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# Kidney damage in burn disease. Part 1. Pathomorphophysiology (literature review)

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**Abstract.** *Acute kidney injury (AKI) is a common complication in critically ill burn patients and is associated with serious adverse outcomes, including increased length of hospital stay, development of chronic kidney disease, and increased risk of mortality. The incidence of AKI among burn patients in the intensive care units is 38 (30–46) %. A high percentage of the total burn surface area and a number of individual predisposing factors are considered to be the leading risk factors for AKI. Pathophysiological and morphological changes in the body under the combination of burn disease and kidney damage have certain discrepancies with the classical course of the pathological process in some nosological forms. Despite significant progress in the technologies of fluid resuscitation, intensive care and renal replacement therapy in recent years, the morbidity and mortality rate in such patients remain quite significant. A better understanding of clinical characteristics, early detection and prevention of risk factors for kidney damage in burns, as well as timely medical intervention can effectively reduce morbidity and progression of the pathological process, and also optimize the prognosis in the long run.*

**Keywords:** *review; acute kidney injury; burn disease; chronic kidney disease; pathomorphology; pathophysiology*

A burn is not only a regional, but also a systemic injury significantly affecting the entire body, especially with an increase in the surface area and depth of the burn [1]. Acute kidney injury (AKI) is a common complication in critically ill burn patients admitted to the intensive care unit (ICU) and is associated with serious adverse outcomes, including increased length of hospital stay, development of chronic kidney disease (CKD), and increased mortality risk with burns of 9–50 % of the skin surface [2–6]. Electric burns are deeper and their area does not correspond to the severity of the injury [7–9]. The AKI incidence after burns varies widely in the literature [10], being 4.64 % in all hospitalized patients and 20.73 % in those with burns of more than 20 % total body surface area (TBSA) [11]. Lesions of no more than 40 % TBSA mostly lead to the development of stage 1 AKI, while patients with large burns, over 40 % TBSA, may develop severe forms [8, 12]. The frequency of AKI development among burn patients in the ICU is 38 (30–46) % [8, 11–17]. Although the morbidity in patients with mild, moderate, and severe AKI doesn't differ much, the mortality is significantly higher compared to those without AKI and increases significantly with the increasing severity of the pathological condition [5, 12, 14, 18, 19]. Even those victims who are admitted to the specialized burn centers have a mortality rate of 3–8 %, and 75 % of these deaths occur within 72 hours of hospitalization [20]. The relationship between AKI and 30-day mortality in the ICU was specified [21–23]. In this study cohort, AKI was independently associated with high 28- and 90-day mortality. Thus, in patients with severe burns, renal dysfunction serves as an additional predictor of a significant risk of mortality [2, 13, 18, 24]. Historically, AKI has had little effect on the fatal outcome in the burn population. Most studies report a mortality of 80–85 % and the earliest report demonstrated a 100% mortality [6, 8, 12]. Since the 1950s, the AKI incidence in burn patients has ranged from 1 to 40 %. Different criteria for detecting AKI provide an explanation for this wide range of incidence and hinder research efforts to accurately define



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or classify patients with AKI. Burn patients are often not considered ones with renal dysfunction until they require renal replacement therapy (RRT) [12, 19]. Approximately 12–50 % of these patients received RRT, but the mortality rate remained high [12, 14, 18, 19]; the main cause of mortality in burn medicine is sepsis — 50–60 % [20].

