SPECIFICITY OF ANTIBIOTIC THERAPY IN PATIENTS WITH CHRONIC KIDNEY FAILURE

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Abstract

Chronic kidney diseases disrupt kidney function, but also other organs which affect both the pharmacodynamics and the pharmacokinetics of many drugs. Prescribing drugs to patients with chronic kidney disease requires knowledge of changes in the absorption, distribution, metabolism and excretion of drugs and their metabolites. Avoiding nephrotoxic drugs is the most important principle that we must follow in patients with chronic kidney disease. If the administration of nephrotoxic drugs is necessary, regular control of glomerular filtration rate, serum electrolyte concentration, and serum drug concentration is required if possible. The dosing of drugs in patients with chronic renal insufficiency is very delicate, both when determining the initial dose and during the maintenance dose, so it is necessary to adjust the doses for each patient individually, depending on the degree of kidney damage. For most drugs, there are recommendations from the Agency for Drugs and Medical Devices of the Republic of Serbia on how to correct the dose of the drug in chronic kidney failure. If such a recommendation does not exist, general rules are used: the maintenance dose can be adapted to kidney function by reducing the dose, extending the intervals in which the unchanged dose of the drug is administered, or a combination of these two methods. In patients with chronic kidney damage, the infection accelerates the progression towards the terminal stage, when it is necessary to apply one of the methods to replace kidney function. The infection should be treated with appropriate doses of antibiotics and/or antifungals and for a sufficient period of time. Likewise, in dialysis patients, there are various causes of infections that must also be adequately treated in order not to compromise the dialysis method or endanger the patient's life. There are recommendations for the use of antibiotics and antimycotics in these cases, which should be applied and adjusted to the individual patient. In intensive care units, in hemodynamically unstable patients with sepsis and acute chronic kidney failure, instead of intermittent hemodialysis, the following methods can be used: prolonged intermittent hemodialysis (PID) and continuous procedures - continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF). The dosage of antibiotics in these patients is specific and adjusted to the individual patient and his kidney function.

Peritoneal dialysis patients in the terminal phase of chronic kidney failure are at risk of developing peritonitis. The guides describe which antibiotics are used to start the treatment of peritonitis and how the antibiotics are then adjusted, according to the causative agent, after the dialysate culture is obtained. Treatment of peritonitis is mainly by intraperitoneal administration of antibiotics, but it is also possible with oral or parenteral antibiotics, i.e. their combination. The guidelines describe the initial and maintenance doses of antibiotics and antifungals. If treatment is not started on time, the dialysis method may be compromised and the patient may die. If fungi are isolated by culture, the treatment of the patient with peritoneal dialysis is stopped and the dialysis catheter is removed, and the treatment is continued with the administration of antibiotics intravenously.

Keywords: chronic kidney failure, hemodialysis, peritoneal dialysis, antibiotics

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Introduction

Chronic kidney disease (CKD) represents a global world challenge, especially due to its high prevalence of 10%. The rapid increase in the incidence and prevalence of CKD in the last decade represents a challenge, in terms of timely and rapid diagnosis, slowing down disease progression and adequate treatment in the terminal phase[1].

Chronic kidney disease causes disruption of kidney function, but also of other organs, which affects both the pharmacodynamics and the pharmacokinetics of many drugs. Prescribing drugs to patients with CKD requires knowledge of changes, regarding the absorption, distribution, metabolism and excretion of drugs, as well as their metabolites. The choice and dose of the drug must be adapted to each individual patient. Multiple drugs use in patients with CKD increases the risk of their interaction and side effects, and the drugs must be prescribed carefully and adapted to each individual and their kidney function[2].

Pharmacokinetics in chronic renal failure

Pharmacokinetics studies the process in which a drug undergoes during metabolism and it includes absorption, distribution, metabolism and elimination of the drug. The part of the administered dose of the drug that reaches the systemic circulation in unchanged form (100% is only after intravenous administration of the drug) is its bioavailability. Bioavailability in chronic kidney failure (CKF) is affected by various disorders as well as the simultaneous administration of various drugs. Absorption of drugs is reduced by alkalization of gastric contents with urea, edema of the mucous membrane of the digestive tract, application of certain phosphate binders, proton pump inhibitors, and antacids. Bioavailability also depends on the metabolism of the drug during its first passage through the liver after absorption in the digestive tract, before it reaches the systemic circulation[3, 4].

