

RENAL IMMATURITY, COMORBIDITIES AND OUTCOMES IN NEONATAL ACUTE KIDNEY INJURY

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ABSTRACT

The kidneys of newborns are morphologically and physiologically different from those of children and adults. Embryonic kidney development begins at the 3rd week after conception and ends at 32-35 weeks prenatally, while in premature infants it continues for some time after birth. Neonatal kidney function is "immature", due to high vascular resistance and low renal blood flow. Therefore, neonatal kidneys are particularly vulnerable to the effects of hypoperfusion. Predisposing factors for the occurrence of acute kidney injury (AKI) in newborns are certain clinical conditions such as prematurity, respiratory distress, sepsis, asphyxia, meconium aspiration, and congenital heart disease. Timely treatment of associated comorbidities reduces the risk of kidney injury in newborns. Diagnosing AKI in newborns is accompanied by certain difficulties due to the lack of blood samples for analysis, especially in premature babies, and variable glomerular filtration due to immaturity of renal function. Early detection of kidney injury provides an opportunity for timely and appropriate treatment, which leads to a better outcome and prognosis of the disease. Renal markers, especially NGAL, enable early diagnosis of AKI even in the first hours of its occurrence, when the disease is not clinically manifested. Due to the possibility of developing chronic kidney disease, monitoring of children at risk is necessary. Extremely premature babies and those with oliguric AKI are susceptible to neurocognitive disorders, anxiety and depression. Therefore, long-term multidisciplinary follow-up of children who manifested acute kidney injury in the neonatal period is warranted.

Keywords: acute kidney injury, newborns, comorbidities, outcomes

KIDNEY FEATURES IN NEWBORNS

Acute kidney injury (AKI) represents a complex disorder of renal function with various clinical manifestations ranging from minimal renal dysfunction to renal failure requiring replacement therapy. Acute kidney injury occurs as a result of a rapid decrease in glomerular filtration, which leads to an increase in the degradation products of nitrogen metabolism and most often to a decrease in the urine output [1-3].

The kidneys of newborns differ morphologically and physiologically from those in children and adults. The embryonic development of the kidneys begins in the 3rd gestational week from the intermediate mesoderm and passes through pronephros, mesonephros, and metanephros. About 20% of the fetus's nephrons develop in the first trimester of intrauterine life, and about 50% by the 5th month. Nephron development is completed between 32

and 35 weeks of gestation, with newborns born at term having a fixed number of nephrons that does not change throughout life. In premature babies, nephrogenesis continues for some time after birth. Nephrons in neonatal kidneys are heterogeneous, with different sizes and functional capabilities, with the apparent difference being overcome only after 12-14 months of postnatal life. Although the fetal kidneys are of no importance as an excretory organ, since the placenta performs renal function until the beginning of extra uterine life, it nevertheless begins to function intrauterine [4, 5].

During the fetal life, glomerular filtration is low and subsequently improves in the first weeks of life. It occurs as a result of active nephrogenesis (postnatal adaptation of the kidney by increasing its length due to hyperplasia and hypertrophy of the glomerular cells, a decrease in the renal vascular resistance, and a progressive increase in the function of the superficial nephrons). In newborns, the glomerular filtration rate in the first days of life is 17-20 ml/min/1.73m², in newborns from 1-2 weeks it is 35-45 ml, in infants from 6 months to 1 year it is 65-91 ml, and in children from 1 to 3 years it is 74-118 ml/min/1.73m² (in adults, GFR is 100-140 ml/min/1.73m²). The postnatal increase in GFR depends on the increase in the filtration surface area, the increase in the ultra filtration pressure, and the increase in the perfusion in the glomeruli. The function of the kidneys of newborns is "immature", but still sufficient to maintain normal life processes in healthy newborns. This "immaturity" results from the fact that they have high renal vascular reserve, high plasma renin activity, low glomerular filtration, low intercortical perfusion, reduced sodium reabsorption in the proximal tubule, and a tendency towards tubular/cortical necrosis [6-8].