Male gender [2] and older age (over 60 years) [2, 5, 10, 13, 20, 24–28] are risk factors for the development of AKI in burn patients. Comorbidities (hypertension and diabetes), which can be exacerbated by the response to catecholamines and endocrine dysfunction, affect the body's ability to resist pathophysiological damage, which increases the incidence of AKI and mortality [2, 5, 13, 18, 20, 25, 27, 28]. Respiratory dysfunction negatively affects kidney function due to a decrease in oxygenation [3]. The presence of inhalation trauma (including poisoning by combustion products) is a significant prognostic indicator of mortality in burn patients with AKI syndrome [4–6, 13, 18, 20, 26]. During the initial hospitalization, AKI in combustiology was associated with an increase in lung failure, mechanical ventilation, pneumonia, myocardial infarction, length of hospital stay, cost of treatment, and mortality [11, 13, 25]. Mechanical ventilation is also a risk factor for the development of AKI in burn patients [5, 13, 18, 25]. Reduction in cardiac output, caused by mechanical ventilation due to the continuous regime of positive pressure in the respiratory system, changes the renal blood flow [3]. Another important factor is cardiac dysfunction [8, 12] caused by atherosclerosis [28], existing coronary disease, congestive heart failure [2, 8, 13], including hemodynamic changes [6] and hypovolemic shock of early burns [2, 8]. Kidney hypoperfusion is accompanied by a consistent decrease in glomerular filtration rate (GFR), and secondary hypoxia leads to irreversible ischemia and tubular necrosis, whose pathophysiological mechanisms are triggered by ischemia or nephrotoxins [8]. Renal hypoperfusion in burns can be caused by intra-abdominal hypertension (abdominal compartment syndrome), which in 82.6 % is caused by excessive fluid resuscitation [2, 8, 10, 13, 21], and the frequency of early AKI increases to 69.9 % [19, 21, 24, 27, 29].

The key triggers contributing to the development of AKI in patients with burns are nephrotoxic drugs, aminoglycosides and some cephalosporins, the use of high doses of methotrexate, glycopeptides, hydroxocobalamin, vasopressors [6, 10, 21, 30], acute or chronic intoxication with alcohol, barbiturates, chlorpromazine, toluene and other solvents [3]. Some of the common drugs used to treat AKI can have negative side effects. It was found that furosemide, depending on the dose, increases the nephrotoxicity of certain drugs and provokes oxidant stress in patients with septicotoxemia [18]. Excessive fluid resuscitation, especially with large doses of ascorbic acid (the lethal synthesis is the formation of nephrotoxic oxalic acid) and blood products, is associated with a greater likelihood of AKI. Additional risk factors are gunshot injury and surgical intervention (including tracheotomy) [5, 13, 18], and also increased preoperative neutrophil-to-lymphocyte ratio, metabolic acidosis, significant water-electrolyte disorders, apoptosis, hemolysis, rhabdomyolysis, hepatic and multiple organ failure — multiple organ dysfunction syndrome (MODS), a history of chronic inflammatory and renal diseases, catheter-associated urinary tract infection, primary increase in the level of nitrogen impurities [2, 5, 6, 8, 13, 18, 26, 28, 31].

A high percentage of TBSA, a high Abbreviated Burn Severity Index, high scores on Acute Physiology and Chronic Health Assessment II and Sequential Organ Failure Assessment (SOFA) are considered to be the leading risk factors for AKI [2, 5, 13, 18, 25, 30]. Stage 1 AKI predominantly develops in patients with burn of less than 40 % TBSA, while more severe AKI occurs in patients with extensive burn injuries (over 40 % TBSA). AKI is associated with combustiological mortality under TBSA of no more than 40 % [12]. Any degree of AKI is independently associated with in-hospital mortality even for small burns (no more than 10 % TBSA), but only severe AKI correlates with mortality in medium-sized burns (10–40 %). AKI is independently associated with a three-fold risk of in-hospital mortality in patients with major burns (over 40 % TBSA) [2, 5, 10, 12, 25]. AKI is also independently associated with an increased length of hospital stay [8, 12, 18, 30]. Burn-induced AKI leads to a significant increase in treatment costs, especially those associated with the use of RRT [13]. The frequency of re-hospitalization of burn patients with AKI 30 days after discharge for outpatient treatment is 29.93 vs. 11.51 % in people without AKI [11]. Mortality increases when long-term RRT is required. Among individuals with burns and AKI, a 1-year mortality was 36.10 % for all patients and 63.07 % in burns over 20 % TBSA compared to 3.16 and 20.00 %, respectively, for patients without AKI.

A recent single-center study showed a mortality rate of up to 81.5 % in a population of burn patients treated with RRT for 7 years [11, 27]. The severity of AKI and the use of RRT were associated with a negative prognosis. A higher risk of mortality was observed in patients with stages 2 and 3 AKI [8]. Improvements in the treatment of acute burns may have contributed to a decrease in mortality in recent years [10], but the problem of multiple organ failure remains relevant, since acute renal failure is the most common cause of death after severe thermal injury [32].

