Hypochloremia Secondary to Diuretics in Preterm Infants: Should Clinicians Pay Close Attention?

Renjithkumar Kalikkot Thekkeveedu, MD1, Sumana Ramarao, MD1, Nilesh Dankhara, MD1, and Pradeep Alur, MD1

Abstract
Diuretic therapy, commonly used in the newborn intensive care unit, is associated with a variety of electrolyte abnormalities such as hyponatremia, hypokalemia, and hypochloremia. Hypochloremia, often ignored, is associated with significant morbidities and increased mortality in infants and adults. Clinicians respond in a reflex manner to hyponatremia than to hypochloremia. Hypochloremia is associated with nephrocalcinosis, hypochloremic alkalosis, and poor growth. Besides, the diuretic resistance associated with hypochloremia makes maintaining chloride levels in the physiological range even more logical. Since sodium supplementation counteracts the renal absorption of calcium and lack of evidence for spironolactone role in diuretic therapy for bronchopulmonary dysplasia (BPD), alternate chloride supplements such as potassium or arginine chloride may need to be considered in the management of hypochloremia due to diuretic therapy. In this review, we have summarized the current literature on hypochloremia secondary to diuretics and suggested a pragmatic approach to hypochloremia in preterm infants.

Keywords
hypochloremia, metabolic alkalosis, preterm infants, bronchopulmonary dysplasia, diuretics

Received October 2, 2020. Accepted for publication January 7, 2021.

Introduction
Bronchopulmonary dysplasia (BPD) is one of the most common morbidities in extremely premature infants. Our understanding of the pathophysiology of BPD is still evolving.1 Hence, several pharmacological agents, such as caffeine, diuretics, bronchodilators, and systemic corticosteroids, are being used in the management of BPD.2,3 Although long term benefits of diuretics in BPD are still debatable, the diuretics are still used extensively in the management of BPD in preterm infants.3,4 Diuretics, both furosemide, and combination of chlorothiazide and spironolactone, may improve airway resistance, specific airway conductance, decrease pulmonary edema, and improve lung compliance in the short term.5-7 Though strong evidence for the routine use of diuretics in the management of BPD is lacking,8,9 the perceived benefits of diuretics10 in a condition that imposes severe morbidity in this vulnerable population have led to their widespread use.

Nevertheless, after much debate, once a clinician considers diuretics for the management of BPD, he faces the prospect of electrolyte abnormalities such as hyponatremia, hypokalemia, and hypochloremia. It is a common knee jerk reaction to initiate sodium chloride supplements11 with or without potassium to correct these electrolyte derangements. However, few questions that invariably pop up are: Is this the ideal approach as it may negate the purpose of diuretic therapy? Should we add a potassium-sparing diuretic? Is it necessary to correct hypochloremia even in the absence of hyponatremia?

As chloride cannot be dealt in exclusion of sodium, we will briefly discuss hyponatremia and its significance during diuretic therapy.

Hyponatremia
Hyponatremia is a fairly common clinical problem in preterm infants. Most authors have defined hyponatremia as

1University of Mississippi Medical Center, Jackson, MS, USA

Corresponding Author:
Renjithkumar Kalikkot Thekkeveedu, University of Mississippi Medical Center, 2500 N State St, W 154, Jackson, MS 39216, USA.
Email: rkalikkot@umc.edu
serum sodium levels of <130 mEq/L. Hyponatremia is seen in up to 30% of very low birth weight infants in the first week after birth (early onset) and the incidence is much higher thereafter, up to 25% to 80% as per various reports (late onset hyponatremia). Renal capacity to regulate sodium absorption and excretion depends on the gestational age and postnatal age. Increased urinary losses, due to impaired absorption of sodium in the renal tubules, is considered as one of the major reasons for hyponatremia in very low birth weight (VLBW, babies with birth weight <1500 g) babies. Hence, diuretic use may be one of the major potentiating factors for late onset hyponatremia in many of these preterm infants. Unlike in adults it is not clear if there is higher incidence of hyponatremia associated with thiazide diuretic use in preterm infants. Studies have associated hyponatremia with poor outcomes such as seizures, poor growth, increased duration of hospital stay, hearing loss, cerebral palsy, and increased mortality. Hyponatremia associated with diuretic use has not been well studied. Nevertheless, it is frequently treated with sodium chloride supplements, in up to 60% to 100% of cases as per some reports. However, due to the concern that interstitial edema is a contributing factor in the pathophysiology of BPD, the role of sodium chloride supplements becomes questionable. Hence, one should exercise caution while routinely using sodium chloride supplements.

