Research Article

Pharmacological correction of intrarenal hemodynamic disorders in acute kidney injury (part 2)

Katherine K. Shramenko[1], Georgiy A. Gorodnik[1], Valentina P. Shano[1], Irina V. Kuznetsova[1], Aleksandr P. Grigorenko[1], Vladimir V. Potapov[1]

1 *Donetsk National Medical University named after M. Gorky, 16 Ilyicha Ave., Donetsk 83003, Russian Federation*

Corresponding author: *Katherine K. Shramenko* (k.shramenko@gmail.com)

Citation: Shramenko KK, Gorodnik GA, Shano VP, Kuznetsova IV, Grigorenko AP, Potapov VV (2018) Pharmacological correction of intrarenal hemodynamic disorders in acute kidney injury (part 2). Research Results in Pharmacology 4(2): 95–104. https://doi.org/10.3897/rrpharmacology.4.28542

Abstract

Introduction: Treatment of acute kidney injury (AKI) is a complex current problem. Mortality in this pathology is over 50%. One of the areas of correction therapy in AKI patients is the improvement of diagnostics and the earliest identification of the underlying cause of AKI. The second promising direction in reducing mortality is prevention of AKI progression (nephroprotection) and resulting multi-organ disorders by individual pharmacological and non-pharmacological intensive therapy.

Objectives: to evaluate the possibilities of individual pharmacological correction and intensive care of patients with AKI of different origin.

Materials and methods: A prospective nonrandomized study. Inclusion criteria: patients with prerenal, renal and subrenal AKI module in stage of oligoanuria and restoration of diuresis. Exclusion criteria: AKI in patients after cardiosurgery and operations on large vessels. Individual pharmacological and non-pharmacological correction (renoprotection) was performed in 250 ICU patients with prerenal (130), renal (81) and subrenal (39) AKI. The effectiveness of individual nephroprotection was assessed by the duration of the oligoanuria stage (indicator of AKI severity).

Results and discussion: The basis of intensive therapy in AKI patients was renal replacement therapy and peridialysis care. Peridialisys support was presented by a complex of therapeutic measures aimed at preventing the progression of AKI (nephroprotection) and the prevention of multi-organ complications. Individual pharmacological and non-pharmacological peridialysis intensive therapy was performed, including: removal of the main cause of forming AKI; maintenance of normal circulation blood volume and effective cardiac output; maintenance of adequate lung ventilation (correction of hypoxia, timely ventilation); correction of hypertension, hypotension, and clinically significant arrhythmia; improvement of renal blood flow and stimulation of diuresis; stopping bleeding and correction of anemia; targeted antibiotic therapy; removal or adequate drainage of the intoxication focus (purulent focus); use of alternative ways of detoxication and efferent methods. It was proved that individual pharmacological and non-pharmacological nephroprotection made it possible to improve the results of treatment. The duration of the oligoanuria stage significantly (p < 0.05) decreased to 14.3±0.9 days in the main group (22.6±1.2 days in the comparison group).

Conclusions: The medical technology of individual intensive therapy with renal replacement therapy and peridialysis care has been developed, including: a diagnostic stage with determination of peculiarities of renal hemodynamic disorders and pharmacological and instrumental (stenting, drainage, etc.) correction of the real cause and manifestations of AKI. Improving AKI diagnostics and carrying out individual pharmacological and non-pharmacological correction improves the results of AKI treatment.

Introduction

Treatment of AKI is an important social problem. The incidence of AKI has increased, accounting for more than 35% of patients in intensive care units (ICU) (Ake et al. 2005, Case et al. 2013). More often, it develops as a component of multi-organ failure (MOF) (Jo et al. 2007, Kellum et al. 2001, Lauschke et al. 2006). AKI is an independent predictor of adverse outcome in critically ill patients and increases hospital mortality 3–10 times (Lameire et al. 2005, Overberger et al. 2007, Ostermann and Chang 2007).

Mortality in this pathology remains high and exceeds 50% (Vaira et al. 2001, Vijayan and Palevsky 2012). Often the difficulty of conducting adequate intensive care is associated with the lack of timely diagnosis and the late establishment of the real cause of AKI (Wystrychowski et al. 2009, Tomilina 2011). The first part of this paper presents the data on the evaluation of the state of renal hemodynamics, using the Doppler method in patients with AKI. The study of renal hemodynamics made it possible to improve diagnostics and establish the immediate cause of AKI. The necessity of individual pharmacological and non-pharmacological nephroprotection in these patients was proved.

In AKI patients, a harmonious nephroprotection system is not developed. There are some works where nephroprotective measures are presented as the use of singular medicines in individual cases. Many issues remain controversial; mutually exclusive views are often have to be dealt with. For example, several authors oppose the use of dopamine in the ICU for the prevention and treatment of AKI (Kolesnik et al. 2010, Kellum and Decer 2001, KDIGO 2012, Lauschke et al. 2006). Others evaluate positively the experience of using this drug, especially in prerenal AKI (Bellomo et al. 2000, Saito et al. 2011). At the same time, it has been proposed to use erythropoietin and iron to correct anemia. According to KDIGO, it is not recommended to use diuretics for the prevention and treatment of AKI, although in cardiorenal and hepatorenal syndromes the use of diuretics for both prophylaxis and treatment of AKI is justified, ensuring a steady increase in the rate and volume of diuresis and a decrease in azotemia.

Improvement of pharmacological and nonpharmacological correction to achieve nephroprotection in patients with various AKI modules is carried out in ICU of the Donetsk Clinical Territorial Medical Unit (DoCTMU) (Shramenko and Shkarbun 2011, Shramenko and Shkarbun 2014).

Objectives

To evaluate the opportunity of individual pharmacological correction and intensive care in patients with different AKI stages.