Burn disease (BD) is a set of clinical symptoms of general pathological reactions of the body due to thermal damage to the skin and underlying tissues. Its course is defined by 4 periods of burn shock, acute toxemia, septicotoxemia, convalescence, according to which the syndrome of AKI is formed [4, 32].

*Severe burn shock* develops with deep burns of 21–40 % TBSA and lasts 48–72 hours. Primarily, AKI under severe burn shock occurs reflexively as a result of significant afferent impulse from the burn zone and vasospasm [31]. In the first hours after a burn, the volume of extracellular fluid decreases by more than 15–20 % due to intensive evaporation from the burn surface [32]. Burn stress and the associated circulatory disturbance cause increases in the levels of catecholamines, angiotensin II, aldosterone, antidiuretic hormone.

This leads to an increase in the reabsorption of water and sodium in the renal tubules, which results in a decrease in di-

uresis, and metabolic acidosis gradually develops [5, 32–34]. The level of atrial natriuretic polypeptide in plasma is elevated for a long time after burns. This polypeptide balances the effects of stress-related hormones through vasodilation and natriuresis [3, 32]. AKI in the first 24 hours of severe burn shock is caused by a decrease in renal perfusion due to dysregulation of pre- and post-capillary tone by a release of stress hormones and inflammatory mediators under [32]:

— circulating blood volume deficiency;
— alteration of the rheological properties of blood;
— an increase in the amount of denatured protein;
— the action of endotoxins and free hemoglobin.

In the presence of endotoxins or thermal damage, myocytes synthesize tumor necrosis factor α, which contributes to the alteration of the myocardial response to catecholamines and left- or biventricular dilatation with a limitation of the ejection fraction [5, 7, 8]. Prostaglandins, leukotrienes $B_4$, $D_4$, thromboxane $A_2$, proteases, and biogenic amines are hyperproduced in burned tissues, which is the basis of degenerative-destructive changes in nephrons up to necrosis with the development of AKI [31]. Kidney hypoperfusion and activation of the sympathoadrenal system cause activation of reactive oxygen radicals with activation of lipid peroxidation; damage to renal tubular cell junctions and inhibition of antioxidant protection is a typical universal pathophysiological mechanism of cell death [36]. The composition of nephron membranes includes a significant amount of polyunsaturated fatty acids, which are easily oxidized under the action of reactive oxygen radicals. Most lipid peroxidation products are cytotoxic and genomotoxic. Oxidant modification of lipoproteins and nucleic acids of the nephron leads to violation of membrane integrity of nephron cells and their death [31]. Lipid peroxidation activation contributes to tubular obstruction and backflow of urine, which leads to an even greater decrease in GFR [8, 12]. Mixed hypoxia induces kidney damage directly and indirectly (extra-renally) through changes in the functions of other organs, which become a source of underoxidized metabolites and oxidant stress. Suppression of mitochondrial oxidative phosphorylation leads to energy deficit with inhibition of phosphofructokinase (the key enzyme of glycolysis). Anaerobic glycolysis leads to lactic acidemia, while the phosphate buffer is depleted, and the release of $H^+$, reabsorption of $Na^+$ and $HCO_3^-$ are realized mostly due to ammoniagenesis. Acidosis reduces the hemoglobin affinity for oxygen, which leads to the activation of acetylcholine, histamine, serotonin, and bradykinin that participate in the development of pain syndrome, capillary diapedesis, and decreased renal perfusion [5, 31]. Kidney shock is the main component in the formation of multiple organ failure syndrome [31].

In *the acute toxemic period*, kidney function cannot be restored, and renal oligoanuria develops [32]. Normalization of renal blood flow after recovery from shock is real with burns of less than 30 % of the body surface. Two main mechanisms are involved in the pathophysiological changes in the kidneys: impaired filtration and tubular dysfunction [3]. The leading factors of BD are endogenous intoxication, dyscirculatory hypoxia, histotoxic ischemia [31, 36].