**Hypochloremia**

Hypochloremia is defined as serum chloride level <96 mMol/L. Though the true prevalence of hypochloremia in preterm infants is unknown, some studies have reported incidence of 16.3% with loop diuretics. There is paucity of literature on the significance of hypochloremia in preterm infants. Most of the recent studies on diuretics usage in preterm infants do not discuss hypochloremia and even the Cochrane review on diuretics use for CLD only briefly mentions hypochloremia as a complication. The current review therefore, addresses this important issue with existing evidence, and suggest a careful approach to the management of this important dyselectrolytemia during diuretic therapy.

**The Physiological Importance of Chloride**

Chloride plays vital roles, including acid-base equilibrium, gastric hydrochloric acid secretion, modulation of the renin-angiotensin-aldosterone system, and thus the systemic blood pressure, and Hamburger shift in carbon dioxide transport at the venous end of the capillaries.

(1) **Renal chloride homeostasis:** The majority of the sodium and chloride reabsorption in the nephron happens in the proximal tubule (50%-70%), followed by the loop of Henle (25%-30%), the distal tubule (5%), and the collecting duct (3%). Within the proximal tubule, passive transport of the chloride and water happens with the active transport of sodium by the sodium-potassium-adenosine triphosphatase (Na\(^+\) K\(^-\)-ATPase). In the thick ascending loop of Henle, the Na\(^+\) K\(^-\)-2Cl membrane carrier actively transports the sodium and chloride from the tubular lumen into the tubular cell. In the distal convoluted tubule, Na\(^+\)-Cl\(^-\) cotransporter transports sodium actively against an electrochemical gradient.

The chloride anion is exchanged for bicarbonate anion in the cortical collecting duct, and hypochloremia increases bicarbonate absorption resulting in metabolic alkalosis. The chloride anion seems to have a significant effect than sodium on the renin-angiotensin system (RAAS). When sodium is infused with bicarbonate without any chloride, the effect on the renin-angiotensin system was minimal. However, there is good evidence that increased chloride delivery to the macula densa inhibits, while reduced chloride delivery stimulates renin release. It will be interesting to see if systemic hypertension that is seen in infants with bronchopulmonary dysplasia is related to hypochloremia and associated RAAS stimulation, at least in part.

(2) **Chloride (Hamburger) Shift:** Hamburger shift is the efflux of chloride with the influx of carbon dioxide into erythrocytes. It is also associated with the unloading of oxygen at the venous end of the capillaries. Since the blood carries most of the carbon dioxide in the form of bicarbonate anion, the chloride shift is essential as it enhances the blood carrying capacity for carbon dioxide/bicarbonate. The significant role of the chloride shift appears to be in lessening of the change in pH that occurs during gas transport. Besides, chloride shift may account for up to 40% of the oxygen unloading at the tissues. However, the clinical impact of hypochloremia on oxygen unloading is unknown. The chloride ion has a role in a myriad of physiological functions. It is thus considered as the queen of electrolytes. Hence, maintaining a normal serum chloride level makes physiological sense.
Clinical Importance of Chloride

Dyschloremia (hypo and hyperchloremia) is well studied in adults than in preterm infants. Hence, adult studies on dyschloremia may throw some light on the importance of chloride in clinical conditions. Several studies have shown that dyschloremia is associated with increased morbidity in adults. A recent meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation concluded that there was a weak but significant association between higher chloride content fluids and unfavorable outcomes. Moreover, chloride rich fluids resulted in volume-dependent increased vasopressor need and possibly increased need for blood products. Studies have also shown that changes in serum chloride concentration, independent of serum sodium and bicarbonate, are associated with increased risks of acute renal injury, morbidity, and mortality.

