

BASIC PRINCIPLES OF ANTIBIOTICS DOSING IN PATIENTS WITH SEPSIS AND ACUTE KIDNEY DAMAGE TREATED WITH CONTINUOUS VENOVENOUS HEMODIAFILTRATION

Aleksandra Nikolić¹, Sasa Jačović², Željko Mijailović^{3,5}, Dejan Petrović^{4,5}

¹Apoteka Kragujevac, Kragujevac, Serbia

²Medicines and Medical Devices Agency of Serbia, Belgrade, Serbia

³Clinic for Infectious Disease, Clinical Center Kragujevac, Kragujevac, Serbia

⁴Clinic for Urology, Nephrology and Dialysis, Clinical Center Kragujevac, Kragujevac, Serbia

⁵Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

Received: 16.12.2018.

Accepted: 25.12.2018.

Corresponding author:

Prof. dr Dejan Petrovic

Faculty of Medical Sciences, University of Kragujevac,
Clinic of Urology, Nephrology and Dialysis, University
Clinical Center Kragujevac, Kragujevac, Serbia

E-mail: dejan.petrovic@fmn.kg.ac.rs

ABSTRACT

Sepsis is the leading cause of acute kidney damage in patients in intensive care units. Pathophysiological mechanisms of the development of acute kidney damage in patients with sepsis may be hemodynamic and non-hemodynamic. Patients with severe sepsis, septic shock and acute kidney damage are treated with continuous venovenous hemodiafiltration. Sepsis, acute kidney damage, and continuous venovenous hemodiafiltration have a significant effect on the pharmacokinetics and pharmacodynamics of antibiotics. The impact dose of antibiotics is increased due to the increased volume of distribution (increased administration of crystalloids, hypoalbuminemia, increased capillary permeability syndrome to proteins). The dose of antibiotic maintenance depends on renal, non-renal and extracorporeal clearance. In the early stage of sepsis, there is an increased renal clearance of antibiotics, caused by glomerular hyperfiltration, while in the late stage of sepsis, as the consequence of the development of acute renal damage, renal clearance of antibiotics is reduced. The extracorporeal clearance of antibiotics depends on the hydrosolubility and pharmacokinetic characteristics of the antibiotic, but also on the type of continuous dialysis modality, dialysis dose, membrane type, blood flow rate, dialysis flow rate, net filtration rate, and effluent flow rate. Early detection of sepsis and acute kidney damage, early target therapy, early administration of antibiotics at an appropriate dose, and early extracorporeal therapy for kidney replacement and removal of the inflammatory mediators can improve the outcome of patients with sepsis in intensive care units.

Keywords: Sepsis, acute kidney damage, antibiotics, continuous venovenous hemodiafiltration (CVVHDF).



UDK: 616.94-085

616.61-008.64

615.33.015.4

Ser J Exp Clin Res 2024; 25(2):93-102

DOI: 10.2478/sjecr-2018-0071

INTRODUCTION

Sepsis is the leading cause of acute kidney damage in patients in intensive care units (1, 2). It is defined as the systemic inflammatory response syndrome to the proven bacterial-induced infection, and a severe sepsis as the sepsis associated with Sequential Organ Failure Assessment - SOFA score ≥ 2.0 . Severe sepsis progresses to a septic shock, which is defined as a persistent hypotension that does not repair after resuscitation with 0.9% NaCl solution of crystalloid at a dose of 40-60 mL/kg in the first hour, requiring the use of the vasopressor norepinephrine in a dose $> 5 \mu\text{g/kg/min}$ for maintenance of mean arterial blood pressure at values $\geq 65 \text{ mmHg}$, associated with clinical data for hypoperfusion (serum lactate concentration greater than 2.0 mmol/L) and organ dysfunction (SOFA score ≥ 2.0) (3, 4). The mortality rate of patients with severe sepsis, septic shock and acute kidney damage is 50-80% (5-9). Patients in intensive care units with severe sepsis, septic shock and acute kidney damage require extended hospitalization, kidney replacement therapy, have high cost of treatment and an increased risk of developing insufficiency of multiple organ systems and unwanted outcomes (5-9). Early detection of sepsis and acute kidney damage, early target therapy, early administration of antibiotics at an appropriate dose, and early extracorporeal therapy to replace the kidney function and removing the inflammatory mediators can correct the outcome in patients with sepsis in intensive care units (5-9). Sepsis, acute kidney damage, and CVVHDF significantly influence the pharmacokinetics and pharmacodynamics of antibiotics (10, 11). The results of the study show that 25-60% of these patients have a substitute therapy concentration of antibiotics in blood (10, 11).

Acute damage and kidney function disorder in sepsis

Based on the Kidney Disease: Improving Global Outcomes classification, acute kidney injury (AKI) is defined as a serum creatinine concentration increase of $\geq 0.3 \text{ mg/dL}$ ($\geq 26.5 \mu\text{mol/L}$) during the course of 48h or as an increase serum creatinine concentrations for ≥ 1.5 times compared to basal serum creatinine concentration over the past seven days and/or as a diuresis of less than 0.5 mL/kg/h for at least 6h (12).

Pathophysiological mechanisms of AKI development in patients with sepsis can be hemodynamic and non-hemodynamic (13-15). Hemodynamic pathophysiological mechanisms include: hypoperfusion of kidneys, increased intra-abdominal pressure, increased central venous pressure and stoppage of blood flow in the venous kidney system (13-15). The non-hemodynamic pathophysiological mechanisms include: enhanced systemic and local response of the host immune system to infection, increased formation and secretion of proinflammatory mediators ("cytokine storm"), dysfunction of the kidney small blood vessels endothelium, kidney parenchyma infiltration by immune system cells (monocytes, neutrophils) activation of epithelial cells of proximal tubules through activation of Toll-like receptors - TLRs and oxidative stress (13-17).