Material and methods

250 patients were the main group (treated from 2009 to 2014 in DoCTMU): 162 male (64.7%) and 88 female (35.3%). The age was from 18 to 85 years, an average of 53±8.2. At the time of admission to the ICU, isolated AKI was only 5%. All the patients after diagnosis clarification were divided into modules: 1) patients with prerenal AKI module (130); 2) patients with renal module AKI (81); 3) patients with subrenal AKI module (39). The module was a relationship of etiology, pathogenetic mechanisms, risk factors, and causes of AKI.

The comparison group consisted of 107 patients with a prerenal (60), renal (32) and subrenal (15) variant of AKI treated at the DoCTMU before 2009, aged 18 to 77 years, an average of 48±7.9. Of which 74 were males (69.2%) and 33 – females (30.8%). Upon admission to the ICU, isolated AKI amounted to 25%. Dialysis treatment was performed in 79 patients (73.8%). In the comparison group, treatment was performed without individual pharmacological and non-pharmacological nephroprotection.

Statistical processing of data

The analysis of the results was carried out in statistical packages MedStat v.4.1 (Lyakh and Guryanov 2012), MedCalc v. 13.2.2 (MedCalc SoftWare bvba, 1993–2014), and Statistica Neural Networks v.4.0 B (StatSoft Inc., 1996–1999).

For the analysis, methods of constructing multivariate models of classification were used. The quality of the constructed models was estimated by their sensitivity and specificity, a 95% confidence interval (95% CI) was calculated. To determine the factors most associated with the results of treatment, the "genetic algorithm" (GA) method was used. To assess the adequacy of multivariate mathematical models and predictive cure rate tests, Area Under Curve (AUC) of their 95% CI was used. To evaluate the possibility of using the constructed models on new data, a method was used to verify their prognostic characteristics on the confirming variety (a random number generator was used for the selection). To assess the degree of influence of factor characteristics on the resulting characteristics,

a method of constructing logistic regression models was used. For the assessment, the odds ratio (OR), as well as their 95% CI, was calculated (Lyakh and Gurianov 2012, Petri and Sabin 2003).

Results and discussion

Intensive therapy in AKI patients integrated renal replacement therapy (hemodialysis) and peridialysis care. The peculiarities of intensive care were determined by the AKI module. However, even within the module, an individual approach was required.

The basis of peridialysis intensive care was therapeutic measures aimed at preventing the progression of renal damage (nephroprotection) and the prevention of multi-organ failures (MOF).

Peridialysis intensive therapy included: removing the cause of AKI; maintenance of normovolemia and effective cardiac output; maintenance of adequate lung ventilation (correction of hypoxia, timely lung ventilation); correction of hypertension, hypotension, and clinically significant arrhythmia; improvement of renal blood flow and stimulation of diuresis; stopping bleeding and correction of anemia; targeted antibiotic therapy; removal or adequate drainage of the intoxication focus (purulent focus); use of alternative ways of detoxication and efferent methods.

Peridialysis support was represented by pharmacological and non-pharmacological measures. Pharmacological intensive therapy was aimed at improving renal blood flow and stimulating diuresis and included: first of all, maintenance of blood volume with adequate infusion mediums, administration of drugs that improve renal blood flow (pentoxifylline, dipyridamole, dopamine, xanthinol nicotinate, euphyllin) and diuresis stimulating (furosemide, torasemide, xypamide); stopping bleeding (etamzilate sodium, tranexamic acid, novoseven, octaplex) and correction of anemia (transfusion of blood components, and the prescription of erythropoietin for patients with AKI having chronic kidney insuffciency (CKI)); antibacterial therapy, maintenance of analgesia, etc. Non-pharmacological nephroprotection was aimed at: prompt restoration of urine passage (stenting, nephrostomy, removal of stones, tumors, etc.); instrumental improvement of systemic blood flow (counterpulsation in cardiogenic shock, puncture of the pericardium in tamponade and severe exudative pericarditis, endovascular intervention in renal artery thrombosis or stenosis, etc.); early removal or drainage of purulent focus; cooling, elastic bandaging in the distal direction, and immobilization in a crush- syndrome.

Among the general principles of peridialysis support were the following: the restrictive infusion therapy and other fluid intake, taking into account renal and extrarenal losses; correction of cardiovascular disorders with a sufficient cardiac output, cardiac index not less than 2.8 L/min/m²; prevention of hypoxia, timely artificial lung ventilation with maintenance of $SpO_2 \geq 90\%$; correction of anemia with maintaining a hemoglobin level of at least 85 g/L; preventive (before the appearance of symptoms of mucosal lesions) protection of the gastrointestinal tract by injection forms of antisecretory drugs; use of alternative ways of detoxification (gastrointestinal lavage, therapeutic diarrhea, etc.); and mandatory drainage and sanation of the intoxication focus in order to stop the damaging effect on the kidneys. Regardless of the AKI module, the general principle of nephroprotection was excluding administration of nephrotoxic drugs.

The main principles of intensive care in AKI patients are presented in Table 1.

Algorithm of individual intensive care

Diagnostics of an AKI module and verification of its immediate cause, taking into account risk factors and using modern visualization and laboratory methods.