Drug distribution implies the distribution of each drug from circulation to extra circulatory spaces. It depends on the physical volume of the organism, the degree of its binding to proteins and the rate of drug elimination. The distribution of the drug is described by the volume of distribution, and each drug has its own characteristic volume of distribution, which depends on the concentration of the drug in the plasma, but not on its anatomical structure. Water-soluble drugs have a relatively small volume of distribution because they are distributed only in the extracellular fluid, while fat-soluble drugs have a much larger volume of distribution, because they penetrate the tissues. Hypovolemia and loss of muscle mass decrease, and edema and ascites increase, the volume of distribution of water-soluble drugs. Many drugs bind to proteins, and the pharmacological effect of the drug usually depends on the free part of the drug not bound to proteins. In patients with advanced renal insufficiency, reduced serum albumin concentration and reduced affinity of albumin for drugs increase the concentration of the free fraction of drugs. In these patients, the metabolism and excretion of the unbound drug is faster, so its clearance is also higher[5].

Metabolism (biotransformation) of drugs implies biochemical changes of a pharmacologically active initial compound into its metabolites, some of which are still pharmacologically active. These processes occur predominantly in the liver, and the resulting metabolites are usually excreted more quickly and easily than the initial compound. In CKF, the activity of certain enzymes and the metabolism of drugs in the liver changes, while the elimination of drugs and their metabolites via the kidneys, decreases. These changes affect the effectiveness of drugs and the frequency of their side effects.

Elimination (excretion of drugs) is most common through the kidneys. The elimination half-life is the time it takes for the drug to lose half of its pharmacological activity, i.e. to halve the concentration of the drug in the plasma. The elimination half-life depends on the volume distribution and clearance of the drug. Drug clearance depends on glomerular filtration, tubular reabsorption and drug secretion. With the progression of insufficiency, the excretory function of the kidneys and the excretion of drugs - decrease[2, 6].

Principles of prescribing drugs to patients with CKD

There are guidelines for prescribing drugs for CKD, but there is no reliable data on their usage in clinical practice. General rules for the use of drugs in patients with CKD, but also in patients with its terminal phase, must be adapted to each individual patient. Before prescribing any drug to a patient with CKD, it is necessary to perform a series of tests that will allow to choose the appropriate drug and its adequate dose. These tests include history, physical examination, laboratory analyzes and functional tests. The anamnesis checks data on kidney disease and other comorbid conditions, previously used drugs and their side effects, that is, drugs that the patient uses, especially if they are nephrotoxic. An objective examination should, among other things, measure body weight and height and check the patient's level of hydration. Laboratory testing should determine the existence of disorders that can affect the pharmacokinetics of the drug (liver function disorders, albumin concentration)[3].

Assessment of kidney function is necessary before administration of drugs, because with a decrease in kidney function, the pharmacokinetics of drugs changes. The assessment of the strength of glomerular filtration can be checked using one of the equations[7, 8]:

1. Cockcroft-Gault formula[9]:

Creatinine clearance = [(140 – years of age) x weight (kg) / 0.814 x s-creatinine (μmol/L)] x 0.85 (for women)

2. Modification of Diet in Renal Disease (MDRD) formula[10]:

Glomerular filtration rate (mL/min/1.73 m^2) = 32.788 x s-creatinine (μmol/L) $^{-1.154}$ x age $^{-0.203}$ x 0.742 (for women) x 1.210 (black race)

Creatinine clearance can also be determined using the classic formula of Endogenous Creatinine Clearance with 24-hour urine collection where[11, 12]:

Creatinine clearance = volume of 24 h urine per unit of time (24 h) x u-creatinine (mmol/L) / s-creatinine (mmol/L)

Selection and drug dosage in patients with CKD

Avoiding nephrotoxic drugs is the first and most important principle that must be followed in patients with CKD. All drugs with a known nephrotoxic effect should be avoided, and in case there is also a disease or condition that increases the risk of acute kidney injury or acutisation of CKD, the use of such drugs should be temporarily suspended. This applies to drugs known to directly damage tubular cells (aminoglycosides, amphotericin, cisplatin, calcineurin inhibitors, radiographic contrast agents), but also to those whose nephrotoxicity depends on hemodynamic disorders (angiotensin convertase inhibitors, angiotensin-2 receptor blockers, nonsteroidal antirheumatic drugs, diuretics). If the administration of nephrotoxic drugs is necessary, then regular control of glomerular filtration rate, serum electrolyte concentration, and serum drug concentration is required, if possible[3, 13].

