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Review

Pharmacological management of acute kidney injury and chronic kidney disease in neonates

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SUMMARY

Both acute kidney injury (AKI) and chronic kidney disease (CKD) are seen more frequently in the neonatal intensive care unit (NICU) as advances in supportive care improve the survival of critically ill infants as well as those with severe, congenital kidney and urinary tract anomalies. Many aspects of the infant's care, including fluid balance, electrolyte and mineral homeostasis, acid–base balance, and growth and nutrition require close monitoring by and collaboration among neonatologists, nephrologists, dieticians, and pharmacologists. This educational review summarizes the therapies widely used for neonates with AKI and CKD. Use of these therapies is extrapolated from data in older children and adults or based on clinical experience and case series. There is a critical need for more research on the use of therapies in infants with kidney disease as well as for the development of drug delivery systems and preparations scaled more appropriately for these small patients.

1. Introduction

Renal injury, both acute and chronic, leads to a host of management challenges for critically ill infants in the neonatal intensive care unit (NICU). Both acute kidney injury (AKI) and chronic kidney disease (CKD) occur more frequently now as advances in supportive care improve the survival of acutely ill neonates as well as those with severe, congenital kidney and urinary tract anomalies. Many aspects of the infant's care, including fluid balance, electrolyte and mineral homeostasis, acid–base balance, and growth and nutrition are affected by kidney insufficiency. Optimal care requires the expertise of neonatologists, nephrologists, dieticians, and pharmacologists. Because of the technical challenges involved in the provision of renal support therapy (RST) for neonates, intensive pharmacologic management is often relied upon in order to prevent or at least delay the need for RST in these patients. Whereas many management strategies for managing neonatal AKI/CKD are the same as those for older children and adults, there are some key differences including the need to promote critical growth, limited options for nutritional delivery, and sparse data on the use of these therapies in infants specifically. This educational review summarizes the therapies widely used for both AKI and CKD and highlights the importance of the multidisciplinary team approach to the care of these patients. Evidence-based clinical practice guidelines from expert panels such as the Kidney Disease: Improving Global Outcomes (KDIGO) work group [1] and the National Kidney Foundation: Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) [2,3] are referenced where appropriate.

2. Management of acute kidney injury

An initial challenge in managing neonatal AKI is identification of those patients suffering from the condition. Current AKI biomarkers including serum creatinine and urine output are limited in this population due to ongoing effects of kidney function maturation and changing glomerular filtration rate (GFR). This dynamic physiology and lack of a stable “baseline” creatinine may lead to late diagnosis. Timely identification of AKI in order to prevent morbidity and mortality requires close kidney function monitoring and heightened awareness for those who may be at risk. Since there are no proven treatments for AKI, management of AKI and its sequelae in neonates remains supportive. A strong emphasis of all care should be on identifying and modifying AKI risk factors early in the course (e.g. maintaining adequate renal perfusion), minimizing additional insults (e.g. discontinuing nephrotoxic medications) and

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managing complications such as electrolyte abnormalities. AKI can lead to derangements in one or all of the following areas, so each should be considered when caring for the infant with AKI.

2.1. Fluid balance

Fluid overload has been associated with increased morbidity and mortality in older pediatric populations [4]; there are also limited but similar data in critically ill infants [5]. Thus, attention to fluid balance is a key aspect of the care of critically ill neonates. Fluid management, especially in the preterm infant, can be difficult as these infants are susceptible to complications with either inadequate or excessive fluid provision [6]. In addition, assessing fluid balance may be more difficult in the preterm infant than in older patients due to immature epithelium and large insensible losses that will not be accounted for in the intake/output balance [7]. Neonates also have immature renal tubular function and may not be able to concentrate their urine adequately in the face of intravascular volume depletion. Daily weights, if available, are often helpful for assessing fluid balance in these patients.

Management of the fluid-overloaded infant includes diuretics, fluid restriction and, in the most severe cases, RST. Review of the amount and content of fluid inputs should occur early, as soon as decline in urine output is recognized. There should be early consideration for decrease in non-nutritive fluids (e.g. “maintenance” fluids). Reviews of central venous nutrition to determine whether the same nutritional content can be formulated in a smaller volume, and of all medications with the pharmacist to see whether carrier fluids can be concentrated further, should also be performed early.

A trial of diuretics may be considered when urine output is declining, though there is no evidence to show that diuretics are useful for the treatment or prevention of AKI [1]. Diuretics are among the most frequently prescribed medications in the NICU [8]. Given the challenges involved with providing RST to small infants, these medications are often used initially for management of fluid overload and electrolyte abnormalities (e.g. hyperkalemia) in the setting of AKI.