Impact on the cause of AKI in order to restore the rate of diuresis and daily diuresis: replenishment of blood volume (BV); removal and inactivation of toxic substances;

Table 1. The main principles of intensive care in AKI patients

№	Principles, determined by the clinical situation	Appropriate intensive care	The universal principle
1.	Arrest of pathogenic action of the ethiologic factor	Stopping bleeding, removal of exo- and endotoxines, surgical lavage of purulent focus, restoration of blood circulation in vessels, restoration of urine passage, etc.	Nephroprotection. Prevention of MOF
2.	Pathogenic preventive therapy of complications	Prevention of hypoperfusion, hypoxia, correction of anemia, prevention of bleeding, antibiotic therapy, etc.	
3.	Replacement and supporting therapy	Renal replacement therapy, artificial lung ventilation, alternative ways of detoxication, efferent methods (extracorporeal antibiotic therapy, ultraviolet irradiation, plasmapheresis)	
4.	Syndrome therapy in life-threatening situations	Cardiopulmonary resuscitation, correction of cardiac rhythm disturbances, normalization of blood pressure, reduction of pulmonary edema, correction of hemorrhagic complications, etc.	

unblocking the kidney and urinary tract; stimulation of diuresis with diuretics and drugs improving renal blood flow; alkalization of plasma and urine on therapeutic grounds; X-ray endovascular intervention with stenting and selective thrombolysis, etc.

Prevention the development or progression of multi-organ failures: 1) prevention of hypoxia, timely respiratory support; 2) prevention and correction of infectious complications, both conservatively and by plasmapheresis with extracorporeal antibiotic therapy with a broad spectrum of powerful targeted antibiotics (de-escalation variant), ultraviolet blood irradiation; 3) prevention of fatal hyperkalemia and correction of dyselectrolytemia; 4) prevention and correction of cardiovascular disorders (antihypertensive drugs, cardioprotectors, antiarrhythmic drugs); 5) prevention and treatment of hemorrhagic complications; preventive (before any symptoms of mucosa damage appear) protection of the gastrointestinal tract by injection forms of H_2-histamine receptors blockers and proton pump inhibitors; prescription of a complete complex of haemostatic agents, including octaplex; 6) parenteral nutrition (including nephrotect).

Timely implementation of replacement renal therapy when creating conditions for the most effective and safe treatment (drainage or removal of the focus of intoxication, correction of hemodynamic disorders, etc.).

The medical technology of individual renal replacement therapy with peridialysis care, developed on the basis of the improved diagnostics, includes several stages.

Ctage I. Optimized diagnosis of AKI

Identification and clarification of the cause of AKI based on: anamnesis, clinical picture of the disease; clinical and laboratory parameters; data of a complex renal ultrasonography with ultrasound dopplerography; if necessary, CT, MRI, echocardiography, etc.

Assessment of AKI severity by SAPS, RIFLE scales according to clinical and laboratory data, including s-NGAL and dopplerographic renal blood flow parameters. Determination of prerenal, renal or subrenal modules of AKI. Differentiation of genuine prerenal AKI and prerenal AKI by cause factor. Consultations with relevant specialists: urologist, cardiosurgeon, nephrologist, thoracic surgeon, vascular surgeon, transplantologist, etc.

Stage II. Optimized Intensive care of AKI

Pre-dialysis: 1) removal of AKI cause; 2) in patients with **prerenal** and **renal AKI**, keeping normal BV, improvement of renal blood flow and stimulation of diuresis; prevention of hypoxia, timely respiratory support, maintenance of oxygenation and cardiac output according to protocols. Twenty-four-hour testing for dosage and effecacy of some drugs, such as dopamine, furosemide to assess the possibility of restoring kidney function; in patients with **genuine perenal AKI**, depending on the immediate cause, certain measures are to be taken: resto-

ration of BV by targeted infusions of, for example, 2.5% sodium chloride solution; pericardial puncture, renal artery stenting, etc.); 3) in patients with subrenal AKI – urgent restoration of urine passage (stenting, nephrostomy, etc.).

Renal Replacement Therapy. Hemodialysis and its modifications.

Daily individual hemodialysis regimen and dosing. The decision to start hemodialysis therapy has to be based on the analysis of a specific clinical situation, the vollemic, electrolyte and metabolic statuses of the patient, including renal blood flow and s-NGAL. Priority must be given to short (2.5-3 hours), frequent (daily, every other day) hemodialyses with peridialysis intensive therapy, aimed at the prevention of dialysis disequilibrium syndrome, cardiovascular, hemorrhagic and other complications. Early or prophylactic hemodialyses should be performed only in patients with toxic nephropathy. In other cases, safe conditions for the procedure should be provided: stabilization of hemodynamic parameters, correction and prevention of hemorrhagic complications, sanation of the purulent focus by drainage or surgical removal. Alternative ways of detoxication are to be used. If there are purulent septic complications, severe endogenous intoxication (crush syndrome, destructive pancreatitis, leptospirosis, etc.) and autoimmune diseases, hemodialysis needs to be combined with extracorporeal antibiotic therapy, plasmapheresis, ultraviolet blood irradiation.

Individual tactics of intensive care in accordance with immediate cause of AKI

If the immediate cause of AKI is diagnozed, early targeted intensive care can be provided. As examples of individual intensive care, patients with some diagnoses in different modules are presented:

Prerenal AKI: 1) rhabdomyolysis; 2) renal artery thrombosis in solitary functioning kidney; 3) hypovolemic shock due to loss of water and electrolytes;

Renal AKI: toxic nephropathy;

Subrenal AKI due to bilateral (usually, with a solitary functioning kidney) or unilateral block and absence of urine passage.

Prerenal AKI module

In the group of patients with rhabdomyolysis (RM) of any origin, targeted intensive care included: early hemodilution and alkalization of plasma (to shorten the duration of the oligoanuria stage, to reduce the need for dialysis treatment and to improve the outcome of AKI). Nephroprotection in RM also included adequate analgesia, improvement of the rheological properties of the blood, correction of hemodynamic and respiratory disorders, stimulation of the gastrointestinal tract, and the use of efferent methods. Stripe incisions in the damaged areas of the body in compression syndrome were not a nephroprotective measure. They were complicated by bleeding, infecting and did not shorten the duration of oliguria.