Treatment of acute damage and disorders of kidney function caused by sepsis

In patients with sepsis and AKI, the severity of renal impairment and the presence of absolute criteria for the treatment of acute dialysis should be assessed: resistant hyperkalemia ($\text{K}^+ > 6.5 \text{ mmol/L}$ with or without electrocardiographic changes), resistant hypervolemia (furosemide resistant edema), severe metabolic acidosis (pH arterial blood ≤ 7.15), complications of high azotemia (uremic encephalopathy, uremic pericarditis) (18, 19). In the absence of absolute criteria, treatment with dialysis should be initiated if the severe form of AKI (KDIGO3 stage) is diagnosed, and in patients with severe sepsis and rapid deterioration of AKI, treatment with dialysis should be initiated at stage 2 (KDIGO2) (modulation of response of systemic and local immune system to infection) (20-22). Before making a decision to initiate treatment with dialysis in patients with sepsis and mild to moderate AKI (KDIGO 1/2), there should be assessment of the severity of the clinical condition of the patient including the renal function reserve, potency for complications, and the presence of clinical conditions that adversely affect the kidney function (intraabdominal hypertension, mechanical ventilation with positive ventilation pressure, nephrotoxic antibiotics, radiocontrast agents) (20-22). Patients with severe sepsis/septic shock who are hemodynamically unstable, with AKI and multiple organ systems failure, increased serum inflammation mediator concentrations ($\text{IL-6} \geq 1000 \text{ pg/mL}$), increased catabolism and hypervolemia, require treatment with CVVHDF with PMMA (Polymethylmethacrylate), standard and modified AN69ST membrane (Acrylonitrile 69 Surface-Treated) (20-26). CVVHDF with PMMA membrane, which has the ability to adsorb the inflammatory mediators, is administered at a dose of 35 mL/kg/h, during 24-72 hours, and substantially ensures hemodynamic stability and homeostasis of the systemic and local immune system response of the host to infection (preventing the development of "cytokine storms"). When the concentration of IL-6 (Interleukin-6) is reduced below 1000 pg/mL, the treatment is continued with standard CVVHDF, with an ultrafiltration of 35 mL/kg/h (dose of CVVHDF = 35 mL/kg/h) (20-29). For evaluation of the efficiency of the filter (AN69ST), serial measurement of effluent and blood concentrations of urea in patients - FUN/BUN (measurement at every 12h) is used. The filter is effective if the ratio FUN/BUN is ≥ 0.80 , and values less than 0.80 indicate the risk of thrombosis of the filter (30, 31). CVVHDF-AN69ST is effective if the ratio of delivered and prescribed dialysis is $\geq 80\%$ (the effective treatment time should be $\geq 20\text{h}$) (30, 31).

The effect of sepsis, acute kidney damage, and CVVHDF on the pharmacokinetics of antibiotics

In patients with AKI, the absorption of antibiotics from the gastrointestinal tract is reduced due to: the use of a proton pump blocker, mucous membrane edema due to hypervolemia, disorders of structure and function of the bowels, altered gastrointestinal motility, cholestasis in sepsis and shock

conditions (antibiotics are administered in the form of i.v. bolus or i.v. infusion) (10, 11). The volume of antibiotic distribution in these patients has been increased due to: increased administration of crystalloid solutions (early target therapy), reduced serum albumin concentrations (increased fraction of free antibiotic concentration in blood), decreased antibody affinity for binding to plasma proteins and increased capillary permeability syndrome to proteins (10, 11). Hypoalbuminemia is present in 40-50% of patients with sepsis and acute kidney damage. There is a particularly high increase of volume of distribution of hydrosoluble antibiotics, such as aminoglycosides, β -lactam antibiotics and glycopeptide antibiotics: vancomycin and daptomycin (10, 11). Increased antibiotic distribution volume requires a higher loading dose compared to the standard impact dose (maintenance of antibiotic therapeutic concentration) (10, 11). The maintenance dose depends on the metabolism of the antibiotic in the liver and the degree of renal function (antibiotic excretion). It is calculated from the following equation: $MD = \text{standard dose} \times (CL_{Cr} \text{ of the patient} / \text{normal } CL_{Cr})$, where CL_{Cr} is the clearance of endogenous creatinine (10, 11).

In the early stage of sepsis, glomerular hyperfiltration is developed. Glomerular hyperfiltration - Augmented Renal Clearance - ARC is defined as $CL_{Cr} > 130 \text{ mL/min/1.73m}^2$ (32-35). The prevalence of ARC in patients in intensive care units with sepsis and brain injury (subarachnoid bleeding) is 50-85% (32-35). Inflammation mediators released during the Systemic Inflammatory Response Syndrome - SIRS increase the minute heart volume, reduce vascular resistance, and increase kidney perfusion ($\uparrow GFR$) (32-35). Glomerular hyperfiltration affects the pharmacokinetics of hydrophilic "time-dependent" antibiotics. Increased clearance of antibiotics shortens its half-life ($t_{1/2}$) and reduces the area under the concentration-time curve (AUC_{0-24}), which directly affects the achievement of the target therapeutic values of pharmacodynamic parameters (inadequate therapy) (32-35). In the presence of ARC, the standard dose of beta lactam antibiotics is not sufficient to maintain the free antibiotic concentration above the minimum inhibitory concentration ($fT > MIC \geq 100\%$) over the dosage interval (32-35). The optimal dose of meropenem in patients with ARC is 2.0 g/8h, in the form of i.v. infusion for 3.0h, and the dose of cefepime is 2.0 g/6-8h, in the form of i.v. infusion over 3.0h. The standard dose of vancomycin is not sufficient to provide $AUC/MIC > 400$. In patients with ARC, impact i.v. dose of vancomycin should be 25-30 mg/kg and then continued with a maintenance dose of 45 mg/kg/24h (administered every 8 hours or as a continuous IV infusion), with appropriate monitoring of the therapeutic levels of vancomycin in plasma (target therapeutic concentration: 15-20 mg/L) (31-34). In the late stage of sepsis, due to the development of acute kidney damage, renal clearance of antibiotics is reduced (32-35).

