the study that dose regimen was acceptable to treat infections caused by *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter spp* up to MIC 2 mg/L.[30] Another study was conducted by Novelli *et al,* included 10 septic patients with abdominal infection, pancreatitis, peritonitis and polytrauma under treatment with meropenem in the same dose regimen and type of infusion. In this study, target of 40% *f*ΔT>MIC was achieved for all patients up to MIC 2 mg/L, including coverage of Enterobacteriaceae and *P. aeruginosa* isolates.[31] In addition, Kitzes-Cohen *et al* investigated seven critically ill patients using the same dose regimen prescribed in most studies included in this review, 1g q8h, 0.5 hr.-infusion. It was reported that the target of 40% *f*ΔT>MIC was achieved up to the clinical breakpoint (ECOFF) for all patients.[32]

In contrast, with study protocols described previously,[21,23,24,27] PK changes occurred by increases on volume of distribution and biological half-life by twice, remaining unchanged total body clearance were obtained for patients from these studies, considering data reported in healthy volunteers, probably due to vasopressors.[21,30-32] In summary, the review of the selected articles related to the intermittent 0.5hr.-infusion of 1g q8h regimen occurred in six studies, against the 0.5g q6h regimen in only one study.[21,29-32]

The comparison of these protocols allows us to state that the variability in the coverage of meropenem in the treatment of septic shock was due to the different targets considered by the authors of the articles reviewed; remembering that the former target to express the effectiveness of carbapenem agents was 40% *f*ΔT> MIC instead the new target 100% *f*ΔT> MIC recommended by Abdul Aziz more recently.[17,28] Anyway, there is a consensus in the literature that after infusion of 0.5hr, meropenem coverage against Gram-negative pathogens up to MIC 2mg/L is guaranteed for targets considered in this review, despite the superiority of 100% *f*ΔT>MIC target applied by Kupa *et al*, and Gonçalves-Pereira *et al*, suggesting caution during septic shock therapy against Gram negative strains of intermediate susceptibility MIC 4- 8mg/L.[18,23,24]

Meropenem extended infusion

As in the last two decades it was reported the selection of mutants that occurred by eradicating susceptible strains (MIC 0.25-2.0mg/L) *K. pneumoniae. P. aeruginosa and Acinetobacter spp,* highly prevalent Gram-negative in most ICUs.[17] Several controlled protocols were conducted in critically ill patients undergoing meropenem therapy using strategies related to infusion duration of 3 hours instead of the 0.5 hr.-infusion recommended previously. The impact on antimicrobial coverage was also investigated, in addition testing new targets to achieve the desired clinical outcome of 50% and 60% up to 100% *f*ΔT> MIC, instead 40% *f*ΔT> MIC recommended previously for carbapenem agents for systemic administration and hospital use.[28]

So more recently it was investigated through controlled prospective studies the increased coverage resulting from the extended 3 hrs.-infusion for meropenem based on new target tested in septic patients with preserved renal function. Results of clinical protocols of meropenem 1g q8h done by extended infusion were presented in table 2.

The extended 3 hrs.-infusion was included in the routine of systemic administration of meropenem to septic patients with major burns in the hospital's ICU, and a target of 60% *f*ΔT> MIC was tested previously by Silva Junior *et al*, to investigate the robustness for eradication of *K. pneumoniae* strains MIC 4-8 mg/L, intermediate susceptibility according to the Clinical Laboratory & Standards Institute data base (CLSI). New strategies have been proposed to avoid the development of KPC MIC > 16 mg/L, even after few cases in the hospital's ICUs.[27] Subsequently, three other prospective

clinical protocols were performed in septic burn patients to investigate meropenem effectiveness based on the new target of 100% *f*ΔT>MIC proposed after an extended 3hrs.-infusion to guarantee the desired outcome.[18]

In a study carried out by Kupa *et al*, it was reported change in pharmacokinetics by increases on volume of distribution and prolongation of half-life, that impacted the pharmacodynamics occurred in the population of 13 critically ill burn patients (TBSA 13-38%), after thermal or electrical trauma, that were investigated at the earlier stage during the septic shock therapy. Patients have preserved renal function (CLcr 60-120 ml/min), and the most part of them received vasopressors. As in previous studies, there was a pronounced increase in the volume of distribution and a prolonged biological half-life of meropenem in these patients. In contrast, total body clearance was reduced for patients investigated in the early phase of septic shock, probably due to reduced expression of biotransporters by SIRS (OAT1, OAT3 and MRP4), involved in renal tubular secretion of beta-lactams. All patients reached the therapeutic target considered 100% *f*ΔT>MIC after the extended infusion against pathogens up to MIC 4 mg/L.[23,25,26]

