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Review

Acute kidney injury in neonatal age

Giovanni Ottonello, Angelica Dessì, Paola Neroni, Maria Elisabetta Trudu, Danila Manus, Vassilios Fanos

Neonatal Intensive Care Unit, Neonatal Pathology, Puericulture Institute and Neonatal Section, AOU and University of Cagliari, Italy

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The role of the clinical pathological dialogue in problem solving
Guest Editors: Gavino Faa, Vassilios Fanos, Peter Van Eyken

Abstract

Acute kidney injury (AKI) is a pathology characterized by a sudden decrease in kidney function that results in the accumulation of nitrogenous waste products and alteration of the regulation of extracellular fluid volume, electrolytes, and acid-base homeostasis. Previously known as acute renal failure (ARF), in the most recent classifications the term "failure" is used only in conditions requiring renal replacement therapy, peritoneal dialysis or hemodialysis. The diagnosis and therapy of AKI, especially in the neonatal period, still present great difficulties and are the subject of ongoing research in the attempt to improve the prognosis of a pathology still featuring high rates of morbidity and mortality.

Keywords

Acute kidney injury, acute renal failure, newborn, preterm, RIFLE, biomarkers, therapy.

Corresponding author

Giovanni Ottonello, Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, Azienda Ospedaliera Universitaria, University of Cagliari, SS 554, km 4.5, 09042 Monserrato, Cagliari, Italy; email: ottogia@gmail.com.

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Introduction

Acute kidney injury (AKI) is a complex pathology characterized by a sudden decrease in kidney function caused by a heterogeneous group of morbid conditions involving the kidney primarily or secondarily. Commonly found in all age groups, it presents a peak in the neonatal population hospitalized in neonatal intensive care units (NICUs); in particular it affects preterms. AKI is characterized by clinical manifestations that may vary from a minimum kidney insult to conditions of complete kidney failure that require renal replacement therapy. Prognosis depends on the gravity of the triggering event, on the rapidity and accuracy of the diagnosis, on the immediacy of treatment and the appearance of possible severe iatrogenic complications. At present, AKI is the subject of many studies on the pediatric and neonatal populations aimed at overcoming some of the problems of diagnosis and therapy [1-5]. The objective is to improve the prognosis of a pathology which (despite being reversible in most cases), if not recognized early and suitably treated, may lead to permanent kidney injury, and is made even more serious by high morbidity and mortality.

Definition of acute kidney injury

Much effort has been made in the last ten years to better define and classify a common syndrome known as "acute renal failure" (ARF), now named "acute kidney injury" (AKI). AKI is characterized by a "sudden and rapid" decrease in kidney function, with repercussions on hydroelectrolytic homeostasis, the acid-base balance and the excretion of nitrogen catabolites. In 2004, the Acute Dialysis Quality Initiative (ADQI) proposed an AKI classification system called "risk, injury, failure, loss, end-stage kidney disease" (RIFLE), to obtain a definition of AKI that could be adopted as universally as possible [6]. The criteria on which RIFLE was based were represented by an acute and reversible increment in serum creatinine (SCr) levels, whether associated or not with an alteration of urine output (UO): oliguria/anuria. In this classification, the term "failure" is reserved only to conditions requiring renal replacement therapy, peritoneal dialysis or hemodialysis. Three years later, RIFLE criteria were modified for application to children, thus originating the pediatric RIFLE criteria (pRIFLE) [7]. The authors adapted glomerular filtration rate (GFR), declined criteria from adults and maintained the same UO definition. The main difference was a lower SCr cut-off for the F (Failure) category. However, the presence of a series of characteristics totally specific to neonates (especially if preterm), such as higher total body water, immature tubular cells and maternal SCr influence, did not allow the correct application of the pRIFLE classification to the neonatal population. In particular, no study succeeded in correctly applying the UO values to this population. Only following a recent study, in which UO and its impact on outcomes in a critically ill neonatal population was investigated [8], were the criteria for UO defined. Once they were incorporated in pRIFLE, it became possible to formulate a neonatal RIFLE classification (nRIFLE) [9] (**Tab. 1**).