The incidence of AKI in newborns has the highest rate compared to other age groups, and it ranges from 6 to 24%, with a mortality rate of over 35%. The occurrence of AKI in newborns is influenced by various factors, such as gestational age, birth weight, and comorbid conditions present during or immediately after birth [9-11]. In the three-year clinical-epidemiological prospective study of Naunova Timovska et al., conducted at the University Children's Hospital in Skopje, in which newborns with various pathological conditions and the development of acute kidney injury were evaluated, the estimated incidence of acute kidney injury was 6.4% [12]. By gender, male newborns predominate, and the high rate of kidney injury in boys is likely the result of some predisposing factors, such

as neonatal sepsis and respiratory distress, which occur more frequently in boys. According to the gestational age, the majority of newborns with AKI were born at term. In the studies by Momtaz et al., and Kapoor et al. term newborns are represented in 79.5% and 68% of cases with AKI. A contrary finding, for a predominance of premature babies, are presented in the studies of Mathur et al. (76%) and Choker et al. (69%) [13-15]. There are several pathophysiological mechanisms responsible for the occurrence of renal excretory failure in newborns: changes in the renal perfusion or reduced blood flow to the kidneys, changes in the glomerular permeability or reduced glomerulo-capillary filtration surface area (Kf), obstruction of the tubules with cellular debris, as well as increased reabsorption through the damaged tubular cells, i.e. tubulo-glomerular reflux (back-leak) [16-18].

The most common type of kidney injury in newborns is prerenal kidney injury, which occurs in 70 to 80% of the cases. It occurs due to various hemodynamic disturbances that attack the immature neonatal kidneys. Namely, the kidneys of newborns, due to the immaturity of the blood flow autoregulation mechanism, are less able to compensate for changes in renal arterial pressure, so hypovolemia and hypotension very often lead to renal hypoperfusion and reduced glomerular filtration. In the study by Naunova Timovska et al., 78% of newborns with kidney injury demonstrated prerenal AKI. It was confirmed by a natriuresis of less than 20 mEq/L, a fractional sodium excretion (FENa) of less than one, and an adequate response to the fluid bolus therapy. Prerenal AKI is most likely the result of the reduced effective blood flow in the kidneys, i.e. inadequate renal perfusion with a subsequent decrease in the glomerular filtration. These conditions occur due to various hemodynamic disturbances affecting the neonatal kidneys. In this case, the already existing parenchymal renal damage does not reverse despite the restoration of the renal perfusion [19-21].

In terms of the 24-hour urine output, the majority (80-90%) of newborns with renal AKI are oliguric, with a diuresis of less than 1-1.5 ml/kg/24, while more than half of neonates with prerenal AKI are non-oliguric. This finding is likely a result of the high prevalence of perinatal asphyxia in newborns with prerenal AKI, which predisposes to the development of a non-oliguric type of renal injury. Newborns with renal AKI have a significantly higher mortality rate than newborns with prerenal AKI. This finding is likely a result of the

more severe clinical condition and greater uremia in newborns with renal AKI, which subsequently leads to the involvement and failure of multiple organs and organ systems [22, 23].

COMORBIDITIES ASSOCIATED WITH ACUTE KIDNEY INJURY

In newborns, due to the high vascular resistance and plasma renin activity, renal blood flow is proportionally lower. Therefore, their kidney is particularly vulnerable to the effects of hypoperfusion. The physiological characteristics of the neonatal kidney – low glomerular filtration rate (GFR), reduced intercortical perfusion and reduced sodium reabsorption in the proximal tubule, resemble those encountered in acute tubular necrosis, which is why some describe the neonatal kidney as “halfway to acute renal failure.” In addition, various comorbid conditions that are often encountered in newborns, and which further reduce circulation, as well as certain therapeutic interventions and nephrotoxic drugs, can secondarily impair the renal function and lead to kidney injury [24, 25].

