Postępy Nauk Medycznych, t. XXVI, nr 2, 2013

*Maria Roszkowska-Blaim, Agnieszka Kisiel

Role of biomarkers in the early diagnosis of acute kidney injury in neonates

Rola biomarkerów we wczesnej diagnostyce ostrego uszkodzenia nerek u noworodków

Department of Pediatric Nephrology, Medical University of Warsaw
Head of Department: prof. Maria Roszkowska-Blaim, MD, PhD

S u m m a r y

Acute kidney injury (AKI) is sudden, usually reversible renal dysfunction with reduction of glomerular filtration rate (GFR) and impaired of renal ability to maintain homeostasis. Acute kidney injury is associated with increased risk for poor outcome in critically ill neonates. Precise incidence of AKI in neonates is unknown, literature data suggest that this condition is diagnosed in 8-24% of all critically ill newborns. Despite significant advances in the therapeutics the mortality rate is still high and ranging between 10-61%.

Underestimation of AKI in the neonatal period may be caused by the specific clinical course – more commonly nonoliguric than oliguric and the use of creatinine as the only biochemical marker of kidney disfunction. Serum creatinine is known as a late marker of renal failure.

In this article authors present the classification of AKI in neonates with etiology and clinical presentation and summarize the diagnostic performance of the early predictive biomarkers of AKI: cystatin C (CysC), neutrophil gelatinase-associated lipokalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), liver fatty acid-binding protein (L-FABP). They indicate the use of novel biomarkers in the diagnosis of AKI allows to detect preclinical kidney damage in the neonatal period.

Further studies are required in large neonates populations that would identify optimal panels of diagnostic tests for AKI, allowing better patient selection, more rapid introduction of specific treatment, and improvement in prognosis.

Key words: acute kidney injury, biomarkers, neonates

S t r e s z c z e n i e

Ostre uszkodzenie nerek (AKI – ang. *acute kidney injury*) jest nagłą, zwykle odwracalną dyfunkcją nerek z obniżeniem filtracji kłębuszkowej (GFR – ang. *glomerular filtration rate*) oraz uszkodzeniem zdolności nerek do utrzymania homeostazy. Ostre uszkodzenie nerek wiąże się ze wzrostem ryzyka niepomyślnego wyniku leczenia krytycznie chorych noworodków. Precyzyjna liczba incydentów AKI u noworodków nie jest znana, wg danych z literatury, AKI jest wykrywane u 8-24% wśród wszystkich ciężko chorych noworodków. Pomimo znaczącego postępu w leczeniu, stopień śmiertelności jest nadal wysoki i wynosi 10-61%.

Niedoszacowanie AKI w okresie noworodkowym może być spowodowane specyficznym przebiegiem klinicznym, częściej nieoligurycznym niż oligurycznym oraz stosowaniem kreatyniny jako jedynego biomarkera dysfunkcji nerek. Stężenie kreatyniny jest późnym markerem uszkodzenia nerek.

W tym artykule autorzy przedstawiają klasyfikację AKI z uwzględnieniem etiologii i objawów klinicznych, oraz podsumowują znaczenie diagnostyczne wczesnych biomarkerów AKI jak: cystatyna (CysC), neutrofilowa żelatynaza związana z lipokaliną (NGAL), cząsteczka 1 uszkodzenia nerek (KIM-1), interleukina 18 (IL-18), białka wiążące kwasy tłuszczowe typ wątrobowy (L-FABP). Stosowanie nowych biomarkerów w diagnostyce AKI, pozwala wykryć przedkliniczny stan uszkodzenia nerek w okresie noworodkowym.

Niezbędne są dalsze badania na dużej populacji noworodków, co pozwoliłoby wybrać optymalny panel diagnostyczny testów do rozpoznania AKI, pozwalający lepiej wyselekcjonować pacjentów, szybciej zastosować odpowiednie leczenie i poprawić rokowanie.