(1) Lessons from adult literature: Hypochloremia activates the renin-angiotensin-aldosterone system (RAAS) despite the significant volume expansion in congestive heart failure (Figure 2). There is strong evidence that hypochloremia is associated with increased mortality in adults, especially with heart failure. The BEST trial, which included 2702 patients, concluded that serum chloride was strongly and independently associated with worsened survival in patients with chronic heart failure. The study also showed that chloride levels but not sodium might have a significant effect on the outcomes in critically ill patients. Another study consisting of 3314 acute ischemic stroke adult patients showed that hypochloremia was independently associated with all-cause mortality with a hazard ratio of 2.43 (confidence interval 1.41-4.19; P=.001). Several case reports have shown that diuretic-induced metabolic alkalosis and low chloride levels are associated with compensatory hypoventilation in adults even with normal lung function.

Moreover, hypochloremia and low normal serum chloride levels, even without overt hypochloremia, are reported to be associated with increased mortality in the general population as well. A pilot study demonstrated that supplementation with lysine chloride not only corrected chloride levels but also reduced the NT-pro-BNP levels suggesting that hypochloremia may represent more than just a marker of disease severity; rather, it may be amenable to therapeutic modification. There is an ongoing trial studying if therapeutic intervention with lysine chloride improves the outcomes in heart failure patients. Thus, there is compelling evidence that hypochloremia is associated with poor prognosis in adult patients.

(2) Association with mortality and morbidity in infants and children:

(i) Hypochloremia and mortality: There is a paucity of studies on hypochloremia and its effects in preterm infants with chronic lung disease. In a retrospective study of 23 preterm patients with BPD, Perlman et al. analyzed the factors associated with death in infants with bronchopulmonary dysplasia requiring hospitalization beyond 100 days. Incidence and duration of moderate and severe hypochloremia were significantly higher in those who died. The mean duration of moderate hypochloremia (chloride < 80 mEq/L) in those who died was 25.45 ± 14.1 days versus 11.4 ± 11.8 days in those surviving. Eighty-two percent of infants who died had severe hypochloremia (serum chloride < 70 mEq/L) with a mean duration of 16.8 ± 6.58 days. In contrast, only 50% of those that survived had a chloride < 80 mEq/L and for a brief period (6.2 ± 3.1 days, mean ± SD). Interestingly only 10% experienced hyponatremia, and there were no differences in the mean arterial carbon dioxide levels between the groups.

In another study evaluating the mortality risk in chronically ventilated bronchopulmonary dysplasia infants, it was noted that the degree of hypochloremia was a useful predictor of survival even after controlling for other major confounding factors like mean airway pressure and inspired oxygen concentration.

(ii) Hypochloremia and metabolic alkalosis: Normal serum chloride concentrations in preterm infants are 110.5 ± 5.0 mmol/L. Hypochloremia is a significant clinical finding in patients receiving chronic diuretic therapy, and it often stays under-corrected. Chloride and bicarbonate levels are inversely related to each other to maintain anion balance. In infants with chronic lung disease, respiratory acidosis due to chronic retention of CO₂ causes the proximal tubule to increase its secretion of hydrogen ion. This process leads to the absorption of sodium along with...
bicarbonate anion resulting in compensatory hypochloremic metabolic alkalosis. Hypochloremia is further exaggerated by the use of chronic diuretics, which worsens metabolic alkalosis and thus augmenting the carbon dioxide retention resulting in a vicious cycle (Figure 1). Of note, serum potassium levels are not significantly affected by chronic hypercapnia.

