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Article

The influence of sepsis on antimicrobials tissue penetration: The use of microdialysis technique to access free drug distribution

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Sepsis is described as a life-threatening organ dysfunction caused by a host's response to infection, leading to an unbalance in body homeostasis. It is one of the leading causes of death in developed countries. Considering that in critically ill patients, such as those with sepsis, plasma concentrations do not necessarily reflect tissue concentrations, one way to assess tissue concentrations is through the microdialysis technique, which allows direct measurements of free drug at the site of action. This review was carried out after searching the Pubmed, Scielo and Web of Science databases, using the following descriptors: (microdialysis AND (sepsis OR septic shock OR severe sepsis OR septicemia)) OR (microdialysis AND (sepsis OR septic shock OR severe sepsis) OR septicemia) AND (antimicrobial OR antibiotic OR antifungal)). The physiological changes generated by sepsis may imply changes in pharmacokinetic parameters, such as in clearance, which may be reduced in these patients and in volume of distribution, which presents an expansion, mainly due to edema. Both events contribute to a high inter-individual variability in tissue penetration of antimicrobials which is generally observed in patients with sepsis.

Keywords: Sepsis. Antimicrobials. Microdialysis. Tissue penetration. Pharmacokinetics. Pharmacodynamics.

INTRODUCTION

Sepsis has been recently defined as a life-threatening organ dysfunction caused by a response of the host to the infection, leading to a misbalance of body homeostasis (Angus, Poll, 2013; Singer *et al.*, 2016). This disease is one of the major causes of death in developed countries (Nguyen *et al.*, 2000) and this topic has emerging importance in medicine due to increasing incidence in hospitals, caused by bacteria resistance and inefficiency in antimicrobial treatment (Hotchkiss, Karl, 2003; Micek, Hampton, Kollefc, 2018). At a global level, 48.9 million sepsis cases were registered in 2017 and 19.7% of global deaths had sepsis as the cause (Rudd *et al.*, 2020). One of clinicians' challenges is the choice of antimicrobial therapy regimen to cover up the larger range of microorganisms, who are spread all over blood and tissue, mostly at the site of infection (Micek, Hampton, Kollefc, 2018). For that reason, the antimicrobial treatment of choice will depend on the spectrum of action and the pharmacokinetics properties of the drug, aiming broad blood and tissue distribution.

Considering that in critically ill patients, as those with sepsis, the concentration in plasma does not necessarily reflect tissue concentration (Liu *et al.*, 2011), in the last years, researchers showed the relevance of studying what happens within tissues (Venkatesh, Morgan, Cohen, 2010). That is why many studies were conducted to evaluate drug tissue distribution in a sepsis scenario, but a great part of those used biopsy (Condon *et al.*, 1997; Wagenlehner *et al.*, 2006) to determine drug concentration at the site of infection. The disadvantage of these studies was not being able to define free drug concentration, which are the fraction of action of the drug. Therefore, microdialysis

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(MD) became very popular in the last years for being an advanced technique of semi-invasive sampling, that can be use in any tissue for free interstitial concentration measuring, being applied to many pre-clinic and clinic studies (Nandi, Lunte, 2009). This technique allows the distinction of interstitial space fluid (ISF) and the others compartments (Joukhadar *et al.*, 2001a), allowing the determination of free drugs level in ISF. The ratio of antimicrobial exposition in tissue and free drug exposition in plasma give the penetration factor (fT). This factor, combined with evaluation of plasma and tissue concentration profiles and other pharmacokinetic parameters, can help to define antimicrobial treatment for each patient. Considering the pathophysiology of the disease and variability between patients, selection of best antimicrobial drug for sepsis situation and the individualization of the regimen for each patient, can contribute to reduction of sepsis mortality.

For the reasons mentioned above, this article review was conducted after a research in Pubmed, Scielo and Web of Science databases, using the same follower descriptors: *(microdialysis AND (sepsis OR septic shock OR severe sepsis OR septicemia)) OR (microdialysis AND (sepsis OR septic shock OR severe sepsis OR septicemia) AND (antimicrobial OR antibiotic OR antifungal)).* No time intervals were applied or any other filters. In Pubmed, Scielo and Web of Science, 119, 2 and 162 articles published between 1993 and 2021 were extracted, respectively, and, after authors reading of titles and abstracts, 24 articles were finally selected for complete reading. Four of the 24 articles were excluded for not fulfilling the prerequisites to be used in this review. In the end, 18 articles were in fact selected for writing this systematic review.

Microdialysis as a technique for tissue penetration evaluation

MD technique is done through a probe with a dialysis membrane, that is semipermeable to small molecules (molecular weight < 20,000 Da) (Shippenberg, Thompson, 2001). Through this probe, an isotonic solution relative to the body fluid, is perfused during the experiment time interval. By the osmolar difference between the perfusate and the fluid around the membrane, some molecules pass through the membrane, then, they dilute in perfusate solution. Perfusate containing the analyte of interest flows through the output tube, where it can be collected for posterior quantification. The main advantage of MD is that it allows for multiple determinations of pharmacologically active drug, that is the free fraction (or the fraction not bound to plasma proteins), at the target site in the same patient (Joukhadar, Derendorf, Muller, 2001b). However, tissue biopsies only can provide the total drug concentration in a tissue portion at a single moment (Mouton *et al.*, 2008).

The membrane probe is able to sample a fraction of the drug in the ISF, so is necessary to perform a probe calibration procedure to quantify how much is possible to harvest the drug in the microdialysate by classic approaches such no netflux and retrodialysis. The majority of the articles selected for this review used the retrodialysis technique. In retrodialysis, before the drug administration, a solution containing a certain concentration of the drug, or another internal standard, is perfused through the probe and then the analyte in dialysate is quantified. This percentage of recovery is used for calculation of microdialysis concentration of the drug in ISF. Also, the high-performance liquid chromatography, with tandem mass spectrometry detector, was the most used method to quantification. Still, other detectors were used, like UV spectroscopy and fluorescence, depending on molecules and matrix characteristics.