Predisposing factors for the occurrence of AKI in neonates are certain clinical conditions (prematurity, respiratory distress, sepsis, perinatal asphyxia, meconium aspiration syndrome, congenital heart diseases). The timely treatment of the associated comorbid conditions, as well as the reduction of nephrotoxic drugs, reduces the risk of kidney injury in neonates. In the clinical studies of Selewski et al., and Gopal et al., the most common comorbid condition associated with AKI is the perinatal asphyxia, with a predominance of the male term infants born with a low Apgar score at the fifth minute of life. There is a strong association of asphyxia with the male gender, hence its predominance in these newborns. The connection between the perinatal asphyxia and the kidney damage stems from the fact that it is accompanied by the occurrence of hypoperfusion, which occurs due to the redistribution of the blood volume to the vital organs and their protection in conditions of threatening hypoxia. This adaptation mechanism that occurs in asphyxia is known as the “diving seal reflex.” The resulting hypoperfusion leads to ischemic damage to the renal parenchyma and tubulointerstitium. Therefore, hypoperfusion is the key factor in the occurrence of renal damage

in asphyxiated newborns. Hence the importance of its timely correction in order to prevent renal damage [26, 27].

More than half of the newborns with AKI associated with asphyxia are non-oliguric, with urine output greater than 1-1.5 ml/kg/h, likely due to tubulointerstitial damage. Early recognition of renal damage in asphyxiated newborns, followed by adequate fluid intake, is necessary for faster recovery and better outcome. The predominance of non-oliguric kidney injury is presented in the studies of Gopal et al., and Gupta et al. Notably, in a one-year study conducted on 75 newborns, Gopal reported the presence of nonoliguric kidney injury in 63% of the asphyxiated newborns. In Gupta’s study, 78% of the asphyxiated newborns had nonoliguric kidney injury [43-45]. Because of other associated comorbidities with AKI, such as congenital heart disease, meconium aspiration syndrome, sepsis, and prematurity, newborns are often oliguric, with a urine output of less than 1-1.5 ml/kg/h [28,29].

The other comorbidity associated with kidney damage in newborns is neonatal sepsis, confirmed by neutropenia in the hematogram, elevated inflammatory markers, and a positive blood culture. Due to the immaturity of the immune system in newborns, sepsis is a significant cause of morbidity and mortality in the neonatal period. Impaired renal function and subsequent renal damage probably occur due to the development of septic shock, disseminated intravascular coagulation, heart failure, and acute tubular necrosis. Acute kidney injury is also associated with prematurity, which today represents a significant global public health problem. The number of babies born before 28 weeks of gestation is increasing. Most likely, this is due to the shift in the age limit of women giving birth, who are increasingly choosing to have children after the age of 30, as well as the more frequent use of in vitro fertilization. With the modernization of neonatal intensive care units and the use of new technologies and protocols, more effective treatment of premature babies is now provided. In this way, survival is drastically improved and early and late complications of prematurity are reduced. Other comorbid conditions associated with AKI in newborns are congenital heart diseases and meconium aspiration syndrome. Evidence suggests that newborns with AKI have multiple comorbid conditions, suggesting that the etiology of acute kidney injury in the neonatal period is multifactorial [30, 31]. In

the study by Naunova Timovska et al., the most common associated comorbid condition in newborns with prerenal AKI was perinatal asphyxia, registered in 36% of cases. That was followed by the following comorbidities: prematurity registered in 25%, sepsis in 18%, meconium aspiration syndrome in 13% and congenital heart diseases in 8% of newborns with AKI. Renal AKI was found in 20% of newborns, and the most common comorbid condition associated with renal AKI was sepsis evaluated in half of cases.