In the group of patients with renal artery thrombosis of solitary functioning kidney, the individual intensive care included the following steps.

1. Diagnosis. The reasons for diagnosing renal artery thrombosis were: clinical manifestations – back pain, oliguria; risk factors: atherosclerosis, hypertension, permanent atrial fibrillation, anamnesis of myocardial infarction or transient ischemic attack, malignant neoplasms, old age, cirrhosis of one of the kidneys.
2. The assignment of renal ultrasound examination in the regime of Doppler mapping, as one of the modern visualization methods, made it possible to diagnose renal thrombosis to high precision, quickly and safely. Kidney ultrasound in the usual regime was non-informative in this pathology.
3. Carrying out X-ray endovascular intervention, including several stages: catheterization of the renal artery; tromoboaspiration and balloon angioplasty of the vessel; selective thrombolysis (actilize 100 mg for 1 hour). Endovascular intervention was advisable despite the duration of oligoanuria, as in this case AKI was prerenal (formation of collaterals, preservation of tubular epithelium and parenchyma). High level of plasma creatinine was not a counterindication for the introduction of radiocontrast agents.

In all 13 patients of this group, diuresis was recovered immediately after the endovascular intervention, despite prolonged anuria (up to 7 days). Hemodialysis was not required. Such a nephroprotective therapy was organ-preserving; it prevented cirrhosis of the kidney and the need for program hemodialysis and provided a good quality of life for the group of patients. with extremely severe module of the sisease.

Individual tactics of intensive care was used in patients with AKI due to loss of water and electrolytes. The main diagnosis at admission was established only in 52% of patients. In order to clarify the diagnosis, the immediate cause and severity of AKI, all patients had ultrasound dopplerography applied, if necessary, CT of the abdominal cavity and fibrogastroscopy were conducted. In retrospect, the patients were divided into 2 subgroups, according to the degree of disturbance of renal blood flow. According to the dopplerography data, 23 patients did not have severe disorders of blood flow in their kidneys. Although Vps was below normal (58±2.3 cm/sec), Ved did not decrease significantly, being on averahe 20±1.6 cm/sec. Thus, the systolic-diastolic ratio remained within the normal values of 2.9. Along with the rates of arterial blood flow, RI was within 0.65±0.2, which did not differ significantly from the data in the control group.

Such a state of renal blood flow testified against severe damage to the renal tubules and parenchyma, which made it possible to perform conservative nephroprotective therapy, despite an increase in plasma creatinine above 600 µmol/L. The therapy was aimed at replenishment of BV and correction of dyselectrolytemia. Infusion thera-

py included 2.5% sodium chloride solution 4ml/kg/day, sterofundin – 6 ml/kg/day, GIK – 8ml/kg/day. The lack of potassium was restored with intravenous administration of potassium chloride, asparcam, and panangin, with daily monitoring the laboratory parameters. Gastrointestinal lavage with enterosoption and cleansing enema was used twice a day. Within 24 hours, there was a decrease in the levels of urea by 10.0±1.4 mmol/L and creatinine by 30-40 µmol/L in this subgroup. Within 2-3 days, such a therapy led to recovery of diuresis and a decrease in azotemia.

In 9 patients, a significant worsening of renal blood flow was detected according to the data of dopplerography. Vps and Ved were reduced to 52.0±2.3 and 11.1±1.3 cm/s, respectively. RI was 0.79±0.03, indicating a severe form of AKI, although the indicators of urea and creatinine were comparable to those in the subgroup with relatively preserved renal blood flow. After the diagnosis was clarified, 7 patients of this subgroup had to undergo a surgical intervention (gastrectomy – 3, drainage of omental bursa – 3, removal of the gall bladder –1). In 4 patients, despite complex intensive therapy, diuresis did not recover. Renal replacement therapy was started, which was combined with plasmapheresis and extracorporeal antibiotic therapy. The mortality rate was 9.3%. A 30-day survival rate was 100%.

So, individual tactics of nephroprotection in this subgroup included: 1) assessment of kidney hemodynamic disorders and possibility for conservative renal blood flow restoration; 2) correction of dyselectrolytemia (2.5% solution of sodium chloride, GIK, sterofundin); 3) creation of conditions for safely renal replacement therapy (removal or drainage of the purulent focus, restoration of patency of the gastrointestinal tract, etc.); 4) increasing the effectiveness of antibiotic therapy by combining hemodialysis with plasmapheresis and extracorporeal antibiotic therapy by means of powerful antibiotics (de-escalation variant); 5) parenteral nutrition (including nephrotect).

Thus, only within the group of AKI caused by the loss of water and electrolytes, various renal hemodynamic disorders were revealed. Tactics and success of nephroprotection and intensive care depend on the ability of the kidneys to restore, and a need for surgery to restore the function of other organs in order to stop their damaging effects on the kidneys.

Renal module AKI

The largest subgroup of renal AKI was represented with the patients with *toxic nephropathy* (57). Of these, 15 were poisoned with toxic substances, and 42 had drugs nephropathy. The lowest blood flow rates and the highest RI were found in the group of patients with toxic nephropathy. A decrease in Vps and Ved in this group reached 32 and 1.7 cm/s, respectively, and the RI increased to 0.95. The thickness of the parenchyma, according to renal ultrasound, was more than 2.5 cm, and in some patients reached 3.5 cm. Echogenicity of the parenchyma

was higher in all the patients. s-NGAL at admission was 32.99±0.34 ng/ml (13.6±0.8 in the control group), which was significantly higher than in the subrenal and prerenal AKI groups. The above indicated a severe damage to the renal tubulointerstitial apparatus and was confirmed by the longest stage of oligoanuria, up to 30 days. All the patients with such disorders need renal replacement therapy.