Pathophysiology of sepsis and diagnosis criteria

Sepsis is a highly heterogeneous syndrome that is defined as a systemic inflammatory response syndrome (SIRS) caused by an infection. Sepsis complicated by organ dysfunction was termed severe sepsis, which could progress to septic shock, (defined as sepsis and refractory hypotension). In the most recent 'Sepsis-3' consensus definition, sepsis is defined as a life-threatening organ dysfunction that is caused by a deregulated host response to infection, and the term severe sepsis has been avoided (Singer *et al.*, 2016). In sepsis, a host response is trigger in the presence of an infectious agent, causing a misbalance in homeostasis due to an extremely inflammatory

phenomenon, as activation of cytokines (Ilias *et al.*, 2018), nitric oxide production and expression of adhesion molecules to endothelium, where important alterations in coagulation and fibrinolysis process can happen (Michie, 1996; Schouten *et al.*, 2008). At the same time, the body regulates against this response, triggering an anti-inflammatory response, which is fundamental to patient recovery (Hotchkiss, Karl, 2003). However, the imbalance between these two forces, inflammatory and anti-inflammatory, is responsible for organ dysfunction (Nedeva, Menassa, Puthalakath, 2019).

High levels of serum lactate is an indication of cardiovascular compromise. Circulatory alterations, like vasodilatation and increase of capillary permeability, contribute to relative hypovolemia and hypotension, being a good predictor of sepsis worsening, as septic shock (Seymour, Rosengart, 2015). Edema will occur with reduction of plasma oncotic pressure, due to increase of glucose and albumin or metabolic changes, leading to leakage of liquid to ISF, causing distribution volume (V) increment (Venkatesh, Morgan, Cohen, 2010). This larger V, together with albumin increase, will elevate antimicrobial bound to protein and, consequently, reduce the active free fraction of the drug (Fly, 1996; Power *et al.*, 1998). This fluid retention could also be due to renal dysfunction and may cause V increase, but mostly, renal dysfunction can cause clearance (CL) reduction and this delay of depuration increase time of half-life ($t_{1/2}$) of drugs in septic patients. Renal dysfunction in sepsis is multifactorial, so the cause may be hypovolemia and hypotension, which leads to poor organ oxygenation (Silva Júnior *et al.*, 2006). In this situation, acute tubular necrosis and lesion through cellular apoptosis happens, prompting a urinary deficit and increase of serum urea and creatinine levels (Michie, 1996).

This particular physiopathological situation of critically ill septic patients makes infection disease management difficult with standard antimicrobial protocols of treatment (Roberts *et al.*, 2010). Impairment on tissue penetration can lead to alterations in the achievement of concentration levels in the site of infection and in drug exposition in plasma and tissue, given by area under the curve (AUC_{0-t}). This can shift expected treatment outcomes, prompting failure and patient's death.

Sepsis diagnosis is usually made using the criteria of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee. They define that a sepsis situation, must include at least the manifestations of: low or high temperature, less than 36 °C and more than 38 °C; heart rate more than 90 beats per minute; respiratory rate over 20 breaths per minute or hyperventilation (CO_2 pressure less than 32 mm Hg); alterations in white blood cells count, with elevated presence of immature neutrophils (Bone *et al.*, 1992). Prognosis are predicted using different criteria, as Acute Physiology And Chronic Health Evaluation (APACHE) (Knaus *et al.*, 1985), especially version II, Simplified Acute Physiology Score (SAPS) (Gall, Lemeshow, Saulnier, 1993), and, specifically for sepsis, Sequential Organ Failure Assessment (SOFA) (Vincent *et al.*, 1996) and Sepsis Severity Score (SSS) (Osborn *et al.*, 2014). All those are models who score the disease using different variables (Osborn *et al.*, 2014 [30]) for evaluation of severity, risk of death and for patients monitoring during treatment (Khwannimit, Bhurayanontachai, Vattanavanit, 2017).

Sepsis initial site of infection and main pathogens

Sepsis could be related to any kind of infection. A 2017 study made with data collected around the world, showed that diarrheal diseases and lower respiratory infections were the main causes of sepsis through patients of any age (Rudd, 2020 [6]). However, sepsis is also related to pneumonia, intra-abdominal infection and urinary infection (Kaukonen *et al.*, 2014). Also, there are highly frequent infections related to catheters, soft tissue abscess, meningitis and endocarditis (Ilias *et al.*, 2018). For these reasons, the World Health Organization defines that, cases of severe infection, such as diarrhea, lower respiratory tract infection, bacteremia, fungus infection, malaria, dengue and any communicable disease have sepsis as the fate and death as a common prognosis (WHO, 2020).

Severe infections are commonly caused by resistant pathogens, who are more difficult to treat with conventional antimicrobial therapy (WHO, 2020). Microorganisms as *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter spp.* and *Staphylococcus aureus* are frequently resistant

to third generation of cephalosporins, as carbapenems, to aminoglycosides and to methicillin (MRSA) (WHO, 2017). In cases of intra-abdominal infections, more than one microorganism could be isolated from the infection and, among them, are Gram-positive and Gram-negative bacteria (Nord, 1994; Ilias *et al.*, 2018). In a Turkey study, Gram-negative (65.9%) bacteria, like *Klebsiella* spp. and *E. coli*, were the most isolated in sepsis cases compared to Gram-positive, still, *Staphylococcus spp.* were one of the main pathogen isolated (21.9%) (Tanriover *et al.*, 2006). However, in another European study, *S. aureus* (30%), each 14% were methicillin-resistant, *Pseudomonas spp.* (14%), and *E. coli* (13%) were the main pathogens isolated from septic patients (Vincent *et al.*, 2006). In Brazil, the largest South American country, also Gram-negative bacteria were predominant in isolates from pediatric patients with sepsis (37.5%), while *S. aureus* were about 27.5% of the cases, followed by *Neisseria meningitides* (12.5%) (São Pedro, Morcillo, Baracat, 2015). In cases of fungus infections, *Candida spp.* is prevalent as an agent in immunosuppressed patients, leading to sepsis (Eggimann, Garbino, Pittet, 2003; Sekyere, 2018; Tanriover *et al.*, 2006).

ANTIMICROBIALS IN SEPSIS: PHARMACOKINETICS AND PHARMACODYNAMICS

In this systematic review, organized in subtopics, the most important groups of antimicrobials used in the sepsis treatment were evaluated in terms of their pharmacokinetics and pharmacodynamics properties, comparing the PK differences observed in healthy volunteers and septic patients. The pharmacokinetic parameters were organized by respective study in Table I.