The extracorporeal antibiotic clearance (CL_{EC}) depends on the following: molecular weight, plasma protein binding degree, and the volume of antibiotic distribution. Hydrosoluble antibiotics with low molecular weight ($MW < 500 \text{ Da}$), low volume of distribution ($V_d < 1.0 \text{ L/kg}$) and low plasma

protein binding ($PB < 80\%$, $f_u > 0.20$) have large extracorporeal clearance (36-39). The group of antibiotics with low molecular weight, low volume of distribution, low plasma protein binding rates and small non-renal clearance, which are being removed in significant amounts during the CVVHDF session, include: aminoglycoside antibiotics, vancomycin, phosphomycin, and flucytosine (36-39). High-volume antibiotics ($V_d > 1.0 \text{ L/kg}$) and/or high plasma protein binding rates ($PB > 80\%$, $f_u < 0.20$) have small extracorporeal clearance since a significant antibiotic fraction is found in the extravascular section (36-39). Flucloxacillin binds to plasma proteins in high percentage ($PB \geq 94\%$, $f_u < 0.06$) and therefore it is not removed in significant amounts during the CVVHDF session (36-39). The two most important parameters for antibiotic dosing in patients treated with CVVHDF are pharmacokinetic properties of antibiotics and CVVHDF doses, expressed as the total effluent flow rate (Q_{ef}) (36-39). With CVVHDF, Q_{ef} represents the sum of the dialysis flow rate (Q_d), the rate of the solution for substitution flow rate (Q_s), and the rate of net ultrafiltration (Q_{nuf}): $Q_{ef} = Q_d + Q_s + Q_{nuf}$. Q_{ef} significantly influences the pharmacokinetics of antibiotics, the prediction of extracorporeal antibody clearance, and the achievement of the target therapeutic concentration of antibiotics in plasma of the patients (36-39). According to the KDIGO recommendations, Q_{ef} in patients with AKI should be 20-25 mL/kg/h, and in patients with sepsis and AKI 35 mL/kg/h (36-39). The total clearance of antibiotics in patients with AKI and CVVHDF is calculated from the formula: $CL_{tot} = CL_{EC} + CL_R + CL_{NR}$, where: CL_{EC} is extracorporeal clearance, CL_R is renal clearance and CL_{NR} non-renal clearance. The diffusion clearance ($Q_d \times S_d$) of the antibiotic in CVVHDF depends on the molecular weight of the antibiotic, the blood flow (Q_b), and the dialysate flow (Q_d), while convective clearance ($Q_{ef} \times S_c$) depends on the total effluent flow rate (Q_{ef}) and the coefficient of scaling (36-39). The saturation coefficient (S_d) is calculated from the formula: $S_d = C_d/C_p$, where: C_d is the antibiotic concentration in the dialysate, and C_p is the plasma antibiotic concentration. The coefficient of scaling - S_c is calculated from the equation: $S_c = C_{ef}/C_p$, where: C_{ef} is the concentration of antibiotics in the effluent, and C_p is the plasma antibiotic concentration (36-39). In CVVHDF, extracorporeal clearance is calculated from the formula: $CL_{CVVHDF} = Q_{ef} \times S_d$, where: Q_{ef} is the total effluent flow rate and S_d is the saturation coefficient (35-38). Extracorporeal clearance significantly contributes to the overall antibiotic clearance if it is greater than 25% ($Fr_{EC} > 25\%$). Contribution of the extracorporeal clearance to the total antibiotic clearance is calculated from the equation: $Fr_{EC} = CL_{EC} / (CL_{EC} + CL_R + C_{NR})$, where: CL_{EC} is extracorporeal clearance, CL_R is renal clearance, and C_{NR} is non-renal clearance (36-39).

Factors that affect antibiotic clearance during the CVVHDF session include factors specific to: patients, antibiotics (pharmacokinetics, pharmacodynamics), and CVVHDF modality of dialysis. Factors specific to the CVVHDF modality of the dialysis include: dialysate flow rate (Q_d), replacement rate of the substitution solution (Q_s), net ultrafiltration rate (Q_{nuf}), total ultrafiltration rate ($Q_{uf} =$

$Q_s + Q_{nuf}$), total effluent flow rate ($Q_{ef} = Q_d + Q_s + Q_{nuf}$), dialysis membrane type (high-velocity membranes), and the dilution method (pre-conditioning, post-dilution). Pre-dialysis (substitution solution used before the filter) reduces antibiotic clearance. Vancomycin clearance is 25% higher if the solution for substitution is applied after the filter (post-dilution) (36-39). Another factor affecting the antibiotic clearance during the CVVHDF modality of the dialysis is the age of the filter (duration of treatment). The Sieving coefficient of scaling of the antibiotic decreases during the CVVHDF session (it is highest in the first dialysis hours) due to the precipitation of proteins along the membrane surface and the reduction in the number of non-thrombosed filter capillaries (36-39). Larger Q_{ef} and Sc provide higher clearance of antibiotics, and this may result in subdosing, the absence of target antibiotic therapeutic concentration, and a lower survival rate of these patients (36-39).