Nephroprotection, in order to shorten the duration of the oligoanuria stage and to reduce the duration of dialysis therapy, included the following measures. The key point of nephroprotection was the early removal of the poisonous substance, both by conservative measures (tube lavage, gastrointestinal lavage, cleansing enema, enterosorption), and active detoxication methods (early hemodialysis, plasmapheresis). In the toxicogenic stage antidote therapy (unitiol, tetacin-calcium, sodium thiosulfate, acetylcysteine) was used. In a number of cases, gastrointestinal lavage and therapeutic diarrhea were sufficient to stabilize the patients's condition. Due to such a therapy, in some patients plasma urea levels could decrease by more than 10 mmol/L per day and the level of creatinine – by 30-40 µmol/L. Hyperhydration was also corrected, as well as events of pulmonary edema, by means the alternative removal of fluid through the gastrointestinal tract. The parameters of renal hemodynamics, according to the data of Dopplerography , were restored within 2-3 weeks and were not significantly different from those of the control group.

The peculiarity of toxic AKI because of taking medicines (in more than 70% of cases) was the development of medical nephropathy on the background of initially unavoidable risk factors (old age, CKD, diabetes, severe hypertension, etc.). In 50% of patients, there were avoidable risk factors: dehydration, anemia, hypotension, hyperthermia, recent use of radiocontrast agents, long-term antibiotic therapy, repeated use of rifampicin. combination of several nephrotoxic drugs and taking anti-viral drugs (acyclovir). In ultrasound examination of kidneys in patients of stage I, it was revealed an increased thickness of the parenchyma over 2.6 cm, increased echogenicity of the kidneys; some patients had punctate granular deposits in the parenchyma (signs of interstitial nephritis).

Nephroprotective therapy in this subgroup can be presented by the patients with *contrast-induced AKI*. All the patients were consulted before planning intravascular contrast administration. In each specific case, the risk of intervention was assessed. If it was possible to avoid this survey, it was canceled, especially if there were uncorrectable risk factors for AKI developing. Such factors were: chronic kidney disease with signs of chronic renal insufficiency, diabetes, congestive heart failure, recent myocardial infarction, age over 75 years. In cases when X-ray contrast examination was strongly recommended, when conducting nephroprotection, avoidable risk factors of the development of contrast-induced AKI were taken into account: dehydration, high osmolality of the contrast medium, administration of more than 100 ml of contrast, recent use of radiocontrast agents, and simultaneous administration of other nephrotoxic drugs.

It was recommended to stop the introduction of diuretics, ACE inhibitors, sartans, statins 24-48 hours before the study. If possible, infusion of 0.9% sodium chloride solution (2 ml/kg/h) and infusion of 4.2% soda-buffer solution (1 ml/kg/h) were recommended as early as possible before the intervention (2-3 hours in advance). In the case of an urgent situation, 400 ml of a 0.9% sodium chloride solution and 100 ml of a 4.2% soda-buffer solution were administered immediately prior to the X-ray vascular examination. It was also recommended to continue hemodilution with a 0.9% solution of sodium chloride during the X-ray contrast test at a rate of 0.5 ml/kg/h (if it wasn`t volume overload). In patients with a diuresis rate of less than 0.3 ml/kg/h, pulmonary heart disease, hemodilution and plasma alkalization were started immediately after the X-ray contrast examination at a rate of 0.5 ml/kg/h for 8-12 hours. Patients with hypernatremia did not undergo alkalization of the plasma. It was also recommended that acetylcysteine be administered intravenously by stream infusion – 5-10 mg/kg before the intervention and 5-10 mg/kg afterwards. Such prophylaxis proved effective. Only 2 patients developed severe AKI, requiring dialysis treatment. In other cases, an increased level of plasma creatinine and a decrease diuresis rate were was short-term and did not require renal replacement therapy.

Thus, when it was necessary to prescribe a particular drug, nephroprotection consisted in assessing AKI risk factors to avoid nephrotoxic effect. This rule applies to most of the groups of medicines used in intensive care: antibiotics, anti-tuberculosis drugs, nonsteroidal anti-inflammatory drugs, radiocontrast agents, ACE inhibitors, diuretics, and antiviral drugs. The following measures were considered as nephroprotective measures: choice of alternative treatment or examination without a nephrotoxic drug; the administration of the lowest possible dose of the drug (antibiotic, contrast); correction of dehydration, anemia, and hypotension; providing hemodilution, antidote therapy; managing treatment-induced diarrhea, active detoxication (early hemodialysis, plasmapheresis, extracorporeal antibiotic therapy, ultraviolet blood irradiation). The lethality in the toxic AKI group was 15.8%. A 30-day survival rate was 85%. The duration of the oligoanuria was 17.2±0.8 days.

Subrenal module of AKI

The study included 39 patients with subrenal AKI. Despite that fact that the patients in this group had been sick for a long time before AKI developed, the diagnosis when the patients were urgently admitted to hospital was not always established. It was because in many cases the patients did not seek medical care before their condition became critical. The main complaints when entering the ICU were a lack of urine, nausea, vomiting, diarrhea, chills, and inability to breathe deeply. The pain syndrome was often absent. Because of an urgent situation, it was not always possible to collect a thorough anamnesis. Treatment of these patients began with a clarification of

a cause of AKI by an ultrasound examination using Doppler scanning.