In addition, it was investigated by De Camargo *et al,* septic major burns patients in a comparative study protocol in ICU teenagers with young adults. Then, it was included 20 septic burn patients TBSA 40% (32%-58%), with preserved renal function, or receiving vasopressors in the early phase of septic shock with augmented renal clearance. These patients were distributed in two groups: G1: 12-17yrs, and in G2: young adults 18-26 yrs. Significant difference between groups regarding volume of distribution and biological half-life occurred, remaining unchanged total body clearance; however, there was no difference between groups in antimicrobial coverage against pathogens up to MIC 4mg/L. It is important to highlight that G1-teeanager patients had early weaning from vasopressors and mechanical ventilation, compared to the group of young adults. The clinical endpoint was achieved, with clinical and microbiological cure for all patients of both groups after extended 3hrs.-infusion based on drug serum levels and 100% *f*ΔT>MIC PK/PD target.[33]

Then, in another study reported by Messiano *et al* that was conducted in 15 severe burn adult septic patients (TBSA 35%) with preserved renal function. Protocol was carried out in these in two sets of meropenem serum levels, after 48hrs of antimicrobial therapy (set 1) and 10 days afterwards (set 2). Patients received vasopressors only in the early phase of septic shock, set 1. After the extended 3hrs.-infusion of the recommended dose, the impact of pharmacokinetic changes on meropenem coverage occurred only at the early stage (set 1) of septic shock by comparison with the late stage (set 2). Authors described in the set 1, a pronounced increase in the apparent volume of distribution and prolongation of the biological half-life ensuring coverage of meropenem against isolates including *P. aeruginosa and K. pneumoniae* up to MIC 8 mg/L, only in the early stage of septic shock for all patients.[34] Nonetheless, it becomes important to highlight that in the treatment period, between the 10th and 14th day, late stage of meropenem therapy, coverage was guaranteed only up to MIC 1 mg/L for all patients, and in 80% (12/15) of them against isolates MIC 2mg/L, since no changes on kinetic parameters were found by comparison with data reported in healthy volunteers.[22,34] Based on data reported, it becomes relevant to consider that the septic patient with preserved renal function, or even receiving vasopressors at the early phase of shock, shows important change in the pharmacokinetics of meropenem administered by extended 3hrs.-infusion, that impacts positively the coverage in the most critical phase of infection therapy, guaranteed against Gram-negative isolates up to MIC 8 mg/L.[34]

It was previously evidenced through controlled prospective studies, that the pharmacokinetics of hydrophilic antimicrobials is altered in critically ill burn during the clinical course of septic shock resulting from SIRS, and in patients with polytrauma, or in the postoperative period of major surgeries such as thoracic or abdominal surgery. Then, regardless of the type of intermittent or extended infusion, in the same dose regimen, 1g q8h, serum levels lower than those bactericides required in the circulatory stream, soft tissues and bone, contribute to the development of bacterial resistance in these patients.[18]

A review of other studies related to pharmacokinetics, considering former targets of 40% or 50% *f*ΔT>MIC in the coverage of meropenem after an extended infusion, describes the results obtained from prospective controlled studies conducted in critically ill patients, table 2.[36-38]

Finally, all changes in pharmacokinetics recorded in critically ill septic patients in this review of clinical protocols were compared to baseline data reported in healthy volunteers, same dose regimen and type of infusion, to investigate the changes that occur in critically ill patients during septic shock.[22] It is also important to point out that, in general, we found agreement related to data in the literature regarding changes in pharmacokinetics that occurred in different proportions in critically ill patients with preserved renal function, after intermittent versus extended infusion. It is also noteworthy that after the extended infusion of 3 hours, the increase in the apparent volume of distribution recorded during SIRS, had consequently, the proportional increases in the biological half-life, especially in the early period of septic shock. Regarding meropenem coverage based on the target of 100% *f*ΔT>MIC against isolates up to MIC 8 mg/L, the superiority of extended 3hrs.-infusion compared to intermittent 0.5 hr.-infusion was evidenced by target achieved in most of the studies reported in this review.