TABLE I - Pharmacokinetic parameters and penetration factor of antimicrobials in sepsis

Antimicrobial	Study group	Tissue of ISF	PK parameters	fT	References
Piperacilin	Shock septic patients (n=7) Volunteers (n=6)	Muscle and adipose subcutaneous tissue	V_{sepsis} = 40.7 ± 8.69 L* $V_{healthy}$ = 9.61 ± 1.79 L CL_{sepsis} = 8.16 ± 1.98 $L.h^{-1}$ $CL_{healthy}$ = 7.86 ± 0.9 $L.h^{-1}$	Muscle fT_{sepsis} = 0.19 ± 0.03* $fT_{healthy}$ = 0.55 ± 0.09 Subcutis fT_{sepsis} = 0.10 ± 0.02* $fT_{healthy}$ = 0.31 ± 0.07	Joukhadar *et al*. 2001
Cefpirome	Sepsis patients (n=12) Volunteers (n=6)	Skeletal muscle	V_{sepsis} = 25.9 ± 7.1 L* $V_{healthy}$ = 14.6 ± 1.3 L CL_{sepsis} = 4.5 ± 0.66 $L.h^{-1}$ $CL_{healthy}$ = 4.68 ± 0.48 $L.h^{-1}$	fT_{sepsis} = 0.63 ± 0.04 $fT_{healthy}$ = 0.83 ± 0.08	Joukhadar *et al*. 2002
Cefpirome	Sepsis patients (n=11) Volunteers (n=7)	Adipose subcutaneous tissue	V_{sepsis} = 21.9 ± 4.5 L* $V_{healthy}$ = 15.8 ± 5.6 L CL_{sepsis} = 4.8 ± 1.56 $L.h^{-1}$ $CL_{healthy}$ = 6.3 ± 1.86 $L.h^{-1}$	fT_{sepsis} = 0.42 * $fT_{healthy}$ = 0.80	Sauermann *et al*. 2005

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Antimicrobial	Study group	Tissue of ISF	PK parameters	fT	References
Aztreonam	Rats with cecal ligation and puncture (CLP) surgery (n=9) Control of health rats (n=5)	Skeletal muscle and intraperitoneal fluid	V_{sepsis} = 0.503 ± 0.328 L $V_{healthy}$ = 0.473 ± 0.075 L CL_{sepsis} = 0.702 ± 0.474 $L.h^{-1}.kg^{-1}$ $CL_{healthy}$ = 0.768 ± 0.108 $L.h^{-1}.kg^{-1}$	Muscle fT_{sepsis} = 1.00 ± 0.30 $fT_{healthy}$ = 0.95 ± 0.12 Intraperitoneal fluid fT_{sepsis} = 0.92 ± 0.41 $fT_{healthy}$ = 0.89 ± 0.14	Chauzi *et al*. 2018
Avibactam	Rats with cecal ligation and puncture (CLP) surgery (n=9) Control of health rats (n=5)	Skeletal muscle and intraperitoneal fluid	V_{sepsis} = 0.312 ± 0.040 L $V_{healthy}$ = 0.285 ± 0.043 L CL_{sepsis} = 0.612 ± 0.072 $L.h^{-1}.kg^{-1}$ $CL_{healthy}$ = 0.636 ± 0086 $L.h^{-1}.kg^{-1}$	Muscle fT_{sepsis} = 1.01 ± 0.14 $fT_{healthy}$ = 0.91 ± 0.11 Intraperitoneal fluid fT_{sepsis} = 0.94 ± 0.21 $fT_{healthy}$ = 0.88 ± 0.11	Chauzi *et al*. 2018
Imipenem	Rats with cecal ligation and puncture (CLP) surgery Control of health rats	Intraperitoneal fluid	V_{sepsis} = 0.310 ± 0.049 L $V_{healthy}$ = 0.289 ± 0.047 L CL_{sepsis} = 0.654 ± 0.126 $L.h^{-1}.kg^{-1}$ $CL_{healthy}$ = 0.714 ± 0.138 $L.h^{-1}.kg^{-1}$	fT_{sepsis} = 0.89 ± 0.28 $fT_{healthy}$ = 1.01 ± 0.19	Lefeuvre *et al.* 2006
Meropenem	Shock septic patients (n=6)	Intraperitoneal fluid	V_{sepsis} = 7.11 ± 2.36 L CL_{sepsis} = 6.72 ± 4.2 $L.h^{-1}$	fT_{sepsis} = 0.73 ± 0.15	Karjagin *et al.* 2007
Meropenem	Sepsis patients (n=10)	Adipose subcutaneous tissue	For intermittent infusion and continuous infusion V = 7.9 L CL = 13.6 (CV 95%: 12.2-14.9) $L.h^{-1}$	Intermittent infusion fTday1= 0.73 fTday3= 0.45 Continuous infusion fTday1= 0.15 fTday3= 0.67	Roberts *et al*. 2009b
Levofloxacin	Sepsis patients (n=7)	Skeletal muscle	V_{sepsis} = 124.6 ± 39 L CL_{sepsis} = 8.79 ± 5.50 $L.h^{-1}$	fT_{sepsis} = 0.85	Zeitlinger *et al*. 2003

