ACUTE KIDNEY DAMAGE: DEFINITION, CLASSIFICATION AND OPTIMAL TIME OF HEMODIALYSIS

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AKUTNO OŠTEĆENJE BUBREGA: DEFINICIJA, KLASIFIKACIJA I OPTIMALNO VREME ZA HEMODIJALIZU

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ABSTRACT

Acute damage to the kidney is a serious complication in patients in intensive care units. The causes of acute kidney damage in these patients may be prerenal, renal and postrenal. Sepsis is the most common cause of the development of acute kidney damage in intensive care units. For the definition and classification of acute kidney damage in clinical practice, the RIFLE, AKIN and KDIGO classifications are used. There is a complex link between acute kidney damage and other organs. Acute kidney damage is induced by complex pathophysiological mechanisms that cause acute damage and functional disorders of the heart (acute heart failure, acute coronary syndrome and cardiac arrhythmias), brain (whole body cramps, ischaemic stroke and coma), lung (acute damage to the lung and acute respiratory distress syndrome) and liver (hypoxic hepatitis and acute hepatic insufficiency). New biomarkers, colour Doppler ultrasound diagnosis and kidney biopsy have significant roles in the diagnosis of acute kidney damage. Prevention of the development of acute kidney damage in intensive care units includes maintaining an adequate haemodynamic status in patients and avoiding nephrotoxic drugs and agents (radiocontrast agents). The complications of acute kidney damage (hyperkalaemia, metabolic acidosis, hypervolaemia and azotaemia) are treated with medications, intravenous solutions, and therapies for renal function replacement. Absolute indications for acute haemodialysis include resistant hyperkalaemia, severe metabolic acidosis, resistant hypervolaemia and complications of high azotaemia. In the absence of an absolute indication, dialysis is indicated for patients in intensive care units at stage 3 of the AKIN/KDIGO classification and in some patients with stage 2. Intermittent haemodialysis is applied for haemodynamically stable patients with severe hyperkalaemia and hypervolaemia. In patients who are haemodynamically unstable and have liver insufficiency or brain damage, continuous modalities of treatment for renal replacement are indicated.

Keywords: *acute kidney injury, definition, classification, renal replacement therapy, haemodialysis, continuous dialysis*

SAŽETAK

Akutno oštećenje bubrega ozbiljna je komplikacija kod bolesnika u jedinicama intenzivnog lečenja. Uzroci za nastanak akutnog oštećenja bubrega kod ovih bolesnika mogu biti prerenalni, renalni i postrenalni. Najčešći uzrok razvoja akutnog oštećenja bubrega u jedinicama intenzivnog lečenja je sepsa. Za definiciju i klasifikaciju akutnog oštećenja bubrega u kliničkoj praksi koriste se RIFLE, AKIN i KDIGO klasifikacija. Između akutnog oštećenja bubrega i drugih organa postoji složena ukrštena povezanost. Akutno oštećenje bubrega složenim patofiziološkim mehanizmima uzrokuje akutno oštećenje i poremećaj funkcije srca (akutna srčana slabost, akutni koronarni sindrom, srčane aritmije), mozga (grčevi celog tela, ishemijski moždani udar, koma), pluća (akutno oštećenje pluća, akutni respiratorni distres sindrom) i jetre (hipoksični hepatitis, akutna insuficijencija jetre). Značajnu ulogu u dijagnostikovanju akutnog oštećenja bubrega imaju novi biomarkeri, kolor dopler ultrazvučna dijagnostika i biopsija bubrega. Prevencija razvoja akutnog oštećenja bubrega u jedinicama intenzivnog lečenja uključuje adekvatan hemodinamski status bolesnika i isključivanje nefrotoksičnih lekova i agenasa (radiokontrstna sredstva). Komplikacije akutnog oštećenja bubrega (hiperkalemija, metabolička acidoza, hipervolemija, azotemija) leče se medikamentima, infuzionim rastvorima i terapijom za zamenu funkcije bubrega. U apsolutne indikacije za akutnu hemodijalizu spadaju rezistentna hiperkaliemija, teška metabolička acidoza, rezistentna hipervolemija i komplikacije visoke azotemije. U odsustvu apsolutnih indikacija, hemodijaliza je indikovana kod bolesnika u jedinicama intenzivnog lečenja u stadijumu tri AKIN/KDIGO klasifikacije, a kod pojedinih bolesnika i u stadijumu 2. Intermitentna hemodijaliza se primenjuje kod hemodinamski stabilnih bolesnika sa teškom hiperkalemijom i hipervolemijom. Kod bolesnika koji su hemodinamski nestabilni, kod kojih postoji insuficijencija jetre ili oštećenje mozga indikovani su kontinuirani modaliteti terapije za zamenu funkcije bubrega.