Epidemiology

Epidemiological investigations into neonatal AKI are few and the data in the literature are

Table 1. Comparison between acute kidney injury (AKI) classification system in children and newborns (modified from: Ricci and Ronco, 2013 [9]).

	Creatinine	Urine output	
RIFLE	***pRIFLE and nRIFLE***	***pRIFLE***	***nRIFLE***
Risk	Increased creatinine x 1.5 or GFR decreases > 25%	UO ≤ 0.5 mL/kg/h x 8 h	UO < 1.5 mL/kg/h x 24 h
Injury	Increased creatinine x 2 or GFR decreases > 50%	UO ≤ 0.5 mL/kg/h x 12 h	UO < 1 mL/kg/h x 24 h
Failure	Increased creatinine x 3 or GFR decreases > 75%	UO ≤ 0.3 mL/kg/h x 24 h or anuria x 12 h	UO < 0.7 mL/kg/h x 24 h or anuria x 12 h
Loss	Persistent failure > 4 weeks		
End stage	End-stage renal disease (persistent failure > 3 months)		

AKI: acute kidney injury; RIFLE: risk, injury, failure, loss, end-stage kidney disease; pRIFLE: pediatric RIFLE; nRIFLE: neonatal RIFLE; GFR: glomerular filtration rate; UO: urine output.

extremely variable owing to the different diagnostic criteria used in defining the disease. Some studies indicate a range of incidence from 8 to 24% among neonates hospitalized in NICUs [1, 2], a third of whom represented by those born preterm [3]. Although many cases properly treated recover from the injury, albeit with frequent long-term results [4], for the oliguric forms of AKI a mortality reaching 60% has been reported. This percentage increases when associated with congenital cardiac malformations or important kidney anomalies [1].

Risk factors and etiology

Risk factors for development of neonatal AKI include very low birth weight (less than 1,500 g), a low 5-minute APGAR score, maternal drug administration (nonsteroidal anti-inflammatory drugs and antibiotics), intubation at birth, respiratory distress syndrome, patent ductus arteriosus, sepsis, phototherapy and neonatal medication administration (nonsteroidal anti-inflammatory drugs, antibiotics, diuretics, etc.) [5]. These different etiological causes act through many different and sometimes common pathophysiological mechanisms.

Diagnosis and new biomarkers

Despite the different international classification systems, AKI diagnosis is still a problem for pediatric and neonatal ages. It is in fact based on two parameters, SCr (marker of GFR) and UO, which are late consequences of injury and not markers of the injury itself: in particular, SCr concentrations may not change until 25-50% of the kidney function has already been lost and, at a lower GFR, SCr will overestimate renal function owing to tubular secretion of creatinine. The use of SCr in the diagnosis of AKI is also subject to different limitations in the neonatal period: in the first 48-72 hours of life the neonatal SCr reflects the mother's and not the infant's renal function and these values may decline at varying speeds over days, depending on gestational age [10]. Bilirubin levels in the neonatal period may remain high for some days after birth and, if the Jaffe method of SCr is used, this may alter its interpretation [11, 12]. As concerns UO, it must be taken into account that AKI in neonates is more frequently non-oliguric [10]. Moreover, the total body water content is greater in newborns than in adult patients: especially in preterm infants total body water can be as high as 80% of bodyweight [13]. This difference in water content, in addition to immature tubular development, may explain why UO in newborns is normally greater than in other populations. It has also been demonstrated that UO of less than 0.5 mL/kg per hour is a non-sensitive marker of AKI and this level must be increased up to 1.5 mL/kg per hour [8]. For these reasons the most recent studies on AKI have focused on identifying new biomarkers, characterized as early, noninvasive and sensitive indicators of AKI. Currently, the most promising early noninvasive biomarkers of AKI are serum and urinary neutrophil gelatinase-associated lipocalin (NGAL) [14], urinary interleukin-18 (IL-18) [15], kidney injury molecule-1 (KIM-1) [16, 17], and serum cystatin C [18]. Normal values in children are available [19]. The diagnostic use of these markers, singly or together, may improve our ability to diagnose AKI and improve its outcome. Results of interest for early identification of novel markers of AKI have been obtained with metabolomics, considered the most innovative of the "omics" sciences. In a recent study by Atzori et al., newborns and infants with nephrouropathies (renal dysplasia, vesicoureteric reflux, urinary tract infections and AKI) were distinguished from healthy children with a magnetic resonance study of the metabolic profiling of urine [20]. Berger et al. applied a metabolomic analysis for the study of kidney injury with complications deriving from heart-lung surgery in a group of neonatal and pediatric patients, enabling a timely diagnosis of this complication [21].