The antibiotic dose adjustment factor in the CVVHDF patients is calculated from the equation: $Q = 1 - (fe \times (1 - KF))$, where: fe is the fraction of the medicine excreted in urine in an unchanged form, KF - the ratio of the current clearance of endogenous creatinine and normal endogenous creatinine clearance (normal clearance of endogenous creatinine = 120 mL/min). The new adjusted dose - D_R is calculated from the formula: $D_R = D_{norm} \times Q$, where: D_{norm} is the dose predicted for normal kidney function and Q is the dose adjustment factor (40, 41).

Pharmacokinetic and pharmacodynamic properties of antibiotics

Based on the pharmacokinetic and pharmacodynamic characteristics, antibiotics can be divided into three groups. The first group consists of antibiotics whose antibacterial effect depends on the concentration of medicine in plasma ("concentration dependent" antibiotics), the second group consists of antibiotics whose antibacterial effect depends on the length of exposure to the antibiotic ("time-dependent" antibiotics), and the third group consists of antibiotics whose antibacterial effect depends on the plasma drug concentration, but also on the duration of exposure to the antibiotic ("concentration-dependent" and "time-dependent" antibiotics) (40-43).

The first group of antibiotics include: aminoglycosides, daptomycin, and fluoroquinolones. The antibacterial effect of these antibiotics is achieved only when the maximum plasma antibiotic concentration is reached. The main pharmacodynamic parameter for assessing the efficacy of these antibiotics is to measure the maximum plasma antibiotic concentration (C_{max}) and the ratio of the maximum plasma antibiotic concentration to the minimum inhibitory antibiotic concentrations (C_{max}/MIC). The main parameter for evaluating the efficacy of antibiotics from the second group is the determination of the percentage of $T > MIC$ (Minimal Inhibitory Concentration) (the estimated time during 24 hours when the plasma antibiotic concentration is greater than its minimum inhibitory concentration ($\%T > MIC$)) (39-42). This

antibiotic group includes beta-lactam antibiotics (40-43). The third group consists of antibiotics whose antibacterial effect depends on the concentration, but also on the time of exposure to the antibiotic (40-43). The antibacterial effect is assessed by measuring the ratio of the area under the concentration-time curve for 24 hours and the minimum inhibitory antibiotic concentration (AUC_{0-24}/MIC) (40-43). This group of antibiotics includes: fluoroquinolones, tigecycline, linezolid, and glycopeptide antibiotics (vancomycin) (40-43).

Gentamicin (Gentamicin) is a hydrosoluble antibiotic, with molecular weight - $MW = 477$ Da, a small volume of distribution - $V_d = 0.25$ L/kg, and a low plasma proteins binding level - $PB = 10-20\%$ ($f_u = 0.80-0.90$). It belongs to the group of antibiotics whose antibacterial effect depends on its plasma concentration ("concentration-dependent" antibiotic group) (40-43). The therapeutic concentration of gentamicin in plasma is $1.0-2.0$ $\mu\text{g/L}$. Its maximum blood concentration is $6-8$ mg/L, and it is achieved 30 minutes after the application of the impact dose of $2-2.5$ mg/kg (IV infusion) (40-43). After the applied impact dose, it is continued with $1.0-1.5$ mg/kg/24h (40-42). The target value of the C_{max}/MIC ratio should be at least $8-10$ ($C_{max}/MIC = 8-10$) (40-43).

Amikacin is a hydrosoluble antibiotic, with molecular weight - $MW = 585.6$ Da, a small volume of distribution - $V_d = 0.22-0.29$ L/kg and a low plasma protein binding level - $PB < 20\%$ (40-44). It is used to treat serious infections caused by Gram negative microorganisms in patients in intensive care units. It belongs to a group of antibiotics whose antibacterial effect depends on the concentration of the medicine in the plasma ("concentration-dependent" antibiotic). It is administered at a dose of 7.5 mg/kg/12h, in the form of an IV infusion, for 30 minutes and requires dose adjustment depending on the degree of renal function (40-44). Amikacin is removed in significant amounts during the CVVHDF session. CL_{CVVHDF} of amikacin is calculated from the formula: $CL_{CVVHDF} = Q_{ef} \times f_u$, where: Q_{ef} is the total effluent flow rate, and the f_u - fraction of amikacin not bound to plasma proteins ($f_u = 0.80$). Q_{ef} represents a dose of CVVHDF modality of dialysis. It is calculated from the equation: $Q_{ef} = Q_d + Q_s + Q_{nuf}$. In patients with AKI in the absence of sepsis, the dose of dialysis is $Q_{ef} = 20-25$ mL/kg/h, and in patients with severe sepsis, septic shock and AKI, the dose of dialysis is - $Q_{ef} = 35$ mL/kg/h (43). The average CL_{CVVHDF} of amikacin is 2.86 ± 0.41 L/h, and the coefficient of scaling for amikacin is - $Sc = 0.83 \pm 0.05$ (44). Amikacin is a small hydrophilic antibiotic, which is significantly removed during the CVVHDF session. The recommended dose of amikacin being 10 mg/kg does not provide optimal therapeutic concentration in patients treated with CVVHDF. The results of the study show that in these patients, amikacin should be administered at an impact dose of $15-30$ mg/kg, in the form of an IV infusion for 30 minutes and then continue with the appropriate dose every 24h or 36h (7.5 mg/kg/24-48h) (44, 45). The target pharmacodynamic parameters for assessing the efficacy of amikacin are: $AUC/MIC \geq 70$, $C_{max}/MIC = 8-10$ (≥ 8) and $MIC \leq 2.5$ mg/L (45, 46).