Słowa kluczowe: ostre uszkodzenie nerek, biomarkery, noworodki

Acute kidney injury (AKI) is sudden, usually reversible renal dysfunction with reduction of glomerular filtration rate (GFR) and impaired excretion of waste products, leading to water-electrolyte and acid-base imbalance. Although precise incidence of AKI in neonates is unknown, literature data suggest that this condition is diagnosed in 8-24% of all critically ill newborns in neonatal intensive care units (1, 2), and

preterm infants comprise about one third of the affected patients (2).

AKI in neonates may be underestimated as the disease is often nonoliguric, and postpartum neonatal creatinine level reflects its maternal level (3). In addition, after birth GFR is low in both preterm and full-term infants; GFR increases within first month of life, but velocity of this increase is lower in preterm neonates (4). AKI is associated with increased morbidity and mortality, and prolonged hospitalizations both in children (5, 6) and adults (7). It has been suggested that in neonates, AKI is a risk factor for mortality and long-term chronic kidney disease. Despite advances in treatment, neonatal mortality in AKI is 10-61% (8).

The term "acute renal failure" (ARF) was introduced in 1951 by Homer W. Smith (9), and several dozen varying definitions of ARF have been used in the literature since that time. A classification of ARF in adults, based on creatinine level and diuresis, has been introduced only in 2004 and is known as the RIFLE criteria (Risk of kidney injury, kidney Injury, renal Failure, Loss of kidney function for > 4 weeks, End-stage kidney disease requiring renal replacement therapy for > 3 months) (10, 11). In 2007, a novel 3-stage Acute Kidney Injury Network (AKIN) classification was proposed. According to the AKIN classification, AKI is a rapidly developing (within 48 hours) renal dysfunction defined as an increase in creatinine level by 0.3 mg/dL or 50%, or reduction in urine output to < 0.5 mL/kg/hour for 6 hours (12). With this terminology, AKI is renal dysfunction secondary to structural and functional intrarenal changes, and the term of ARF is reserved for conditions requiring renal replacement therapy.

In 2007, Acan-Arikan published first pediatric RIFLE classification (pRIFLE) for children above 2 years of age, based on the estimated creatinine clearance (using Schwartz formula) and hourly diuresis (5).

In clinical practice, renal dysfunction in neonates is diagnosed based on abnormal results of biochemical tests and reduced urine output. First neonatal AKI classification was proposed by Koralkar in 2011(13). Table 1 shows AKI classification criteria in neonates and children above 2 years of age.

Etiology of acute kidney injury

No large studies on the etiology of AKI in neonates have been published. In the prenatal period, an important cause of AKI development in utero is exposure to nephrotoxic drugs such as angiotensin-converting enzyme inhibitors (ACEI) (15), angiotensin-receptor blockers (ARB) and non-steroidal anti-inflammatory drugs (NSAIDs) (16) which inhibit prostaglandin secretion, leading to vasodilatation and renal hypoperfusion. Congenital and genetic kidney disease such as renal dysplasia/hypoplasia and cystic kidney disease including autosomal recessive polycystic kidney disease (ARPKD) and autosomal dominant polycystic kidney disease (ADPKD) may lead to renal failure (8).

In the postnatal period, risk factors for AKI include preterm birth, perinatal asphyxia, respiratory distress syndrome (RDS) requiring ventilation support and surfactant administration and sepsis(17). Table 2 shows the most common causes of acute kidney injury in the neonatal period.

Table 2. Causes of AKI in neonates.