Non-inflammatory AKI is the most dangerous complication, which reduces the chances of survival with TBSA over 15–20 % [30]. Inflammation due to ischemia is a common response to burns [18], but the levels of hormones and inflammatory mediators are significantly different from those in other injuries [2]. Increased synthesis of Toll-like receptors 2 and 4, which recognize pathogen-associated microbial structures, promotes the release of chemokines and activation of the alternative complement pathway, which stimulates the synthesis of interleukin-6, tumor necrosis factor α and chemokines and promotes the development of leukocytosis and direct vasoactive effect [27]. Some studies indicate that the basis of AKI is a persistent inflammatory reaction not associated with a decrease in renal perfusion [11, 18]. After tissue damage, inflammatory cells accumulate at the site of injury and differentiate into many subtypes whose proportions can change over time. In early AKI, most macrophages are polarized to the M1 subtype to clear microbes and necrotic tissue, and later — to the M2 subtype (to promote tissue regeneration) [3, 32]. Dysregulation of blood coagulation status can cause the development of disseminated intravascular coagulation syndrome, which is a frequent complication of BD. Disseminated intravascular coagulation syndrome develops more often and is more severe against the background of renal-hepatic dysfunction and in most cases ends fatally [31].

In the period of *septicotoxemia*, inflammatory mediators participate in the formation of microthrombi in the capillaries of glomeruli and renal tubules. Kidney function after a burn is impaired due to a decrease in cardiac output, respiratory failure, acidosis, sepsis, and toxemia under cellular immunity dysregulation [5, 8, 18, 20]. A decrease in the renal blood flow is accompanied by tubular necrosis [3]. Severe burns can cause systemic inflammatory response syndrome/cytokine storm, and systemic inflammatory response syndrome can lead to multiple organ failure. Even after a patient is discharged from the hospital, inflammation can persist for months or years. Constant inflammation caused by burns is the main factor in the development of AKI and cell aging, which accelerates the development of CKD [6, 8, 10, 18].

Sepsis is the main cause of AKI, MODS and increased burn mortality. The high/low flow state is determined by the presence of bacteria that induce a cytokine response with direct effects on the initiation of endothelial damage, procoagulation, and vasoplegia, which contribute to excessive hypotension. To balance the hypotonic state, cardiac output increases due to activation of the sympathetic and renin-angiotensin-aldosterone systems. For sepsis, significant tubular inflammation and microvascular damage, rapid and frequent development of bacteremia are typical [12, 13, 18, 25, 30, 37–39]. Plasma toxins in patients with burns caused by septic shock and AKI can increase the permeability of renal vessels for albumin, reduce the expression of nephrin and have a pro-apoptotic effect on podocytes and tubular cells; 10 % of burn patients develop an infectious complication of BD — pyelonephritis [27, 32, 39].

During the *convalescence* period, kidney damage can be restored slowly. Proximal cells of the tubular epithelium

have strong proliferative properties and can gradually regenerate. Other cells (podocytes) have a weaker ability to regenerate, so their loss and exfoliation occur constantly. In general, kidney function gradually declines with age ontogenetically. As patients with mild kidney disease age and experience some risk factors or accidental injury, kidney function further will decline rapidly, eventually progressing to CKD, sometimes even end-stage renal disease [8, 18, 39]. Renal damage is due in part to aging-related, profibrotic and inflammatory factors that contribute to renal fibrosis and vascular damage, which accelerates the progression of CKD [18]. Peripheral lipolysis after local thermal injury contributes to both hepatomegaly and fatty infiltration of the liver and is associated with an increased incidence of sepsis [20].

The absence of AKI symptoms does not mean that the kidneys are not damaged [18]. Burns can accelerate the progression of CKD due to pre-existing AKI, aging, and persistent inflammation even after the patient is discharged from the hospital [18]. In patients who have suffered deep burns, kidney function remains reduced both after surgical restoration of the skin and for a long time after clinical recovery [32].

Severe burns lead to kidney damage, but are not necessarily accompanied by significant changes in kidney function (subclinical renal processes). This explains why AKI occurs only in some patients with severe burns and a history of kidney disease, since the reserve capacity of their kidneys is reduced [18].