Review of piperacillin-tazobactam studies based on duration of infusion

Intermittent infusion

Pharmacokinetics changes of piperacillin reported in different studies was investigated by comparison with the reference values reported by Occhipinti *et al*, in a study carried out in healthy volunteers after a 4.5 g q8h regimen of piperacillin combined with tazobactam, a beta-lactamase inhibitor.[39] Then, evidence of alteration in pharmacokinetics of clinical studies considered was related to higher or lower coverage against susceptible Gram-positive and Gram-negative pathogens. Targets recommended in the past by Kays *et al* for piperacillin-tazobactam coverage were 50% *f*ΔT> MIC against Gram-positive strains, while a target of 70% *f*ΔT> MIC was applied against Gram-negative strains.[40] More recently, the new target of 100% *f*ΔT>MIC was proposed for critically ill septic patients undergoing therapy with piperacillin-tazobactam to guarantee clinical cure reaching the desired outcome.[18] A serial of clinical protocols based on serum levels and PK/PD approach after intermittent infusion, table 3, or extended infusion was summarized in table 4. In addition, only three studies considering septic patients undergoing therapy with piperacillin-tazobactam done by intermittent 0.5hr.-infusion, 4.5 g q8h were found.[43,45,46] Another five protocols with piperacillin-tazobactam done by intermittent 0.5hr.-infusion, 4.5g q6h, related to drug effectiveness were compared.[41-44,47]

The most recent pilot study was conducted by De Souza *et al* in septic patients treated with piperacillin-tazobactam that was carried out in 40 major burns from a tertiary hospital in Sao Paulo, Brazil,

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using the recommended dose of 4.5g q6h in 22/40 patients that received intermittent 0.5hr.-infusion. Coverage was investigated based on the new recommended PK/PD target of 100% *f*ΔT>MIC. In this study, it was isolated from bloodstream, bronchoalveolar lavage for pneumonia unrelated to mechanical ventilation, wound and bone, as sites of infection from septic major burn patients. Among the isolates, the most relevant pathogens in terms of incidence and prevalence in ICU of burns of hospital were *K. pneumoniae, Enterobacter cloacae* among the Enterobacteriaceae, and *P. aeruginosa and Acinetobacter spp, non-Enterobacteriaceae*. In this protocol, piperacillin coverage occurred in 18/22 patients against pathogens up to MIC 2 mg/L, and in just one patient against MIC 8 mg/L strains; it is noteworthy that any patient showed coverage against MIC 16 mg/L strains after the intermittent 0.5hr.- infusion.[41] In addition, it was investigated by Udy et al, 47 septic patients in intensive care therapy. All patients received the dose regimen, 4.5g q6h, by intermittent infusion of 0.33 h (20 minutes) for the treatment of nosocomial pneumonia. PK/PD target of 100% *f*ΔT>MIC was considered by the authors, and clinical cure was achieved for 32/47 patients against pathogens up to MIC 4 mg/L, falling to 23/47 patients (MIC 8mg/L), and for 16/47 patients against MIC 16 mg/L strains.[42]

In another study reported by Silva Jr *et al* was carried out in 35 septic major burn patients (TBSA>40%) that received intermittent infusion in two regimens; 26 patients received the conventional dose regimen recommended in hospital, 4.5g q8h, and another nine patients received the 4.5 g q6h regimen. In this study, the target 70% *fΔ*T>MIC initially recommended by Kays (1999) was considered. Piperacillin coverage after intermittent 0.5hr.-infusion, regimen of 4.5 q8h occurred for all patients (26/26) against Gram-negative pathogens up to MIC 2 mg/L, falling to 23/26 patients including *P. aeruginosa* (MIC 4 mg/L). In contrast, considering intermediate susceptibility pathogens (MIC 8 mg/L), target was achieved in 14/26 patients. Microbiological study revealed positive cultures for several Gram-positive isolates with high incidence of S. aureus. High prevalence of Enterobacteriaceae up to MIC 2 mg/L was registered, while *P. aeruginosa* MIC 2-4 mg/L and *Acinetobacter spp* (MIC 8-16 mg/L) were the most prevalent Gram-negative in infections recorded in severely burned ICU patients. Additionally, when regimen 4.5g q6h was tested in another nine patients, clinical and microbiological cure occurred for all patients (9/9) up to MIC 16 mg/L against Gram-negative strains after the 0.5h intermittent infusion, since pathogens with MIC 8-16mg/L were isolated only in two patients.[40,43]

