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Drug Induced Acute Kidney Injury in Neonates

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Abstract

Purpose of review—Acute kidney injury (AKI) is an independent risk factor for morbidity and mortality in critically ill neonates. Nephrotoxic medication exposure is common in neonates. Nephrotoxicity represents the most potentially avoidable cause of AKI in this population.

Recent findings—Recent studies in critically ill children revealed the importance of recognizing AKI and potentially modifiable risk factors for the development of AKI such as nephrotoxic medication exposures. Data from critically ill children who have AKI suggests that survivors are at risk for development of chronic kidney disease. Premature infants are born with incomplete nephrogenesis and are at risk for chronic kidney disease (CKD). The use of nephrotoxic medications in the neonatal intensive care unit (NICU) is very common; yet the effects of medication nephrotoxicity on the short and long-term outcomes remains highly understudied.

Summary—The neonatal kidney is predisposed to nephrotoxic AKI. Our ability to improve outcomes for this vulnerable group depends on heightened awareness of this issue. It is important for clinicians to develop methods to minimize and prevent nephrotoxic AKI in neonates through a multi-disciplinary approach aiming at earlier recognition and close monitoring of nephrotoxin induced AKI.

Keywords

nephrotoxic medication; vancomycin; aminoglycosides; ibuprofen; NSAIDS; acyclovir; amphotericin B

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Introduction

Acute Kidney Injury (AKI) in the intensive care setting is an important contributing factor to the morbidity and mortality of critically ill neonates [1*, 2–4*,5]. Recent studies evaluating the epidemiology of AKI have shown that it is common in the neonatal intensive care unit (NICU) with incidence varying between 18–70%, depending on the studied population [3,4*–7]. Critically ill neonatal populations known to be at increased risk of developing AKI include those with congenital heart disease, perinatal asphyxia, sepsis, premature birth, and those who receive extra-corporeal membrane oxygenation. The current approach to diagnose AKI in neonates is based upon a rise in serum creatinine (SCr) or changes in urine output. SCr has a number of challenges as a biomarker for kidney function that results from the unique neonatal physiology including the presence of maternal creatinine, creatinine reabsorption in the proximal tubules, overall lower glomerular filtration rates (GFRs), and maturational differences. In recent years there has been an evolution in AKI definitions from arbitrary definitions to standardized staged definitions. The neonatal modified Kidney Diseases: Improving Global Outcomes (KDIGO) has been adopted by many researchers to define neonatal AKI (Table 1) [8]. This definition relies on a rise in SCr from a previous trough or a decrease in urine output, and defines three levels of AKI.

Utilizing modern definitions of AKI a number of studies have shown that AKI occurs commonly in critically ill newborns and is associated with adverse outcomes. In 2011, Koralkar et al reported an 18% incidence of AKI in very low birth weight (VLBW) infants. The mortality in infants with AKI was significantly higher than those without AKI (42% vs 5%, P< .001). After adjusting for potential confounders, those with AKI had a significantly higher chance of death (hazard ratio 2.4, 95% confidence interval [CI] 0.95–6.0; P< .06) [6]. AKI is a major complication in children who undergo cardiopulmonary bypass surgery. In a recent prospective multicenter study, AKI occurred in 64% of the neonates with congenital heart disease undergoing cardiopulmonary bypass. ICU length of stay and duration of mechanical ventilation were longer in those newborns who developed AKI [9]. In a multicenter study, noncardiac neonates on extracorporeal membrane oxygenation (ECMO) had an AKI incidence of 26%, and AKI was associated with an adjusted mortality rate that was 3.2 times higher [10]. These findings are similar to those reported by Gadepalli et al in neonates with congenital diaphragmatic hernia on ECMO where AKI occurred in 71% of neonates, and those with the highest stage of AKI had a mortality of 73% [3]. Another neonatal population at particularly high risk of developing AKI is those infants with perinatal asphyxia. A recent single-center study found that 36 (38%) of 96 newborns undergoing therapeutic hypothermia had AKI. Even after controlling for important potential confounders, children with AKI on average were ventilated 4 days longer (P< .001) and were hospitalized 3.4 days longer (P= .023) [11].