Prerenal failure	
↓ **Intravascular volume**	Dehydratation Gastrointestinal disorders Salt wasting renal/arenal disease Nephrogenic or central diabetes insipidus Third space losses (*sepsis, traumatized tissue*)
↓ **Intravascular blood volume**	Congestive heart failure Pericarditis Cardiac tamponade
Intrinsic AKI	
Acute tubular necrosis	Hypoxic/ischemic injury
	Nephrotoxic drugs: aminoglycosides, intravascular contrast, NSAIDs
	Endogenous toxins: hemoglobinuria, myoglobinemia
Interstitial nephritis	Drugs: antibiotics, anticonvulsants
	Idiopathic
Vascular lesions	Cortical necrosis Renal artery/venous thrombosis
Infectious causes	Sepsis Pyelonephritis
Postrenal failure	
CAKUT	Obstruction in a solitary kidney Bilateral ureteral obstruction
	Ureteral obstruction

NSAIDs – non-steroidal anti-inflammatory drugs
CAKUT – congenital anomalies of kidney and urinary tract

Table 1. Classification for AKI in neonates and children.

Classification for AKI in neonates*		**pRIFLE (> 2 years old)****			
AKI stages	**Serum creatinine ($_sCr$)**	**AKI stages**		**eGFR (mL/min/1.73 m²)**	**Urine output (mL/kg/h)**
1	↑ $_sCr$ ≥ 0.3 mg/dL (26.5 μmoL/L) from previous value = 48 h ↑ $_sCr$ ≥ 150-200% from previous value	**R**	Risk	↓ by 25%	< 0.5/8 h
2	↑ $_sCr$ ≥ 200-300% from previous value	**I**	Injury	↓ by 50%	< 0.5/16 h
3	↑ $_sCr$ ≥ 2.5 mg/dL (221.0 μmoL/L) ↑ $_sCr$ ≥ 300% from previous value or renal replacement therapy	**F**	Failure	↓ by 75% or < 35	< 0.3/24 h or anuria/12 h

AKI – acute kidney injury; eGFR – estimated GFR according to Schwartz formula (14)
Adapted: *(12), **(4)

Clinical presentation of acute kidney injury in neonates

Regardless of patient age, AKI may be traditionally categorized as:

1. prerenal failure due to impaired adaptation to intravascular volume reduction or hypotension,
2. intrarenal failure resulting from the effect of cytotoxic factors that impair nephron structure and function,
3. postrenal failure due to obstructed urine outflow.

The most common type of AKI in neonates is prerenal failure, found in 85% of cases. Intrarenal failure was reported in 11% of cases, and postrenal failure in only 3% of cases (18).

The clinical presentation of AKI includes reduction in urine output to < 0.5-1.0 mL/kg body mass/hour. In the neonatal period, AKI is more commonly nonoliguric than oliguric, and edema is not a characteristic feature but may be caused by water retention due to unrecognized oliguria. In addition, some children present with arterial hypertension (19).

AKI may be diagnosed in the absence of characteristic clinical signs, based on typical abnormal biochemical findings such as increased levels of nitrogen waste products including creatinine, electrolyte disturbances including hyponatremia, hyperkalemia and hypocalcemia, and metabolic acidosis. Hyponatremia may be dilutional in oliguric AKI or depletional in non-oliguric AKI.

Evaluation of acute kidney injury in neonates

Traditional methods

Commonly used parameters of renal dysfunction include serum creatinine, urinary sodium, urine osmolality, and fractional sodium excretion (FE_{Na}) which allows distinguishing between intrarenal and prerenal failure. In oliguric acute tubular necrosis (ATN) in full-term infants, FE_{Na} is always > 2.5-3.0%, and in preterm infants (≤ 32 weeks of gestation) with high plasma sodium level and urinary sodium excretion, diagnostic cut-off FE_{Na} for ATN is > 6% (tab. 3). The diagnosis of prerenal AKI is confirmed by an increase in urine output following fluid replacement (8).

Table 3. The differential diagnosis of AKI: prerenal from intrinsic renal based on urine osmolality, urine sodium concentration and fractional Na excretion in newborns.