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Antimicrobial	Study group	Tissue of ISF	PK parameters	fT	References
Moxifloxacin	Shock septic patients (n=10)	Muscle and adipose subcutaneous tissue	V_{day1}= 131.1 ± 28.7 L V_{day3}= 121.2 ± 23.2 L V_{day5}= 118.6 ± 39.8 L CL_{day1}= 16.2 ± 5.9 L.h^{-1} CL_{day3}= 15.7 ± 7.4 L.h^{-1} CL_{day5}= 14.9 ± 4.2 L.h^{-1}	Muscle fT_{day1}= 0.90 fT_{day3}= 0.95 fT_{day5} = 1.14 Subcutis fT_{day}= 1.05 fT_{day3}= 0.91 fT_{day5} = 0.93	Nowak *et al*. 2019.
Linezolid	Sepsis patients (n=12)	Adipose subcutaneous tissue	IV single V = 61.4 L CL = 9.91 L.h^{-1} IV multiple V = 79.8 L CL = 8.44 L.h^{-1}	Muscle fT= 0.99 Subcutis fT= 0.89	Buerger *et al*. 2006
Linezolid	Severe Sepsis patients (n=8) Shock septic patients (n=16) Volunteers (n=10)	Muscle and adipose subcutaneous tissue	Severe sepsis V = 57.15 ± 17.8 L CL = 14.83 ± 7.55 L.h^{-1} Shock septic V = 60.37 ± 13.92 L CL = 9.81 ± 4.32 L.h^{-1} Volunteers V = 51.47 ± 9.51 L CL = 8.59 ± 3.38 L.h^{-1}	Severe sepsis fT_{muscle}= 1.0 $fT_{subcutanous}$= 1.35 Shock septic fT_{muscle}= 1.0 $fT_{subcutanous}$= 0.9 Volunteers fT_{muscle}= 1.22 $fT_{subcutanous}$= 1.71	Thallinger *et al*. 2007
Fosfomycin	Sepsis patients (n=9)	Skeletal muscle	V_{sepsis}= 31.5 ± 4.5 L CL_{sepsis}= 7.2 ± 1.33 L.h^{-1}	fT_{sepsis} = 0.7 (0.4-1.0)	Joukhadar *et al*. 2003
Fosfomycin	Shock septic patients (n=5) Volunteers (n=7)	Lung	$V_{healthy}$= 18.1 L $CL_{healthy}$= 5.24L.h^{-1}	fT_{sepsis} = 0.63 ± 0.31 $fT_{healthy}$= 0.53 ± 0.31	Matzi *et al*. 2010
Vancomycin	Sepsis patients (n=7)	Adipose subcutaneous tissue	V_{sepsis}= 10.87 ± 3.73 5 L CL_{sepsis}= 3.33 ± 1.19 L.h^{-1}	fT_{sepsis} = 0.37 (0.3-0.53)	Abraham *et al*. 2018
Metronidazole	Shock septic patients (n=6)	Skeletal muscle	V_{sepsis}= 53.5 ± 4.0 L CL_{sepsis}= 3.37 ± 1.61 L.h^{-1}	fT_{sepsis} = 0.87	Karjagin *et al*. 2005
Fluconazole	LPS-induced sepsis model (n=12) Control of health rats (n=16)	Skeletal muscle and Lung	V_{sepsis}= 0.17 L CL_{sepsis}= 0.0118L.h^{-1}	Muscle fT_{sepsis} = 1.18 $fT_{healthy}$= 1.12 Lung fT_{sepsis} = 1.32 ± 0.04 $fT_{healthy}$= 1.38 ± 0.39	Mauric *et al*. 2011

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Antimicrobial	Study group	Tissue of ISF	PK parameters	fT	References
Metronidazole	Shock septic patients (n=6)	Adipose subcutaneous tissue	V_{sepsis} = 20.4 (15.5-26.7) L CL_{sepsis} = 0.5 (0.2-0.6) $L.h^{-1}$	fT_{sepsis} = 0.53 ± 0.30	Sinnollareddy *et al.* 2015

CL= clearance; V = volume of distribution; fT = penetration factor given by $fAUC_{tissue}/fAUC_{plasma}$

*Significant statistical difference between groups.

[#] Significant statistical difference between IV bolus and continuous infusion.

The Figure 1 shows the mechanism of action of the drugs revised in the current study.

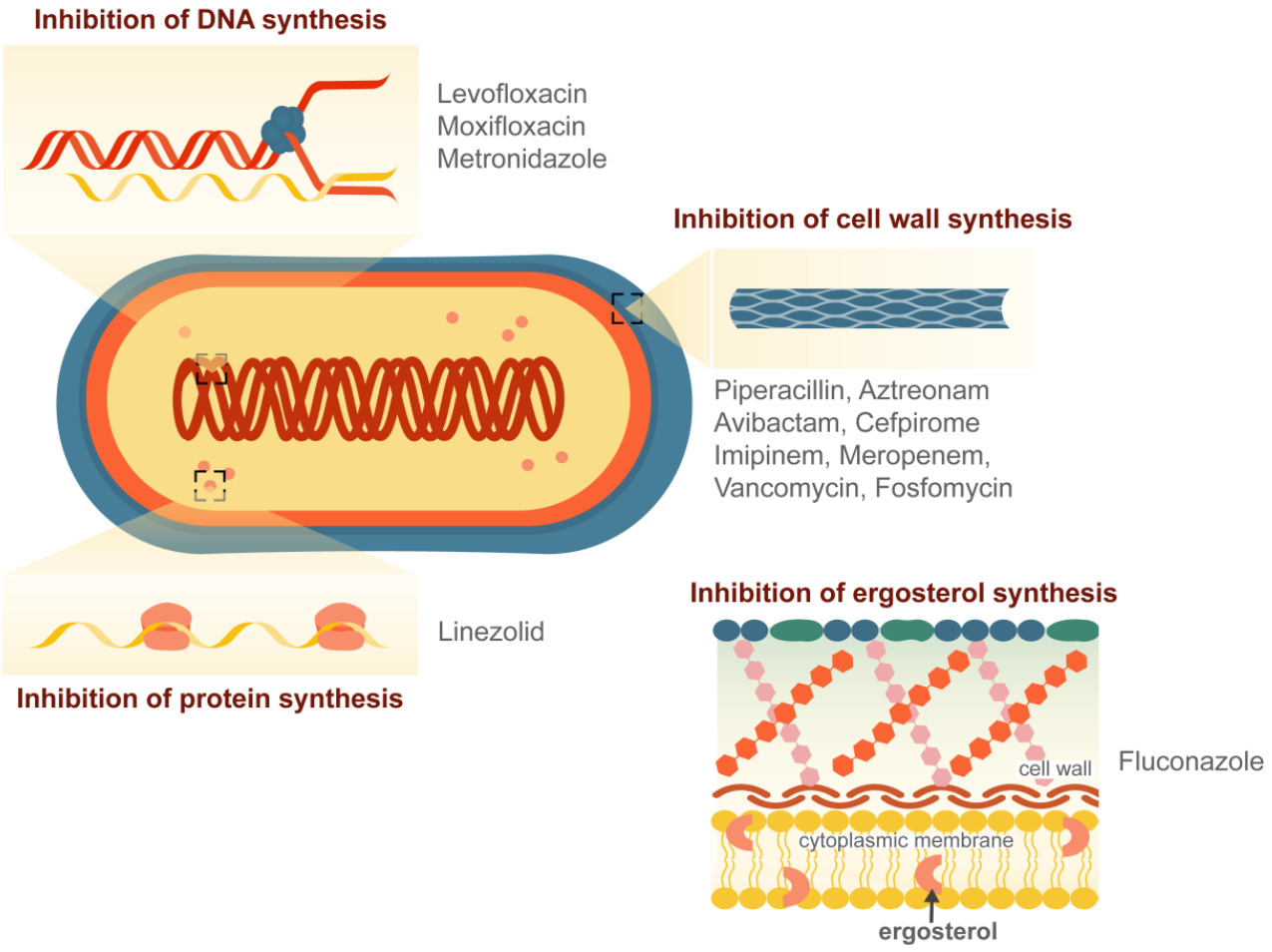

FIGURE 1 - Mechanism of action of antimicrobials used in sepsis treatment.