Drug interaction is the next aspect that must be considered when prescribing drugs for patients with chronic kidney disease. The cytochrome P450 enzyme system is involved in the metabolism of numerous drugs, and many drugs can induce or inhibit this system. The simultaneous use of these drugs, which are either substrates of cytochrome P450 (cyclosporine, tacrolimus, sirolimus) or act as its inducers (barbiturates, carbamazepine, phenytoin, rifampin) or inhibitors (calcium channel blockers, macrolides, azole antifungals), causes reduced effectiveness or the appearance of side effects of drugs. This is the reason that the simultaneous use of drugs, that in any way affect the cytochrome P450 system should be avoided, and if their simultaneous use is necessary, the dose should be adjusted and the patient should be carefully monitored.

The dosing of drugs in patients with CKD is very delicate, both when determining the initial dose and the maintenance dose, and it is necessary to adjust the doses for each patient individually, depending on the degree of kidney damage. Achieving the desired concentration of the drug in the plasma depends on the elimination half-time of the drug. Although the half-life of elimination increases with decreasing renal function, for most drugs it is not recommended to reduce the initial dose of the drug in patients with CKD. Namely, the initial dose of the drug depends on the desired concentration of the drug and the volume of distribution, and as these two sizes are similar in healthy people and most patients with CKD, the initial dose of most drugs, should not differ. Some authors suggest correcting the initial dose if the patient has hypoalbuminemia or hypervolemia or if drugs with a narrow therapeutic index are used[2].

The maintenance dose of the drug in patients with CKD is reduced according to the severity of kidney impairment. There are recommendations of the Agency for Medicines and Medical Devices of the Republic of Serbia for most drugs in terms of dose correction in CKD[14]. If such recommendations do not exist, general rules are used: the maintenance dose can be adapted to kidney function by reducing the dose, extending the intervals in which the unchanged dose of the drug is administered, or a combination of these two methods. In adjusting the maintenance dose in patients with CKD simple formulas have been proposed that can be used in daily practice[4]. To calculate the appropriate dose, the following formulas are used (taking a value of 120 mL/min as a normal creatinine clearance):

$$\text{Maintenance dose} = \frac{\text{Creatinine clearance} \times \text{normal dose}}{\text{Normal Creatinine clearance}}$$

To extend the in between dose intervals we use the following formula:

$$\text{Dose intervals} = \frac{\text{Normal creatinine clearance} \times \text{normal interval}}{\text{Patients creatinine clearance}}$$

However, measuring the concentration of the drug in the blood is the best way to check and adjust the dose, and it is available for a large number of drugs. The methods used for this measure is mainly the total concentration of the drug, which may differ from the active or free fraction of the drug[2].

Drug administration in patients treated with dialysis

Many drugs are removed by hemodialysis (HD). Their clearance depends on the characteristics of the drug, but also on the applied dialysis method. The drug's dialyzability is influenced by the drug's molecular weight, charge, solubility in water, binding to proteins, volume of distribution, and excretion through other organs. The type of dialyzer membrane and its surface, composition and temperature of dialysis solution, blood flow rate, dialysis solution and speed of ultrafiltration are factors that influence the dialysis of drugs[7, 15]. In patients on regular HD, drugs

are most often administered after HD. Continuous hemodialysis procedures achieve a creatinine clearance of 20-30 mL/min. However, we are lacking in recommendations on drug dosing during these procedures that have been verified in controlled studies. That is why careful control of both the disease and the concentration of the drug in the plasma is necessary.

The drug clearance during peritoneal dialysis (PD) is lower, and it is considered that patients on PD can be dosed with drugs in the same way as those with a glomerular filtration rate below 15 mL/min/1.73 m^2. There are not many papers on drug dosing for patients on automatic PD (APD), which is more effective in removing drugs than continuous ambulatory PD (CAPD)[7, 15].