Ključne reči: *akutno oštećenje bubrega, definicija, klasifikacija, terapija za zamenu funkcije bubrega, hemodijaliza, kontinuirana dijaliza*

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INTRODUCTION

Acute kidney injury (AKI) is a common, serious complication in critical patients in intensive care units (incidence of acute kidney damage is 25%) (1, 2). There are numerous causes of acute kidney damage in these patients, including sepsis, abdominal surgery, liver failure and severe weakness of the heart. Organ function disorders, triggered by acute renal damage, play a key role in the survival of critical patients requiring renal replacement therapy. The mortality rate of haemodynamically unstable patients in intensive care units, with shock and insufficiency of multiple organ systems (including acute kidney damage requiring haemodialysis), is high at 60–80% (1, 2).

Definition and classification of acute kidney damage

For the diagnosis and assessment of the severity of acute kidney damage, three classifications are used: Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) 2004, Acute Kidney Injury Network (AKIN) 2007 and Kidney Disease Improving Global Outcomes (KDIGO) 2012 (2). According to the recommendations of RIFLE and AKIN, acute renal impairment is defined as an increase of serum creatinine concentration ≥ 26.5 μmol/l (≥ 0.3 mg/dl) over 48 h compared to basal creatinine concentration and/or diuresis of less than 0.5 ml/kg/h for at least 6 h (2). Based on the KDIGO classification, acute kidney damage is defined as an increase of creatinine concentration in serum by ≥ 0.3 mg/dL (≥ 26.5 μmol/l) for 48 h or as an increase of serum creatinine concentration ≥ 1.5 times compared to basal creatinine concentration for the previous seven days and/or diuresis less than 0.5 ml/kg/h for at least 6 h (Table 1) (2). Significant constraints of these three classifications are the definition and assessment of the severity of acute renal damage based on the serum creatinine concentration (loss of muscle mass, increased concentration of substances affecting analytical measurement of serum creatinine concentration, impaired renal function and impaired liver function), defining basal serum creatinine concentration (serum creatinine concentration just before the episode of acute kidney damage) and decision-making on the initiation of treatment with renal replacement therapy (RIFLE-F, AKIN-3 and KDIGO-3). The optimal time for starting a therapy to replace the kidney function in clinical practice is still not clearly and precisely defined (in the absence of absolute indications for haemodialysis) (2). In patients with liver cirrhosis, acute kidney damage is defined based on the ICA-AKI criteria (Table 2) (3-5).

Table 1. Classification of acute kidney damage: RIFLE, AKIN, and KDIGO

RIFLE	Creatinine Criterion	Diuresis Criterion
Risk (1)	≥ 26.4 μmol/l or > 150–200% compared to basal value	> 0.5 ml/kg/h for ≥ 6 h
Injury (2)	> 200–299% compared to basal value	> 0.5 ml/kg/h for ≥ 12 h
Failure (3)	> 300% compared to basal value or > 354 μmol/l with↑ > 44 μmol/l or treatment with dialysis support therapy	> 0.3 ml/kg/h for ≥ 24 h or anuria for 12 h
Loss (4)	Persistent acute kidney damage - a complete loss of kidney function over a period of more than 4 weeks	
ESRD (5)	Final stage of kidney disease over a period of time longer than three months	
AKIN	Creatinine Criterion	Diuresis Criterion
AKIN 1	≥ 26.4 μmol/l or > 150–200% compared to basal value	> 0.5 ml/kg/h for ≥ 6 h
AKIN 2	> 200–299% compared to basal value	> 0.5 ml/kg/h for ≥ 12 h
AKIN 3	> 300% compared to basal value or > 354 μmol/l with↑> 44 μmol/l or treatment with dialysis support therapy	> 0.3 ml/kg/h for ≥ 24 h or anuria for 12 h
KDIGO	Creatinine Criterion	Diuresis Criterion
KDIGO 1	1.5–1.9 times compared to basal value	< 0.5 ml/kg/h for 6–12 h
KDIGO 2	2.0–2.9 times compared to basal value	< 0.5 ml/kg/h for ≥ 12 h
KDIGO 3	3.0 times compared to basal value or serum creatinine concentrations at a value greater than 4.0 mg/dl or starting RRT	< 0.3 ml/kg/h for ≥ 24 h or anuria for ≥ 12 h