DIAGNOSIS OF ACUTE KIDNEY INJURY

The following findings are used to diagnose acute kidney injury: Medical history (personal and maternal for use of medications during pregnancy or childbirth), Clinical finding, Laboratory tests in blood and urine (blood count, gas analysis, electrolytes in serum and urine, creatinine in serum and urine, urea, 24-hour urine output, pH and urine osmolarity), ECG, ultrasound of the renal and urinary system, MCUG, Renal biopsy. Disturbances in the water balance, electrolytes and acid-base status, as well as the accumulation of waste products, indicate a decrease in the kidney function, with the kidneys insufficiently excreting urine with an inappropriate composition. To assess the kidney function and the capacity of the kidneys to purify the blood, creatinine clearance and glomerular filtration rate (GFR) are determined. Normally functioning kidneys have a creatinine clearance and GFR of 120 ml/min. Creatinine clearance decreases with age, decreasing by about 50% in adulthood. In neonates, the most common indicators of renal dysfunction are serum creatinine values greater than 130 $\mu\text{mol/l}$ in neonates younger than 33 weeks of gestation and greater than 90 $\mu\text{mol/l}$ in neonates older than 33 weeks of gestation, with or without the presence of oliguria ($<1\text{--}1.5\text{ ml/kg/h}$). If the urine output is less than $1\text{--}1.5\text{ ml/kg/24h}$, it is oliguric AKI, and if it is greater than $1\text{--}1.5\text{ ml/kg/24h}$, it is non-oliguric AKI [32–34].

Diagnosing AKI in newborns is accompanied by certain difficulties due to: fewer blood samples for determining serum creatinine levels, especially in extremely premature babies due to the small blood volume and the potential

risk of anemia; higher serum creatinine values in the first 72 hours of life reflecting the presence of maternal creatinine in the newborn's circulation; low and variable GFR due to immaturity of the renal function; lack of reference values for serum creatinine in newborns [35].

Renal biomarkers are used for the early diagnosis and follow-up of the outcome of kidney injury. They enable timely recognition of the newborns at risk for kidney injury, in which clinical symptoms and signs of the disease have not yet been manifested. Until now, the diagnosis of the kidney injury was based on the determination of the serum creatinine values, which is the most commonly used parameter for monitoring glomerular filtration. However, its use in the neonatal period is very limited due to the difficulties in interpretation. Namely, during the first 2 to 3 days of life, serum creatinine reflects the function of the maternal kidneys, i.e. maternal creatinine, showing higher values that subsequently decrease in the following days. On the other hand, serum creatinine levels may increase as early as 48–72 hours after the initial kidney injury, after a 25–50% decrease in the kidney function has occurred and when there are clear clinical signs of the disease. Therefore, serum creatinine is considered a late functional marker of kidney injury [36, 37].

Starting from the fact that acute kidney injury is a serious life-threatening condition, especially in the neonatal period, the importance of early diagnosis of this disease arises in the initial stage, when the changes are reversible and the disease has a transient course. Early detection of kidney injury provides the opportunity to initiate timely and adequate treatment that would ensure a better outcome and better prognosis of the disease. Namely, previous research has shown that determining renal biomarkers in the early stages of AKI, in addition to the timely detection of the kidney damage, also plays a major role in predicting the clinical course and prognosis of the disease. It has been established that renal biomarkers can detect renal injury within the first 2 to 3 hours of its occurrence, when the disease is not clinically manifested, and creatinine values are within the reference limits. Known biomarkers that detect AKI in newborns are Cystatin C (CysC), Kidney injury molecule 1 (KIM-1), Interleukin-18 (IL-18), N acetyl B-D glucosaminidase (NAG), B2-microglobulin ($\beta 2\text{M}$), Retinol-Binding Pro-

tein (RBP), Neutrophil Gelatinase Associated Lipocalin (NGAL) [38,39].

Wider application of NGAL in the evaluation of critically ill newborns with various pathological conditions is justified, as an early, sensitive marker for the detection of acute kidney injury. NGAL has shown high sensitivity and predictive value in neonates at risk of AKI. Under normal conditions, very small amounts of the NGAL glycoprotein are excreted in the urine, but they increase rapidly in the first hours after the onset of kidney injury. A sudden increase in the urinary NGAL occurs in those newborns who do not have clinical signs of AKI, and before the onset of an increase in serum creatinine [40,41].

Many studies have evaluated the predictive power of NGAL marker. Mishra et al. showed that NGAL was an early marker of subclinical AKI in pediatric patients after cardiopulmonary bypass; its elevation preceded any increase in creatinine, and the increase was sustained throughout the duration of AKI. In the prospective observational study of Eldegwi et al. the diagnostic performance of NGAL as an early predictor of AKI was assessed in 70 premature babies receiving nephrotoxic drugs, whereas a two-center prospective cohort study of Stoops et al. showed the performance of NGAL to detect AKI in 148 infants [42-45].