Dosing of antibiotics and antimycotics in patients with CKD and on dialysis

In patients with CKD, or those treated with HD and PD, it is important to take care of antibiotic doses, having in mind that the worsening of kidney function occurs, among other things, as a result of an infection that should be treated with appropriate doses of antibiotics and for a long period of time. Likewise, in dialysis patients, various causes of infections must also be adequately treated, to preserve the dialysis method and save the patient's life. Table 1 shows the recommendations for antibiotics and antimycotics dosing in patients with CKD and on dialysis[1, 16].

Table 1. Recommendations for antibiotics and antimycotics dosing in patients with CKD and on dialysis

Drug	Dose reduction or extension of dose intervals			Drug dosing in pts on dialysis	
	GFR > 50 mL/min	GFR 10–50 mL/min	GFR < 10 mL/min	HD	PD
Amikacin	5-6 mg/kg/12 h	3-4 mg/kg/24 h	2 mg/kg/24-48 h	5 mg/kg after HD	5 mg/L/24 h
Amfotericin B	q 24 h	q 24 h	q 24 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Ampicilin	250 mg- 2 g/4-6 h	250 mg-2 g/6 h	250 mg-1 g/6 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Vancomycin*	1 g/12-24 h	1 g/24-96 h	1 g/4-7 days	avoid	avoid
Gentamicin*	5-7 mg/kg/24 h	2-3 mg/kg/24 h	2 mg/kg/24 h	3 mg/kg after HD	3-4 mg/L/24 h
Erythromycin	100%	100%	50-75%	as GFR < 10 mL/min	as GFR < 10 mL/min
Etambutol	q 24 h	q 24-36 h	q 48 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Imipenem	100%	50%	25%	as GFR < 10 mL/min	as GFR < 10 mL/min
Isoniazid	100%	100%	75-100%	as GFR < 10 mL/min	as GFR < 10 mL/min
Kanamycin	7.5 mg/12 h	7.5 mg/24-72 h	7.5 mg/48-73 h	50% of normal dose	15-20 mg/L/24 h
Clarithromycin	100%	75%	50-75%	as GFR < 10 mL/min	as GFR < 10 mL/min
Levofloxacin	100%	50%	25-50%	as GFR < 10 mL/min	as GFR < 10 mL/min
Lincomycin	q 6 h	q 6-12 h	q 12-24 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Meropenem	500 mg-2 g/8 h	500 mg-1 g/12 h	500 mg-1 g/24 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Norfloxacin	q 12 h	q 12-24 h	q 24 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Ofloxacin	100%	50%	25%	as GFR < 10 mL/min	as GFR < 10 mL/min
Penicillamine	100%	avoid	avoid	avoid	avoid
Penicillin G	100%	75%	20-50%	as GFR < 10 mL/min	as GFR < 10 mL/min
Piperacillin	na 6 h	na 6-12 h	na 12 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Rifampin	100%	50-100%	50-100%	as GFR < 10 mL/min	as GFR < 10 mL/min
Streptomycin*	q 24 h	na 24-72 h	q 72-96%	as GFR < 10 mL/min	as GFR < 10 mL/min
Sulfomezhoxazole	q 12 h	q 18 h	q 24 h	1 g after HD	1 g/24 h
Tetracycline	100%	100%	50%	as GFR < 10 mL/min	as GFR < 10 mL/min
Tobramycin*	5-7 mg/kd/24 h	2-3 mg/kg/24 h	2 mg/kg/48-72 h	3 mg/kg after HD	3-4 mg/L/24 h
Trimethoprim	q 12 h	q 12 h	q 24 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Fluconazole	100%	100%	50%	as GFR < 10 mL/min	as GFR < 10 mL/min
Cefazolin	na 8 h	na 12 h	50% na 24-48 h	15-20 mg/kg after HD	as GFR < 10 mL/min
Cefaclor	100%	100%	50-100%	250-500 mg/8 h	250 mg/8-12 h
Cefalexin	250-500 mg/6 h	250-500 mg/8-12 h	250-500 mg/12-24 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Cefotaxime	q 6 h	q 6-12 h	1 g /8-12 h	as GFR < 10 mL/min	as GFR < 10 mL/min
Ceftazidime	100%	1-2 g/24 h	0.5-1 g/48 h	1 g after HD	0.5-1 g /24 h
Ciprofloxacin	100%	50-100%	50%	250 mg/12 h	250 mg/8 h

