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Neonatal acute kidney injury – Severity and recovery prediction and the role of serum and urinary biomarkers☆

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ABSTRACT

Neonatal acute kidney injury is common, in part due to incomplete renal maturation and also due to frequent exposure to risk factors for acute kidney injury such as perinatal asphyxia, extracorporeal-membrane-oxygenation, cardiac surgery, sepsis, prematurity and nephrotoxicity. However the current method by which acute kidney injury is diagnosed is sub-optimal and not universally accepted which impairs the accurate estimation of the true incidence of neonatal acute kidney injury. Serum Cystatin-C, urinary NGAL, KIM-1 and IL-18 are promising neonatal acute kidney injury biomarkers however the diagnosis of acute kidney injury remains serum creatinine/urine output-based in many studies. Emerging biomarkers which require further study in the neonatal population include netrin-1 and EGF. Increased awareness amongst clinicians of nephrotoxic medications being a modifiable risk factor for the development of neonatal acute kidney injury is imperative. The burden of chronic kidney failure following neonatal acute kidney injury is unclear and requires further study.

1. Introduction

Acute kidney injury (AKI), previously known as acute renal failure, is defined as a sudden decline in kidney function accompanied by an acute and reversible increment in serum creatinine (SCr) levels associated or not with a reduction in urine output (UO) and resulting in derangements in fluid balance, electrolytes and waste product clearance [1,2]. The diagnosis of AKI is reliant on a rise in SCr or decrease in UO both of which are suboptimal markers of renal injury. Considerable research has been directed at developing a more standardised and accurate definition of AKI and the neonatal modified KDIGO criteria are gaining acceptance [3]. The incidence of neonatal AKI in published studies is quite variable (6.5% to 17.7%) depending on the definition of AKI employed [4,5].

Perinatal asphyxia (PA), sepsis, congenital heart disease (CHD) surgery, prematurity, nephrotoxicity and respiratory failure requiring extracorporeal membrane oxygenation (ECMO) constitute the most common causes of AKI in the neonatal period. The approximate rates of AKI associated with each of these pathologies are as follows: 38–41.7% in PA; 64% in infants receiving ECMO; 62–64% in CHD surgery; 6.1–6.8% in sepsis; 18– (VLBW)39.8% in prematurity i.e. very low birth weight infants; 26.2% in VLBW infants with nephrotoxicity [6–9].

Considering the limitations associated with defining neonatal AKI by rising SCr values and/or decreasing UO, the search for accurate, reliable, sensitive and specific biomarkers of neonatal AKI is intensifying. Serum and urinary neutrophil gelatinase-associated lipocalin (NGAL), cystatin-C (CysC), urinary kidney injury molecule-1 (KIM-1), urinary interleukin-18 (IL-18), urinary epidermal growth factor (EGF) and urinary netrin-1 are of particular interest in the neonatal population. In the following paragraphs, a review of the aetiology of neonatal AKI and the merits of each aforementioned biomarker in the context of the common causes of neonatal AKI will be discussed.

2. Hypoxia-ischaemia related AKI

PA is one of the most common causes of neonatal AKI. Redistribution of cardiac output occurs post an asphyxial insult and in order to maintain cerebral, cardiac and adrenal perfusion, renal blood flow decreases. Hypoperfusion results in a prerenal failure stage which can progress to acute tubular necrosis and parenchymal injury. Furthermore, hypoxia-ischaemia can release reactive oxygen species into the circulation and this free radical storm can further damage presensitised renal tissue [1,10]. Application of the new neonatal modification of the KDIGO/AKIN criteria by three recent studies, gives an incidence of AKI in 38–41.7% of PA infants [11–13].