Daptomycin has a molecular weight - MW = 1650 Da and volume of distribution - Vd = 0.1 L/kg. It is associated with a high percentage of plasma protein binding (PB = 90-92%, fe = 0.08-0.10) (47, 48). It is used to treat infections caused by Methicillin (MRSA) resistant *Staphylococcus aureus*, Vancomycin Resistant *Enterococcus* (VRE) and other Gram-positive microorganisms. It belongs to the group of "concentration-dependent" antibiotics, and the most important pharmacodynamic parameter for assessing the effectiveness of antibacterial action is the ratio of the area under the concentration-time curve (AUC) and the minimum inhibitory concentration (MIC) - AUC_{0-24}/MIC (MIC = 3-4 µg/mL) (47, 48). The efficacious antibacterial effect of daptomycin exists if AUC_{0-24}/MIC is ≥ 666 (47, 48). In patients with endogenous creatinine clearance greater than 30 mL/min it is administered at a dose of 6 mg/kg every 24 hours (IV infusion over 30 minutes), and when the endogenous creatinine clearance drops below 30 mL/min, it is administered in the same dose, but every 48h (47, 48). The recommended dose of daptomycin in patients treated with CVVHDF is the same as in patients with clearance greater than 30 mL/min (6 mg/kg/24h) (46, 47). One group of authors recommends that the dose of daptomycin in patients with severe sepsis, septic shock and AKI treated with CVVHDF should be 8 mg/kg/48h (47, 48). Daptomycin acts toxically to skeletal musculature: it causes weakness and pain of transverse-striated musculature, and creatinine kinase concentration is ten times higher than the upper normal limit (47, 48). Serum creatinine phosphokinase (CPK) monitoring is required in patients using daptomycin (47, 48).

Linezolid (Linezolid) has a molecular weight - MW = 337 Da, a small volume of distribution - Vd = 0.6-0.8 L/kg and low percentage of plasma protein binding - PB = 30% (fu = 0.70) (49, 50). It is a moderately lipophilic antibiotic that belongs to the group of "time-dependent" antibiotics. The linezolid dosing regimen may be intermittent or continuous. Intermittently, linezolid is applied IV at a dose of 600 mg/12h, and continuously, as an impact dose of 300 mg, and then continued at a dose of 900 mg/24h, in the form of a continuous IV infusion. In patients with severe sepsis treated with CVVHDF, high-dose linezolid can be administered intermittently or continuously. Intermittently, intravenously at a dose of 600 mg/8h or continuously, as a high dose of 600 mg, and then continued at a dose of 1200 mg/24h, in the form of a continuous IV infusion (49, 50). The best parameter for assessing the antibacterial effect of linezolid is the AUC_{24}/MIC ratio, which should be 50 for *Staphylococcus pneumoniae* ($AUC_{24}/MIC = 50$), and 85 for *Staphylococcus aureus* ($AUC_{24}/MIC = 85$). The maximum antibacterial effect of linezolid is achieved when $T > MIC$ is $\geq 85\%$ and AUC_{0-24}/MIC ratio is > 100 (49, 50).

Vancomycin has a molecular weight - MW = 1450 Da, volume of distribution - Vd = 0.47 - 1.1 L/kg and plasma protein binding percentage - PB = 10-50% (51-53). Depending on the antibacterial effect, it belongs to the third group of "concentration-dependent" and "time-dependent" antibiotics. The best parameter for the evaluation of the efficacy of

vancomycin is AUC_{0-24}/MIC ratio, which should be greater than 400 mg/hxL (provides eradication of Methicillin-resistant *Staphylococcus aureus*) (51-53). Vancomycin is applied IV at an impact dose of 15-20 mg/kg, and then continued at 10-40 mg/kg/day, depending on the degree of renal function. The therapeutic concentration of vancomycin in plasma is 15-20 mg/L (51-53). In patients treated with standard intermittent hemodialysis, the dose of vancomycin depends on the diabetic membrane flow rate: "low-flux" versus "high-flux" (54). The results of clinical trials show that vancomycin is removed in significant amounts during the CVVHDF session ($> 50\%$ of the total amount of vancomycin is eliminated via kidneys). The dose of CVVHDF significantly affects the clearance of vancomycin. With the increase in the CVVHDF dose, vancomycin clearance is increased by at least 30%. CVVHDF clearance of vancomycin corresponds to the clearance of endogenous creatinine of 25-50 mL/min. Bearing this in mind, some authors consider that the vancomycin impact dose should be 35 mg/kg (IV infusion for 4h), and further treatment should be continued continuously i.v. through the infusion of vancomycin at a dose of 14 mg/kg/24h (51-54).