Parameters	AKI	
	Prerenal	Intrinsic renal (ATN)
	Newborns (full term/preterm)	
Urine osmolality (mOsm/L)	> 350	< 350
Na/urine (mEq/L)	< 20-30	> 30-40
FE_{Na} (%)	> 2.5	2.0

FE_{Na} – fractional Na excretion; ATN – acute tubular necrosis

Biomarkers

AKI is associated not only with reduced GFR but also with functional changes in renal tubular epithelium, interstitial tissue, and intrarenal microcirculation. AKI in neonates is largely asymptomatic, and the diagnosis is based on the determination of serum creatinine, a biomarker of renal function. The main source of creatinine is phosphocreatinine in the muscle tissue. In full-term infants, serum creatinine reflects maternal creatinine levels during the initial 48-72 hours after birth, and then gradually decreases to 0.4 mg/dL by about 2 weeks. In preterm infants, creatinine level initially rises during the first 2-4 days and later normalizes by 2-3 weeks. Unfortunately, creatinine level is a late marker of renal dysfunction, rising only when lesions involve 50% of the renal parenchyma (20). GFR in full-term infants is 20 mL/min/1.73 m^2 and doubles within the initial two weeks after birth, while in preterm infants it is low, depends on the gestational age and doubles only by 3 weeks after birth or even later. The rate of GFR changes depends on renal hemodynamic changes that occur regardless of the gestational age and body mass (4). Despite the above limitations, serum creatinine level continues to be widely used as a clinical biomarker of renal function also in neonates.

Intensive search continues for an ideal biomarker to improve the diagnosis of AKI. Such a biomarker should be characterized by:

1. an ability to be determined in easily obtainable biological specimens, preferably using least invasive methods (e.g. urine);
2. high sensitivity for the detection of even mild renal dysfunction;
3. a wide reference range that would allow predicting prognosis;
4. specificity for AKI, with area under ROC curve > 0.90;
5. independence from GFR (21).

In addition to the diagnosis of preclinical AKI, different biomarkers and their panels allow determination of the AKI subtype (prerenal, intrarenal, postrenal failure), location of kidney damage (proximal tubule, distal tubule, interstitium, glomerulus), etiology (ischemia, toxins, sepsis), and prognosis (disease duration, severity of AKI, indications for dialysis therapy, mortality risk), as well as monitoring treatment effects (22).

Based on the recent literature, a short review of the biomarkers that have been studied in neonates is given below, focusing specifically on cystatin C, neutrophil gelatinase associated lipocalin (NGAL), interleukine-18 (IL-18), kidney injury molecule 1 (KIM-1), and liver fatty acid-binding protein (L-FABP).

Cystatin C (CysC) is a 120-aminoacid cysteine protease inhibitor with a small molecular mass of 13 kDa, synthesized in all nuclear cells. CysC molecules are freely filtered at the glomerulus, and then nearly completely reabsorbed and metabolized by proximal tubular cells (23).

CysC may be determined both in serum and urine using the nephelometric method. CysC level is not dependent on age, gender, race, and muscle mass (23), and in the first days of the neonatal period it also does not depend on maternal CysC level (24). Normal values in neonates are shown in table 4.

In AKI, determination of CysC level allows more rapid selection of patients requiring renal replacement therapy as compared to serum creatinine (25). Advantage of CysC determination over creatinine was shown in children after cardiac surgery, as creatinine level rose by 50% only after 1-3 days after the surgery, while a rise in CysC level allowed the diagnosis of AKI on average 12 hours after the surgery (26).

Jędrasiak and Grygalewicz showed an increased CysC level in umbilical cord blood in neonates delivered vaginally compared to those delivered by Cesarean section, with a significant correlation with lactic acid levels (27). Urinary CysC level shows an inverse relationship with the gestational age (28, 29) and birth weight (28). CysC level peaks in the first days of life, more so among preterm infants, decreases by the third day, and then remains stable until the end of the first month (23, 30).

Determination of urinary CysC level in the first days after birth allows precise identification of AKI patients – AUC = 0.82-0.92 (3, 28). Increased urinary CysC level in neonates with perinatal asphyxia allows identification of kidney damage in children who do not fulfill the criteria of AKI based on serum creatinine level (31).