RIFLE - Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease, AKIN - Acute Kidney Injury Network, KDIGO - Kidney Disease Improving Global Outcomes, ESRD - End-stage Renal Disease

Table 2. New diagnostic criteria for acute kidney damage in patients with cirrhosis of the liver (achieved by ICA consensus)

Basal concentration of serum creatinine	Stable concentration of serum creatinine ≤ 3 months. If the previous concentration of serum creatinine is not available, take as a baseline the concentration of serum creatinine at admission
Definition of AKI	↑concentration of creatinine in the serum ≥ 26.5 μmol/l (≥ 0.3 mg/dl) ≤ 48 h or an increase of 50% in the ratio compared to the basal value
Stages of AKI	Stage 1: ↑ SCr ≥ 26.5 μmol/l (≥ 0.3 mg/dl) or↑ SCr ≥ 1.5–2.0 times compared to the basal value
	Stage 2: ↑ SCr > 2.0–3.0 times compared to the basal value
	Stage 2: ↑ SCr > 3.0 times compared to basal value or SCr ≥ 352 μmol/l (4.0 mg/dl) with acute↑ ≥ 26.5 μmol/l (≥ 0.3 mg/dl) or initiation of kidney replacement therapy
Progression of AKI	Progression of AKI to a higher stage or need for treatment with kidney replacement methods
Regression of AKI	Regression of AKI in lower stage
Response to treatment	Absent: no AKI regression
	Partial: regression of AKI: ↓ SCr to a value of ≥ 26.5 μmol/l (≥ 0.3 mg/dl) above the baseline
	Complete: AKI regression:↓ SCr to a value of < 26.5 μmol/l (< 0.3 mg/dl) above the baseline

ICA - International Club of Ascites, AKI - Acute Kidney Injury, SCr - serum creatinine concentration
Modified by reference [2].

Acute kidney damage in patients with liver cirrhosis is defined as an increase in serum creatinine concentration ≥ 26.5 μmol/l (≥ 0.3 mg/dl) compared to basal creatinine concentration over a period of ≤ 48 h or as an increase in serum creatinine concentration ≥ 50% relative to the basal value (3-5). The baseline serum creatinine concentration is precisely defined as the serum creatinine concentration within seven days prior to hospitalisation or serum creatinine concentration over a three month period prior to hospitalisation (if there are more measurements of serum creatinine concentration, the one nearest to hospitalisation is taken) or the serum creatinine concentration at the time of admission to the hospital (if there is no serum creatinine concentration noted within a period of three months prior to hospitalisation) (3-5). Type 1 hepatorenal syndrome, as a specific form of acute kidney damage, is defined on the basis of the hepatorenal syndrome-acute kidney injury (HRS-AKI) criteria (Table 3) (3-5). In patients with liver cirrhosis, serum creatinine levels overestimate the volume of glomerular filtration due to loss of muscle mass (reduced creation of creatinine from creatine in muscles), increased creatinine clearance in the proximal tubules of the kidneys, liver damage and increased serum bilirubin concentration (impact on analytical measurement of serum creatinine concentration). As a result, all of these factors have complicated and delayed the diagnosis of acute kidney damage. Pregnancy-related acute kidney injury (PR-AKI) is defined as a serum creatinine concentration > 71 μmol/l in pregnant women in the absence of clinical data for chronic kidney disease (normal serum creatinine concentration in the third trimester of pregnancy is 62–71 μmol/l) (6, 7). The definition and classification of acute renal disease associated with pregnancy is not entirely clear and precisely defined due to open issues, such as low basal serum creatinine concentration due to increased glomerular filtration in pregnancy by approximately 50% (adaptive changes in pregnancy) and defining an optimal method for measuring glomerular filtration volume (6, 7).