Beta-lactam antibiotics are widely used as the first-line antibiotics for the treatment of infections in patients in intensive care units. The use of standard doses in patients treated with continuous dialysis modalities may result in an inadequate therapeutic concentration of these antibiotics in the serum (subdosage, increased risk of development of resistance). The group of beta-lactam antibiotics include: ceftazidime (CEF), cefepime (CEF) and piperacillin/tazobactam (TZP) (55-57). They belong to the group of "time-dependent" antibiotics. The best pharmacodynamic parameter for the evaluation of the antibacterial effect is $\%T > MIC$ ($T > MIC \geq 40\%$ for CEF, $T > MIC > 75\%$ for TZP) (55-57). The results of the tests carried out so far indicate that the standard intermittent dose of ceftazidime does not provide the target values of the pharmacodynamic parameters in all patients with severe infection treated with CVVHDF (56, 57). CVVHDF removes a significant amount of ceftazidime. The maximum effective serum ceftazidic concentration is 4-5 times higher than the MIC ($> 4-5 \times MIC$) (MIC for ceftazidime is ≤ 4 mg/L) (56, 57). Ceftazidime is the third generation of cephalosporins, with molecular weight of 636.6 Da. It binds with plasma proteins in low percentage (fu = 0.90), and about 90% of ceftazidime is excreted in the urine in an unchanged form (fe = 0.90), and the coefficient of scaling of ceftazidime in the CVVHDF session is $Sc = 0.81 \pm 0.11$. The CL_{CVVHDF} of ceftazidime is calculated from the equation: $CL_{CVVHDF} = Sc \times Q_{ef} = fu \times Q_{ef}$, where: Sc is the coefficient of scaling, fu is the fraction of ceftazides not bound to plasma proteins, and Q_{ef} - the total effluent flow rate (dose of CVVHDF modality of dialysis). The average CL_{CVVHDF} of ceftazidime is 33.6 ppm 4.0 mL/min (56, 57). CL_{CVVHDF} in total clearance of ceftazides participates with 55%. One of the dosing regimens recommended in patients with severe infection treated with CVVHDF is ceftazidime administration in the form of an impact dose of 2.0 g IV

infusion, and then continued treatment with a continuous 3.0 g/24h IV infusion over 72h (during CVVHDF) (56, 57).

Cefepime is a fourth-generation cephalosporin, which has a wide range of effects on Gram-positive and Gram-negative bacteria. It has a small volume of distribution - $V_d = 0.3 \text{ L/kg}$ and binds in low percentage to plasma proteins ($f_u = 0.97$). The Sieving coefficient (the coefficient of cefepime scaling is - $Sc = 0.93$, and the saturation coefficient - $S_d = 1.03$. CL_{CVVHDF} of cefepime is significant and is calculated from the equation: $CL_{CVVHDF} = f_u \times Q_{ef}$, where: f_u is fraction of cefepime not bound to plasma proteins ($f_u = 0.97$) and Q_{ef} - the total effluent flow rate (dialysis dose). Q_{ef} is calculated from the equation: $Q_{ef} = Q_d + Q_s + Q_{nuf}$. In patients with AKI, in the absence of sepsis, $Q_{ef} = 20\text{--}25 \text{ mL/kg}$, and in patients with severe sepsis, septic shock and AKI, $Q_{ef} = 35 \text{ mL/kg/h}$ (56, 57). The dose of cefepime in patients treated with CVVHDF should be IV 1.0 g/12h or IV 2.0 g/24h (56, 57). Cefepime belongs to the "time-dependent" group and the antibacterial effect is effective if $T > MIC \geq 40\text{--}50\%$ and $AUC_{0-24}/MIC \text{ ratio} \geq 100$ (57, 58).

Piperacillin/tazobactam, Tazocin® is one of the most frequently used combinations of antibiotics for the treatment of serious infections in patients in intensive care units. They have a wide range of antibacterial effects involving Gram-positive and Gram-negative bacteria (*Pseudomonas aeruginosa*) (59, 60). They are applied in a standard dose of 4.5g (Piperacillin 4.0 g + Tazobactam 0.5g), in the form of an IV infusion for 20 minutes, at different dosing intervals: 4h, 6h and 8h (59, 60). It belongs to the group of "time-dependent" antibiotics, and the antibacterial effect is effective if $T > MIC \geq 100\%$ (59, 60). Both piperacillin and tazobactam have a low molecular weight, low plasma protein binding rates and are removed during the CVVHDF session in high percentage. The extracorporeal cleansing of piperacillin/tazobactam is calculated from the equation: $CL_{CVVHDF} = Sc \times Q_{ef}$, where: Sc is Sieving coefficient/coefficient of scaling ($Sc = f_u$), f_u - fraction of piperacillin/tazobactam not bound to plasma proteins and Q_{ef} - flow rate of total effluent (dose of CVVHDF modality of dialysis) (59, 60). Extracorporeal clearance has a significant role in the total clearance of piperacillin/tazobactam ($\geq 25\%$ of total clearance) (59, 60).

Colistin is used to treat Gram-negative bacteria that are resistant to a large number of antibiotics - MDR (Multi Drug-Resistant): *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (61-63). Colistin has a small volume of distribution - $V_d = 0.3\text{--}0.4 \text{ L/kg}$ and in high percentage is excreted in an unchanged form via kidneys ($f_e = 80\%$) (59-61). Antibacterial effect depends on the concentration of colistin in plasma (belonging to the group of "concentration-dependent" antibiotics) (61-63). It is administered intravenously in the form of an inactive colistin methanesulfonate (CMS), which is designated as CBA (Colistin Base Activity) in most countries (80 mg CMS = 30 mg CBA, conversion factor is 2.7). In some countries, colistin is expressed in international units (1.000.000 IU = 30 mg CBA). These diverse descriptions have led to confusion in daily clinical work. Impact dose in