As a rule, The ultrasound examination revealed an enlarged calyceal system. In 65% of the cases, there was a need for CT examination of the abdominal cavity and retroperitoneal space in order to clarify the source of obstruction for urine passage. In 87% of the patients, renal hemodynamic disorders were not severe. Vps was reduced to 64.01±0.25 cm/sec; Ved was 20.3±0.3 cm/sec; the S/D ratio was higher than the data in the control group, reaching 3.12±0.08, and RI was up to 0.69±0.02. In 13% of the cases, a hemodynamically significant decrease in the rates of arterial blood flow and an increase in RI to 0.75 was recorded, which indicated more severe AKI. Such disorders in combination with thick parenchyma did not exclude the development of terminal hydronephrosis even before a patient's admission to the ICU. s-NGAL at admission was higher – 14.56±0.42 ng/ml (13.6±0.8 in the control group), although it was significantly (p <0.001) lower than in the prerenal and renal AKI patients. At the same time, plasma creatinine reached an extremely high level of up to 2200 µmol/L; the ureal level went up to 60 mmol/L. Immediately after the diagnosis was established, urinary passage restoration was performed: percutaneous nephrostomy (13), stenting (17), open surgery (3), removal of ligatures and restoration of ureteral passability (3), bladder and ureteral plastic reconstruction (3). In the stage of restoration of diuresis (polyuric phase), massive infusion therapy was conducted with balanced polyionic solutions (if possible with solutions for hemodiafiltration). To prevent the development of disequilibrium syndrome, 10% and 20% glucose solution was administered 8-10 ml/kg/day. Dialysis treatment was required for 5 patients because of terminal hydronephrosis. The mortality rate was 5.1%.

To assess the influence of various factors on the outcome in AKI patients, a multifactor analysis was carried out. The results of treatment in AKI patients were evaluated as: the number of those who survived and the number of those who died.

When analyzing the risk of development of long-term oligoanuria (OA) ("long" means "lasting over 5-days"), first, a linear neural network forecasting model was constructed using 16 factor variables: age, sex, AKI module (pre-renal, renal, subrenal), duration of disease before admission to the ICU, time of diagnosis, duration of oligoanuria in days before admission to the ICU, presence of multi-organ disorders, the nature of multi-organ disorders (primary, secondary), development of AKI against chronic renal insufficnency, presence of risk factors (no – 0, yes – 1), nephroprotection before admission to the ICU (0 – was not carried out, 1 – was carried out), conducting nephroprotection in the ICU (1 – early, 0 – late), the need for hemodialysis (HD) (without HD – 0, with HD – 1), the number of hemodialyses, the need for artificial lung ventilation, the urea level at admission to the ICU, the creatinine level at admission to the ICU, the highest level of urea, and the highest level of creatinine.

The sensitivity of the model on the training set was 90.0% (95% CI 78.5% – 97.4%), and specificity 91.7% (95% CI 80.1% – 98.5%). On the confirming set, the sensitivity of the model was 71.4% (95% CI 43.3% – 92.6%), and specificity – 93.8% (95% CI 75.4% – 100%).

To identify the factors most associated with the risk of developing long-term oligoanuria, the selection of significant features using the genetic algorithm (GA) method was carried out. As a result of the analysis, 3 factors were selected: AKI module (prerenal – 1, renal – 2, subrenal – 3) (X1), nephroprotection before admission to the ICU (0 – was not conducted, 1 – was conducted) (X2), and nephroprotection in the ICU (1 – early, 0 – late) (X3). Using the selected set of factor features, a linear neural network model for predicting the risk of developing long-term oligoanuria was constructed. The sensitivity of this model on the training set was 85.0% (95% CI 72.0% – 94.5%), specificity was 77.8% (95% CI 62.4% – 90.0%). On the confirming set, the sensitivity of this model was 64.3% (95% CI 35.8% – 100%), specificity was 81.3% (95% CI 57.1% – 96.7%).

Sensitivity and specificity on the training and confirmatory sets are not statistically significant (p = 0.20 and p = 0.93, respectively, when comparing by criterion c^2), which indicates the adequacy of the model constructed.

To evaluate the significance of 3 out of the total 16 factor factors and to assess the adequacy of the constructed models for predicting the risk of developing long-term oligoanuria in the treatment of AKI patients, the method of comparing ROC curves was used (Figure 1).

During the analysis, it was established that the area under the ROC curve for the linear neural network model
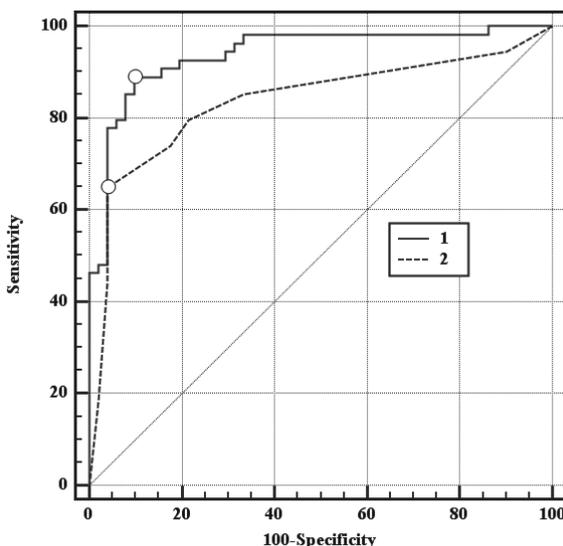

Figure 1. ROC curves of models predicting the risk of development of long-term OA when treating AKI patients (o – indicates the optimal values of sensitivity and specificity of models , the curves are constructed on all 106 cases): 1 – linear neural network model built on all 16 factor features, 2 – linear neural network a model based on 3 selected factor features

constructed on all 16 factors was $AUC_1 = 0.94\pm0.02$, for the linear neural network model constructed on the 3 selected factor features, $AUC_2 = 0.84\pm0.04$.