Piperacillin, Cefpirome and Aztreonam

Piperacillin is a largely prescribed antimicrobial in ICUs, as are many other β-lactams (Rello *et al.*, 2011). This class presents hydrophilic characteristics, (Tjandramaga *et al.*, 1978) which is why it is expected to distribute well in ISF. Joukhadar *et al.* (2001a), compared 7 septic shock patients with 6 healthy volunteers after a single intravenous (IV) administration of 4g of piperacillin. Plasma and ISF (microdialysis) samples from skeletal muscle and subcutaneous tissue were collected and concentration-time profiles analyzed. The main findings were the surprising lower concentrations of piperacillin in both tissues, compared to plasma concentrations, in septic patients. This could be due to great V of septic patients compared to volunteers (40.72 ± 8.69 vs. 9.61 ± 1.79 L, respectively). More astonishing was the difference in tissue penetration of septic patients: almost three times lower than in controls. Also, it was observed that the half-life of the elimination phase ($t_{1/2\beta}$) was higher in septic patients due to slower clearance. The extreme conditions present in shock septic patients explain all these findings, especially the use of vasopressors that are very needed in shock situations. In 2009a, Roberts *et al.* in a prospective randomized trial, with 13 septic patients compared the administration of piperacillin associated with tazobactam, a β-lactam inhibitor, in constant infusion with IV bolus. Plasma and ISF (microdialysis) samples of subcutaneous tissue were collected and concentration-time profiles showed a mean plasma concentration higher with continuous infusion when compared to IV bolus (16.6 vs. 4.9 $mg.L^{-1}$, respectively), even the continuous infusion dose was 25% less than IV bolus dose. Therefore, for an adequate regimen of treatment, a dose increase may not be necessary. Equilibration times between tissue and plasma concentrations, for 50% and 90%, were extremely high (173 and 570 h, respectively) for continuous infusion, so the equilibrium was not achieved during the experiment, maybe because of vascular alterations compromising drug distribution. Tissue penetration was almost three times higher for continuous infusion than IV bolus. Those differences between these two regimens could impact the effect, as can be seen by pharmacodynamics simulation results: continuous infusion more frequently achieved the therapeutic target of 100% T > MIC, that means time above minimum inhibitory concentration (MIC), PK/PD index usually applied to □-lactams, for bacteria with MIC's over 2 - 4 $mg.L^{-1}$.

As well as piperacillin, cefpirome belongs to the class of β-lactam; it is a four-generation cephalosporin, which has a wide spectrum, being indicated for the treatment of seriously ill patients. Joukhadar *et al.* (2002), performed microdialysis on the skeletal muscle of 12 septic patients compared with 6 healthy volunteers after a single IV administration of 2g of cefpirome. The $C_{máx}$ and $AUC_{0\text{-}4\ h}$ in skeletal muscle were significantly lower and $T_{máx}$ were significantly higher in patients with sepsis compared with the control group (62 ± 4* vs. 127 ± 15 $mg.L^{-1}$, 0.16 ± 0.012* vs. 0.259 ± 0.024 $g.h.L^{-1}$and 1.45 ± 0.18 vs. 0.72 ± 0.1 h, respectively). In septic patients, mean $AUC_{0\text{-}4\ h}$ values for free cefpirome in plasma and skeletal muscle were consistently lower than those in healthy volunteers, however, the fT, was not significantly different between both groups. Yet, the fluid overload, as expressed by a higher volume of distribution in patients with sepsis when compared with healthy controls (25.9* ± 7.1 and 14.6 ± 1.3 L), decreases directly drug concentrations in plasma and interstitial space. The authors conclude that after an equilibration period of 2 hours, the concentration-time profile of cefpirome in skeletal muscle is identical to plasma concentrations in patients and volunteers.

Another study of cefpirome was made by Sauermann *et al.* (2005). They performed microdialysis of subcutaneous adipose tissue in 11 patients with sepsis and compared against 7 healthy individuals after administration of 2 g of cefpirome. The $t_{1/2\beta}$ of cefpirome was significantly longer for patients than for healthy controls (3.05 ± 0.9 and 1.58 ± 0.5 h*) in plasma and subcutaneous adipose tissue (5.16 ± 2.41 and 1.55 ± 0.37 h*). For tissue, the $C_{máx}$ was lower in patients than in the healthy subjects (41 ± 17* and 116 ± 48 $mg.L^{-1}$, respectively) and showed reduction in $AUC_{0\text{-}4\ h}$ of septic patients (0.115 ± 0.043* and 0.219 ± 0.087 $g.h.L^{-1}$, respectively), further the patients exhibit increasing in the distribution volume (21.9 ± 4.5* and 15.8 ± 5.6 L, respectively). Plasma to tissue balance was considerably delayed in patients with sepsis compared to healthy patients. Thus, the penetration of cefpirome into subcutaneous adipose tissue occurs quickly in healthy subjects, and it

was strongly delayed in septic patients. In PD, the lowest and the highest tissue concentrations of cefpirome were tested by dynamic time-kill curves experiments against *S. aureus* and *P. aeruginosa*. T>MIC appeared to be slightly higher in septic patients, due their slower clearance, though, no statistical difference was found.