The compensatory hypoventilation may increase the duration or time to wean off of mechanical ventilation. Therefore, treating metabolic alkalosis by maintaining normal chloride levels may help to disrupt this vicious cycle.

(iii) Hypochloremia and growth: The young growing rats, when fed with chloride deficient diet, had a significantly lower weight and length gain and decreased protein synthesis, compared to the controls fed with normal chloride diet. Tuschman reported similar observations in 3-week old rats. Perlman et al also noted in their study that despite similar calories, sodium, chloride, and fluid intake, weight gain, and head growth were poor in those preterm infants with hypochloremia. In another report of 30 infants fed with chloride deficient formula, it was shown that chloride deficiency is associated with failure to thrive, lethargy, and hypercalcemia. Growth failure associated with chloride deficiency was also reported by other researchers.

Some have reported even poor cognitive functioning at 2 years of age in the infants exposed to chloride deficient formula in infancy. Extended assessment at 9 to 10 years of age showed that infants who experienced hypochloremic metabolic alkalosis were at risk for deficits in language skills that require expressive language abilities. The underlying mechanisms for growth failure and neurodevelopmental abnormalities associated with Cl-deficient diet is not studied.

(iv) Hypochloremia and nephrocalcinosis: Animal studies have raised an exciting interaction between hypochloremia and nephrocalcinosis. Tuchman et al showed that 50% of the rats on chloride depleted diet developed nephrocalcinosis after furosemide administration, and 94% of the rats developed the same if both sodium and chloride were depleted, independent of the furosemide use. Similarly, nephrocalcinosis was observed in association with hypochloremia in a case series of infants ingesting chloride deficient formula, Bartter syndrome, congenital chloride diarrhea, and pyloric stenosis.

(3) Hypochloremia and diuretic resistance: Hypochloremia has also been shown to decrease the efficacy of loop diuretics, which often leads to diuretic dose escalation and increased adverse effects without an improved diuretic response. Diuretic resistance is defined as a failure to achieve the therapeutically desired reduction in edema or blunted natriuresis despite a full dose of diuretic. Hypochloremia exaggerates this diuretic resistance. Hanberg et al, in their study in acute heart failure patients, have noted that hypochloremia was associated with poor diuretic response (OR = 7.3, 95% CI 3.3-16.1, P < .001). The diuretic efficiency, which was calculated as the increase in sodium output per doubling of the loop diuretic dose, was also substantially decreased in patients with hypochloremia. PROTECT trial involving 2033 patients observed that lower chloride was associated with decreased diuretic response. The diuretic response, which was defined as weight change on day 4 per 40 mg of intravenous furosemide (or equivalent doses) administered from baseline to day 3 was significantly lower with hypochloremia. This trial also reported that there was less weight change, a need for higher diuretic doses, a smaller percentage change in BNP levels from baseline, and the more frequent requirement for adjuvant thiazide diuretics or inotropes during hospitalization in patients with hypochloremia. The trial also showed that unlike the chloride levels, sodium levels did not correlate with mortality.
As previously discussed, hypochloremia is also involved in renin release at the macula densa in the distal tubule through the NKCC2 (Na-K-Cl cotransporter) pathway. Increased chloride delivery to the macula densa inhibits renin release, while lower chloride stimulates renin release and thus increased fluid retention and increased need for diuretics. WNK (with no lysine K) is a serine-threonine kinase that regulates Na-K-Cl and Na-Cl cotransporters in the kidneys. Binding of chloride to the active site of WNK in the thick ascending loop of Henle and distal convoluted tubule inhibits autophosphorylation and therefore decreases the availability of both sodium-potassium-chloride cotransporter and sodium-chloride cotransporter. This interaction consequently reduces renal salt reabsorption. Thus, hypochloremia may enhance fluid absorption (Figure 2). Hypochloremia may also reduce glomerular filtration rate and thus decreasing the delivery of bicarbonate to the distal nephron and attenuating further Na and fluid losses.