Table 3. Diagnostic criteria for type 1 hepatorenal syndrome (HRS-AKI) in patients with liver cirrhosis

HRS-AKI criteria
• Diagnosis of liver and ascites cirrhosis
• Diagnosis of AKI according to ICA-AKI criteria
• Absence of a response after two consecutive days of discontinuation of the diuretic or plasma volume expansion with albumin 1.0 g/kg/day
• Absence of shock
• Absence of nephrotoxic medicines/agents (NSAIDs, aminoglycosides, and iodine contrast agents)
• Absence of macroscopic signs of kidney structure damage:
• Absence of proteinuria (> 500 mg/24 h)
• Absence of microhaematuria (> 50 RBC/HPF)
• Normal findings on ultrasound examination of the kidney

HRS-AKI - Hepatorenal Syndrome-Acute Kidney Injury, ICA - International Club of Ascites, ICA-AKI - International Club of Ascites-Acute Kidney Injury, NSAIDs - Non-Steroidal Anti-Inflammatory Drugs, RBC - Red Blood Cells, HPF - High Power Field
Modified by reference [2].

The influence of acute kidney damage on the function of other organs

Studies show that there is a complex correlation between acute kidney damage and other organs/systems of organs, including the heart, brain, lung, and liver. Knowledge of the pathophysiological mechanisms of the cross-linked association between acute kidney damage and other organs represents a new potential strategy for the treatment of critical patients in intensive care units (8).

Acute damage to the kidneys and heart

Acute kidney damage can cause acute heart damage and dysfunction (acute reno-cardiac syndrome or cardiorenal syndrome, type 3) (9, 10). Acute heart damage and function disorders include acute heart failure, acute coronary syndrome, cardiogenic shock and cardiac arrhythmias (9, 10). The mechanisms of the effects of acute kidney damage on acute heart damage and function disorders are divided into two groups: direct and indirect. Direct mechanisms are the result of microinflammatory effects on cardiomyocytes (9, 10). After acute kidney damage caused by ischaemia-reperfusion of the kidneys, there is a reinforced response of systemic and local immune systems results in the accumulation of neutrophils in the interstitium of the myocardium (neutrophils amplify the release of free oxygen radicals, proteases and myeloproteases that directly damage the myocardium), increased expression of pro-inflammatory mediators (interleukin (IL)-6 and tumour necrosis factor (TNF)-α) and cardiomyocyte apoptosis (9, 10). Among indirect mechanisms of the effects of acute kidney damage on the development of acute heart damage and heart function disorders there are: oliguria and increase in volume of extracellular fluid (volume overload, hypervolaemia, hypertension, ascites, and intra-abdominal hypertension), electrolyte balance disorders (hyperkalaemia, hyperphosphataemia, and hypocalcaemia) and development of disorders of cardiac rhythm, acid-base balance disorders (metabolic acidosis) and negative inotropic effects (reduced contractility of the left ventricle) (9, 10). For the detection of acute heart damage and function disorders, the measurement of the concentration of serum natriuretic peptides (BNP/NT-pro-BNP) and troponins (cTnI/cTnT) and ultrasound of the heart (echocardiography) are used (9, 10). Excess liquid in patients (fluid overload (FO)) is defined as the difference between the total uptake and loss of liquid divided by the body mass (excess fluid exists if the FO ≥ 10%) (11-13). For evaluation of the early detection of excess fluid, ultrasound of the lungs (estimated fluid in the extravascular lung section–estimation of lung congestion) and the inferior vena cava (indirect assessment of central venous pressure) are used (11-13). With ultrasound examination of the lungs, the vertical hyperechogenic lines are visualised (lung comets), and lung congestion is absent if the sum of lung comets is < 5. A mild degree of congestion of the lungs is present if the sum of the ultrasonic lung comets = 5–15, moderate degree if the sum = 15–30, and with a severe level of lung congestion, the sum of ultrasound comet lungs is greater than 30 (11-13). Through ultrasound examination of the inferior vena cava, the diameter of the inferior vena cava (VCId), the index of the inferior vena cava (VCIi, the ratio of the diameter of the inferior vena cava and the patient's body surface area - VCId/TP mm/m^2) and the index of the collapsibility of the inferior vena cava (VCIci, (VCIci = (VCIexp - VCIinsp)/VCIexp) x 100%) are measured. Euvolaemia exists if VCIci = 50–75%, and VCIci < 50% indicates hypervolaemia (12, 13). Removal of excess liquid is achieved using Henle's loop diuretics and extracorporeal ultrafiltration techniques. In patients with known resistance to the effect of loop of Henle diuretics, their continuous intravenous infusion is applied. If there is no response (increase in diuresis), extracorporeal ultrafiltration is administered: slow continuous ultrafiltration (SCUF) and isolated/sequential ultrafiltration (SUF) (9, 10). Slow continuous ultrafiltration is applied continuously (8 h) with a small blood flow (Qb = 50–100 ml/min) and rate of ultrafiltration (Quf = 100–300 ml/h). With isolated/sequential ultrafiltration, the blood flow is Qb = 200–300 ml/min, and the rate of ultrafiltration is Quf = 500–1000 ml/h (since there is a risk of development of haemodynamic complications) (9, 10).