the IV bolus is 10,000,000 IU (300 mg CBA); it is applied for 30 minutes, and then continues with IV application at a dose of 3,000,000 IU/8h (12h after the impact dose) for two weeks (conventional dosing regimen). The dosage should be adjusted to the degree of renal function (61-63). According to the EMA and FDA recommendations, dosing of colistin should provide a target mean concentration of colistin balance of 2.0 mg/L ($C_{ss} = 2.0 \text{ mg/L}$). The AUC/MIC ratio is used to assess the antibacterial effect (61-63). In patients treated with CVVHDF, the extracorporeal clearance of colistin can be calculated from the following formula: $CL_{CRRT} = Q_{ef} \times ER$, where: Q_{ef} is the total effluent flow rate, and the ER is the extraction index. The extract index of colistin is calculated from the formula: $ER = 2 \times C_{eff}/(C_{in} + C_{out})$, where: C_{eff} is the concentration of colistin in the effluent, C_{in} is the concentration of colistin before the filter, and C_{out} is the concentration of colistin after the filter. The coefficient of scaling for colistin is - $Sc = 0.35$. Extracorporeal clearance of colistin is significant and accounts for 43-59% of total colistin clearance. The concentration of colistin after the filter $\geq 70\%$ of the colistin concentration before the filter may indicate a reduced elimination of colistin during a dialysis session (61-63). An increased risk of nephrotoxicity occurs if the concentration of colistin is in balance (after seven days of administration) $> 3.0 \text{ mg/L}$. The nephrotoxic effect occurs as a result of the accumulation of colistin in the epithelial cells of the proximal tubule (tubulointerstitial damage), within 72h after the administration of colistin (63, 64). As the consequence of the increased accumulation of colistin in the epithelial cells of the proximal tubule, the development of acute kidney damage occurs. The most common are AKI Stages 1 and 2, and less than 3% of patients require dialysis treatment (64). The main risk factors for the development of the nephrotoxic effect induced by the use of colistin are the following: age, liver disease, basal intensity of glomerular filtration, and hemoglobin concentration in blood. The blood hemoglobin concentration changes the oxygenation of the kidney tissue and increases the risk of AKI (64).

Meropenem is a carbapenem hydrophilic antibiotic used to treat severe infections caused by Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa* and *Acinetobacter* species (65). Meropenem has a low molecular weight, a small volume of distribution ($V_d = 0.30\text{--}0.35 \text{ L/kg}$), low percentage of binding to plasma proteins ($f_u = 0.98$) and is significantly removed during the course of the CVVHDF (65). It belongs to the group of "time-dependent" antibiotics, and the antibacterial effect is effective if $T > MIC \geq 40\%$ (65). The minimum inhibitory concentration of meropenem is $\leq 2.0 \text{ mg/L}$ ($MIC \leq 2.0 \text{ mg/L}$) (65). It is applied at a dose of 500-1000 mg/8-12h. When determining the dosing regimen, conditions that affect the pharmacokinetics of meropenem should be considered: hypoproteinemia, different residual diuresis, different continuous dialysis modalities, and different doses of the same CRRT modality of the dialysis. For sensitive microorganisms, in which the minimum inhibitory concentration of meropenem is $MIC \leq 2.0 \text{ mg/L}$, the target pharmacodynamic parameter that assesses the effectiveness of the antibacterial effect of meropenem should be T

$> \text{MIC} \geq 40\%$. In these patients, meropenem is administered at a dose of 500 mg/8h in the IV infusion for 30 min. However, in the case of severe infections of microorganisms that require minimal inhibitor meropenem concentration of $\text{MIC} = 2.0\text{--}4.0 \text{ mg/L}$, $T > \text{MIC}$ should be $\geq 100\%$ (65). In these patients, meropenem is administered at a dose of 500 mg/8h, in the form of an extended intravenous infusion over 3h (65). Resistance to meropenem is defined as the minimum inhibitory concentration of meropenem - $\text{MIC} > 4.0 \text{ mg/L}$ (65).

Ertapenem is a carbapenem antibiotic used to treat severe infections caused by Gram-negative bacteria (65). It is associated with a high percentage of plasma proteins (85-95% in healthy volunteers, $f_u = 0.05\text{--}0.15$), and in patients with AKI, the free medicine fraction increases to 20-40% ($f_u = 0.20\text{--}0.40$) (66). It belongs to the group of "time-dependent" antibiotics, and the main pharmacodynamic parameter for assessing the efficacy of ertapenem is $\text{AUC}_{0-24}/\text{MIC}$ ratio ($\text{AUC}_{0-24}/\text{MIC} \geq 40\%$) (66). In patients with endogenous creatinine clearance less than 30 ml/min, IV dose of ertapenem is 500 mg/24h, in patients with standard hemodialysis is also 500 mg/24h, and it is applied after a hemodialysis session, whereas in patients treated with continuous dialysis modalities (CVVHDF), ertapenem is administered at a dose of 1.0 g/24h (66).

Doripenem is a new carbapenem antibiotic with little available data for optimal dosing in patients with sepsis and AKI treated with continuous dialysis modalities (67). It belongs to the group of "time-dependent" antibiotics, and the main pharmacodynamic parameter for assessing the effectiveness of its antibacterial effect is $T > \text{MIC} \geq 40\%$ (67). It is low in molecular weight ($\text{MW} = 438.5 \text{ Da}$), low in percentage of plasma protein binding ($\text{PB} = 10\%$, $f_u = 0.90$), has an unchanged form of excretion in urine ($f_e = 0.70$), and is significantly removed in the course of CVVHDF. The extrapolation index of doripenem is calculated from the equation: $\% \text{ER} = ((\text{Ca} - \text{Cv}) \times 100)/\text{Ca}$, where: Ca is the concentration of doripenem in the patient's blood before the filter and Cv is the concentration of doripenem in blood after the filter. $\text{CL}_{\text{CVVHDF}}$ of doripenem moderately contributes to its overall clearance (30%) (67). In patients with normal kidney function, it is administered at a dose of 500-100 mg/8h, in the form of an IV infusion over 60 minutes, and in patients treated with CVVHDF for sensitive microorganisms ($\text{MIC} \leq 4.0 \text{ mg/L}$), a dose of 500 mg/12h is administered (67).