Pathophysiological classification

The causes of neonatal AKI are multiple and the three classic categories into which they are divided are: pre-renal, renal (intrinsic or organic) and post-renal.

Pre-renal acute kidney injury

Pre-renal AKI (also known as vasomotor nephropathy) is the most common form in the neonatal period, with an incidence of 85% of cases of AKI [22, 23]. Injury, typically functional and not anatomic, is secondary to pathological states that reduce directly or indirectly the volume of arterial blood (cardiac insufficiency, severe systemic vasodilatation, hypovolemia). The kidney is normally able to compensate for physiological variations in arterial blood pressure and maintain renal blood flow (RBF) and GRF constant by means of an intrinsic system of "self-regulation"

("myogen" and "tubuloglomerular feed-back"). In presence of a serious and sudden hypovolemia, the organism reacts at the systemic level with a neuroendocrine response:

- the sympathetic adrenergic system is activated and produces a redistribution of blood volume that ensures suitable perfusion to vital organs such as the brain and heart by limiting the supply to muscles, skin, visceral organs and kidney; it increases heartbeat, myocardial contractibility and there is lung hyperventilation;
- the endocrine compensation of hypoperfusion causes the secretion of a series of hormones having a metabolic action and control over total blood volume: vasopressin (neurohypophysis), adrenocorticotrope and somatotrope (adeno-hypophysis), cortisol (adrenal cortex), glucagon (endocrine pancreas) and activation of the renin-angiotensin system (kidney).

At the local kidney level the combined action of different vasoactive substances, such as the catecholamines, the renin-angiotensin-aldosterone system (RAAS), the prostaglandins (PG), the endothelin (ET), nitric oxide (NO), adenosin (AD), thromboxane (TXA2) and atrial natriuretic peptide (ANP), causes glomerular vasodilatation (kidney-protective) and glomerular vasoconstriction (kidney-aggressive): the delicate balance of these factors (vasodilation-vasoconstriction) regulates and stabilizes RBF and GRF. When a state of AKI continues or is not properly treated, an imbalance is created among the different renal vasoactive factors, with a prevalence of the phenomena of preglomerular vasoconstriction and postglomerular vasodilation which, associated with an increased retention of water and salt secondary to the increase in the circulation of aldosterone and vasopressin, cause a state of kidney imbalance with a reduction of GRF. Hypotension and hypovolemia are the most common causes of neonatal AKI. They can be caused by primary cardiac insufficiency and be a part of a hypoxic-ischemic syndrome, or may be the consequence of a wide variety of neonatal pathophysiological situations [23]. A serious hypoxia following severe respiratory distress also accompanies hypotension and hypovolemia which, by negatively influencing glomerular hemodynamics, may lead to AKI [24, 25]. Hypercapnia and acidosis, commonly found in such situations, contribute to aggravating renal dysfunction [26], just as recourse to mechanical ventilation may bring about a decrease in venous return and cardiac output which combine to worsen hypovolemia and hypotension [24]. Septic shock is associated with systemic peripheral vasodilation and systemic hypotension, with secondary renal vasoconstriction by activation of the sympathetic nervous system and the release of a series of vasoactive mediators [23, 27] such as RAAS, ET, NO and TXA2. During pregnancy or in the neonatal period the use of some drugs, such as the non-steroidal anti-inflammatory drugs (NSAIDs), may lead to AKI through a common pathological mechanism of renal vasoconstriction. NSAIDs (e.g. indomethacin used in persistence of the ductus arteriosus) act by blocking cyclooxygenase (COX) and the prostaglandin synthase, substances having a strong vasodilating action [28]. During treatment with indomethacin or ketoprofen (both non-selective COX inhibitors), administered in the prenatal period as tocolytics or maternal pain killers, or to the neonate to promote closure of the ductus arteriosus, important reductions of RBF and GRF have been observed. ACE-inhibitors (captopril and enapril) are used in the treatment of hypertension both during pregnancy and in the neonate [29]. These drugs, by blocking the synthesis of angiotensin II (AG II), create a situation of potential danger for the kidney: in fact, both in the fetus and the neonate AG II plays a role of primary importance in maintaining RFG and GRF [30]. Still, among frequently prescribed nephrotoxic drugs, we must keep in mind antibiotics such as the aminoglycosides and antifungals, such as amphotericin B which, besides having a direct cytotoxic action, also act as renal vasoconstrictors [31, 32].