Acute damage to the kidneys and brain

Acute kidney damage can cause acute brain damage (14-16). Acute brain damage is caused by direct and indirect mechanisms. Direct mechanisms include the accumulation of uremic toxins and microinflammatory conditions, and the most significant indirect mechanisms are disorders of fluid and electrolyte balance (hypervolaemia, hyponatraemia, and hypernatraemia), acid-base balance disorders (metabolic acidosis), lack of thiamine, and the effect of kidney function replacement therapy—dialysis-associated brain injury (DABI) (a rapid decrease in the urea concentration in the serum, intradialysis hypotension) (14-16). Quickly reducing the concentration of urea in the serum may cause dialysis disequilibrium syndrome (DDS), which is caused by brain oedema. to prevent the development of disequilibrium syndrome, the duration of first round of haemodialysis should be limited to 2.0–2.5 h, the blood flow should be limited to 200 ml/min, and the sodium concentration in the solution for haemodialysis should be modelled after the sodium concentration in the serum of the patient (the concentration of sodium in the solution for haemodialysis should not be greater than 10 mmol/l than the sodium concentration in the serum of the patient) using a low-flux membrane of low efficiency (coefficient of mass transfer (CoA) < 300–600), and the target urea reduction ratio (URR) should be 0.40 (short-term low-efficiency haemodialysis) (14-16). In patients with a high risk of developing disequilibrium syndrome (traumatic brain injury and intracerebral haemorrhage), the intravenous administration of mannitol during haemodialysis treatment (1.0 g/kg → increases the serum osmolarity by 8.5–10 mOsm/kg H_2O) and

a continuous dialysis modality should be considered (14-16). Intradialysis hypotension causes ischaemia-reperfusion of the subcortical white matter of the brain, leukoaraiosis (neuronal loss, demyelination, and gliosis), and development of stunning of the brain, which all result in cognitive dysfunction (significant memory loss) (17, 18).

Acute damage to the kidneys and lungs

Respiratory complications are common in patients with acute kidney damage (cardiogenic pulmonary oedema, non-cardiac pulmonary oedema/acute respiratory distress syndrome, and respiratory failure, which requires mechanical ventilation) (19, 20). Cardiogenic lung oedema in patients with acute renal impairment is due to hypervolaemia and metabolic acidosis and is successfully treated with a loop of Henle diuretics and extracorporeal ultrafiltration. Non-cardiac pulmonary oedema/acute respiratory distress syndrome in patients with acute kidney damage is due to the increased systemic and local response of the immune system, neutrophil infiltration of lung parenchyma and apoptosis of endothelial and epithelial cells of the lung (19, 20). A syndrome of increased permeability of capillaries for proteins, capillary leak syndrome (CLS) has an important role in the development of non-arterial oedema of the lungs in patients with acute kidney damage (21). The diagnosis of non-cardiac pulmonary oedema (acute respiratory distress syndrome) is based on the following criteria: rapid onset, bilateral infiltrates on chest radiography, normal function of the heart (the filling pressure of the capillaries of the lung (pulmonary capillary wedge pressure (PCWP) is less than 18 mmHg) and the ratio of the partial pressure of oxygen in the arterial blood and the oxygen fraction in the inhaled air (PaO2/FiO2) is < 200 (Acute Respiratory Distress Syndrome, ARDS), respectively, as well as < 300 in acute lung injury (ALI) (22, 23). Patients with acute kidney and lung damage require mechanical ventilation. Positive pressure ventilation (PPV), with its haemodynamic and non-haemodynamic mechanisms, can exacerbate acute kidney damage (kidney hypoperfusion) (22, 23). In these patients, the lung protective ventilation strategy (LPVS) with a small breathing/respiratory volume (a volume of 6 ml/kg of ideal body weight) is recommended, where the plateau pressure at the end of the inhalation should be less than 30 cm H_2O using the lowest positive pressure at the end of exhalation (PEEP = 5–10 cm H_2O) to achieve satisfactory oxygenation (PaO_2 = 55–80 mmHg or $SaHbO_2$ = 88–90%) (22, 23). In severe forms of acute respiratory distress syndrome (severe hypoxaemia: PaO_2/FiO_2 > 80 mmHg and uncompensated hypercapnia: pH < 7.20), extracorporeal removal of carbon dioxide ($ECCO_2R$) is the indicated therapy (24, 25).