Thus, a decrease in the number of factor features from 16 to 3 does not lead to a significant change in the predictive qualities of the model, which indicates a high significance of the selected factor features (AKI module (prerenal – 1, renal – 2, subrenal –3) (X1), nephroprotection before admission to the ICU (0 –was not conducted, 1 – was conducted) (X2), nephroprotection in the ICU (1 – early, 0 – late) (X3) to predict the risk of long-term oligoanuria.

To determine the strength and direction of the influence of the 3 selected factor features, a logistic regression model was constructed; the model is adequate ($\chi2 = 50.5$ for the number of degrees of freedom $k = 4$, $p<0.001$). The results of the analysis of the regression coefficients of the model are shown in Table 2.

The analysis of logistic regression model coefficients implies that in the case of renal AKI module (2), the risk of developing long-term oligoanuria ($p = 0.001$) increases, OR = 8.7 (95% CI 2.3 –

32.9), compared with the prerenal (1) module. It was found that the risk of developing a prolonged oligoanuria reduced statistically significantly ($p = 0.032$) with nephroprotection before admission to the ICU, OR = 0.3 (95% CI 0.1–0.9). There was also a decrease ($p = 0.014$) in the risk of developing long-term oligoanuria with early nephroprotection in the ICU, OR = 0.06 (95% CI 0.01–0.56).

So, three factor features, associated with the risk of developing long-term oligoanuria were identified: AKI module (prerenal – 1, renal – 2, subrenal – 3) (X1), nephroprotection before admission to the ICU (0 – was not conducted, 1 – was conducted) (X2), nephroprotection in the ICU (1 – early, 0 – late) (X3). The sensitivity of this model was 64.3% (95% CI 35.8% – 100%), specificity was 81.3% (95% CI 57.1% – 96.7%).

It was established that the risk of developing long-term oligoanuria in the renal AKI module increases ($p = 0.001$), OR = 8.7 (95% CI 2.3–32.9), compared with the prerenal (1) AKI module. There was also a decrease ($p = 0.032$) in the risk of developing long-term oligoanuria during nephroprotection before admission to the ICU, OR = 0.3 (95% CI 0.1–0.9). It was found that in cases of early nephroprotection in the ICU, the risk of prolonged oligoanuria ($p = 0.014$) decreases, OR = 0.06 (95% CI 0.01–0.56).

According to the neural network modeling, the main factors influencing the duration of the OA are: the AKI module (prerenal, renal, subrenal), early nephroprotective measures before admission to the ICU and early nephroprotection in the ICU. It was also revealed that even later, with oliguria having lasted more than 5 days, the administration of nephroprotection contributes to shortening the duration of OA. This confirms our hypothesis that nephroprotection should be carried out at all stages of AKI, since the severity and extent of renal tubules damage in AKI patients can not be evaluated in full, even according to objective studies (kidney biopsy, CT examination, ultrasound dopplerometry, renography, etc.).

One of the main goals of successful treatment of AKI patients is to reduce the duration of oligoanuria. The sooner diuresis is restored, the less danger is there of MOF development and forming irreversible changes in the kidneys. The duration of the OA stage determines the severity of AKI. The influence of various factors was evaluated on the duration of oligoanuria, and it was found that carrying out individual pharmacological and non-pharmacological nephroprotection reduces the duration of the oligoanuria stage.

So, in the comparison group, the oligoanuria stage duration was 22.6±1.2 days. The duration of oligoanuria in the main group reliably decreased ($p<0.05$) to 14.3±0.9 days.

Conclusions

Determination of renal blood flow disorders by dopplerography can improve diagnostics and reveal the immediate cause of AKI. This makes it possible to take nephroprotective measures in the early stages. Early pharmacological and non-pharmacological nephroprotection resulted in the shortening of the oligoanuria stage in AKI patients.

The medical technology of individual intensive therapy with replacement renal therapy and peridialysis care was developed, including: a diagnostic stage with determination of peculiarities of renal hemodynamic disorders and pharmacological and instrumental (stenting, drainage, etc.) correction of the main cause and manifestations of AKI.

Improving the diagnosis and carrying out the individual pharmacological and non-pharmacological nephroprotection provides an improvement in the results of treatment in AKI patients.

Table 2. Coefficients of the 3-factor model of long-term oliguria risk prediction (logistic regression model)

Factor feature	Prediction model coefficients, b±m	Significance of the coefficient difference from 0, p	Odds ratio, OR (95% CI OR)
X1 (2) vs (1)	2.2±0.7	0.001*	8.7 (2.3–32.9)
X1 (3) vs (1)	0.3±0.6	0.684	–
X2	-1.2±0.5	0.032*	0.3 (0.1–0.9)
X3	-2.8±1.1	0.014*	0.06 (0.01–0.56)