Chauzy *et al*. (2018) studied the combination of Aztreonam and Avibactam, β-lactam/β-lactamase inhibitors for the treatment of serious infections (Sy, 2016 [48]). Aztreonam (100 $mg.kg^{-1}$) and Avibactam (25 $mg.kg^{-1}$) were administered to rats that underwent cecal ligation and puncture (CLP) surgery to mimic a model of animal sepsis. Skeletal muscle and intraperitoneal fluid MD were performed. The AUC, of plasma, muscle and intraperitoneal fluid for control rats (131.8 ± 16.8, 123.7 ± 7.5, 116.2 ± 18.7 $mg.h.L^{-1}$, respectively) showed no significant difference when compared to the CLP group (180.6 ± 74.6, 169.9 ± 64.4, 150.6 ± 65.7 $mg.h.L^{-1}$). The peritonitis group showed similar values of penetration factors when compared to the control group, both closed to unit, indicating great distribution. There were no differences in the pharmacokinetic parameters analyzed, demonstrating that this combination of drugs presents good tissue penetration and can be used as an alternative in critically ill patients.

Meropenem and Imipenem

In 2006, Lefeuvre *et al.* investigated imipenem tissue distribution in peritoneal ISF, using an experimental model of induced peritonitis by cecal ligation and punctures in rats. Through plasma and tissue MD, after a 30 $mg.kg^{-1}$ dose of imipenem infused over 30 min, they evaluated the pharmacokinetics. No statistical differences were found in clearance (CL) (0.714 ± 0.138 vs. 0.654 ± 0.126 $L.h^{-1}.kg^{-1}$) or volume of distribution (V) (0.296 ± 0.047 vs. 0.310 ± 0.049 $L.kg^{-1}$) for the control group and peritonitis group. In septic rats, ISF concentrations in tissue were slightly less than plasma concentrations, however, tissue and plasma drug expositions had no differences and, consequently, fT is close to one. These findings showed that imipenem is fully distributed to peritoneal ISF in both groups, indicating that infection have no influence in imipenem penetration in this fluid, in a sepsis model of rats. Nonetheless, posterior clinical studies with meropenem, – another broad-spectrum carbapenem widely prescribed for patients with sepsis (Baldwin, Lyseng-Williamson, Keam, 2008), especially in case of infections in peritoneal cavity, like peritonitis (Wiesholzer *et al*., 2016) – observed impact of sepsis in tissue concentrations.

Karjagin *et al.* (2008) studied meropenem penetration into peritoneal fluid (PF) in patients affected by peritonitis and septic shock and the concentrations in plasma and in PF were analyzed using compartmental approach. Based on the PK parameters estimated, they simulated exposition by different dosing regimens of meropenem. For the usual dose of 1 g every 8 hours, $AUC_{0\text{-}24\ h}$ in plasma and PF was 0.625 and 0.491 $mg.h.L^{-1}$. Moreover, C_{max} for plasma and PF was 98.2 and 32.3 $mg.L^{-1}$ and C_{min} was 12.5 and 11.9 $mg.L^{-1}$.. Effect was evaluated for different regimens through the percentage of time interval between doses that concentration in plasma and PF stayed over MIC. For MIC of 4 $mg.L^{-1}$, the mean of 87% of interval between doses was achieved for any regimen, in plasma and PF. Yet, for MIC of 16 $mg.L^{-1}$, the treatment using the usual dose was not that successful, since the mean of 55% in plasma and 43% in PF were achieved.

Roberts *et al.* (2009b) provides information on the concentrations of meropenem in subcutaneous tissue, where two groups receive different meropenem regimens: one was intermittent bolus and other was continuous infusion, where the dose was 3.5 g at day one, when was given a loading dose, and followed by 3 g/day. Statistical difference was found between parameters at day 1 – where for plasma $AUC_{0-8\ h}$ was 97.2 and 99.0 $mg.h.L^{-1}$ and for subcutaneous tissue $AUC_{40-48\ h}$ was 71.5 and 8.8 $mg.h.L^{-1}$ – and at day 2 – where for plasma $AUC_{0-8\ h}$ was 69.1 and 67.55 $mg.h.L^{-1}$ and for subcutaneous tissue $AUC_{40-48\ h}$ was 30.3 and 38.8 $mg.h.L^{-1}$ – for intermittent bolus infusion and continuous infusion, respectively. The administration of meropenem by continuous infusion maintains statistically significant higher concentrations at steady state (mean 7.5 $mg.L^{-1}$ between day 1 and 2), in subcutaneous tissue and plasma, when compared with trough concentrations of intermittent bolus dosing, where C_{min} was almost zero for this regimen. Tissue penetration was good in both regimens, however, after

day 1 continuous infusion was very low compared with the first day of intermittent infusion, that may be because of the lower loading dose administered in this regimen. Through PK results, PD analysis was made by Monte Carlo simulations to evaluate probability of target attainment (PTA) using 40% $fT > MIC$ as therapeutic target for those regimens and others. Continuous infusion was more efficiently against pathogens with higher values of MIC (4-16 $mg.L^{-1}$). Cumulative fraction of response (CFR), that is the success of treatment probability when PTA against the MIC breakpoints of frequent pathogens, was 100% achieved for more susceptible microorganisms, though for *P. aeruginosa* and *Acinetobacter spp.* showed a significant reduction in values of PTA to intermittent infusion. Another interesting simulation finding was that people with lower renal function have higher PTA, due to higher time of drug exposition.

Levofloxacin and Moxifloxacin

Levofloxacin is a synthetic broad-spectrum antimicrobial, belonging to the class of fluoroquinolones (Zhanel *et al.*, 2002). Zeitlinger *et al.* (2003), performed muscle microdialysis in 7 patients with sepsis after a single 500 mg levofloxacin intravenous dose. High variability was found in concentration-time profiles in tissue, but not for plasma. The means of $AUC_{0\text{-}8\ h}$ (22.1 ± 13.1 and 24.9 ± 6.7 $mg.h.L^{-1}$) and C_{max} (3.6 ± 2.0 and 7.3 ± 1.5 $mg.L^{-1}$) were lower in muscle tissue than the means of total plasma ($p = 0.018$). Despite the high variability, the mean penetration factor was almost close to unit, indicating that levofloxacin is able to penetrate well into the tissues of patients with sepsis. PD analysis was made with dynamic *time-kill* curves, using the concentrations found in plasma and tissue. A Spearman rank order correlations between the decrease of *P. aeruginosa* colonies count and individual tissue parameters as C_{max}/MIC ($R = 0.96$), $AUC_{0\text{-}8\ h}$/MIC ($R = 0.96$) and fT ($R = 0.93$) were significant.