Loop diuretics (e.g. furosemide) act at the $Na^+K^+—2Cl^-$ co-transporter in the thick ascending limb of the loop of Henle. Furosemide blocks chloride uptake and thereby inhibits sodium, chloride, and potassium reabsorption. Pharmacologic tolerance may occur with repeated doses as extracellular volume depletion associated with diuresis may trigger an increase in sodium and water reabsorption in other parts of the nephron (proximal and distal tubules) [9,10]. Side-effects include hypotension with rapid diuresis, hypokalemia, and hypochloremic metabolic alkalosis. In addition, furosemide induces hypercalciuria that may lead to bone demineralization and renal calcifications [11,12]. Ototoxicity is another rare but known complication of chronic furosemide use [13].

Thiazides are another class of diuretics widely used in the NICU. These act at the Na^+/Cl^- transporter in the distal tubule to induce sodium and water excretion. Because less sodium is usually absorbed in this part of the nephron, thiazides are typically less potent than loop diuretics [9]. However, these medications do not promote hypercalciuria and may in fact increase calcium reabsorption in both the proximal and distal tubule [14], actions which may provide relative benefits over loop diuretics.

With severe oligo-anuric AKI, diuretics and fluid restriction may be ineffective for preventing worsening fluid overload. Severe electrolyte derangement may occur as the result of high-dose, frequent diuretic administration. In addition, fluid restriction may lead to inadequate nutrition provision. In these cases, care teams should consider implementing RST.

3. Electrolyte balance

Neonates with AKI may have one, few, or many electrolyte abnormalities depending on the cause of AKI. For example, neonates with oligo-anuric AKI may develop hyponatremia related to fluid overload, or they may develop severe hyperkalemia and hyperphosphatemia due to low GFR. Infants with proximal tubule injury, such as with aminoglycoside toxicity, may maintain their urine output but develop hypokalemia and hypomagnesemia secondary to renal tubular wasting. Identifying the etiology of AKI whenever possible will help the care team anticipate potential sequelae.

3.1. Potassium homeostasis

Hyperkalemia is a potentially life-threatening complication of AKI. Upon recognition that an AKI event has occurred, the potassium content of all fluids and enteral feeds should be reviewed and adjusted and/or discontinued, especially in the oligo-anuric patient. Hyperkalemia may be treated definitively by removing potassium from the body or temporarily by promoting potassium shifts from the extracellular to intracellular compartment. Choice of therapy will depend on the degree of hyperkalemia and presence or absence of electrocardiographic changes. Potassium may be removed from the body via the gut (such as with sodium polystyrene sulfonate, SPS), via urinary excretion if the patient still has urine output (e.g. with loop diuretics), or with dialysis. Intracellular shifts may be achieved through change in pH by administration of sodium bicarbonate or acetate, use of albuterol, or administration of insulin and glucose. If an infant is found to have hyperkalemia and severe acidosis, correction of the acidosis may be a reasonable first step in management.

Sodium polystyrene sulfonate (SPS) is a cation exchange resin that remains in the lumen of the gastrointestinal tract where it exchanges sodium for potassium. Potassium is then excreted in the stool. It is an effective medication for lowering potassium in pediatric patients [15], though a number of serious adverse effects have been described when given directly to infants including colonic necrosis and death [16]. Thus, several authors have described methods, primarily based on in-vitro studies, for pre-treating infant formula or breast milk to decrease the potassium content and thereby avoid giving the SPS to the infant directly [17,18] (Table 1). Importantly, pre-treating the formula also results in a decrease in calcium and magnesium content and a marked increase in sodium content via the ion exchange process. Other nutrient content of the formula (or breast milk) may also be altered with this process [19].

3.2. Sodium homeostasis

Infants with AKI may manifest either hyponatremia or hypernatremia depending on the underlying cause of AKI. Hyponatremia may be the result of total body water overload or total body sodium depletion, as may occur with large chest tube losses or urinary sodium wasting in the infant with congenital kidney or urinary tract disease (e.g. dysplasia or obstructive uropathy). Thus, attention to fluid balance and recent clinical events is essential for managing dysnatremias correctly. Assessment of the effective circulating volume, plasma and urine osmolality, and urine sodium levels may help determine whether hyponatremia is the result of total body sodium depletion or total water excess.

For those infants with AKI who are not symptomatic (no seizures or lethargy), fluid restriction alone may result in correction of hyponatremia. If hyponatremia is severe (<120 mEq/L) or the infant is manifesting changes in mental status, then use of 0.9% saline or 3% sodium chloride may be required. Serum Na^+ levels should be monitored frequently when correcting hyponatremia to avoid

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