Abbreviations: *dose adjustment according to serum concentration of the drug; **GFR** - glomerular filtration rate; **HD** - hemodailysis; **PD** - peritoneal dialysis

Table 2. Antimicrobial dosing recommendations for prolonged intermittent dialysis (PID)

Antibiotics	Dose Recommendation	Mean Blood/Dialysate	Average length of PID (in hours)
Ampicillin/Sulbactam	Mean PID	162/162	7,4
Daptomycin	6 mg/kg IV q 24 h	166/166	7,6
Ertapenem	1 g IV q 24 h	160/160	8
Gentamicin/Tobramycin	2-2.5 mg/kg LD (or higher if the organism MIC is 2 mg/L), then adjusted using TDM	200/300	8
Levofloxacin	250 mg IV q 24 h	161/161	8
Linezolid	600 mg IV q 12 h	200/100	8
Meropenem	1 g IV na 12 h or 0,5-1 g IV q 8 h	100-250/100-200 160/160	8 8
Moksifloxacin	400 mg IV na 24 h	161/161	8
Piperacillin/Tazobactam	4.5 g IV q 8 h ili 4.5 g IV q 12 h + 2.25 g Additional dose after dialysis 3.375 g IV q 8 h (consider in severe infections)	200/200 200/300	6 8
Sulfamethoxazole/trimethoprim	15 mg/kg/24 h in 4 divided doses	140-170/170	7,4
Vancomycin	If previous PID level > 30 mg/L, hold If previous PID level 20-30 mg/L, give 500 mg at 6-8 h If previous PID level < 20 mg/L, give 1000 mg 20-25 mg/kg starting dose, then use DM to guide dosing	160/175 160/160, 300/300, 300/66,7 or 88,3	8 8, 8-10, 8-10

Abbrevations: PID - prolonged intermittent dialysis; IV- intravenous; **LD** - loading dose; **MIC** - minimum inhibitory concentration; TDM - therapeutic drug monitoring

In intensive care units, in hemodynamically unstable patients with sepsis and AKI, instead of intermittent HD, the following methods can be applied: prolonged intermittent hemodialysis and continuous procedures. The dosing of antibiotics in these patients is specific and adjusted to the individual patient and his kidney function[17].

In prolonged intermittent dialysis, conventional dialysis machines are used, but at a lower flow rate of dialysate and blood over a longer period of time than in intermittent HD. This procedure is cheaper than continuous procedures, and it can be used in hemodynamically unstable patients who would not be able to tolerate intermittent HD. The use of antibiotics in these patients is shown in table 2[17].

Continuous therapy for the replacement of kidney function includes: continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF) and is used mainly in patients with sepsis or septic shock. The dosage of antibiotics in these patients is shown in table 3[17].

Peritoneal dialysis patients are at risk of peritonitis. Regardless the sterile conditions when changing the dialysate, there is a possibility of infection - peritonitis, which should be diagnosed in time and antibiotics treatment should start before the culture of the dialysate arrives. The guidelines describe which antibiotics are used to start the treatment of peritonitis and how they should be adjusted, according to the causative agent, after the dialysate culture is obtained. Treatment of peritonitis is mainly performed by intraperitoneal administration of antibiotics. Table 4 shows the doses of antibiotics and antimycotics that are given intraperitoneally for the treatment of peritonitis in patients on continuous ambulatory peritoneal dialysis (CAPD)[17], while table 5 shows the doses of antibiotics with systemic administration of antibiotics in the treatment of peritonitis in patients on PD[18].

Table 3. Antibiotic dosing recommendations for CRRT

Antibiotics	CVVH and CVVHD		CVVHDF	
	1-2 L/h	3 + L/h	1-2 L/h	3 + L/h
Cefepime (0.5 h infusion)	1 g q 8 h (1 L/h) 1 g q 6 h (2 L/h)	1 g q 6 h	1 g q 8 h (1 L/h) 1 g q 6 h (2 L/h)	1 g q 6 h
Daptomycin	6-8 mg/kg q 24 h	8 mg/kg q 24 h	6-8 mg/kg q 24 h	8 mg/kg q 24 h
Meropenem (3 h infusion)	500 mg q 8 h	500 mg q 8 h	500 mg q 6-8 h	500 mg q 6-8 h
Piperacillin/ Tazobactam (4 h infusion)	3.375 g q 8 h	3.375 g q 8 h	3.375 g q 8 h	4.5 g q 8 h
Vancomycin	20-25 mg/kg + 500-700 mg q 12 h with TDM adjustments	20-25 mg/kg with TDM adjustments	20-25 mg/kg + 500-700 mg q 12 h with TDM adjustments	20-25 mg/kg with TDM adjustments