Although in most cases the etiology of AKI is multifactorial, many of the infants in the reported studies were exposed to nephrotoxic medications. Nephrotoxicity represents a potentially avoidable cause of AKI in neonates. In this review, we will summarize what is known about drug induced nephrotoxicity in neonates, discuss common nephrotoxic medications, and highlight the potential long-term implications of neonatal nephrotoxic AKI.

Nephrotoxin induced AKI

Nephrotoxic-medications are becoming increasingly recognized as a common and potentially modifiable cause of AKI in pediatric patients [12–15**]. In hospitalized children, predisposing factors such as age, pharmacogenetics, severity of illness, dosage, duration, and concomitant medication determine and influence the severity of nephrotoxic insult. There have been several recent studies in older children that have investigated the epidemiology impact of AKI induced by nephrotoxic medication. Moffett et al. showed that increasing total nephrotoxic-medication exposure and intensity of exposure, increased the predictive values for development of AKI in hospitalized non-critically ill children. In this cohort, higher age was noted as a protective factor, and therefore, infants were at higher risk of developing AKI; in addition, patients with AKI had an increased length of stay in hospital. They noted that the majority of nephrotoxic medications to which patients were exposed were antimicrobial agents (52%) [14].

Aminoglycosides exposure is a frequent cause of AKI. Zappitelli et al showed that one-third of patients exposed to aminoglycosides developed AKI in a cohort of non-critically ill hospitalized children, which resulted in longer stay and higher total hospital costs. Longer treatment, higher baseline estimated GFR, being on a drug (versus surgical) treatment, and prior aminoglycosides treatment were independent risk factors for AKI in this study [16].

Under a single-center, and now a multicenter collaborative, Goldstein et al. lead an initiative collaboration to address the issue of pediatric nephrotoxic AKI. The Nephrotoxic Injury Negated by Just-in-time Action (NINJA) mission statement is that “nephrotoxic medications should only be used for as long as they are needed”. NINJA is a surveillance program whereby all non-critically ill patients are screen for exposure to 3 or more nephrotoxic medications or 3 or more days of aminoglycoside exposure. Those who are identified as exposed using these criteria are monitored daily for SCr. Goldstein et al. showed that an electronic health record driven SCr nephrotoxin-AKI surveillance process resulted in a 42% reduction in the number of days with AKI (AKI intensity) [15**]. Additionally, these investigators also showed that implementation of daily SCr measurements as part of a hospital-wide quality initiative led to earlier and increased detection of aminoglycoside-associated AKI, compared to every other day SCr measurement, in a cohort of hospitalized patients with cystic fibrosis [17]. Despite the evidence that drug-induced renal dysfunction is a common condition in pediatrics, and that strategies to decrease the damage from nephrotoxic medications can improve outcomes, there is a paucity of information available regarding the epidemiology of this problem in neonates.

Neonatal nephrotoxic AKI

The neonatal kidney has complex developmental characteristics as nephron development continues until 34 to 36 weeks of gestational age; this could make understanding the pathophysiology, incidence and outcomes after nephrotoxic medications different in pediatric compared to adult patients. Aspects of the neonatal renal physiology that may increase the likelihood of nephrotoxicity include the fact that most of the medications are predominately excreted through the kidneys, and there is a progressive concentration of

filtered and secreted compounds in the tubular lumen [18]. Interestingly, the unique neonatal renal physiology may theoretically protect the kidney from some nephrotoxicity. For example, certain drugs requiring renal tubular transport as an initial toxic pathway (e.g., aminoglycosides, vancomycin) may not achieve their “full” toxic potential, as in an older child, because of immature transport function [19]. Additionally, nephrotoxic medication taken during fetal life or during postnatal nephrogenesis could interfere with nephron generation, contributing to a particular magnitude of damage. Such adjunctive damage could further increase the risk of CKD in children born prematurely [20].