Sometimes in clinical settings, doubts arise: was there kidney damage in a patient with severe burns without diagnosed AKI? When studying only biomarkers of biological fluids, their normal levels do not exclude kidney damage. Specific morphological signs are:

— mesangial expansion;

— proliferation and hypertrophy of glomerular mesangial cells;

— increase in endothelial cells of capillaries and accumulation of neutrophils or monocytes in their lumen.

Severe burns cause narrowing or occlusion of capillary loops with glomerular acute glomerulopathy. Renal tubules show varying degrees of degeneration, necrosis, and conglomerate formation, and acute glomerulopathy is associated with azotemia. Renal proximal tubular epithelial cells are capable of repair by proliferation, but damage to podocytes is usually permanent. Therefore, in the long term, it is believed that severe burns can lead to renal dysfunction due to glomerulopathy [18, 39].

AKI occurs either immediately as a result of hypovolemic severe burn shock, or later, when sepsis develops [2–4]. Kidney damage associated with burns is usually classified as early (0–3 days after injury) or late AKI (no less than 4 days after injury) [2, 5, 6, 21]; a progressive type of AKI was defined separately [19, 30]. Early AKI occurs in 22.2 % of patients, late — in 17.7 %, and in 7.2 %, the process has a progressive course [30].

*Early AKI*, formerly known as acute renal failure, is a frequent fatal complication in patients with severe burns. In 74 % of victims, the average period of AKI development is 3 days (interquartile range, i.e. the difference between the penultimate and first quartiles of the distribution, which is equal to 1–7 in the graphic representation) [2, 22, 23]. When the full thickness of the skin is dead (third-degree burns), water loss increases to 200 ml/m$^2$/g; this increase in water deficit leads to hypertonic dehydration [31]. Early AKI is usually associated with inadequate primary fluid resuscitation, hypoperfusion, inflammation, release of proinflammatory cytokines, hemodynamic changes, release of stress hormones, increased inflammatory mediators, denatured protein liberalization, cardiac dysfunction, rhabdomyolysis, etc. [4, 6–8, 37, 40]. This leads to ischemia and ischemia-reperfusion injury of tubules and glomeruli and, ultimately, induces AKI [2, 3, 5]. Rhabdomyolysis is a serious condition responsible for 10 % cases of AKI [2, 3, 5]. The odds ratio of developing AKI in burn patients with and without rhabdomyolysis was 16.074/3.056, respectively [7, 40]. Until recently, it was thought that the early development of burn-related AKI was associated with negative short-term consequences, both for mortality and morbidity [8, 12]. Although early renal dysfunction is reversible, tissue damage is irreversible [43]. AKI itself does not increase metabolic rate, but post-traumatic stress reaction induces an early hypercatabolic state that accelerates hormonal dysregulation, which has pronounced effects on the pulmonary, renal, hepatic, cardiovascular, and coagulation systems [3, 8, 20].

In recent years, the incidence of early stage 3 AKI has decreased significantly due to advances in fluid resuscitation and RRT technologies, but the overall incidence of AKI remains high. Recent studies suggest that persistent renal tissue damage may result from AKI after burn injury, even though early AKI-related renal dysfunction is mild and reversible [7]. Patients with AKI spent more than one week longer in the ICU compared to people without AKI [13]. In the early post-burn period due to the formation of stage 3 AKI, the mortality rate is 35–55 % [8, 13, 24], but survival in early AKI is better (79.6 %) than in the late one (64.1 %) [19]. Prevention of early AKI includes correction of hypovolemia and avoidance of nephrotoxic drugs [18].