Neutrophil gelatinase-associated lipokalin (NGAL) is a 24 kDa, 178-aminoacid protein bound covalently with neutrophil gelatinase. It is secreted into urine by the cells of the thick ascending limb of loop of Henle and the collective tubule. By regulating intracellular iron balance, it is a growth and differentiation factor for many types of cells. In the kidney, it participates in the differentiation of mesenchymal cells into renal epithelium both during nephrogenesis and post-damage reepithelialization. Physiologically, NGAL is detected in urine in very small amounts (32).

Normal urinary NGAL level in full-term and preterm infants are presented in table 4. Studies in preterm infants showed a negative correlation between urinary NGAL level and birth weight (33) and the gestational age (29, 33, 34). NGAL expression increases significantly in response to toxic factors, particularly ischemia/hypoxia (35). An increase in both urinary and serum NGAL level was noted already by 2 hours after cardiac surgery with cardiopulmonary bypass in neonates and older children. An increase in NGAL level preceded a rise in serum creatinine level by 1-3 days. A correlation was shown not only with the incidence of AKI but also with the severity and duration of renal failure (36). Urinary and serum NGAL levels were sensitive markers of AKI in infants with perinatal asphyxia evaluated 1-3 days after birth (31).

Krawczeski showed that in neonates, cut-off serum and urinary NGAL levels for the diagnosis of AKI were 100 ng/mL and 185 ng/mL, respectively (36). Lavery et al. confirmed high specificity of urinary NGAL level as a marker of AKI in newborn (34).

A significant increase in urinary NGAL level was also seen in neonates with a very small birth weight and microbiologically confirmed sepsis (37).

Kidney injury molecule-1 (KIM-1) is a 90 kDa transmebrane glycoprotein with a soluble ectodomain cleaved by metalloproteinases. It was isolated and described by Ichimura in 1998 (38). It is synthesized in minimal amounts in a healthy kidney. In response to ischemia or toxic factors, increased KIM-1 mRNA expression is noted on the apical membrane of the epithelial cells in the most damaged area of the proximal tubule. Following tubular damage, KIM-1 ectodomain is excreted into urine where it may be determined using immunologic methods, e.g. ELISA. This molecule plays a major role in the restoration of structural and functional integrity following kidney damage (22, 39).

KIM-1 is a specific marker of proximal tubule damage by both ischemia and nephrotoxic substances, which affects the usefulness of urinary KIM-1 level determination in the differential diagnosis of AKI causes (35). Increased KIM-1 mRNA expression can be noted already in mild renal damage prior to morphological alteration, and thus it is a much more sensitive marker compared to creatinine and urea (35).

In the first days of life, urinary KIM-1 level shows an inverse correlation with the gestational age (29). Serafidis showed that absolute values of urinary KIM-1 level in term neonates were higher in the 1 day of life and systematically decreased within 10 days after birth (31) (tab. 4).

The usefulness of KIM-1 level determination in the diagnosis of AKI was shown in neonates, particularly with serial assessment in the subsequent days after birth. Among preterm infants with RDS (respiratory distress syndrome) and AKI, a significant increase in urinary KIM-1 level was shown in the third day of life. Urinary KIM-1 level in the first day of life correlated with

Table 4. Reference ranges of urinary cystatin C, NGAL, KIM-1 and IL-18 in neonates according to gestational age (29, 31).

Biomarkers	≤ 26 w	26.1-28 w	28.1-30 w	30.1-36 w	> 36.1 w
Cystatin C (ng/mL)	911 (570-1454)	457 (195-1069)	230 (87-608)	133 (27-657)	1 dol 61.4 (41.9-137.7) 10 dol 31.7 (17.9-41.1)
NGAL (ng/mL)	351 (271-456)	231 (161-333)	145 (96-218)	85 (53-134)	1 dol 6.8 (3.1-15.2) 10 dol 1.1(0.9-1.9)
KIM-1 (pg/mL)	226 (184-277)	158 (117-212)	155 (122-213)	143 (99-207)	1 dol 302 (139.1-512.9) 10 dol 38.7 (27.1-65.9)
IL-18 (pg/mL)	42 (2.0-67)	41 (21-81)	30 (14-63)	67 (29-155)	not aviable