The complex nature of neonatal critical illness often requires the use of multiple therapeutic agents, most of which are not labeled for use in infants because clinical trials for safety, dosing, and efficacy of drugs are lacking in this population. Neonates remain an understudied population. In the Food and Drug Administration (FDA) database for pediatric studies submitted between 1997 and 2010 involving 406 pediatric labeling changes, only 6% included new neonatal information [21]. A retrospective review of a national database showed that only 35% of the most commonly prescribed medications in the NICU are FDA approved for infants. In this large cohort, the 10 most commonly reported medications, by exposure, were ampicillin, gentamicin, caffeine citrate, vancomycin, beractant, furosemide, fentanyl, dopamine, midazolam, and calfactant. For extremely low birthweight (ELBW) infants, the 10 most commonly reported medications by exposure were gentamicin, ampicillin, caffeine citrate, vancomycin, furosemide, dopamine, beractant, indomethacin, fentanyl, and albuterol [22**].

In a recent investigation of very low birth weight (VLBW) infants, Rhone et al highlighted the degree by which neonates are exposed to nephrotoxic medications. In this study, 87% of neonates were exposed to at least one nephrotoxic medication, and on average these neonates were exposed to 14 days of nephrotoxic medications during their NICU stay. The greatest exposure occurred among the smallest, most immature infants [23**]. Clearly, the potential to cause harm from medications is present, and strategies to understand ways to mitigate this risk are greatly needed.

Nephrotoxic medications

Acyclovir

It is used in neonates for the treatment of herpes simplex viral infections and in suspected neonatal sepsis. Acyclovir is excreted in the urine through filtration and secretion, and is relatively insoluble in urine. Nephrotoxicity can be seen in 17–35% of patients and warrants diligent monitoring throughout treatment [24, 25*]. Acyclovir nephrotoxicity is classically attributed to tubular obstruction secondary to drug crystallization, but direct tubular toxicity from acyclovir metabolites may also contribute to nephrotoxic potential [26–29]. Furthermore, acyclovir is transported by shared organic acid transporters with certain beta-lactam antibiotics (particularly ceftriaxone), which may increase nephrotoxicity [28, 30]. Nephrotoxicity classically occurs within 48 hours of exposure and is more likely in those with impaired renal function, concurrent nephrotoxic exposures, and reduced intravascular volume. In order to mitigate the nephrotoxic potential, clinicians should aggressively hydrate

patients, administer the medication over 1–2 hours, adjust dose in those with decreased renal function, and avoid concurrent nephrotoxic medication exposure.

Aminoglycosides (AG) — still remain as a mainstay for the treatment of neonates with suspected sepsis or documented serious gram negative infections. The utilization of AG is complicated by nephrotoxicity and ototoxicity. AG are freely filtered into the urine and are almost entirely excreted by the kidneys [31**]. AG accumulate in the proximal tubules by endocytosis and cationic transporters [32]. Approximately 10–15% of filtered AG accumulate in the renal cortex in concentrations that may exceed measured systemic concentrations [33]. Intracellular AG damage proximal tubular cells by lysosomal accumulation, membrane disruption, disruption of protein production, disruption of mitochondrial adenosine triphosphate production, and oxidative stress [32]. AG toxicity may be also typified by distal tubular dysfunction, polyuria, and anti-diuretic hormone resistance.

AG nephrotoxicity is classically non-oliguric in nature and develops later in the treatment course. As a result of their impact on tubular function, AG induced nephrotoxicity may result in a number of electrolyte abnormalities including hypomagnesemia, hypokalemia, hypophosphatemia, and acidosis. Risk factors for nephrotoxicity applicable to neonates include low birth weight, concurrent nephrotoxic medications, prematurity, hypovolemia, sepsis, and hypoxic ischemic encephalopathy [31,34*]. At its most extreme, AG nephrotoxicity may lead to acute tubular necrosis, oliguria and complete renal failure.

Estimated rates of AG associated nephrotoxicity in neonates vary depending on the definition utilized and the population studied, but is generally lower than in older children and adults. The true incidence of AKI related to AG exposure is unclear in neonates, but epidemiological studies will benefit from the utilization of modern definitions. Recent studies have evaluated the impact of AG on urinary markers of proximal tubule damage. These studies have shown that AG exposure results in the elevation of urinary biomarkers, including those that signify proximal tubular damage, irrespective of rise in serum creatinine [31**,35*,36]. These data suggest there may be damage resulting from AG exposure that is not detected by a rise in serum creatinine, which warrants further study.