*Late-onset AKI* causes irreversible damage to renal tissue and lowers the threshold for further damage, even if renal function can be restored [8]. Infection progressing to sepsis is a major concern due to loss of the skin barrier along with marked dysregulation of the humoral and innate immune systems [5, 18, 20]. This type of AKI is associated with both early and late organ failure [19] and occurs mostly in the context of sepsis and MODS, or as a result of fluid overload and the use of nephrotoxic drugs [4, 5, 8, 12, 18]; it is characterized by greater severity and worse prognosis [2]. Late AKI occurs more than 3 days after the burn and, despite its multifactorial origin, is usually secondary to sepsis; it is caused by fluid overload, multiple organ dysfunction syndrome and the use of nephrotoxic drugs, and is associated with higher mortality than early AKI. Increased vascular permeability causes significant dyshydria manifested by both local and generalized edema. This leads to hypovolemia and centralization of blood circulation, causing oliguria in the early stages of BD. Retention of sodium in collagen fibers and disruption of the sodium-potassium pump are also

involved in the occurrence of generalized edema [3]. Tubuloglomerular feedback can play a beneficial role, as there is a limitation in the flow of sodium to damaged tubules when glomerular filtration rate is reduced [8].

The literature describes 5 possible ways of explaining the effect of fluid overload on the occurrence of late AKI [12, 13]:

1. Intra-abdominal hypertension, defined as an increase in intra-abdominal pressure of more than 12 mm Hg, is an important risk factor. With the development of abdominal compartment syndrome, renal perfusion and GFR decrease.

2. Interstitial edema leads to increased interstitial pressure, limitation of renal oxygenation, and disruption of cellular junctions. The response of the kidneys to the compartment is inadequate due to the restriction of the renal capsule. This contributes to the occurrence of renal congestion, a decrease in renal perfusion, and a significant decrease in GFR [8].

3. Endothelial dysfunction leads to disruption of the glycocalyx and capillary leakage, which causes interstitial edema, and also reduces the systemic intravascular volume, which results in a decrease in renal perfusion and AKI [8].

4. Atrial natriuretic peptide is synthesized as a result of hypervolemia, which leads to distension of the atria and blood vessels. Atrial natriuretic polypeptide activation contributes to the disruption of the glycocalyx and subsequent capillary leakage [8].

5. Swelling of the intestinal wall contributes to the entry of bacteria into the systemic circulation, which leads to sepsis and AKI [12].

Intoxication with products of tissue decay in combination with bacteriotoxemia create favorable conditions for the development of degenerative inflammatory changes in the kidneys [42].

Late AKI can form even before the diuresis changes. In patients with late AKI on the day of initial diagnosis, urine output did not decrease (100 ml/h), but serum creatinine (sCr) increased up to 156 μmol/l. It is likely that renal blood flow was not reduced, but sCr clearance was already markedly reduced. This confirms that the hyperproduction of inflammatory mediators and microcirculatory dysfunction are mainly caused by sepsis and infection and contribute to the development of late AKI [8, 42].

The frequency of sepsis, septic shock, the need for vasopressors, and also mortality in patients with late AKI were significantly higher than in those with early AKI [2]. Patients with late AKI had the longest length of stay in the ICU (~ 71 days) [19]. Compared to early AKI, patients with late AKI had a higher 28-day (34.9 %) and 90-day mortality (57.1 vs. 27.4 %), a higher incidence of sepsis (74.2 vs. 32.6 %) and septic shock (55.6 vs. 13.7 %) [2, 8].

Prevention of late AKI involves prevention and early recognition of sepsis, as well as avoidance of nephrotoxins [18].

Patients with *advanced AKI* had more comorbidities, the worst rates of organ failure, and the lowest survival (18.8 %) compared to the early or late AKI group [19, 30]. Patients with progressive AKI had the shortest length of stay in the ICU (27 days), as many of them die relatively early [19].

In terms of cost of treatment and ongoing use of expendable resources, among patients receiving hemodialysis, only 23.1 % with late AKI required dialysis at discharge compared to 62.5 % of patients with advanced AKI [19].

Most combustiologists use specific consensus classifications to determine AKI [14].

The classification of AKI severity includes 3 main stages:

— stage 1 — an increase in serum creatinine level no less than 0.3 mg/dL or 1.5–1.9 times higher than the initial value;

— stage 2 — an increase in the level of creatinine in the blood serum more than 2–2.9 times higher than the initial level;

— stage 3 — an increase in serum creatinine level more than 3 times or more than 4 mg/dL compared to the initial level, or the need to initiate RRT [8].