Since hypochloremia is associated with poor growth, nephrocalcinosis, and increased mortality, there is a compelling need to maintain the chloride levels within the physiological norms. Besides, normal chloride levels are also essential for the optimal diuretic response.

Management of Hypochloremia

It is important to consider other causes of hypochloremia like pyloric stenosis, Bartter syndrome, adrenal insufficiency, pseudohypoaldosteronism, cystic fibrosis, cerebral salt wasting syndrome, chloride diarrhea), or hypochloremia due to water excess (eg, SIADH), as management in each condition is different. The current review focuses on the management of hypochloremia secondary to diuretic therapy.

In the management of hypochloremia, one should consider holding of diuretics temporarily, use of higher ratio of Cl to acetate in TPN etc. before Cl supplementation is considered. Chloride administration promotes bicarbonate excretion through chloride-bicarbonate exchange pumps in the nephron. Treatment of hypochloremic alkalosis is mainly in the form of administration of potassium chloride, sodium chloride, arginine chloride, or acetazolamide.

Many neonatologists prefer to use sodium chloride supplementation as the first-line therapy for correcting hyponatremia and hypochloremia. Sodium supplementation can also create unwanted side effects. Adult data suggests that high dose sodium supplementation induces increased arterial tone by impairing endothelial function or by diminishing nitric oxide bioactivity. Long-term sodium intake also induces structural changes in the arterial wall and activation of the renin-angiotensin system. Evidence is sparse to conclude if sodium supplementation has similar implications in the neonatal population. There are some reports, however, of significantly thicker and stiffer systemic arteries in preterm infants with BPD, compared to gestational age and sex-matched preterm infants with no BPD or term infants. There is also a high incidence of systemic hypertension in infants with BPD, which is associated with a significantly longer duration of home oxygen therapy and significantly higher mortality. It needs to be further studied if this phenomenon is the result of sodium supplementation or hypochloremia.

(1) Potassium sparing diuretics: As potassium abnormalities are common with diuretics, a potassium-sparing diuretic, such as spironolactone, is frequently used. Spironolactone is a synthetic steroid and a competitive antagonist of the aldosterone receptor. Aldosterone acts on the distal tubule and collecting duct to increase reabsorption of sodium in exchange for potassium and hydrogen ions. The blockade of the mineralocorticoid receptor by spironolactone decreases potassium secretion, and it also decreases sodium and chloride reabsorption in the principal cells. The natriuresis and the resultant diuresis produced by spironolactone accounts for less than 2% of the filtered sodium, making it a very weak diuretic.

Combining spironolactone with chlorothiazide therapy does not seem to change the clinical outcomes in
neonates compared to monotherapy with chlorothiazide. Hoffman et al,74 compared the diuretic therapy as a combination with chlorothiazide alone. They randomly assigned 33 preterm infants with chronic lung disease to a 2-week course of thiazide with spironolactone versus thiazide alone. The authors did not find any difference in pulmonary compliance, resistance, tidal volume, or fraction of inspired oxygen between the groups.

Hypokalemia with diuretic use is multifactorial in origin. Thiazide diuretics increase distal sodium delivery, leading to enhanced sodium reabsorption in the collecting tubule, which favors the secretion of potassium. Thiazides also lower the luminal calcium concentration along distal tubules. This activates epithelial Na channels (which are inhibited by calcium) and favors potassium secretion by increasing the electrochemical gradient for potassium secretion.75 Increased urinary potassium excretion associated with diuretic-induced hypomagnesemia and metabolic alkalosis also may contribute to hypokalemia.76 Finally, hyperaldosteronism, which may be associated with hyponatremia, also may promote potassium loss.77