In adult studies the hierarchy of nephrotoxicity for AG is gentamicin > tobramycin > amikacin > netilimicin. In order to prevent toxicity practitioners should diligently monitor drug levels and renal function while on therapy. Because of differential accumulation of AG in the renal cortex, toxicity may occur despite therapeutic drug levels. In an effort to maximize therapeutic benefits and minimize toxicity, extended interval AG dosing regimens have been adopted. Extended interval dosing is recommended based on favorable pharmacokinetics, but has yet to be shown to impact rates of nephrotoxicity in neonates [37].

Amphotericin B

The frequency of neonatal fungal infections has been increasing in neonates and represents a source of significant morbidity and mortality in neonates. Amphotericin B is used as empiric therapy for neonatal fungal infections. Nephrotoxicity represents the most significant side effect to Amphotericin B and results from a combination of vasoconstriction and direct distal tubular toxicity [38]. The direct toxicity and increased tubular membrane permeability

accounts for the characteristic electrolytes abnormalities that can be seen with amphotericin B (hypokalemia, hyponatremia, acidosis hypomagnesemia). The nephrotoxicity associated with amphotericin B in neonates is typically milder than in older children and it is transient in nature, but may be associated with significant morbidity. Liposomal formulations of amphotericin B were developed to reduce the toxicity associated with amphotericin treatment and have been shown to be less nephrotoxic in neonates [39,40]. The reported incidence of nephrotoxicity utilizing liposomal formulations in neonates ranges from 0–20% and it is commonly transient in nature [39–41]. Risk factors for nephrotoxicity include longer treatment duration, nephrotoxic medications, and severity of illness [42,43]. The risk of nephrotoxicity can be diminished by avoiding concurrent nephrotoxic medication exposure and potentially by increasing sodium intake (> 4 mEq/kg/day) [44].

Angiotensin converting enzyme inhibitors (ACE)

The renin-angiotensin system (RAS) is critical to fetal renal development and contributes significantly to renal vascular resistance during the neonatal period through its vasoconstrictive activity. In the kidney angiotensin acts primarily as a vasoconstrictor at the efferent arteriole (post-glomerulus) to maintain glomerular filtration. The implications of blockade of the renin-angiotensin system on the developing fetus are well known and include a spectrum of disorders ranging from papillary atrophy to pulmonary hypoplasia and renal failure [45,46*]. These outcomes were worse with exposure to angiotensin receptor blockers and when the exposure occurred in the second and third trimesters. Given the potential deleterious impact on postnatal renal development, it may be appropriate to avoid the use of ACE-inhibitors in neonates < 32 weeks of age, in whom nephrogenesis may not be complete [47]. In a study of captopril treatment in neonates with congenital heart disease, AKI occurred in 14% of patients and was reversible in all patients [47]. AKI induced by ACE-inhibitors is typically reversible with dose adjustment, increased renal perfusion, or medication discontinuation. Since neonatal kidneys are known to be sensitive to RAS blockade, ACE inhibitors should be started at low doses and titrated slowly with diligent monitoring of electrolytes and renal function. In order to mitigate the risk of AKI with ACE inhibition practitioners should closely monitor intravascular volume (including those on diuretic therapy) and be cautious about concomitant utilization of non-steroidal anti-inflammatory drugs (NSAIDs).