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Human CysC is a low molecular weight protein, belonging to the cystatin superfamily of protease inhibitors, which is produced at a constant rate in all nucleated cells. CysC is freely filtered through the glomerular membrane, then completely reabsorbed and degraded by the proximal tubule. Serum CysC (sCysC) is being promoted as a more accurate estimate of neonatal glomerular filtration rate (GFR) [14]. sCysC levels have been shown to be significantly higher in severely asphyxiated infants compared to mild-moderately asphyxiated newborns. Neurological follow-up during the first year of life found that more severe neurodevelopmental deficits were associated with significantly higher sCysC levels on day of life (DOL) 3 [15]. Furthermore, umbilical and DOL 3 sCysC levels were shown to be significantly higher in infants exposed to PA (n = 50) compared to controls (n = 50). Area under the receiver operating characteristic curve (AUROC) for prediction of AKI was excellent for both umbilical and DOL 3 samples (0.92 and 0.7) [16]. However in a smaller study conducted by Sarafidis et al. 2 years previously, sCysC levels were significantly higher in PA infants (n = 13) compared to controls (n = 22) only on DOL 1 and not at later time points (DOL 3 and 10) [17]. In contrast, PA infants had significantly higher urinary CysC (uCysC) levels at all time points compared to controls, suggesting that uCysC may be a more sensitive marker of perinatal hypoxia-ischaemia. Although not a distinct term PA infant cohort, Li et al. and Askenazi et al. showed that uCysC was highly predictive of AKI in an unwell neonatal population with AUROC of 0.92 and 0.82 respectively [4,18].

NGAL is a ubiquitous 25-kDa protein covalently bound to gelatinase from human neutrophils and a member of the lipocalin superfamily with various immunological functions. At the early phase of ischaemia-induced AKI there is a rapid up-regulation of NGAL mRNA in Henle's loop and proximal tubules, causing an increase in the synthesis and excretion of NGAL into the urine, constituting the renal pool of total body NGAL. Other non-renal tissues release NGAL into plasma following ischaemic injury and this constitutes the systemic pool of NGAL. In normal conditions, serum NGAL (sNGAL) is filtered by the glomerulus and rapidly reabsorbed by the proximal tubule [19]. sNGAL's role in prediction of multifactorial neonatal AKI was recently subjected to a systematic review and meta-analysis which identified only 5 eligible studies comprising 159 critically ill neonates [20]. The AUROC was 0.87 and overall pooled sensitivity and specificity of all studies were 0.81 (95% CI 0.7–0.89) and 0.86 (95% CI 0.73–0.93). The slightly lower sensitivity compared to specificity and an approximate 19% false-negative rate infers that another biomarker may be required to improve sensitivity when an infant tests NGAL-positive for AKI.

NGAL prediction of AKI in a specific PA population has been assessed by a number of studies. Sarafidis et al. demonstrated that asphyxiated infants have significantly higher sNGAL levels compared to controls and PA-AKI infants have significantly higher levels compared to PA-no-AKI infants [17]. In a similarly small sized study, Raggal et al. demonstrated that sNGAL measured at 6 h of life was significantly higher in asphyxiated term newborns (n = 30) (median concentration 95 ng/mL) compared to controls (n = 20) (median concentration 39.75 ng/mL). sNGAL levels also correlated positively with severity of HIE. Within the HIE group, sNGAL levels were significantly higher in neonates diagnosed with AKI defined as SCr > 133 μmol/L for >48 h than non-AKI infants. A cut-off value of 157 ng/mL for sNGAL was suggested as indicative of AKI in asphyxiated term newborns with a sensitivity and specificity of 83.3% and 94.4% [21].