In the pre-renal form, the kidney will maintain:

- a valid capacity to concentrate urine (specific weight > 1,018 and osmolarity > 500 mOsm);
- reduced concentration of urinary sodium (< 10 mEq/L) with a fractional excretion of sodium (FENa) < 2%;
- substantially negative urinary sediment;
- increase in the serum azotemia/creatinine ratio.

Renal acute kidney injury

Renal AKI is the form that by definition accompanies an intrinsic organic injury to the renal parenchyma; it has an incidence of approximately 11% [22, 23]. Anatomopathologically, it is characterized by the presence of a tubular lesion named "acute tubular necrosis" (ATN). While in the pre-renal form there remains a postglomerular blood flow sufficient to prevent the onset of

tissue injury, in this case, following a serious and prolonged ischemia, a series of anatomic alterations takes place that may diffusely involve the entire nephron. If the effects of the different pathologies that cause pre-renal AKI (hypoxic/ischemic syndrome, sepsis…) last a long time or they are not treated properly, they may evolve into a true form of "renal" insufficiency, with intrinsic damage that can be documented histopathologically. Thrombosis of renal vessels may be the cause of renal "organic" distress. Thrombosis of the renal artery is often a complication of the positioning of an umbilical catheter [33]: thrombotic formations that form on the catheter surface may cause emboli that localize in the renal arteries and produce areas of parenchymal infarction. If the thrombosis is bilateral, it may present clinically with an AKF. Thrombosis of the renal vein is not frequent: its incidence is approximately 2.2 per 100,000 live births [34]. In the neonatal period its predisposing conditions are found in states of blood concentration (dehydration, polycythemia), sepsis, perinatal asphyxia and congenital deficit of protein C. The bilateral form is associated with irreversible renal insufficiency. The nephrotoxic action of certain drugs may come about not only through the vasomotor mechanisms described above, but also with a direct toxic action on the tubular epithelium, as in the case of the aminoglycosides that inhibit lysosomal phospholipase with tubular phospholipidose and cell necrosis or, as recently reported, through the use of intravenously administered immunoglobulin.

In the pre-renal form, the kidney will maintain:

- diluted urine typically iso-osmotic with the plasma (specific weight < 1,010 and osmolarity < 300 mOsm);
- high concentration of sodium (> 30 mEq/L) and a FENa > 2.5-3%;
- urinary sediment with cylinders of red blood cells and tubular cells;
- serum azotemia/creatinine ratio of 1:1.

Post-renal acute kidney injury

Post-renal AKI is the least frequent form in the neonatal period, with an incidence of 3% of cases [22, 23]: it originates from the presence of an obstacle in urinary outflow. The obstruction causes ARF if it is able to block the urinary flow in both kidneys, as in the case of the persistence of the posterior urethra valve, or when the kidney contralateral to the obstruction is not functioning.