Fluoroquinolones (Levofloxacin, Ciprofloxacin) are lipophilic antimicrobials, which fall into the group of "concentrations-dependent" antibiotics (target $\text{C}_{\text{max}} = 4\text{--}5 \text{ } \mu\text{g/mL}$) (68-70). The main pharmacodynamic parameters for assessing the effectiveness of the antibacterial effect of fluoroquinolones are $\text{C}_{\text{max}}/\text{MIC}$ ratio ≥ 10 and $\text{AUC}_{0-24}/\text{MIC}$ ratio $\geq 100\text{--}125$ (good ciprofloxacin dosing indicator) (68-70). Levofloxacin is applied IV at a dose of 250 mg/24h or 500 mg/48h, while ciprofloxacin is administered IV. at a dose of 400 mg/12h (i.e. infusion over 60 min) (per os 500 mg/12h). In patients with endogenous creatinine clearance less than 30 mL/min is administered IV. The dose of ciprofloxacin is 400

mg/24h (per os 500 mg/24h). If the patient is treated with intermittent standard hemodialysis, ciprofloxacin is administered at a dose of 400 mg/24h (per os 500 mg/24h), the medicine is applied after HD, and in patients treated with CVVHDF, IV infusion of administered ciprofloxacin is 400 mg/12-24h (68-70). The CVVHDF fluoroquinolone clearance is calculated from the equation: $\text{CL}_{\text{CVVHF}} = \text{Sc} \times \text{Quf}$, where: Sc is the coefficient of scaling (sieving coefficient), and Quf - the rate of the total ultrafiltrate flow. The coefficient of scaling is calculated from the equation: $\text{Sc} = 2 \times \text{Cuf}/(\text{Ca} + \text{Cv})$, where: Cuf is the concentration of the medicine in the ultrafiltrate or effluent ($\text{Cuf} = \text{Cef}$), Ca is the concentration of the medicine before the filter and Cv is the concentration of the medicine after the filter. The total flow rate of the total ultrafilter is calculated from the equation $\text{Quf} = \text{Qs} + \text{Qnuf}$, where: Qs is the rate of flow of the solution for substitution and Qnuf is the rate of net ultrafiltration. The coefficient of scaling for levofloxacin is 0.67, and for ciprofloxacin 0.63 (0.70 ± 0.06) (68, 69). The contribution of CL_{CVVHF} to total system clearance is calculated from the equation $(\text{CL}_{\text{CVVHF}}/\text{CLs}) \times 100$, where CLs is the total system clearance (68, 69). With CVVHDF, fluoroquinolone clearance is calculated from the equation: $\text{CL}_{\text{CVVHDF}} = \text{Sd} \times \text{Qef}$, where: Sd is the saturation coefficient, and Qef is the flow rate of the total effluent. The coefficient of saturation is calculated from the equation: $\text{Sd} = \text{Cef}/(\text{Ca} + \text{Cv})$, where: Cef is the concentration of the medicine in the effluent, Ca is the concentration of the medicine before the filter and Cv is the concentration of the medicine after the filter. The flow rate of the total effluent - $\text{Qef} = \text{Qd} + \text{Qs} + \text{Qnuf}$, where: Qd is the dialysis flow rate, Qs is the rate of flow of the solution for substitution and Qnuf is the net ultrafiltration rate. The coefficient of saturation for levofloxacin is 0.56, and for ciprofloxacin 0.63. $\text{CL}_{\text{CVVHDF}}$ of ciprofloxacin can be calculated from the equation: $\text{CL}_{\text{CVVHDF}} = f_u \times \text{Qef}$, where: f_u is the fraction of ciprofloxacin not bound to the plasma protein ($f_u = 0.60\text{--}0.78$), and Qef - flow rate of the total effluent ($\text{Qef} = 35 \text{ mL/kg/h}$). An increase in the dose of CVVHDF ($\uparrow \text{Qef}$) increases the clearance of ciprofloxacin. $\text{CL}_{\text{CVVHDF}}$ of creatinine is equivalent to the clearance of $\text{CL}_{\text{CVVHDF}}$ of ciprofloxacin. In the situations of inability to measure ciprofloxacin plasma concentrations, $\text{CL}_{\text{CVVHDF}}$ creatinine should be determined. The contribution of $\text{CL}_{\text{CVVHDF}}$ to the total system clearance is calculated from the equation $(\text{CL}_{\text{CVVHDF}}/\text{CLs}) \times 100$, where CLs is the total system clearance. $\text{CL}_{\text{CVVHDF}}$ of fluoroquinolones contributes to 40% of the total system clearance. The results of the studies showed that the optimal IV dose of levofloxacin in patients treated with CRRT/CVVHDF is 250mg/24h, and for ciprofloxacin 400 mg/24h (68, 69). In patients with severe sepsis, septic shock and AKI treated with CVVHDF, with a filter containing AN69 membrane and a dialysis dose of $\text{Qef} = 35 \text{ mL/kg/h}$, to achieve pharmacokinetic and pharmacodynamic goals ($\text{C}_{\text{max}}/\text{MIC} \geq 10$, $\text{AUC}_{0-24}/\text{MIC} \geq 100$ for $\text{MIC} \leq 0.50 \text{ mg/L}$) a dose of 400 mg/12h of ciprofloxacin is required, and in patients with concomitant liver insufficiency it is 400 mg/24h (in order to optimize and individualize ciprofloxacin, the function of the liver should also be evaluated) (69, 70).

ACKNOWLEDGMENTS

The authors would like to thank the Ministry of Education, Science and Technological Development of the Republic of Serbia for the project N^o175014, whose funds were used as one of the sources for the financial support of this scientific paper.

CONFLICT OF INTEREST

The authors declare no financial or commercial conflict of interest.

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