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EDITORIAL COMMENTARY

Diuretic use, acute kidney injury, and premature infants: the call for evidence-based guidelines

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Introduction

Acute kidney injury (AKI) is a common morbidity among infants cared for in the neonatal intensive care unit (NICU) and has been recognized to be associated with increased length of stay, risk of chronic kidney injury, and mortality. A series of publications derived from the Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study, a multicenter, retrospective cohort study of ill neonates, has provided a wealth of knowledge regarding the epidemiology of AKI in this population [1–3]. Notably, infants with AKI had a four-times higher independent odds of death and longer hospital length of stay than those without AKI [1]. Moreover, recent studies suggest AKI is a risk factor for the development of chronic kidney disease later in life [4, 5]. However, as evidence accrues regarding the role that AKI plays in the morbidity and mortality of critically ill neonates and infants, we continue to lack robust evidence-based guidelines for prevention and mitigation of this life-threatening event.

To understand the impact of AKI on the health of babies and ultimately to improve outcomes, we need a better appreciation of the risk factors for the development of AKI as well as current management approaches for infants once AKI has occurred. The management of oliguria and fluid overload is a key aspect of care of babies with AKI, and diuretics are often used in this context to promote urine output. Indeed, as shown in an article in this issue of *Pediatric Nephrology* by Mohamed and colleagues [6], the (off-label) use of diuretics in premature infants with AKI is common, occurring in 76% of premature infants with AKI in their cohort and with considerable variation in prescribing practices across centers. That such broad application occurs in the absence of either evidence-based clinical guidelines for use or robust outcomes data shines a light on an important area for improvement in the care of this vulnerable population.

Understanding the use of diuretics in neonates and infants with AKI

Mohamed and colleagues have utilized the Pediatric Hospital Information System (PHIS) database to enlighten providers regarding the utilization of diuretics in preterm infants with AKI [6]. Review of records from over 70,000 infants < 37 weeks gestation and admitted within the first week of life identified 2379 infants with AKI, using the International Classification of Disease, Tenth Revision, code N17 (acute kidney failure, unspecified). The severity or stage of AKI was not available nor were specific creatinine values. Multiple demographic variables were available and included in the analysis, as were diagnoses of oliguria/anuria and high-risk conditions associated with AKI (e.g., congenital heart disease and genitourinary structural abnormalities). As mentioned above, 76% (1801/2379) of infants with AKI received at least one dose of diuretics while only 16% (11,075/69,242) of those without a diagnosis of AKI were treated with this medication class. Among infants with AKI, treatment with diuretics was associated with younger gestational age and lower birthweight. For infants receiving diuretics (and 99% of these received furosemide), the median duration was 18 days, with slightly over half of these receiving diuretics for ≥ 5 consecutive days. In neonates with AKI, treatment with diuretics was significantly associated with increased mortality, need for mechanical ventilation, and length of stay. Interhospital variation in the use of diuretics was also high, with diuretics prescribed to less than half of patients with AKI in some hospitals to almost all patients with AKI in others

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(range 42–96%). While infants with AKI received diuretics at a far higher rate than those without AKI, the authors could not ascertain the reasons for diuretic administration or the timing of occurrence of AKI with dosing of diuretics. For example, infants with developing or established chronic lung disease may have been treated with diuretics for pulmonary purposes, and not in response to a diagnosis of AKI. The authors appropriately highlight that there are many questions to answer based on the data they have presented in this paper.

Is there a rationale for the widespread use of diuretics?

The relatively high use of diuretics in the NICU population has previously been established. In a review of a large national dataset (Pediatrix Medical Group data warehouse) from 1996 to 2005, Clark et al. reported furosemide to be the 7th most commonly prescribed drug in the NICU, with 8–9% of NICU patients receiving at least one dose [7]. A later analysis of this same database (1997–2011) found that 37% (39,357/107,542) of infants < 32 weeks gestation and < 1500 g birth weight were exposed to at least one diuretic; furosemide was the most commonly used (93% with ≥ 1 recorded dose) [8]. Using the same PHIS database as in the current study, Bamat et al. identified that for infants < 32 weeks gestation with grade 2 or 3 bronchopulmonary dysplasia, almost 95% of infants were exposed to loop diuretics at least once during hospital admission, with the duration of use ranging from 7.3 to 49.4% of all hospital days [9]. Neither these nor other studies have been able to establish that use of diuretics improves short- or long-term outcomes.