Another fluoroquinolone investigated was moxifloxacin, which belongs to the fourth generation of this class. Nowak *et al.* (2019), monitored concentrations in plasma and ISF of muscle and subcutaneous tissue, in 10 patients with sepsis, after 400 mg of moxifloxacin one time per day, through 2 hours infusion. Plasma samples collection and microdialysis were performed for a long period of time, at 1, 2 and 3 days after beginning of treatment. As a result, a rapid balance between free concentrations in plasma and tissue was observed, where no significant difference was found in the parameters between plasma and tissue through the study days. Maximum tissue concentrations were reached 1 hour behind plasma, however, values of C_{max} were very close. Like for levofloxacin, a high variability was observed in concentrations measured by microdialysis in tissue, more than in plasma. Using concentration-time profile of each patient, $fAUC_{0\text{-}24\ h}$/MIC was calculated employing European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for *Enterobacteriaceae* and *Staphylococcus spp.* All the values of ratio were over 30 hours for each patient, at muscle, at subcutaneous tissue and plasma, through all study days, reaching the target if it was considered concentrations between 30-100 for maximum effect. However, for day 5, muscle showed a higher mean of $fAUC_{0\text{-}24\ h}$/MIC than plasma, due to moxifloxacin accumulation in this tissue after multiple doses.

Linezolid

Linezolid belongs to a class of synthetic antibacterial agents called oxazolidinones and has been approved for the reserve treatment of serious infections caused by resistant aerobic and gram-positive anaerobic pathogens (Ford, Zurenko, Barbachyn, 2001). Also, is often administered to patients who have sepsis and septic shock (De Gascun *et al.*, 2006).

Buerger *et al.* (2006) performed MD on subcutaneous adipose tissue and skeletal muscle in 12 patients with sepsis. Two studies were carried out, where patients received 600 mg of linezolid through 30 min infusion every 12 hours. At day one, after administration of the first dose, plasma samples were collected and microdialysis was performed. Three days after the first dose, the same procedure was made, for single dose and multidose comparison. Free fraction of linezolid was calculated individually for all patients and an average of 86.6% (CV=7.9%) was obtained. Although high variability, the penetration factor of linezolid found was

almost close to the unit in both adipose and muscular tissue, meaning that sepsis cannot affect linezolid tissue distribution. The pharmacokinetic parameters estimated for single and multiple doses was distribution volume at steady state (V_{ss}) = 61.4 vs. 79.8 L, CL = 9.91 vs. 8.44 L/h, respectively, showed no significant differences. In the same way that the AUC was not different between groups.

With those findings, it is possible to conclude that this dosing regimen presents a larger interval between doses, so cannot produce linezolid accumulation, so every dose function as a single dose and steady state is in fact never reached.

In PK/PD analysis, 70% of patients achieved the therapeutic target of 40% *f*T>MIC. Though, for more rigorous targets like >80% *f*T>MIC, only 40% of patients could achieved. Still, if the index of *f*AUC/MIC is considered for bacteriostatic effect (ratio of 48-147) and bactericidal effect (ratio >51), almost every patient stay above this target. So, for effectiveness, a reduction in this time of interval is necessary to avoid subtherapeutic dose.

Thallinger *et al*. (2008), employing data from Buerger *et al.* (2006) patients and increasing this number for statistical purposes, compared the concentration-time profiles and pharmacokinetics to health individuals from a previously study (Dehghanyar *et al*., 2005) to evaluate the influence of sepsis severity in tissue penetration. $AUC_{0-24\ h}$ was calculated for both groups and, in the same way of $AUC_{0-8\ h}$, no significant difference were found. The free fraction of linezolid in plasma was completely balanced with the tissue interstitial fluid. The penetration factors found were approximately 1 in all groups, however, in healthy individuals was observed a tendency of linezolid deposit in adipose tissue. Linezolid is a lipophilic molecule and it volume of distribution varied between 50 and 60 liters, so the authors suggest that this drug does not distribute exclusively to the fluid in the extracellular space, also penetrates into the cells, making it less susceptible to major changes in the volume of the extracellular fluid, which can be found in patients with sepsis.

Fosfomycin

Fosfomycin is a broad-spectrum bactericidal antimicrobial that is not structurally related to other classes of antimicrobials. It has high *in vitro* activity against gram-positive bacteria such as *S. aureus* and *Staphylococcus pyogenes* and gram-negative bacteria such as *P. aeruginosa* (Grif *et al*., 2001). The tissue penetration capacity of fosfomycin may be partially related to its high hydrophilicity, small molecular weight and low protein binding. (Popovic *et al*., 2009).

Joukhadar *et al.* (2003) studied the concentrations of fosfomycin in ISF of muscle and showed that it was fully balanced with plasma at 1.3 hours after drug administration. When analyzing 9 patients with sepsis who underwent muscle microdialysis, after a single intravenous dose of 8.0 g of fosfomycin, the results of $AUC_{0-4\ h}$ and C_{max} for muscle and plasma (501 ± 69 vs. 721 ± 66 mg.h.L^{-1}, and 247 ± 38 vs. 357 ± 28 mg.L^{-1}, respectively) were significantly lower. Although the exposition in tissue is smaller than in plasma, *S. pyogenes* time-kill curves showed an almost 2 $\log_{10}$/mL decrease when exposed to the concentrations found in plasma and ISF. In addition, the fT of muscle was very good, even better than in lungs, studied by Matzi and collaborators (2010), where, after microdialysis probe insertion into healthy and infected lung tissue, a single intravenous dose of 4 g of fosfomycin was administered in a cohort of septic patients and healthy volunteers. Observed mean values of C_{max}, T_{max} and $AUC_{0-4\ h}$, showed no significant difference between groups. The fT of infected lung tissue was also very similar to the healthy ones. The main find was that equilibration is fully obtained among free fosfomycin in plasma and in extracellular space fluid of tissues, in either healthy volunteers or septic patients. There was considerable variability in tissue and plasma pharmacokinetic profiles, exposing individuals to the potential risk of sub-therapeutic exposure, but severe inflammation in septic patients seems not be clinically relevant on fosfomycin ability to penetrate infected lung tissue.