Asphyxiated infants have also been demonstrated to have significantly higher concentrations of urinary NGAL (uNGAL) compared to controls. While asphyxiated neonates with AKI have significantly higher uNGAL levels compared to controls over the first 10 days of life. Furthermore, Sarafidis et al. found significantly higher uNGAL levels in the PA-no-AKI group compared to controls on DOL 10 perhaps eluding to ongoing subclinical AKI which is not identified by the flawed SCr based definition of AKI [17]. More recently, Essajee et al. showed uNGAL to be a good predictor of AKI in 108 term asphyxiated neonates with an AUROC of 0.724 when a cut-off of 250 ng/mL was used (56% AKI prevalence). Furthermore, a uNGAL level > this cut-off value on day 1 was associated with severe HIE and mortality with an identical odds ratio (OR) = 8.9 [22]. Hoffman et al. included 25 infants with HIE receiving TH in a study investigating a panel of urinary biomarkers for ability to predict AKI in critically ill neonates [23]. The HIE group had significantly higher uNGAL levels compared to controls at all 3 time points (baseline = within 24 h of initiation of TH, at 48 h after initiation of TH and at >24 h post rewarming). However in contrast to previous studies, the uNGAL levels were not significantly different between infants with and without AKI and the ROC curves showed poor sensitivity and specificity to diagnose AKI. The panel of biomarkers also included EGF, which is a polypeptide hormone that binds to its receptor epidermal growth factor receptor (EGFR). Activation of EGFR in the proximal tubule of the kidney plays an important role in the recovery phase after acute kidney injury [24]. Urinary EGF levels in the recovery phase following HIE (when tubular turnover could be expected to be at its maximum rate) were significantly elevated in the AKI group compared to the non-AKI HIE controls and showed good sensitivity and specificity for identifying those infants with ongoing AKI.

IL-18 is a pro-inflammatory cytokine released by the proximal tubule into urine in response to tubular injury [4]. IL-18 has been infrequently studied in infants with PA. Li et al. demonstrated that urinary IL-18 levels were significantly higher in non-septic critically ill infants with AKI compared to controls and was predictive of AKI even after controlling for demographic variables such as gestational age, gender, birth weight etc. (OR = 6.15) [4].

KIM-1 is a type-1 transmembrane glycoprotein that is not detected in urine under normal conditions. Following ischaemic or toxic injury, there is epithelial cell dedifferentiation and KIM-1 is shed from proximal tubule cells and secreted into the urine where it enhances phagocytosis of apoptotic and necrotic cells [19]. Two small studies of urinary AKI biomarkers in asphyxiated newborns showed that urinary KIM-1 (uKIM-1) did not differentiate significantly between asphyxiated and control infants, or between AKI and no-AKI infants [17,18]. However, a more recent, larger study by Cao et al. demonstrated significantly higher levels of uKIM-1 in asphyxiated infants (n = 80) compared to controls (n = 40) within 48 h of birth [25]. Within the PA group, infants with AKI had significantly higher levels of uKIM-1 than no-AKI infants and the AUROC for prediction of AKI within 12 h of birth was 0.90. The results of this larger, more robust study suggest that uKIM-1 may be an early, promising marker of AKI following PA.

Netrins are a family of laminin-like proteins, which were initially identified for their role in embryonic axonal guidance. In adult studies, urinary netrin-1 (uNetrin-1) levels have been shown to rise in response to acute kidney injury and at a faster rate than traditional markers of renal impairment, highlighting a potential clinical role for netrin-1 as a biomarker of renal function [26]. Cao et al. also showed that asphyxiated infants had significantly higher levels of uNetrin-1 within 48 h of birth compared to controls and uNetrin-1 was predictive of AKI (AUROC = 0.88) [25]. There are few studies which examine netrin-1 in the neonatal AKI setting however Cao et al.'s study supports the need for more in depth analysis of this promising AKI biomarker.

3. ECMO-related AKI

Irrespective of the indication for neonatal ECMO, these infants are critically unwell and are at high risk of AKI. Renal injury occurs both through the pathway of renal hypoperfusion secondary to systemic hypotension which can progress to acute tubular necrosis and secondly due to the inflammatory response and free radical environment that accompanies exposure to the extracorporeal circuit [27]. AKI incidence rates in newborns on ECMO have been reported to be as high as 64–71% with associated mortality rates for those neonates with more severe stages of AKI (Failure stage of RIFLE criteria) of 65–73% [28,29]. Neither of these studies examined biomarkers of AKI in this population of

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