In addition, Bourget et al investigated also major burn patients, TBSA 26-34%, in a study conducted in 10 critically ill patients using the same dose regimen prescribed in many studies included in this review, 4.5g q6h, intermittent infusion 0.5 h. Authors reported that the target of 70% *f*ΔT> MIC was achieved for all patients up to MIC 2mg/L against Enterobacteriaceae isolates, *P. aeruginosa,* and *Streptococcus spp*.[44] However, it is important to highlight that the goal of 70% *f*ΔT> MIC recommended by Kays *et al*., against Gram-negatives was considered in the protocols reported by Silva Jr et al, and Bourget et al.[43,44]

In contrast, in the period between 2005-2014, another targets 50% *f*ΔT>MIC, 50% *f*ΔT>4xMIC were applied in the studies. It is important to highlight that different target was considered in these studies to measure the piperacillin effectiveness through the PK/PD approach in critically ill septic patients, since the target of 50% *f*ΔT>MIC was recommended by Kays *et al*, only against Gram-positive strains.[40]

It was investigated by Jeon *et al*, 50 severely major burn patients to evaluate the piperacillin effectiveness through the PK/PD approach by applying another target of 50% *f*ΔT>4xMIC against Enterobacteriaceae isolates, recording a higher prevalence of *K. pneumoniae* (MIC 16 mg/L) in 45/50 patients.[44] In addition, Taccone *et al* investigated 27 septic patients with bacteremia receiving the same dose regimen the 4.5g q8h. In this protocol, the target considered was also 50% *f*ΔT> 4xMIC against Gram-negative strains with coverage of 12/27 patients against MIC 16 mg/L isolates. In this study, authors reported coverage for treating infections caused by *Enterobacteriaceae, Pseudomonas aeruginosa, Hafnia alvei.*[46] Finally, Li (2005) in a prospective protocol to study conducted in 132 septic patients with complicated abdominal infection, receiving 3,375 g q6h by intermittent infusion. In this study, also the target considered was 50% *f*ΔT>4xMIC. It was reported by authors that clinical cure occurred by eradication of Gram-negative strains achieved for all patients up to MIC 2 mg/L, including coverage of Enterobacteriaceae isolates, *P. aeruginosa, and Bacterioides spp*.[47]

In summary, the review of the selected articles that applied the intermittent infusion of 0.5 hr., dose regimen of 4.5g q6h regimen was investigated in four studies, and dose regimen of 3.375g q6h in one protocol of study.[41-44,47] In addition, dose regimen 4.5g q8h were investigated in another three protocols of study.[43,45,46] Comparison of these protocols allows us to state that the variability in antimicrobial coverage in the treatment of septic shock was due to the different targets considered by the authors of these articles. It is also noteworthy that the target initially recommended to express the effectiveness of beta-lactam agents such as piperacillin and first to fourth generation cephalosporin derivatives was 50% *f*ΔT> MIC only against Gram-positives, and 70% *f*ΔT> MIC against Gram-negatives.[40,43,44] However, other targets have been considered such as 50% *f*ΔT>4xCIM against Gram-negatives. In this last case, it is important to be very careful regarding the neurotoxicity of beta-lactams and carbapenem agents in targets of 50% *f*ΔT>4xMIC, still little investigated.[45,46,47]

Anyway, the consensus in the scientific literature regarding the 0.5 h intermittent infusion is that it guarantees beta-lactam coverage, including piperacillin-tazobactam against Gram-positive and Gram-negative up to MIC 2mg/L for all 50% targets, 70%, 100% *f*ΔT>MIC considered in this review, despite the superiority in drug effectiveness and safety guaranteed for the target of 100% *f*ΔT>MIC referred by Souza *et al* and Udy *et al* for the regimen of 4.5 g q6h in septic shock therapy against intermediate susceptibility pathogens MIC 8-16 mg/L.[17,18,41,42]