*All values for premature infants are expressed as geometric mean (29)
**All values for term neonates are expressed as median value (31)
NGAL – Neutrophil gelatinase associated lipocalin; KIM-1 – kidney injury molecule 1; IL-18 – interleukin 18; w – week; dol – day of life

serum creatinine level at 3 days, confirming the usefulness of urinary KIM-1 level as an early marker of AKI. Increased urinary KIM-1 level at 7 days was a significant predictor of increased mortality risk (40).

Among neonates with perinatal asphyxia, urinary KIM-1 level did not differ compared to the control group during the first 1-3 days after birth, with a significant increase in urinary KIM-1 level noted only at 10 days (31).

Interleukin-18 (IL-18) is a 24 kDa proinflammatory cytokine synthesized by proximal tubule cells in response to nephrotoxic factors (41). It may be determined both in urine and serum using the ELISA method. In neonates, urinary IL-18 level does not depend on the gestational age (29). Reference values for the neonatal population are shown in table 4.

Clinical studies showed that IL-18 is a sensitive early marker of hypoxic tubular damage (41). A large increase in IL-18 level was found in children with AKI following cardiovascular procedures (42). In critically ill pediatric patients treated in an intensive care unit, an increase in urinary IL-18 level preceded a rise in serum creatinine level and was a predictor of both the severity of kidney damage and the mortality risk (43).

However, the diagnostic value of IL-18 level as an AKI biomarker in neonates has not been clearly established. Although urinary IL-18 level was a significant predictor of AKI in critically ill neonates – AUC 0.72 (28), urinary IL-18 levels in neonates with a very small birth weight did not differ significantly between the patients with AKI and the group without renal damage (44).

Liver fatty acid-binding protein (L-FABP) is a small, 14.4 kDa cytoplasmic protein binding long-chain fatty acids that are subsequently transported to mitochondria and peroxisomes to be oxidized or stored in the sarcoplasmic reticulum. Among nine identified FABP isoforms, two proteins, i.e. cardiac isoform H-type fatty acid binding protein (H-FABP) and L-FABP are present in trace amounts in kidneys. Hofstra showed that L-FABP is reabsorbed in the proximal tubule, and H-FABP is reabsorbed in the distal tubule. L-FABP excretion increases in kidney damage, particularly in AKI, e.g., following cardiac surgery, in idiopathic membranous nephropathy, contrast-induced nephropathy, and chronic kidney disease (45).

In preterm neonates, a 10-fold increase in urinary L-FABP level was shown as compared to healthy adults. A negative correlation was also shown with the gestational age and birth weight (46).

The use of biomarkers in the diagnosis of AKI in neonates allows detecting preclinical kidney damage in children who would not even be suspected to have renal dysfunction based on the conventional diagnostic methods. A systematic review by Coca showed that candidate biomarkers to predict AKI in adult patients include CysC, IL-18, and KIM-1, biomarkers allowing early detection of AKI include urinary NGAL, IL-18, and glutathione S-transferase P, and the best predictors of mortality include urinary N-acetyl-beta D-glucosaminidase, KIM-1, and IL-18 (47). In the present paper, only selected biomarkers of AKI that had been studied in neonates were reviewed. However, further studies are required in large pediatric patient populations that would identify optimal panels of diagnostic tests for AKI, allowing better patient selection, more rapid introduction of specific treatment, and improvement in prognosis.

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received/otrzymano: 10.12.2012
accepted/zaakceptowano: 14.01.2013

Address/adres:
*Maria Roszkowska-Blaim
Department of Pediatric Nephrology
Medical University of Warsaw
ul. Marszałkowska 24, 00-429 Warszawa
tel./fax: +48 (22) 621-98-63
e-mail: dblaim@o2.pl