Non-steroidal anti-inflammatory drugs (NSAID)

Neonates have high levels of circulating prostaglandins, which play an integral role in renal water clearance and afferent arteriolar vasodilatation. Prostaglandins are vasodilators and increase renal blood flow by vasodilation of the afferent arteriole. Prostaglandin levels are high during the neonatal period and act as a key counter-regulatory mechanism to offset the highly vasoconstrictive milieu following birth. Inhibiting prostaglandin synthesis can profoundly decrease neonatal renal blood flow and GFR, causing transient oliguria. Prenatal exposure to NSAID medications can adversely impact renal function with a range of effects from transient oliguria to oligohydramnios depending on timing and duration of exposure [48]. NSAID-induced AKI following birth is most frequently related to exposure to ibuprofen or indomethacin and is typically transient in nature; however, occasionally this may be complicated by oliguria, fluid overload, and electrolyte abnormalities. The

nephrotoxic side effects are less severe with ibuprofen [49–51]. In order to prevent NSAID induced AKI practitioners should ensure adequate intravascular volume, consider using the lowest effective dose, and avoid the use of concomitant nephrotoxic medications.

Vancomycin

The role of vancomycin as a nephrotoxin remains controversial, particularly in the context of monotherapy with appropriate medication levels [52,53*]. The exact mechanism of nephrotoxicity remains unclear, but animal models suggest that nephrotoxicity may be related to oxidative effects on the proximal tubule damage [54]. Risk factors for AKI in neonates who receive vancomycin include higher vancomycin troughs, concomitant nephrotoxins and/or diuretics, positive blood cultures, low birth weight, patent ductus arteriosus, and higher severity of illness [53*,55]. Animal models and adult studies have suggested that vancomycin used in conjunction with aminoglycoside or piperacillin-tazobactem may lead to increased nephrotoxicity [54,56*,57] Given the ability to monitor vancomycin levels and its potential for nephrotoxicity, vancomycin monitoring protocols should be instituted with a daily review of nephrotoxic medications.

Prevention of nephrotoxic associated AKI

There are currently no approved treatments for established AKI, and therapies are limited to the management of sequelae of AKI. In lieu of successful treatment strategies there has been renewed interest in the prevention of AKI. Nephrotoxic medication exposure, and by extension nephrotoxin associated AKI, represents an obvious area for intervention in neonates given the high exposure burden. In order to decrease the incidence of nephrotoxin associated AKI in neonates, the development of algorithms to screen, monitor and intervene to reduce harm produced by medication could significantly improve outcomes. These programs would regularly evaluate infants who are at risk for nephrotoxic injury, develop lab monitoring processes for those at risk, and institute intervention strategies to limit the damage caused by nephrotoxic medications. Such approach relies on daily evaluations by a multi-disciplinary team that includes input from nurses, physicians, residents, and pharmacists.

The most obvious first step in this algorithm is avoiding nephrotoxic medication when feasible, and identifying appropriate alternative medications. When nephrotoxic medications cannot be avoided a careful inventory of risk factors should be done, including: prior nephrotoxicity, renal function, severity of illness, volume status, nephrotoxic medication burden, and gestational age. The team should focus on mitigating modifiable risk factors when feasible, including reducing nephrotoxic burden, optimizing intravascular volume, reassessing diuretic need, avoiding harmful medication interactions (e.g., NSAIDs and ACE), and using the minimal effective dose (e.g. daily versus multiple-daily AG doses).

Once a patient is on nephrotoxic medication(s) diligent monitoring of kidney function becomes paramount. Regular monitoring of kidney function and drug levels (where applicable) should be protocolized to monitor for development and progression of AKI. Utilization of the electronic medical records represents a potential avenue for monitoring,

which has been successful in older pediatric patients. If AKI develops while on a nephrotoxic medication it is important to also consider other potential causes of AKI.

Long-term effects of prematurity and AKI on CKD

In recent years long-term follow-up data has begun to identify prematurity as a known risk factor for the development of chronic kidney disease. A meta-analysis performed by White et al. reported that premature infants (birthweight < 2500 grams) have nearly twice the odds of having low glomerular filtration rate, microalbuminuria, end-stage renal disease and hypertension than their term counterparts [58]. Carmody and Charlton recently published a comprehensive overview of the links between prematurity/low birth weight and subsequent chronic kidney disease in adulthood [59]. Preterm delivery disrupts nephrogenesis, which is normally not completed until approximately 34–36 weeks gestation. A small number of autopsy studies have suggested that nephrogenesis continues for only a short time after birth [60–62]. The remaining nephrons undergo hypertrophy to compensate for decreased nephron mass, and the resultant “hyperfiltration” eventually becomes deleterious and leads to glomerulosclerosis with sodium retention, systemic hypertension, proteinuria and progressive chronic kidney disease [63]. Thus, these infants are already “primed” for kidney injury/chronic kidney disease based on their premature birth.