In the last decade, a revised classification of AKI based on KDIGO (Kidney Disease: Improving Global Outcomes) guidelines was proposed for such patients in order to optimize the understanding of the risk of progression to CKD:

— AKI develops within no more than 7 days, is characterized by an increase in serum creatinine by more than 50 % within 7 days or by no less than 0.3 mg/dL within 2 days, or oliguria lasting more than 4 hours (at this stage, structural changes are not determined);

— acute renal dysfunction is characterized by a duration of no more than 3 months, the presence of AKI or GFR less than 60 ml/min/1.73 $m^2$, or a decrease in GFR by more than 35 % from the initial value, or an increase in sCr by 50 % above the initial value (various structural abnormalities, albuminuria, hematuria, pyuria, etc. may be noted). After 3 months of renal dysfunction, CKD is diagnosed (GFR less than 60 ml/min/1.73 $m^2$).

Early prediction and risk stratification of AKI in patients with severe burns play an important role in timely intervention and improvement of prognosis [41]. The severity and incidence of AKI were assessed according to the KDIGO criteria [41]. Severe AKI was defined as stage 2 AKI. Because preinjury sCr was not measured in most patients, baseline sCr was the first available. Life-threatening organ dysfunction can be represented by an increase in the SOFA score of no less than 2 points [41, 43], but when this tool was used, the AKI score did not include urine output, so it was defined as a SOFA score without a renal component [44]. According to the RIFLE and AKIN criteria, the mortality of patients with severe burns and AKI ranges from 29 to 35 % [12].

Despite the fact that after an episode of AKI, kidney function is restored in most patients, the risk of developing CKD remains high [8]. One year after injury, AKI has been associated with the development of CKD, conversion to chronic dialysis, rehospitalization, and high mortality [11, 16, 45]. Patients who have survived AKI are prone to the development of CKD and have increased long-term morbidity and mortality [1, 13, 15]. About 35 % of patients need temporary continuation of hemodialysis, 10 % of them need RRT lasting more than 6 months. Burns increase the risk of developing cardiovascular failure, a disease in which CKD develops in the late stage; the morbidity index is 3.11 ‰ for women and 1.89 ‰ for men. Severe burns are a high-risk factor for developing end-stage renal disease. About 35 % of patients

treated with RRT during hospitalization required chronic hemodialysis as continuous RRT can alleviate the decline in renal function after AKI [6].

In response to a burn injury, a blood circulation disorder immediately develops in the kidneys, which is manifested in the movement of the main mass of blood to the system of juxtamedullary pathways and stagnation in them. In this setting, dystrophic and, in the elderly people, due to nephrosclerosis — necrotic damage to the epithelium of renal tubules with interstitial edema appears very quickly. Secondary nephrotic syndrome in large burns is caused by some kidney diseases (glomerulonephritis). Nephrosis, pyelitis, and urolithiasis are observed in the advanced stages of BD. In some patients, pathological changes in the kidneys are quite persistent and remain for a long time. This is most often associated with septic and circulatory complications of BD [42, 46].

Electron microscopy of the kidneys revealed that 3 hours after a severe burn injury, the endotheliocytes of the proximal parts of the nephron undergo a rearrangement of submicroscopic architecture, which is the characteristic of functional stress [47]. Cell death occurs only in some renal tubules, especially as a result of apoptosis rather than necrosis. In addition, disruption of the actinic cytoskeleton is characterized by cell detachment and reduced adhesion of the cell matrix, which leads to the accumulation of tubular cells in tubules. Loss of binding proteins and adhesion molecules leads to backflow of filtrate to the renal interstitium. This anomaly is especially noticeable in severe forms of acute tubular necrosis, which are determined [8, 42, 48, 49]:

— with the expansion of the lumen of the proximal tubules and variety of their forms;

— the partial loss of eosinophilic substance on the apical surface of the nephrothelium;

— the partial destruction of the fringe.