PROGNOSIS, OUTCOMES AND FOLLOW-UP

A good prognosis is shown in newborns with prerenal AKI (if treatment is started in time) and with postrenal AKI (if obstruction of the distal urinary tract is removed in time). A poor prognosis is shown in newborns with renal AKI, with the appearance of residual renal failure (reduced glomerular filtration, tubular dysfunction or retarded kidney growth) or permanent loss of renal function with transition to end-stage renal failure, i.e. end-stage renal disease [45,46].

It is known that the total glomerular filtration rate is determined by the filtering capacity of each individual nephron. In cases where kidney damage occurs, the number of nephrons decreases, resulting in compensatory hypertrophy of the remaining nephrons. They operate under increased intracapillary hydraulic pressure, which

subsequently leads to damage to the capillary wall. This inevitably leads to the appearance of progressive glomerulosclerosis, proteinuria, hypertension and terminal renal failure. Terminal renal failure is a severe disability that impairs the quality of life of patients and their families, and the expensive and long-term treatment financially depletes health funds and the families of affected babies [47, 48].

Because of the potential risk of developing chronic kidney disease, long-term follow-up is desirable for children who have AKI in neonatal period. The follow-up includes the assessment of:

- Growth and development, through appropriate growth curves. The finding of body weight curve below 5th percentile indicates growth retardation; between the 85th and 95th percentile shows overweight, while body weight above 95th percentile represents obesity, an overweight.

- Blood pressure measurement. Hypertension is defined as systolic blood pressure and/or diastolic blood pressure above the 90th percentile or above the 95th percentile for the appropriate age group on at least three separate occasions. Hypertension is classified as prehypertension (blood pressure between the 90th and 95th percentile), stage 1 (blood pressure between the 95th and 99th percentile plus 5 mmHg), and stage 2 (blood pressure above the 99th percentile plus 5 mmHg).

- Assessment of renal function. The assessment is performed through certain laboratory parameters (urea and creatinine in serum, urinalysis of the first urine with calculated protein/creatinine ratio) and ultrasonographic examination of the kidneys. The reference value for the calculated protein/creatinine ratio is taken to be a value less than 0.5 mg/mmol [49].

The follow-up of children with AKI in neonatal age shows that glomerular filtration and tubular function are still normalized. However, renal blood flow remains permanently impaired, suggesting that there is still some irreversible loss of nephrons, and that glomerular filtration is maintained by hypertrophy of the remaining nephrons. The children with neonatal AKI are at risk of chronic kidney disease in the future, especially extremely premature in whom the kidney disease may progress during the first year of life. This is due to the vascular endothelial cells damage that leads to progress to fibrosis, glomerulosclerosis, and loss of kidney function.

The findings in the majority of short term monitored children show that they still have normal growth and development, proper blood pressure, and appropriate renal function. This is most likely due to the prerenal AKI, as a dominant kidney injury in neonatal period. But, at the same time, these findings do not exclude the occurrence of chronic kidney disease in the future. Therefore, a long term follow up of children with AKI is necessary to timely identify those with possible development of chronic kidney disease [50-53]. In the study by Naunova Timovska, only 52% of children are followed up for one year after the initial kidney injury, partly because of the unfavorable outcome in infancy, and partly because of non-acceptance of the health status control. The majority of the monitored children have had normal growth, blood pressure, and kidney function. In 8% of the monitored children, microproteinuria is registered, as an important predictor of developing chronic kidney disease. This finding indicates that children with microproteinuria are at risk for progression of kidney disease. Therefore, long-term monitoring of children at risk is necessary, in order to timely diagnose chronic kidney disease and to undertake appropriate treatment to prevent further loss of kidney function and transition to end-stage renal failure.