Therapy and prognosis

The ideal therapy for correcting "vasomotor nephropathy" must immediately correct the events that determine its development and block any precipitating factors that may be present before the onset of an intense and lasting renal vasoconstriction. Research is moving in this direction by experimenting on molecules capable of contrasting the endogenous vasoconstrictors and favoring the vasodilating factors: several experimental studies have emphasized the role of the ACE-inhibitors, which have a direct influence on glomerular circulation, blocking AG II mediated vasoconstriction [35] and an indirect influence that allows the dilatory action of AD to take place on the efferent arteriole [36]. The efficacy of the antagonists of free radicals [37] and calcium antagonists [38] also appears to be demonstrated, while the effects of the blocking of ET on the protection of the microcirculation are scarce: although it is a hundred times more powerful than adrenalin, ET responds to dose-dependent mechanisms that have not yet been clarified. Theophillin appears to have an important therapeutic effect in the prophylaxis of AKI in the post-asphyxial neonate. Theophillin, by antagonizing the AD receptors, is capable of contrasting renal vasoconstriction both preventively and during AKI (thus limiting injury and allowing a faster functional recovery) [39-41]. Despite the many and promising studies on neonates (preterm and term), theophillin still does not have an official role in the guidelines for the treatment of AKI and its use requires further research. Instead, a series of support measures to be applied during AKI are of indisputable therapeutic value: management of liquids, blood pressure monitoring, respiratory support, prevention of glycemic disturbances, limitation of the use of nephrotoxic drugs and careful monitoring of their serum levels.

There are few studies on the long-term prognosis of neonatal AKI. The available works describe the possibility of long-term kidney disturbances, such as chronic renal insufficiency, hypertension and a defect in renal concentration. Therefore, it is important to emphasize the need for a prolonged and careful follow-up of all neonates who suffered from AKI, especially if they were born preterm [42]. **Tab. 2** lists the elements that the kidney requires to function properly. In general terms, from the prognostic viewpoint we distinguish AKI with conserved diuresis (with a reduction in weight) for which we are more optimistic since survival is good,

Table 2. What does the kidney need to function properly?

- Water, in pre-renal forms (imagine that the kidney is like a sponge – it is at home in the water)
- Oxygen (the tubule in particular, which has an extremely high metabolic consumption)
- Calories (practical dilemma: if we provide calories, we have an overload of volume; if we reduce volume, we give few calories)
- Sodium (sodium is not only a growth factor for the organism, but is essential for the proper functioning of the kidney)
- Adequate protidemia
- Possible diuretic at a generous dose

Attention to: liquids, blood pressure, respiratory support, glycemic distress, nephrotoxic drugs

and AKI with contracted diuresis (oligo-anuria with weight increase): in the latter case we are "chin-deep in water" since survival is poor, especially in presence of multiple organ failure.

At present, many experimental studies are under way (on animals and humans) involving metabolomics, a methodology that appears to be especially promising in the study of AKI, in the early diagnosis of the form, the definition of its severity and the monitoring of its progress, as well as in the revealing of nephrotoxicity. In particular, metabolomics appears to possess those predictive characteristics that may in the near future rewrite the history of AKI [43-46].