Piperacillin-tazobactam extended infusion

Selection of mutants previously reported in the last consensus of the Sepsis Surviving Campaign for *K. pneumoniae, P. aeruginosa* and *Acinetobacter spp* was based on the high incidence and prevalence in ICUs. Then, several controlled protocols of study were conducted in critically ill patients undergoing piperacillin-tazobactam therapy using strategies related to infusion duration from 2 up to 4 hours, instead of the one initially recommended of 0.5hr on the package insert for the drug infusion.[12,17,18] Goal was to evaluate the target to be reached against Gram-negative intermediate susceptibility strains, MIC 8-16 mg/L to ensure antimicrobial coverage up to MIC 32 mg/L. The impact on antimicrobial coverage was also investigated, in addition to testing new targets to achieve the desired clinical outcome of 50%, 90% to 100%*f*ΔT> MIC, instead of 70%*f*ΔT> MIC, initially recommended by Kays (1999) for beta-lactams of systemic administration and hospital use against Gram-negative strains.[17,18,40]

Recently, it was investigated through a controlled prospective study on the increased coverage resulting from the extended 3-hrs.-infusion of piperacillin based on new effectiveness indices tested in septic patients with preserved or augmented renal clearance. It

was proved, in a study the superiority on coverage for this type of infusion in the protocol conducted by Souza *et al*, in a two-arm study involving 18 critically ill burn patients receiving the regimen 4.5g q6h by extended infusion of 2 hours in nine patients by comparison with infusion of 3 hours in another nine patients; the PK/PD target considered by the authors was 100% *f*ΔT> MIC. There was an evident improvement in the clinical outcome with the use of this infusion in patients receiving 3 hrs.-infusion since coverage was guaranteed up to MIC 16-32 mg/L for all patients by comparison with 2 hrs.-infusion. This fact was due to trough serum levels increased by three folds after extended 3 hrs.-infusion, with increases on volume of distribution and biological half-life, that impacted positively piperacillin effectiveness achieved after 3hrs.-infusion. Consequently, coverage occurred for all patients compared up to MIC 32 mg/L by comparison with the same dose regimen done by 2hr.-infusion up to MIC 4mg/L (9/9 patients), with reduction against intermediate susceptibility isolates, MIC 8 mg/L (7/9) and MIC 16 mg/L in only one patient.[41]

In another controlled protocol of study 16 septic patients with preserved renal function and febrile neutropenia were included by Sime *at al*. Only two blood samples collection based on one compartment open model and noncompartmental data analysis were done. Total body clearance was reduced, but the volume of distribution and the biological half-life were not reported. Antimicrobial coverage against MIC 16 mg/L pathogens was achieved in 11/16 patients and *Enterobacteriaceae* were isolated from these patients. The clinical endpoint was achieved with clinical and microbiological cure of 11/16 patients after the extended 3hrs.-infusion, for 100% *f*ΔT> MIC target considered.[48] In addition, 15 septic patients receiving 4.5g q6h by 3-hrs.-infusion undergoing pneumonia therapy for the PK/PD target of 100% *f*ΔT> MIC considered were investigated by De Waale *et al*. Coverage was achieved for all patients (15/15) up to MIC 8 mg/L, falling to 7/15 against MIC 16 mg/L isolates. It was shown alteration on pharmacokinetics by increases in the volume of distribution by trice, despite the biological half-life remaining unchanged. Therefore, total body clearance reported by authors were like data reported in healthy volunteers, probably due to vasopressors required at the earlier stage of septic shock, responsible by augmented renal clearance, in total body plasma clearance with consequent reduction of biological half-life.[38,39]

Finally, Chung *et al* described a study carried out in 11 adult septic patients, with preserved renal function, for the target of 90% *f*ΔT>MIC considered. The impact of pharmacokinetic changes in piperacillin coverage following a dose of 4.5g every 8h by prolonged 4hrs-infusion was recorded during septic shock therapy. Authors described a pronounced three-folds increase in the apparent volume of distribution despite, and a two-folds prolonged biological half-life. Such kinetic changes ensured coverage for all patients at the target of 90% *f*ΔT>MIC considered against *P. aeruginosa* and *Enterobacteriaceae* isolates up to MIC 16mg/L.[49]

Nonetheless, the wide variability of results concerning the total body clearance of piperacillin occurred either using vasopressors in titrated doses according to the greater or lesser need of each patient in relation to the results of the study of Chung *et al*., as well as the use of high doses or even the association of two, even three vasopressor agents in some septic patients included in the study of De Waele *et al*.[38]