Abbreviations: CVVH - continuous renal replacement therapy; **CVVH** - continuous venovenous hemofiltration; **CVVHD** - continuous venovenous hemodialysis; **CVVHDF** - continuous venovenous hemodiafiltration; **ƒAUC:MIC** - area under the concentration-time curve relative to the pathogen MIC; **MIC** - minimum inhibitory concentration; **TDM** - therapeutic drug monitoring

Since in addition to CAPD there is also APD, that is mostly performed at night through a machine, with a possible combination with one daily shift, the treatment of peritonitis in these patients is a little complicated. Namely, these patients are advised to transfer to CAPD with four shifts, which is easier for treatment and administration of antibiotics in each dialysate bag. If they remain on APD, they can be given first-generation cephalosporins intermittently only during the day shift, but then the concentration of antibiotics

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during the night is low. Therefore, it is recommended to give cephalosporin in every shift. Vancomycin can be used intermittently in adults. Oral ciprofloxacin can achieve an adequate dose in the peritoneum in patients on automatic peritoneal dialysis. The dosing of antibiotics in patients on automatic peritoneal dialysis is shown in table 6[19-21]. If the patient develops fungal peritonitis, it is recommended to stop treatment with PD, remove the peritoneal catheter and transfer the patient to HD. Antimycotics are then given intravenously.

Table 4. Intraperitoneal antibiotics and antimycotics dosing in the therapy of peritonitis in patients on CAPD

Antibiotics	Intermittently (1x6 h/24 h)	Continuously (all shifts)
	Aminoglycosides:	
Amikacin	2 mg/kg/24 h	avoid
Gentamicin	0.6 mg/kg/24 h	avoid
Netilmicin	0.6 mg/kg/24 h	avoid
Tobramycin	0.6 mg/kg/24 h	avoid
	Cephalosporins:	
Cephazolin	15-20 mg/kg/24 h	LD 500 mg/L, MD 125 mg/L
Cefepime	1.000 mg/24 h	LD 500 mg/L, MD 125 mg/L
Cefotaxime	500-1.000 mg/24 h	No data
Ceftazidime	1.000-1.500 mg (20 mg/kg)/24	LD 500 mg/L, MD 125 mg/L
Ceftriaxone	1.000 mg/day	No data
	Penicillins:	
Penicillin G		LD 50.000 IU/L. MD 25.000 IU/L
Amoxicillin		MD 150 mg/L
Ampicillin	4 g/24 h	MD 125 mg/L
Ampicillin/Sulbactam		LD 1.000 mg/500 mg, MD 133,3 mg/66,7 mg/L
Piperacillin/Tazobactam		LD 4/0.5 g MD 1/0,125 g
Ticarcillin/Clavulanic acid		LD 3/0.2 g, MD 300/20 mg/L
	Other antibiotics:	
Aztreonam	2 g/24 h	LD 500, MD 250 mg/L
Ciprofloxacin		MD 50 mg/L
Clindamycin		MD 600 mg/in the bag
Daptomycin	300 mg/24 h	LD 100 mg/L, MD 20 mg/L
Fosfomycin	4 g/24 h	
Imipenem/Cisplatin	500 mg/in every secont shift	LD 250 mg/L, MD 50 mg/L
Ofloxacin		LD 200 mg/L, MD 25 mg/L
Polymyxin B		MD 300.000 IU (30 mg)/shift
Qinupristin/Dalfopristin	25 mg/during every second shift	
Meropenem	500 (APD);1.000 mg (CAPD)	MD 125 mg/L
Teicoplanin	15 mg/kg/5 days	LD 400 mg/shift, MD 20 mg/L
Vancomycin	15-30 mg/kg /5-7 days 15 mg/kg /4 days (APD)	LD 20-25 mg/kg, MD 25 mg/L
	Antimycotics:	
Fluconazole	P 150-200 mg / 24-48 h	
Voriconazole	IP 2.5 mg/kg	

