Acute kidney injury in neonatal age

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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.

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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** | **pRIFLE and nRIFLE** | **pRIFLE** | **nRIFLE** |
| **RIFLE** | | | | |
| **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 GFR constant by means of an intrinsic system of “self-regulation”
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), thrombomaxane (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 vasodilatation 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 vasodilatation 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,
The Authors declare that there is no conflict of interest.

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References