The full impact of additional AKI events in the NICU on long-term kidney and health outcomes is not yet known. Previously, it was assumed that those who survived an episode of AKI would recover kidney function without long-term sequelae; however, recent data from animals [64], critically ill children [65,66]l, and adults with AKI suggest that survivors are indeed at risk for development of CKD. A meta-analysis by Coca et al. showed that adults with AKI have higher risk of developing incident CKD (pooled adjusted hazard ratio 8.8, 95% CI 3.1–25.5), end-stage kidney disease (pooled adjusted HR 3.1, 95% CI 1.9–5.0), and mortality (pooled adjusted HR 2.0, 95% CI 1.3–3.1) compared to patients without AKI [67].

The role that nephrotoxin-associated AKI plays in the development of CKD in this population is still unknown. Several case reports have documented that CKD occurs in infants who had AKI; however, these studies were small single center retrospective reports [68]. Unfortunately, follow up after AKI is not commonly done. In a study by Camody et al., 180 out of 455 neonates (40%) had at least one episode of AKI (75 had multiple episodes). Alarmingly, only 13.5 % of infants who were discharged home had a diagnosis of AKI on the hospital discharge summary, and no subjects were referred for follow up with a pediatric nephrologist [4*]. Large multi-center studies designed to determine which factors are associated with long-term CKD are greatly needed to define the most appropriate surveillance protocols as well as to identify those most at risk. This effort will provide us with the needed in-hospital AKI phenotype to determine the degree to which AKI may impact future development of CKD. In turn this will guide follow-up recommendations

Conclusions

Neonatal AKI occurs commonly in the NICU and is associated with adverse outcomes. While the exact rates of nephrotoxin-associated AKI remain unclear, the burden of nephrotoxin exposure in critically ill neonates is high and represents a potentially modifiable risk factor. In order to prevent and/or diagnose nephrotoxin a multi-disciplinary approach utilizing careful monitoring of nephrotoxic medications (i.e., burden, duration), drug levels, renal function, and risk factors (e.g., birthweight, volume status, etc.) is needed. Future work assessing nephrotoxic medications associated with development of AKI needs to focus on utilizing standardized definitions, risk stratification, role for surveillance utilizing the electronic medical record, and the long-term outcomes including the development of CKD in these patients.

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Key points

- Nephrotoxic medications are commonly prescribed to neonates.
- Nephrotoxic-associated AKI can have a profound impact on clinical outcomes in neonates.
- Because premature neonates are born with underdeveloped nephrons and low nephron numbers, the negative impact of nephrotoxins on renal outcomes may be substantial.
- Strategies to identify neonates who are expose to nephrotoxic medications, daily evaluation for signs of AKI, and strategies to prevent toxicity are likely to improve clinical outcomes and resource expenditure.

Table 1

Neonatal acute kidney injury KDIGO classification

Stage	SCr	Urine Output
0	No change in SCr *or* rise < 0.3 mg/dL	≥ 0.5 ml/kg/hour
1	SCr rise ≥ 0.3 mg/dl within 48hrs *or* SCr rise ≥ 1.5–1.9 X reference SCr* within 7 days	<0.5 ml/kg/hour for 6 to 12 hours
2	SCr rise ≥ 2 to 2.9 X reference SCr*	<0.5 ml/kg/hour for ≥ 12 hours
3	SCr rise ≥ 3 X reference SCr * *or* SCr ≥ 2.5 mg/dl** *or* Receipt of dialysis	<0.3 ml/kg/hour for ≥ 24 hours *or* anuria for ≥ 12 hours

Differences between the proposed neonatal AKI definition and KDIGO include:

* Reference SCr will be defined as the lowest previous SCr value

** SCr value of 2.5 mg/dl represents <10 ml/min/1.73m2