Based on results reported by those authors in reviewed clinical protocols, it becomes relevant to consider that the septic patient with preserved renal function, or receiving vasopressors at the early phase of shock (SIRS), shows alteration in the pharmacokinetics of piperacillin given by an extended infusion of 3-hour and of 4 hours, positively impacting piperacillin coverage, and consequently piperacillin effectiveness in the most critical phase of the infection, which was guaranteed against isolates, MIC 16-32 mg/L.[38,41,42,49]

Review of studies related to the pharmacokinetics of piperacillin, considering the targets of 90% *f*ΔT>MIC after 4hrs.-infusion, or 100% *f*ΔT>MIC for coverage of this antimicrobial after prolonged infusion of 2 to 3 hours, describes the comparison of results obtained in five prospective controlled studies conducted in critically ill patients during septic shock therapy. Pharmacokinetic changes recorded in septic patients in protocol considered in this review were always compared to data reported in healthy volunteers, considering dose regimens to investigate changes that occur in critically ill patients during the period of septic shock.[38,39,41,48,49] Reference values for piperacillin pharmacokinetics related to the biological half-life, volume of distribution and total body clearance in healthy volunteers were registered after piperacillin-tazobactam regimens of 4.5g q8h and 3.375g q6h.[39]

It is important to highlight that, in general, we found data from the literature regarding the change in pharmacokinetics that occurred in critically ill patients with preserved or augmented renal function, after the extended infusion of 2 to 4 hours. It is also noteworthy that in 3/4 studies with patients receiving the extended infusion of 3 hours, with an increase in the apparent volume of distribution recorded during SIRS, that consequently had a proportional prolongation in the biological half-life, especially in the early period of septic shock. Nonetheless, it was shown high variability in the total body clearance justified in some studies.[41,48,49]

Regarding antimicrobial coverage based on the target recommended 100% *f*ΔT> MIC against isolates up to MIC 16-32 mg/L, the superiority of the extended after 3hrs.-infusion, or even of 4hrs.-infusion with a target 90% *f*ΔT> MIC considered by Chung et al., were evidenced by piperacillin effectiveness reached in the clinical protocols of studies included in this review by comparison with the extended 2-hrs-infusion.[38,41,48,49]

Conclusion

In this systematic review, the superiority of the extended 3 to 4hrs.-infusions was evidenced by comparison with intermittent 0.5hr.-infusion on drug effectiveness based on the new recommended target 100% *f*ΔT>MIC for meropenem and piperacillin-tazobactam in critically ill patients with renal function preserved or augmented in the articles considered.

Different changes occurred in the pharmacokinetics of these beta-lactams as a function of prolonged infusion period impacting positively target attainment, and consequently, different antimicrobial effectiveness of both meropenem and piperacillin combined with tazobactam would be expected.

It is important to point out that the changes registered in the pharmacokinetics with impact on pharmacodynamics occurred in a different manner for each beta-lactam investigated in the chosen articles. Consequently, meropenem after an extended 3 hrs.-infusion, a three-fold increase in the volume of distribution and half-life were registered, evidencing a linear correlation between them, impacting meropenem coverage and consequently drug effectiveness against Gram negatives isolates up to MIC 4-8mg/L in severe septic ICU patients, mainly at the earlier stage of systemic inflammatory response syndrome.

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On the other hand, changes in pharmacokinetics of piperacillin were related to an increase in the volume of distribution dependent on the SIRS, that in general occurs in critically ill patients at the earlier stage of septic shock. It should also be noted that the biological half-life of piperacillin varies with renal clearance, and therefore depends only on serum clearance of drug. Therefore, the duration of infusion did not change these other two kinetic parameters, since the patients investigated in the clinical protocols of the articles selected for the review study, had preserved renal function or renal clearance increased by the vasopressors required in those patients mainly at the early phase of septic shock.

It is considered that meropenem and piperacillin serum levels should be implemented in the routine of the hospital's central laboratory based on PK/PD tools, as an important laboratory support required, to justify changes in medical conduct, and dose adjustment done in a real-time by clinical intervention to ensure the desired clinical outcome.

Finally, the clinical and microbiological cure by eradicating susceptible pathogens will contribute to the reduction of deaths in ICU patients by combating the selection of mutants, preventing the development of bacterial resistance and MDR in a pandemic planet.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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