Abbreviations: MD - loading dose; **MD** - maintenance dose; **IV** - intravenous

Table 5. Systemic antibiotics and antimycotics dosing during peritonitis therapy in patients on CAPD

Drug	Dosing
Antibiotics	
Amoxicillin	orally 500 m 3 times/24 h
Ciprofloxacin	orally 500-750 mg/24 h orally 750 mg 2 times for CCPD
Clarithromycin	orally 250 mg 2 times/24 h
Colistin	LD IV 300 mg, MD 60-200 mg/24 h
Daptomycin	IV 4-6 mg/kg/48 h
Ertapenem	IV 500 mg/day
Levofloxacin	orally 250 mg/24 h or 500 mg/48 h
Linezolid	IV or orally 600 mg 2 times/48 h, 300 mg 2 times/24 h
Moxifloxacin	orally 400 mg/24 h
Rifampicin	Orally or IV 450 mg/24 h for TT < 50 kg, 600 mg/24 h TT > 50 kg
Ticarcillin/clavulanic acid	IV 3 mg/0.2 mg /12 h
Tigecycline	LD IV 100 mg, MD 50 mg/12 h
Sulfamethoxazole/trimethoprim	orally 160/800 mg 2 times/24 h
Antimycotics	
Amphotericin B deoxycholate	IV 0.75-1 mg/kg/24 h, for 4-6 h
Amphotericin B (liposomal)	IV 3-5 mg/kg/24 h
Anidulafungin	LD IV 200 mg, MD 100 mg/24 h
Caspofungin	LD IV 70 mg, MD 50 mg/24 h
Fluconazole	LD orally 200 mg, MD 100 mg/24 h
Isavuconazole	LD orally or IV 200 mg/8 h 6 doses (48 h), MD 200 mg/24 h
Micafungin	IV 100 mg/24 h
Posaconazole	LD orally 300 mg/12 h – 2 dose, MD 300 mg/24 h
Voriconazole	Orally 200 mg/12 h

Abbreviations: LD - loading dose; **MD** - maintenance dose; **IV** - intravenous

Table 6. Antibiotics and antimycotics dosing during peritonitis therapy in patients on APD

Antibiotics	Intraperitoneal dose
Cephazolin	20 mg/kg IP every second day in the second dialy shift
Cefepime	1 g IP in one daily shift
Fluconazole	200 mg IP in one daily shift every 24-48 h
Tobramycin	LD 1.5 mg/kg IP in the long shift, then 0.5 mg/kg IP in the second dialysate shift
Vancomycin	LD 30 mg/kg IP in the second dialysate shift; repeat 15 mg/kg IP in the second daily shift every 3-5 days (serum level > 15 mg/mL)

Abbreviations: APD- automatic peritoneal dialysis; **LD** - loading dose; **IP** – intraperitoneal

Conclusion

In patients with CKD, and those on HD and PD, antibiotics dosing is of great importance. Improper administration of these drugs in patients with CKD can worsen kidney function and accelerate the reaching of end-stage renal disease when it is necessary to start dialysis treatment. In patients who are already on dialysis, there may be a decrease in residual diuresis or complications in the form of ototoxicity or damage to the balance center. Therefore, it is necessary to either reduce the dose of the drug or extend the dosing interval or combine both in order to prevent the patient from reaching end-stage renal failure or to avoid other complications.