While rationale, or lack thereof, for the use of diuretics in infants with chronic lung disease has been discussed elsewhere, their use in infants with AKI warrants additional consideration [10, 11]. Several studies have shown that neonatal fluid overload is associated with increased morbidity and mortality [12] including in infants supported with extracorporeal membrane oxygenation (ECMO) and following cardiac surgery [13, 14]. In addition, a positive fluid balance in the first week of life has been associated with increased risk of requiring mechanical ventilation (MV) in both preterm (< 36 weeks) and near-term/term (≥ 36 weeks) neonates [2, 15] and increased risk of patent ductus arteriosus [16]. Thus, efforts to promote diuresis and maintain fluid balance in infants with AKI appear justified. Certainly, for the smallest patients, diuretics may represent the only option available for fluid removal given the lack of appropriately sized dialysis technology.

Practitioners may also prescribe furosemide in the setting of AKI in an attempt to ameliorate the severity of injury by increasing renal blood flow through the stimulation of prostaglandins and decreasing renal oxygen consumption [17, 18]. Renal oxygen consumption is proportional to renal tubular sodium reabsorption. It has been estimated that approximately 80% of renal oxygen consumption is related to activity of the Na-H antiporter [19]. While data from pediatric populations are missing, studies from animals and human adults may prove informative. In a sheep model of septic AKI, furosemide significantly increased fractional excretion of sodium (FENa) and renal medullary PO2 without an effect on medullary perfusion, renal blood flow, or renal oxygen delivery, implying decreased oxygen consumption [20]. Despite restoration of medullary PO2, no sustained improvement in kidney function, including creatinine clearance, FENa, or urine volume, was seen. In adults following cardiopulmonary bypass, furosemide significantly increased FENa and urine output, and decreased tubular sodium reabsorption, associated with a 23% decrease in renal oxygen consumption [18]. However, glomerular filtration rate decreased by 12%, possibly by feedback mechanisms resulting in constriction of afferent arterioles. Furosemide has additionally been shown in cardiac surgery patients with normal kidney function to decrease creatinine clearance [21]. Taken together, while experimental data suggest that renal workload may be reduced by diuretics, there is no evidence that diuretic administration can prevent or decrease the severity of AKI. Clinical studies in adult cohorts have shown this finding to be true as well [22–24].

Diuretics and outcomes—what is the relationship?

An additional finding to note in the report of Mohamed et al. was the increased mortality in those infants receiving diuretics. At all gestational ages, infants who survived to and were treated with either a short or long course of diuretics at or before 28 days had lower probability of survival compared to those who did not receive diuretics before 28 days. Reasons for this relationship were not able to be explored given the nature of the investigation. The authors acknowledge, as have others who have identified a similar relationship, that diuretic use may be a marker of severity of illness, being administered to those infants with severe oliguria/anuria or fluid overload. However, in a recent retrospective analysis of 456 patients admitted to a pediatric intensive care unit, of whom 43.4% received furosemide in the first week of admission, Dai et al. reported mortality was twice that in the furosemide-treated group, even after adjusting for severity of illness [25]. In contrast, Zhao et al. used a large, adult intensive care database to match 4427 pairs of patients with AKI who received furosemide and those without diuretics treatment [26]. Furosemide was associated with reduced in-hospital mortality [hazard ratio (HR) 0.67; 95% CI 0.61–0.74; P < 0.001] and 90-day mortality [HR 0.69; 95% CI 0.64–0.75; P < 0.001] in overall AKI patients, though this relationship was not seen in all

subgroups. The authors note that the reduction in mortality was not seen in patients with AKI stage 2–3 according to serum creatinine (rather than urine output) criteria, in patients with mild AKI (0–1 by urine output criteria), and in those with acute-on-chronic kidney injury. The disparate findings within and across studies support the need for additional rigorous investigation specifically in neonatal and infant cohorts with attention to the AKI stages and definitions, biomarkers used to define AKI, fluid balance, and associated comorbidities identified. Benefit (or harm) may be restricted to subsets of patients with AKI (severity, oliguric vs. non-oliguric, fluid overload, etc.) that will need to be more clearly defined to optimize diuretic use.