Acute damage to the kidneys and liver

In the prerenal type of acute kidney damage, a reduced effective arterial volume can cause hypoxic hepatitis (HH) (26, 27). Hypoxic hepatitis is characterised by a sudden and substantial transient increase of aminotransferases in the serum, as a result of reduced flow and utilisation of oxygen by the hepatocytes of the liver (26, 27). The most important predisposing clinical conditions for the development of hypoxic hepatitis are heart failure (liver congestion), septic shock, pre-renal acute kidney damage and respiratory insufficiency. The incidence of hypoxic hepatitis in intensive care units is 2.5–10%, and the pathophysiology is multifactorial and includes blood stasis in the hepatic veins, reduced blood flow through the liver, whole body hypoxia, decreased supply of oxygen to the hepatocytes, reduced utilisation of oxygen by hepatocytes, ischaemia-liver reperfusion, increased central venous pressure and increased intra-abdominal pressure (26, 27). The main clinical manifestations of hypoxic hepatitis are pain under the right chest arch, hepatomegaly, and increased aminotransferase concentrations in the serum, and the most significant complications are spontaneous hypoglycaemia, respiratory failure due to hepatopulmonary syndrome and hepatic insufficiency (increased serum ammonia concentration) (26, 27). HH is diagnosed based on the following criteria: a significant increase of aminotransferase concentrations in the serum (≥ 20 times compared to the upper normal limit), the presence of one of the predisposing clinical conditions (acute cardiac, circulatory or respiratory insufficiency), the absence of other possible causes of necrosis of liver cells (toxic effect of medicines, viral hepatitis, acute Budd-Chiari syndrome, HELLP syndrome, acute fatty liver in pregnancy, or autoimmune hepatitis) (26, 27). A liver biopsy is not required for the diagnosis of HH, and the main histopathological feature is centrilobular cell liver necrosis (CLNC) (26, 27). Rapid diagnosis and timely treatment of the underlying disease are of paramount importance. Optimisation of circulation, maintaining adequate mean arterial blood pressure, and preservation of the microcirculation and oxygenation of tissue is achieved by application of inotropes, vasodilators and diuretics. In patients with acute liver failure, consideration should be given to the benefit of the modality of albumin dialysis with the Molecular Adsorbent Recirculating System (MARS) (26, 27).

Diagnosis of acute kidney damage

The diagnosis of acute kidney damage is based on anamnesis, physical examination, review of the urine sediment (erythrocytes altered in shape and erythrocyte cylinders indicate glomerular disease, leukocytes indicate acute bacterial inflammation of the kidneys, and brown granular cylinders indicate acute tubular necrosis of the kidneys). Fractional sodium excretion (FE_{Na+}) < 1.0% and FE_{urea} < 35% with normal urine sediment suggest a prerenal (functional) type of acute kidney damage (28). Some patients require tests for the evaluation of the immune system: antibodies to the antigens of the cytoplasm of neutrophils (renal vasculitis), antibodies directed against the basement membrane of the glomeruli (fast progressing glomerulonephritis), and antinuclear antibod-