References

1. Al Himali N, Al Suleimani YM, Al-Zakwani I, Abdelrahman AM. Antibiotics utilization patterns and dosage appropriateness among patients receiving hemodialysis. Saudi Pharm J. 2022 Jul;30(7):971-8.
2. Djukanovic Lj (urednik poglavlja). Izbor i doze lekova u hronicnim bolestima bubrega. U:Djukanovic Lj, Dimkovic N, Jovanovic D, Lezaic V, Naumovic R, Simic-Ogrizovic S (urednici): Bolesti bubrega (drugo dopunjeno izdanje), Akademska misao, Beograd; 2021: 668-83. (Serbian)
3. Cervelli MJ, Russ GR. Principles of Drug Therapy, Dosing, and Prescribing in Chronic Kidney Disease and Renal Replacement Therapy. In: Johnson RJ, Feehally J, Floege J (editors). Comprehensive Clinical Nephrology, 5th edition. Philadelphia, PA: Elsevier Saunders; 2015.885-904.
4. Olyaei AJ, Foster TA and Lerma EV. Drug dosing in chronic kidney disease. In: Turne N, Lameire N, Goldsmith DJ, Winearls CG, Himmelfarb J, and Remuzzi G (editors). Oxford University Press; 2016. 2911-8.
5. Matzke GR, Keller F. Drug Dosing Considerations in Patients with Acute Kidney Injury and Chronic Kidney Disease. In: Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL (editors). Brenner and Rector's The Kidney, 10th edition. Philadelphia, PA: Elsevier Saunders; 2016. 2034-55.
6. Olyaei AJ, Steffl JL. A quantitative approach to drug dosing in chronic kidney disease. Blood Purif. 2011;31(1-3):138-45.
7. Matzke GR, Aronoff GR, Atkinson AJ Jr, Bennett WM, Decker BS, Eckardt KU, et al. Drug dosing consideration in patients with acute and chronic kidney disease-a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011 Dec;80(11):1122-37.
8. Djukanovic Lj, Ležaić V. Ispitivanje bolesnika sa oboljenjima bubrega. U:Djukanovic Lj, Dimkovic N, Jovanovic D, Lezaic V, Naumovic R, Simic-Ogrizovic S (urednici): Bolesti bubrega (drugo dopunjeno izdanje), Akademska misao, Beograd; 2021: 19-52. (Serbian)
9. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999 Mar 16;130(6):461-70.
11. Elseviers MM, Verpooten GA, De Broe ME, De Backer GG. Interpretation of creatinine clearance. Lancet. 1987 Feb 21;1(8530):457.
12. Đukanović Lj. Ispitivanje bolesnika sa oboljenjima bubrega. U: Đukanović Lj i Oštrić V (urednici). Bolesti bubrega. Beograd: Zavod za udžbenike i nastavna sredstva;1999, 1-38. (Serbian)
13. KDIGO CKD Work Group: Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guidelines for the evaluation and management of chronic kidney disease. Kidney Int Soppl 2013;3:1-150.
14. Vrcelj-Jovanović S, Radonjić V, Đurović D, Đukić Lj (urednici). Beograd: Agencija za lekove i medicinska sredstva Srbije 2017. Dostupno na: https.//www.alims.gov.rs/ciril/ files/2017/04/NRL_2017_fin.pdf . Pristupljeno 13 maja, 2019.
15. Awdishu L, Bouchard J. How to optimize drug delivery in renal replacement therapy. Semin Dial. 2011 Mar-Apr;24(2):176-82.
16. Thongsanit S, Pietruszka M, Shull S, Gast C. UW Health Renal Function-Based Dose Adjustments – Adult – Inpatient/Ambulatory Clinical Practice Guideline. Madison, WI: University of Wisconsin Hospitals and Clinics Available at: https:// www. uwhealth.org/ cckm/cpg/medications/ Renal-Function-Based-Dose-Adjusments---Adult---Inpatient. Ambulatiry-17.06.27.pdf. Accessed May 20, 2020.
17. Hoff BM, Maker JH, Dager WE, Heintz BH. Antibiotic Dosing for Critically Ill Adult Patients Receiving Intermittent Hemodialysis, Prolonged Intermittent Renal Replacement Therapy, and Continuous Renal Replacement Therapy: An Update. Ann Pharmacother. 2020 Jan;54(1):43-55.
18. Li PK, Chow KM, Cho Y, Fan S, Figueiredo AE, Harris T, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. Perit Dial Int. 2022 Mar;42(2):110-53.
19. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, et al; International Society for Peritoneal Dialysis. Peritoneal dialysis-related infections recommendations: 2010 update. Perit Dial Int. 2010 Jul-Aug;30(4):393-423.
20. Li PK, Szeto CC, Piraino B, de Arteaga J, Fan S, Figueiredo AE, et al. ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. Perit Dial Int. 2016 Sep 10;36(5):481-508.
21. de Vin F, Rutherford P, Faict D. Intraperitoneal administration of drugs in peritoneal dialysis patients: a review of compatibility and guidance for clinical use. Perit Dial Int. 2009 Jan-Feb;29(1):5-15.

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