Note: * – the difference from 0 is statistically significant, $p <0.05$

References

- Ake JA, Jelacic S, Ciol MA (2005) Relative nephroprotection during Escherichia coli O157:H7 infections: association with intravenous volume expansion. Pediatrics 115(6): 673–680. https://doi.org/10.1542/peds.2004-2236 [PubMed]
- Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J (2000) Low-dose dopamine in patients with early renal dysfunction: a placebo controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet. 356(9248): 2139–2143. https://doi.org/10.1016/S0140-6736(00)03495-4 [PubMed]
- Case J, Khan S, Khalid R (2013) Epidemiology of acute kidney injury in the intensive care unit. Critical Care Research and Practice 2013: 479–730. https://doi.org/10.1155/2013/479730 [PubMed] [PMC]
- Jo SK, Rosner MH, Okusa MD (2007) Pharmacologic treatment of acute kidney injury: why drugs haven't worked and what is on the horizon. Clinical Journal of the American Society of Nephrology 2(2): 356–365. https://doi.org/10.2215/CJN.03280906 [PubMed]
- Kellum JA, Decker J (2001) Use of dopamine in acute renal failure: a meta-analysis. Critical Care Medicine 29(8): 1526–1531. https://doi.org/10.1038/sj.ki.5000310 [PubMed]
- Kidney Disease: Improving Global Outcomes (KDIGO) (2012) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International. Official Journal of the International Society of Nephrology 2(1): 1–138. https://doi.org/10.1038/kisup.2012.1
- Kolesnik MO (2010) Protocol for the diagnosis, prevention and treatment of acute kidney injury (AKI). Ukrainian Journal of Nephrology and Dialisis 3: 22–34. [In Russian]
- Lameire N, Biesen Van W, Vanholder R (2005) Acute renal failure. Lancet 365(9457): 417–430. https://doi.org/10.1016/S0140-6736(05)17831-3 [PubMed]
- Lauschke A, Teichgräber UK, Frei U (2006) Low-dose dopamine worsens renal perfusion in patients with acute renal failure. Kidney International 69(9): 1669–1674. https://doi.org/10.1038/sj.ki.5000310 [PubMed]
- Lyakh YuE, Gurianov VG (2012) Mathematic modeling for classification problems in biomedicine. Ukrainian Journal of Telemedicine and Medical Telematics 10(2): 69–76. [in Russian]
- Ostermann M, Chang RW (2007) Acute kidney injury in the intensive care unit according to RIFLE. Critical Care Medicine 35(8): 1837–1843. https://doi.org/10.1097/01.CCM.0000277041.13090.0A [PubMed]
- Overberger P, Pesacreta M, Palevsky PM, et al. (2007) Management of renal replacement therapy in acute kidney injury: a survey of practitioner prescribing practices. Clinical Journal of the American Society of Nephrology 2(4): 623–630. https://doi.org/10.2215/CJN.00780207 [PubMed]
- Petri A, Sabin K (2003) Visual Statistics in Medicine [from English by Leonov VP]. GEOTAR-MED, Moscow, 144 pp. [In Russian]
- Saito O, Sugase T, Saito T, Akimoto T, Inoue M, Ando Y, Muto S, Kusano E (2011) Two cases of renal hypouricemia in which dopamine infusion produced a good recovery from exercise-induced acute kidney injury. Clinical Nephrology 76(2): 83–90. https://doi.org/10.5414/CN106919 [PubMed]
- Shramenko KK, Shkarbun LI (2011) Possibilities of dopplerography in the choice of nephroprotection tactics of acute kidney injury for various etiologies. Emergency Medicine 7–8: 144–146. [In Russian]
- Shramenko KK, Shkarbun LI (2014) Comparative assessment of changes in renal blood flow in various variants of acute kidney injury. Emergency Medicine 4: 78–82. [In Russian]
- Tomilina NA (2011) Acute Renal Failure. Intensive Therapy: National Leadership Vol. 1. GEOTAR-Media, Moscow, 856–879. [In Russian]
- Vaira M, Barone R, Aghemo B, Mioli PR, De Simone M (2001) Renal protection with amifostine during intraoperative peritoneal chemohyperthermia (IPCH) with cisplatin (CDDP) for peritoneal carcinosis. Phase 1 study. Minerva Medica 92(4): 207–211. [PubMed]
- Vijayan A, Palevsky PM (2012) Dosing of renal replacement therapy in acute kidney injury. American Journal of Kidney Diseases 59(4): 569–576. https://doi.org/10.1053/j.ajkd.2011.11.035 [PubMed] [PMC]
- Wystrychowski A, Wystrychowski W, Król P, Obuchowicz E, Cierpka L, Wiecek A (2009) Pentoxifylline augments fasting-induced nephroprotection in acute ischemic kidney injury in rats. Transplantation Proceedings 41(8): 2992–2993. https://doi.org/10.1016/j.transproceed.2009.07.084 [PubMed]

Author contributions

- **Katherine K. Shramenko,** Candidate of Medical Sciences, Associate Professor, Department of Anesthesiology, Intensive Care and Emergency Medicine, Donetsk National Medical University named after M. Gorky, e-mail: k.shramenko@gmail.com, http://orcid.org/0000-0002-6622-9858. The author owns the idea of research, the collection of clinical material, the analysis of the results and conclusions.

- **Georgiy A. Gorodnik,** Doctor of Medical Sciences, Full Frofessor, Head of the Department of Anesthesiology, Intensive Care and Emergency Medicine, Donetsk National Medical University named after M. Gorky. Head of Intensive Care Neurosurgery Unit of Donetsk Regional Clinical Territorial Medical Association, e-mail: dongorodnik@yandex.ru. The author provided consultations when shaping the research idea, processing the clinical material, and making the conclusions.

■ **Valentina P. Shano**, Doctor of Medical Sciences, Full Professor, Professor of the Department of Anesthesiology, Intensive Care and Emergency Medicine, Donetsk National Medical University named after M. Gorky, e-mail: shano_vp@yandex.ru. The author provided consultations when shaping the research idea and making the conclusions.

■ **Irina V. Kuznetsova**, Doctor of Medical Sciences, Full Professor, Professor of the Department of Anesthesiology, Intensive Care and Emergency Medicine, Donetsk National Medical University named after M. Gorky, e-mail: kiv@mail.ru. The author provided consultations when shaping the research idea and making the conclusions.

■ **Aleksandr P. Grigorenko**, Doctor of Medical Sciences, Full Professor, e-mail: A_grigorenko@mail.ru. The author took part in the analysis of the results in the study.

■ **Vladimir V. Potapov**, Clinical resident, Department of Anesthesiology, Intensive Care and Emergency Medicine, Donetsk National Medical University named after M. Gorky, e-mail: potapov@mail.ru. The author participated in the design of the article and the statistical processing of the material