The children with AKI at neonatal age, especially those with oliguric AKI and born extremely preterm, are at risk for long-term neurocognitive disorders (memory deficits, and learning difficulties), anxiety, and depression (noticed in more than 11% of children with severe neonatal AKI). Unfavorable neurodevelopmental outcomes are a result of an imbalance in vascular growth factors; disruption of blood-brain barrier integrity that allows infiltration of toxic products from the injured kidneys into the developing brain, as well as with reduction of dopamine turnover in certain parts of the brain. Long-term neurodevelopmental follow-up after neonatal AKI is warranted [54, 55]. Namely, kidney injury survivors experience persistent psychological distress, cognitive impairment, and reduced QoL, particularly in those with incomplete renal recovery. Incomplete renal recovery, prolonged ICU stay, more dialysis sessions, and higher creatinine titers were linked to worse psychiatric outcomes, while better albumin titers correlated with improved cognition. Early psychiatric assessment and targeted interventions should be integrated into post-AKI care [56].

CONCLUSION

In the neonatal period, various pathological conditions that further reduce the circulation can secondarily impair the renal function of immature kidneys and lead to the occurrence of acute kidney injury. Comorbid conditions in newborns increase the risk of kidney injury in the neonatal period. The occurrence of AKI is often multifactorial, with one or more associated comorbid conditions that worsen the course and outcome of the disease. The timely treatment of the associated comorbid conditions reduces the risk of developing AKI in newborns. Prerenal AKI is the most common type of kidney injury that occurs due to various hemodynamic disorders that attack the immature neonatal kidneys. NGAL is a promising marker that allows early diagnosis of kidney injury, even in the first hours of its occurrence. That is why we propose its wider application in ill newborns with different clinical conditions as an early renal marker for AKI detection. Long-term follow-up of children who have experienced AKI at neonatal age is necessary, due to the possible progression over the years to chronic kidney disease as well as neurodevelopmental disorders and depression. In addition, multidisciplinary follow-up for pediatric patients with AKI is important, such as psychiatric follow-up in treatment centers due to the associated psychiatric disorders with acute kidney injury.

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Резиме**НЕЗРЕЛОСТ НА БУБРЕЗИТЕ, КОМОРБИДИТЕТИ И ИСХОДИ
КАЈ НЕОНАТАЛНО АКУТНО БУБРЕЖНО ОШТЕТУВАЊЕ**

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Бубрезите кај новороденчињата морфолошки и физиолошки се разликуваат од оние кај децата и кај возрасните. Ембрионалниот развој на бубрезите започнува во 3-тата недела по зачнувањето и завршува во 32-35-та недела пренатално, додека кај предвремено родените продолжува одреден период по раѓањето. Функцијата на неонаталните бубрези е „незрела“ поради високиот васкуларен отпор и нискиот бубрежен крвен проток. Затоа, неонаталните бубрези се особено чувствителни на хипоперфузија. Предиспонирачки фактори за појава на акутното бубрежно оштетување (АБО) кај новороденчињата се одредени клинички состојби, какви што се предвременото раѓање, респираторниот дистрес, сепсата, асфиксијата, мекониумската аспирација и вродените срцеви заболувања. Навременото лекување на придружните коморбидитети го намалува ризикот од оштетување на неонаталните бубрези. Дијагностицирањето на бубрежното оштетување кај новороденчињата е придружено со одредени тешкотии поради недостигот на крвни примероци за анализа, особено кај предвремено родените, и варијабилната гломеруларна филтрација, поради незрелоста на бубрежната функција. Раното откривање на бубрежното оштетување дава можност за навремен и соодветен третман, што доведува до подобар исход и прогноза на болеста. Бубрежните маркери, особено НГАЛ, овозможуваат рана дијагноза на АБО дури во првите часови од нејзиното појавување, кога болеста не е клинички манифестирана. Поради можноста за развој на хронична бубрежна болест, потребно е мониторирање на децата со ризик. Екстремно прематурните деца и оние со олигурична АБО се подложни на неврокогнитивни нарушувања, анксиозност и депресија. Затоа, неопходно е долгорочно мултидисциплинарно следење на децата што во неонаталната возраст манифестирале акутно бубрежно оштетување.

Клучни зборови: акутно бубрежно оштетување, новороденчиња, коморбидитети, исходи