The consequence of necrosis of the endothelial cells of the renal capillaries is the formation of paravasal hemorrhages and lympho-leukocyte infiltrates, which is evidence of impaired filtering and reabsorption functions of the kidneys, as well as the progression of the inflammatory process with the accumulation of $NO_2^-$. Intense pink granules, uniform in appearance, are diffusely located in the cytoplasm of epithelial cells, which is a sign of hyaline-droplet protein parenchymal dystrophy. This is due to coagulation of structural proteins of the cytoplasm of nephrocytes with insufficiency of the vacuole-lysosomal apparatus of tubular epitheliocytes [31, 36, 49]. AKI in BD caused by renal ischemia-reperfusion leads to an overload of protein folding mechanisms in the lumen of the tubules of the granular endoplasmic reticulum, resulting in a folding imbalance and accumulation of pathologically folded proteins, which causes endoplasmic reticulum stress. Prolonged endoplasmic reticulum stress activates the apoptotic cell death pathway, which eliminates dysfunctional cells but prevents necrosis. Excessive cytoplasmic vacuolization ends with necrotic death of endothelial cells [31, 36]. As a result of ischemia-reperfusion, the metabolic process in the cells of the tubular epithelium shifts from β-oxidation of fatty acids to glycolysis due to disruption of cellular functions and pathways. Although this shift increases adenosine triphosphate production, it also causes inflammation, lipid accumulation, and tubulointerstitial fibrosis [18].

Macroscopically, the kidneys are enlarged, swollen and soft-elastic, and the fibrous capsule is stretched and easily removed; the yellowish-gray cortex clearly differs from the light-red color of the medulla caused by vascular stasis [50]. During optical microscopy, pronounced desolation of the vessels of the cortical layer and vasodilation of the medullar microcirculatory bed with focal hemorrhages were revealed. The outer contour of Bowman's capsule is indistinct, scalloped, with dystrophy and desquamation of podocytes, endothelial cells, and fragmentation of the basement membrane. The total volume of nephrons is almost twice over normal due to the high content of eosinophilic protein masses in the capsule with freely located cellular elements and fragments of nuclei. Damage to the structure of glomerular capillaries and the absence of gaps between them are associated with compression of the pathological contents of Bowman's capsule [42, 48]. The phenomenon of juxtamedullary shunting occurs [33]: there is a significant decrease in blood flow in the cortical layer of the kidneys, the preservation or increase of medullary blood flow, which plays the role of an emergency fuse for the total cessation of blood filtration by the kidneys and maintains the water-electrolyte balance of the body [48]. In burn patients, AKI is associated with an extremely poor short- and long-term prognosis [6].

Despite the significant progress in the technologies of fluid resuscitation, intensive care and RRT, in recent years the level of morbidity and mortality in such patients remains quite high [7, 50]. A better understanding of clinical characteristics, early identification and prevention of risk factors for AKI in burns, as well as timely medical intervention can effectively reduce morbidity, progression of the pathological process, and optimize the prognosis in the long run [7].

Biochemical markers of AKI and CKD under BD will be discussed in Part 2 of the article.

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## Пошкодження нирок при опіковій хворобі. Частина 1. Патоморфофізіологія (огляд літератури)

**Резюме.** Гостре пошкодження нирок (ГПН) є поширеним ускладненням у важкохворих з опіками, пов'язаними із серйозними несприятливими наслідками, включаючи збільшення тривалості перебування в стаціонарі, розвиток хронічної хвороби нирок та підвищений ризик смертності. Частота розвитку ГПН серед опікових хворих у відділеннях інтенсивної терапії становить 38 (30–46) %. Головними факторами ризику ГПН вважаються високий відсоток опіку загальної поверхні тіла та низка факторів схильності індивідуального характеру. Патофізіологічні й морфологічні зміни в організмі при поєднанні опікової хвороби та пошкодження нирок мають певні розбіжності із класичним перебігом патологічного процесу за окремих нозологічних форм. Незважаючи на значний прогрес у технологіях рідинної ресусцитації, інтенсивної терапії та замісної ниркової терапії в останні роки, рівень захворюваності та смертності у таких пацієнтів залишається досить високим. Краще розуміння клінічних характеристик, раннє виявлення та запобігання факторам ризику пошкодження нирок при опіках, а також своєчасне медичне втручання можуть у перспективі ефективно зменшити захворюваність і прогресування патологічного процесу й оптимізувати прогноз.

**Ключові слова:** огляд; гостре пошкодження нирок; опікова хвороба; хронічна хвороба нирок; патоморфологія; патофізіологія