Beyond diuretics

While kidney support therapy (KST) is used more broadly in older children and adults with severe AKI, oliguria, and fluid overload, the use of KST is much less common in the NICU setting. Indeed, in the AWAKEN study, KST was used in only 4% (25/605) of patients with AKI [1]. Peritoneal dialysis (PD) remains a safe and effective kidney support option for babies with both AKI and CKD, and novel techniques like continuous flow PD may offer more options to provide this therapy safely to some of the smallest babies [27]. In addition, low extracorporeal volume dialysis machines designed specifically for babies as small as 2.5 kg are gradually becoming more available [28]. These new systems may change the risk/benefit profile of heavy diuretic use in those with the most severe AKI. Of course, the provision of dialysis also carries risk (e.g., risks to long-term vascular access options in patients who have vascular catheters placed at such an early age) and higher costs, and will not be available to all babies outside of highly resourced settings. Again, it will be important to study the impact and use of these therapies on outcomes, especially morbidity, mortality, hospital length of stay, and long-term kidney function.

Rational use of diuretics: consideration for quality improvement initiatives

Clearly, the use of diuretics is a mainstay of care of the most critically ill patients in all intensive care units. While the association between diuretic use and mortality as demonstrated in this and other studies may be considered simply a "marker of illness severity," the fact that this medication class is so intricately related with critical illness, mortality, and high-risk conditions suggests that closer scrutiny and more dedicated study is warranted, especially in light of conflicting clinical evidence as shown above. Neonatal intensive care unit therapy has seen tremendous advances and improvement in care through commitment to evidence-based care protocols that are subject to rigorous evaluation and study. The use of diuretics, as suggested by the data in this study, has not seen the same level of attention except in specific conditions such as bronchopulmonary dysplasia. The question of whether or not diuretics cause harm (or at least do not offer meaningful benefit) in the context of neonatal and infant AKI should be addressed more intentionally.

Because of the lack of proven treatments to reverse the course of AKI once it has occurred, more and more attention is being paid to preventive strategies. Moreover, these strategies can be framed in the context of quality improvement efforts whereby they can be tracked, critically appraised, and revised. Harer et al. recently published a well-framed neonatal response to the Acute Disease/Dialysis Quality Initiative (AQDI) outlining NICU-specific AKI quality improvement guidelines and approaches [29]. These include a neonatal "AKI bundle" that lists monitoring fluid intakes, outputs, daily balance, and percent fluid accumulation as key components for the evaluation of potentially modifiable risks and complications of AKI [29]. All of these parameters should be taken into account in assessments of effective diuretic use. In addition, the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) project [30] and its NICU corollary Baby NINJA [31] showed that it is possible to reduce nephrotoxic medication-related AKI frequency and severity by careful assessment of antimicrobial need, combination dosing, and creatinine surveillance, as well as the promotion of alternative, non-nephrotoxic medications using a multidisciplinary team approach and strategic use of the electronic medical record. The use of diuretics should be evaluated similarly through a quality lens—one that includes the context of fluid overload, concomitant use of other potentially nephrotoxic drugs, serum creatinine surveillance, and other AKI mitigation strategies. In this way, specific indications for, duration of use, and timing of diuretic prescription could be developed and optimized specifically for neonatal care. Many additional questions about diuretic use in neonates, including but not limited to the identification of the most effective diuretic(s), the tracking and monitoring of diuretic complications (e.g., electrolyte abnormalities, impact on hearing, bone health, and worsening of AKI), strategies to mitigate fluid overload, and the appropriate time to consider KST instead of diuretics, need to be addressed.

Until further data are available, prudent use of diuretics for neonatal AKI is likely appropriate to address fluid overload, especially in the smallest patients for whom no KST options exist. In such cases, higher doses than typically administered may be necessary. Additionally, furosemide may have a role in the treatment of hyperkalemia. In the absence of such conditions, and with the understanding that diuretics themselves have little benefit to kidney function itself (i.e., diuretics cannot "kick-start" kidney function), harm from diuretic

administration may outweigh potential benefit, and constant attention to response and emerging side effects should be part of the care. At the least, the outcomes of choices regarding diuretic use, both positive and negative, should be examined carefully such that rational decisions can be made and robust evidence-based clinical guidelines can be developed.

Conclusion

Diuretics are widely used in critically ill and high-risk patients. Mohamed et al. have documented high use in premature babies with AKI compared with those who did not have AKI. Mortality rates and other morbidities were higher in babies who received diuretics and who had AKI, though this is not to imply causation. Additional scrutiny is needed to develop rational and evidence-based practices to optimize outcomes and minimize side effects of this medication class that is widely used in the care of critically ill neonates and infants.

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