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Stapleton FB, Jones DP, Green RS. Acute renal failure in neonates: incidence, etiology and outcome. Pediatr Nephrol. 1987;1:314-20.
2. Hentschel R, Lodige B, Bulla M. Renal insufficiency in the neonatal period. Clin Nephrol. 1996;46:54-8.
3. Agras PI, Tarcan A, Baskin E, Cengiz N, Gurakan B, Saatci U. Acute renal failure in the neonatal period. Renal Failure. 2004;26(3):305-9.
4. Abitbol CL, Bauer CR, Montane B, Chanda J, Duara S, Zilleruelo G. Long term follow-up of extremely low birth weight infants with neonatal renal failure. Pediatr Nephrol. 2003;18(9):887-93.
5. Cataldi L, Leone R, Moretti U, De Mitri B, Fanos V, Ruggeri L, Sabatino G, Torcasio F, Zanardo V, Attardo G, Riccobene F, Martano C, Benini D, Cuzzolin L. Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study.Arch Dis Child Fetal Neonatal Ed. 2005;90(6):F514-9.
6. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure-definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the acute dialysis quality initiative (ADQI) group. Critical Care. 2004;8(4):R204-12.
7. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71(10):1028-35.
8. Bezerra CT, Vaz Cunha LC, Libório AB. Defining reduced urine output in neonatal ICU: importance for mortality and acute kidney injury classification. Nephrol Dial Transplant. 2013;28(4):901-9.
9. Ricci Z, Ronco C. Neonatal RIFLE. Nephrol Dial Transplant. 2013;28(9):2211-4.
10. Jetton JG, Askenazi DJ. Update on acute kidney injury in the neonate. Curr Opin Pediatr. 2012;24(2):191-6.
11. Lolekha PH, Jaruthunyaluck S, Srisawasdi P. Deproteinization of serum: another best approach to eliminate all forms of bilirubin interference on serum creatinine by the kinetic Jaffe reaction. J Clin Lab Anal. 2001;15(3):116-21.
12. Rajs G, Mayer M. Oxidation markedly reduces bilirubin interference in the Jaffé creatinine assay. Clin Chem. 1992;138(12):2411-3.
13. Hartnoll G, Bétrémieux P, Modi N. Body water content of extremely preterm infants at birth. Arch Dis Child Fetal Neonatal Ed. 2000;83(1):F56-9.
14. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol. 2003;14(10):2534-43.
15. Parikh CR, Mishra J, Thiessen-Philbrook H, Dursun B, Ma Q, Kelly C, Dent C, Devarajan P, Edelstein CL. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int. 2006;70:199-203.
16. Dhanireddy S, Altemeier WA, Matute-Bello G, O'Mahony DS, Glenny RW, Martin TR, Liles WC. Mechanical ventilation induces inflammation, lung injury, and extra-pulmonary organ dysfunction in experimental pneumonia. Lab Invest. 2006;86:790-9.
17. Liangos O, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H, MacKinnon RW, Li L, Balakrishnan VS, Pereira BJ, Bonventre JV, Jaber BL. Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol. 2007;18:904-12.
18. Trof RJ, Di Maggio F, Leemreis J, Groeneveld AB. Biomarkers of acute renal injury and renal failure. Shock. 2006;26(3):245-53.
19. Finney H, Newman DJ, Thakkar H, Fell JM, Price CP. Reference ranges for plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. Arch Dis Child. 2000.82:71-5.
20. Atzori L, Antonucci R, Barberini L, Locci E, Cesare Marincola F, Scano P, Cortesi P, Agostiniani R, Weljie A, Lai A, Fanos V. 1H NMR-based metabolic profiling of urine from children with nephrouropathies. Front Biosci (Elite Ed). 2010;2:725-32.