ies (systemic lupus erythaematosus) (28). For diagnosis of aHUS/TTP, the number of platelets, concentration of haptoglobin and lactate dehydrogenase in the serum, Coombs test, activity of metalloproteinase enzyme ADAMTS13 and titre of antibodies for factor H of the complement system should be determined (29-30). In the last decade, for the diagnosis of acute kidney damage, the following new biomarkers have been used: cystatin C (marker of glomerular filtration), microalbuminuria (marker of integrity of the glomerulus), neutrophil gelatinase-associated lipocalin (NGAL) (marker of tubular damage), kidney injury molecule-1 (KIM-1) (marker of tubular damage), Liver fatty acid-binding protein (L-FABP) (marker of tubular damage), interleukin 18 (a kidney inflammatory marker), and insulin-like growth factor-binding protein-7 (IGFBP-7) (marker of the stress of tubules) (31-33). The concentration of new biomarkers in the urine increases 24–48 h before the increase in serum creatinine concentration. In critical patients in intensive care units, a concentration of NGAL in urine greater than 150 ng/ml may indicate the development of acute kidney damage in the phase before the increase of the creatinine concentration in the serum (non-creatinine increase-acute kidney injury (NCI-AKI)) (32). For the diagnosis of acute kidney damage and the assessment of renal perfusion, colour Doppler ultrasonography of the kidney is used (34). Colour Doppler ultrasonography and measurement of the resistance index from the blood flow curve through the segmental and interlobular arteries allows the evaluation of kidney perfusion and the distinction of the prerenal type of acute kidney damage from acute tubular necrosis. In patients with the prerenal type of acute kidney damage, the resistance index (RI) is < 0.75, whereas a RI ≥ 0.75 indicates a transition from the prerenal to renal type of acute kidney damage (extending of renal hypoperfusion results in the development of acute tubular necrosis) (34). Patients with acute damage to the kidney who have clinical suspicion of acute glomerulonephritis or renal vasculitis require a kidney biopsy (35).

Treatment of acute kidney damage

Prevention of acute kidney damage in intensive care units includes adequate haemodynamic status of the patient (central vein pressure (CVP) = 8–12 mmHg, diuresis ≥ 0.5 ml/kg/h, mean arterial blood pressure (SAP) ≥ 65 mmHg) and exclusion of nephrotoxic drugs and agents (radiocontrast agents) (36). Complications of acute kidney damage (hyperkalaemia, metabolic acidosis, hypervolaemia, and azotaemia) are treated with medications (Resonium A, 10% calcium chloride/calcium gluconate, and Henle's loop diuretics), infusion solutions (8.4% $NaHCO_3$ and 10% or 50% glucose + quick acting insulin) and kidney replacement therapy (36).

Optimal starting time for kidney replacement therapy

Patients with acute renal impairment in intensive care units require enhanced cooperation between doctors and medical technicians of the following specialties: anaesthesiologist intensivists, nephrologists and medical technicians of the general and nephrological intensive care units (37). For treatment of acute kidney damage in critical patients in intensive care units, the following modalities of kidney replacement therapy (renal replacement therapy (RRT)) are used: acute peritoneal dialysis, acute intermittent haemodialysis, and continuous dialysis modalities (continuous venous vein haemodiafiltration (CVVHDF)) (38-48). Intermittent haemodialysis provides rapid clearance of the substance/electrolyte and a high degree of ultrafiltration. Additionally, intermittent haemodialysis is a first-line modality of therapy for kidney replacement function in haemodynamically stable patients for the treatment of life-threatening hyperkalaemia and hypervolaemia (malignant chamber disorder rhythms of the heart and acute oedema of the lungs in acute renal damage) and poisoning caused by overdosage of medicines (41-48). Continued dialysis modalities are indicated in haemodynamically unstable patients with acute kidney damage caused by cardiogenic or septic shock, as well as in patients with acute kidney damage associated with brain or liver damage (increased intracranial pressure) (41-48). The time to initiate kidney replacement therapy is completely clear when there are complications associated with acute kidney damage that are life-threatening for patients, such as resistant hyperkalaemia, severe metabolic acidosis, oedema of the lungs, and complications of high azotaemia (uremic encephalopathy and uremic pericarditis) (49-52). However, in the absence of absolute criteria, the optimal time to initiate dialysis is not clearly defined (there is no consensus) (49-52). Patients with acute renal impairment of stage 3 of the AKIN/KDIGO classification require treatment with kidney replacement methods. For stage 2 of the AKIN/KDIGO classification, randomised clinical studies are required to precisely define the criteria for initiating treatment with renal replacement methods (49-52). The arguments for early initiation of RRT are better volaemia control (avoiding the accumulation of water, especially in patients where there is resistance to the use of diuretics), better control of the electrolyte and acid-base status, the clearance of toxins of small- and medium-molecular weight (modulation of the immune system and clearance of mediators of inflammation), and avoiding severe complications associated with acute kidney damage (heart rhythm disorders due to hyperkalaemia) (49-52).The arguments for the late initiation of RRT are exposure of patients to complications associated with the placement of central venous catheters, exposure of patients to complications associated with *RRT* (intradialysis hypotension (an iatrogenic episode of haemodynamic instability in patients may aggravate acute kidney damage and slow down/delay kidney function recovery), cardiac rhythm disorders, and antibiotic clearance), complications associated with anticoagulant therapy (haemorrhage due to systemic anticoagulation caused by the use of unfractionated heparin), risk of increased clearance of medications (suboptimal