Vancomycin

Vancomycin is a bacteriostatic glycopeptide antibiotic widely used in the ICU (Tenover, Biddle, Lancaster, 2001), especially against resistant microorganisms (Liu *et al*., 2011 [7]). However, there is only one study, of Abraham *et al.* (2018), who performed microdialysis of vancomycin in a sepsis situation. Subcutaneous tissue

microdialysis was performed after vancomycin infusion in 6 patients with sepsis. A high variability was observed in the concentration-time profiles and the median $AUC_{0-24\,h}$ in total plasma was 346 (328-373) mg.h.L^{-1} and in subcutaneous tissue was 123 (90-148) mg.h.L^{-1}, showing a low tissue penetration, demonstrating that vancomycin can not be completely distribute in tissue.

Fluconazole and Metronidazole

Metronidazole can be used for anaerobic infections which lead to sepsis (Eykyn, Phillips, 1976) and fluconazole is another triazole often used in ICUs for the treatment of critically ill patients (Colombo *et al.*, 2013). Metronidazole penetration properties were studied by Karjagin *et al.* (2005). Patients with sepsis were treated with 500 mg of metronidazole in a single IV dose and muscle microdialysis was performed. $AUC_{0-10\,h}$ for plasma was 66 ± 8.3 mg.h.mL^{-1} and for muscle tissue of 57.9 ± 29.9 mg.h.L^{-1}, where no significant differences were found, so a high muscle penetration factor of metronidazole was observed, indicating that septic shock has no major influence in metronidazole distribution. However, high variability was found in tissue concentrations of these patients. Mean concentrations found in tissue after this 500 mg dose were used to calculate tissue concentrations for 250 and 1000 mg doses, considering linear pharmacokinetics. These profiles were simulated in time-kill curves experiments against *Bacteroides fragilis* strains. As a result, bactericidal effect was observed through significant log decrease for each dose until 10 hours after inoculum exposition to metronidazole.

Mauric *et al.* (2011) suggests that fluconazole has great tissue penetration into the lung and muscle in healthy rats and in LPS-induced sepsis model. A LPS (lipopolysaccharide) model was used to induce systemic inflammation in rats after peritoneum administration. Later to administration of a single intravenous dose of 6 mg.kg^{-1} of fluconazole, MD of pulmonary tissue and skeletal muscle was performed. Over the unit penetration factors for health, inflamed lungs and muscles were observed, as results of the similar values of $AUC_{0-6\,h}$ of plasma and lungs in this two groups: the $AUC_{0-6\,h}$ of healthy rats was 35.5 ± 5.8 mg.h.L^{-1} for plasma, 47.4 ± 8.6 mg.h.L^{-1} for lungs and 39.1 ± 6.4 mg.h.L^{-1} for muscle; sepsis rats had an $AUC_{0-6\,h}$ of 35.3 ± 7.3 mg.h.L^{-1} for plasma, 52.9 ± 6.2 mg.h.L^{-1} for lungs and 41.5 ± 6.7 mg.h.L^{-1}, for muscle. No changes were found in any of the PK parameters analyzed, when animals with sepsis were compared with healthy animals, indicating that severe inflammation did not affect the ability of fluconazole to penetrate tissues. However, the LPS model used in the study does not mimic all forms of inflammation found in sepsis and this can explain why fluconazole penetration in tissues was so good.

In a study done by Sinnollareddy *et al.* (2015), 12 septic patients received 400 mg (5.1 mg/kg) dose of fluconazole, through intravenous infusion. When compared the median $AUC_{0-24\,h}$ of plasma (340.4 mg.h.L^{-1}) to subcutaneous tissue (141.1 mg.h.L^{-1}), the AUC of free plasma was significantly higher, still reflecting in adequate fluconazole tissue penetration. Lag distribution to tissue from plasma was observed through the t_{max} of ISF, almost 3 times higher than t_{max} of plasma. Therefore, the fluconazole was incompletely distributed from plasma to subcutaneous tissue, with high variability among patients. The PK/PD index used for effect analysis was $fAUC_{0-24\,h}$/MIC ≥100 and, for the majority of patients (33-92%), this target was reached for breakpoints established by EUCAST and Clinical and Laboratory Standards Institute (CLSI) to *Candida albicans*, *Candida tropicalis*, and *Candida parapsilosis*. However, with values of MIC's of 4-8 mg.L^{-1}, the percentage of patients who achieved this target decreased considerably (0-42%). Although this PK/PD results showed the efficiency of fluconazol, only one patient of twelve responded well to the treatment.

These findings of Mauric *et al.* (2011) and Sinnollareddy *et al.* (2015) are examples of how important is to study antimicrobial tissue penetration in different populations, also, not always a pre-clinic study could be extrapolated to humans. Simulation tools need to be improved and apply before translation of pre-clinic to clinic studies, because the results of one may not reflect in the other.

CONCLUSION

Sepsis is a life-threatening disease where impaired tissue penetration can occur and this will reflect in treatment outcome. Clearance seems to be slower in

septic patients, which can lead to toxic implications and aggravation of patient state. Also, expansion of ISF volume of distribution due to edema, can result in a decrease of osmotic gradient and fluid overload, with an increase of circulating proteins, which can bind to drugs, cause reduction of free concentrations of the antimicrobials in ISF, as can be seen through lower AUC and, consequently, lower fT. Another important fact is the elevated variability in tissue penetration of antimicrobials (Karjagin *et al.*, 2005; Thallinger *et al.*, 2008; Matzi *et al.*, 2010), once hemodynamic and other manifestations vary through the employment of different strategies of treatment, is the use of vasopressors, like norepinephrine, that delays drug distribution to ISF, by restriction of perfusion capillaries (Zeitlinger *et al.*, 2007).

Considering the complexity of this subject matter and the variety of antimicrobials for this treatment purpose, highlights the necessity for further investigation about tissue penetration and pharmacokinetics of antimicrobials in sepsis scenarios, especially employing MD technique, that can access free drug interstitium concentrations per time. There is a lack of information about some drugs, for example vancomycin, a widely use antimicrobial for critically ill patients, which has only one microdialysis study in septic patients. Pre-clinic studies employing animal sepsis model are also restricted in number, which can result in difficulties to perform clinic studies with previous evidence.

In conclusion, is possible to say that sepsis will implicate in imbalance plasma/tissue concentrations and impact in drug distribution, resulting in pharmacokinetic and, consequently, pharmacodynamics alterations of antimicrobials.

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