21. Beger RD, Holland RD, Sun J, Schnackenberg LK, Moore PC, Dent CL, Devarajan P, Portilla D. Metabonomics of acute kidney injury in children after cardiac surgery. Pediatr Nephrol. 2008;23(6):977-84.
22. Hentschel R, Lodige B, Bulla M. Renal insufficiency in the neonatal period. Clin Nephrol. 1996;46:54-8.
23. Toth-Heyn P, Drukker A, Guignard JP. The stressed neonatal kidney: from pathophysiology to clinical management of neonatal vasomotor nephropathy. Pediatr Nephrol. 2000;14:227-39.
24. Guignard JP, Torrado A, Mazouni SM, Gautier E. Renal function in respiratory distress syndrome. J Pediatr. 1976;88(5):845-50.
25. Karlowicz MG, Adelman RD. Non oliguric and oliguric acute renal failure in asphyxiatd term neonates. Pediatr Nephrol. 1995;9:718-22.
26. Heijden AJ, Guignard JP. Effect of hypercapnic acidosis on renal function in the newborn rabbit. Pediatr Res. 1986;20:798-801.
27. Badr KF. Sepsis-associated renal vasoconstriction: potential targets for future therapy. Am J Kidney Dis. 1992;20(3):207-13.
28. Musu M, Finco G, Antonucci R, Polati E, Sanna D, Evangelista M, Ribuffo D, Schweiger V, Fanos V. Acute nephrotoxicity of NSAID from the foetus to the adult. Eur Rev Med Pharmacol Sci. 2011;15(12):1461-72.
29. Russo A, Mirani A, Periman J, Miller S. Enalapril-induced acute kidney injury in neonates. J Neonatal Perinatal Med. 2013;6(2): 179-81.
30. Chevalier RL. Mechanisms of fetal and neonatal renal impairment by pharmacologic inhibition of angiotensin. Curr Med Chem. 2012;19(27):4572-80.
31. van den Anker JN, Allegaert K. Pharmacokinetics of aminoglycosides in the newborn. Curr Pharm Des. 2012;18(21):3114-8.
32. Le J, Adler-Shohet FC, Nguyen C, Lieberman JM. Nephrotoxicity associated with amphotericin B deoxycholate in neonates. Pediatr Infect Dis J. 2009;28(12):1061-3.
33. Boo NY, Wong NC, Zulkifli SS, Lye MS. Risk factors associated with umbilical vascular catheter-associated thrombosis in newborn infants. J Paediatr Child Health. 1999;35:460.
34. Lau KK, Stoffman JM, Williams S, McCusker P, Brandao L, Patel S, Chan AK; Canadian Pediatric Thrombosis and Hemostasis Network. Neonatal renal vein thrombosis: review of the English-language literature between 1992 and 2006. Pediatrics. 2007;120(5):e1278-84.
35. Huet F, Semama DS, Gouyon JB, Guignard JP. Protective effect of perindoprilat in the hypoxemia-induced renal dysfunction in the newborn rabbit. Pediatr Res. 1999;45(1):138-42.
36. Guignard JP, Semama D, John E, Huet F. Acute renal failure. Crit Care Med. 1993;21(9 Suppl):S349-51.
37. Pedrotti A, Bonjour JP, Guignard JP. Protection from hypoxemia-induced renal dysfunction by the thiophosphate WR-2721. Kidney Int. 1992;41(1):80-7.
38. Guignard JP, Walliman C, Gautier E. Prevention by verapamil of hypoxemia-induced renal vasoconstriction. Kidney Int. 1981;20:139.
39. Bhat MA, Ahah ZA, Makhdoomi MS, Mufti MH. Theophylline for renal function in term neonates with perinatal asphyxia: a randomized, placebo-controlled trial. J Pediatr. 2006;149(2): 180-4.
40. Cattarelli D, Spandrio M, Gasparoni A, Bottino R, Offer C, Chirico G. A randomised, double blind, placebo controlled trial of the effect of theophylline in prevention of vasomotor nephropathy in very preterm neonates with respiratory distress syndrome. Arch Dis Child Fetal Neonatal Ed. 2006;91(2): F80-4.
41. Eslami Z, Shajari A, Kheirandish M, Heidary A. Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia. Iran J Kidney Dis. 2009;3(4):222-6.
42. Polito C, Papale MR, La Manna A. Long-term prognosis of acute renal failure in the full-term neonate. Clin Pediatr (Phila). 1998;37(6):381-5.
43. Mussap M, Noto A, Fanos V, Van Den Anker JN. Emerging biomarkers and metabolomics for assessing toxic nephropathy and acute kidney injury (AKI) in neonatology. Biomed Res Int. 2014;2014:602526.
44. Mussap M, Antonucci R, Noto A, Fanos V. The role metabolomics in neonatal and pediatric laboratory medicine. Clin Chim Acta. 2013;426:127-38.
45. Fanos V, Noto A, Caboni P, Pintus MC, Liori B, Dessì A, Mussap M. Urine metabolomic profiling in neonatal nephrology. Clin Biochem. 2014;47(9):708-10.
46. Fanos V, Fanni C, Ottonello G, Noto A, Dessì A, Mussap M. Metabolomics in adult and pediatric nephrology. Molecules. 2013;18(5):4844-5.