therapeutic concentrations in serum), and high costs of treatment (especially in patients with slow kidney function recovery) (49-52). Based on the results of the clinical trials done so far, three sets of indications for the initiation of treatment with kidney replacement methods have been identified. The first group consists of the traditional indication (hyperkalaemia ($K^+ \geq 6.5$ mmol/l), serum urea concentration ≥ 84 mg/dl, pH of arterial blood < 7.15, serum bicarbonate concentration < 10 mmol/l, acute pulmonary oedema, acute uremic encephalopathy or acute uremic pericarditis) (49-52). The second group of indications constitute a severe form of acute kidney damage (stage 3 AKIN/KDIGO) in the absence of traditional indications, and the third group indicates acute kidney damage (stage 2 AKIN/KDIGO) in extreme situations (severe sepsis and rapid deterioration of acute kidney damage) (49-52). Two randomised clinical studies, Early vs. Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury (ELAIN) and Acute Kidney Initiation in Kidney Injury (AKIKI) showed a different impact of the early onset of dialysis on the survival rate of patients with acute kidney damage in intensive care units (49-52). The ELAIN Study demonstrated improved survival in patients with the early initiation of dialysis (stage 2 AKIN/KDIGO), while the results of the AKIKO Study have not confirmed this (there was not shown the improved survival of patients who started early treatment with dialysis supportive therapy was not shown, while the improved survival of in patients who started late dialysis supportive therapy (stage 3 AKIN/KDIGO) was observed (49-52). Randomised clinical studies of the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network (VA/NIH ATN) and the Randomised Evaluation of Normal versus Augmented Level (RENAL) have shown that patients treated with continuous dialysis modalities have no statistically significantly higher survival rates in comparison to patients with acute kidney damage who are treated with intermittent haemodialysis. With increasing dose of renal replacement therapy (RRT), the survival rates of patients with acute kidney damage are not significantly increased (49-52). According to the recommendations of KDIGO, the dose of individual treatment of intermittent haemodialysis, expressed through the kinetic model of urea, should be $Kt/V \geq 1.20$-1.4, and the dose of the continuous dialysis modality, expressed over the effluent rate, should be 20–25 ml/kg/h. In patients with severe sepsis and acute kidney damage, the dose of continuous modality of CVVHDF, expressed over the effluent rate, should be 35 ml/kg/h (49-52).

CONCLUSION

Acute kidney damage is an independent risk factor for an adverse outcome for patients in intensive care units. Due to the complexity and severity of acute kidney damage syndrome (multiple organ systems insufficiency), patients in intensive care units require a team approach, technical knowledge, well-trained staff, enhanced collaboration between anaesthesiologist intensivists and nephrologists as well as precisely defined treatment protocols that should include therapeutic support for more organ systems. Early detection of patients who have a high risk of developing acute kidney damage, timely application of appropriate prevention and treatment, and adequate monitoring of patients can significantly prevent the development of acute kidney damage and reduce the mortality rate of these patients.

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