It is a common practice among neonatologists to add spironolactone to the diuretic regimen to decrease the degree of hypokalemia and hyperkaliuria with chronic diuretic therapy. The impact of spironolactone on potassium management has not been well understood.8,28 The effect of spironolactone on potassium homeostasis seems to be paradoxical. It is suggested that spironolactone may increase serum potassium concentrations initially, with the potential for decreases in serum potassium during prolonged therapy.78

Routine use of spironolactone may not be more efficacious than potassium supplementation for the maintenance of serum potassium concentrations while on diuretic therapy. Hoffman et al,74 did not find any significant difference in serum electrolytes, the need for potassium chloride, or sodium chloride supplementation between the groups in their randomized study comparing chlorothiazide with a combination of chlorothiazide and spironolactone. A similar experience has been reported in the pediatric population as well. Moffett et al,79 in a retrospective analysis of 448 patients in the pediatric cardiac intensive care unit, reported that Spironolactone supplementation did not reduce the need for potassium supplementation. Likewise, Hobbins et al80 reported that spironolactone did not change the potassium values compared to patients on potassium supplements in 21 infants with congestive heart failure while on concomitant digoxin and chlorothiazide therapy. This lack of effect on potassium may be due to age-related end organ resistance of the distal convoluted tubule in the kidney to aldosterone in the premature infant population.81,82

Thus, despite the addition of the potassium-sparing diuretic, many infants may still require dietary supplementation with potassium chloride.

Besides, the addition of potassium-sparing diuretic prevents the clinician from providing chloride supplementation in the form of potassium chloride because of the risk of hyperkalemia. Thus, the addition of spironolactone may not only be ineffective in improving the clinical outcomes but also may interfere with electrolyte supplementation to improve chloride homeostasis.

(2) Sodium and Potassium supplementation—benefits and side effects: Thiazide diuretics are preferred over loop diuretics in neonates for their calcium sparing effect. Thiazides decrease urinary calcium excretion, while loop diuretics increase urinary calcium excretion.8 Hence, thiazide diuretics may help to prevent the exacerbation of metabolic bone disease of the prematurity while on chronic diuretic therapy.

Potassium supplementation decreases urinary calcium loss. The study showed that potassium supplementation in children with hypercalciuria significantly decreased urinary calcium excretion.83 Similarly, potassium chloride, when added to hydrochlorothiazide, significantly decreased urinary calcium excretion in adults.84 It appears that with potassium supplements, the hypokalemia may also get corrected to some extent. This correction is thought to be due to the shift of sodium from the intracellular to extracellular space, increasing the serum sodium concentration.85-87

Sodium inhibits calcium uptake by the membrane vesicles in the distal convoluted tubules.88 So when sodium supplementation is used to treat thiazide-induced hypokalemia, it may lead to increased sodium concentrations in the distal tubular lumen and may result in increased urinary loss of calcium, thus minimizing the calcium sparing effect of thiazides.89,90

The calcium conserving property makes potassium chloride the preferred choice rather than spironolactone or sodium chloride to treat the diuretic-induced electrolyte disturbances like hypokalemia, hypochloremic metabolic alkalosis, and even mild hyponatremia. However, close monitoring of serum potassium levels is needed to prevent inadvertent hyperkalemia.

(3) Role of arginine chloride: Arginine chloride is an appealing option to treat hypochloremia. Sierra et al89 reported that arginine chloride, especially the oral supplementation, was effective in resolving both hypochloremia and metabolic alkalosis.
in pediatric patients. Arginine chloride was the most common supplement used in one of the level IV neonatal intensive care units. The mean required dose was $2.9 \pm 1.1$ mEq/kg/day. These authors also suggested that the intravenous formulation can be given via the enteral route as well.51 For correction of chloride deficit, Martin and Matzke51 proposed that the dose of hydrochloric acid be calculated as follows: 

$$\text{dose (mEq)} = [0.2 \text{ liters/kg} \times \text{body weight (kg)} \times (103 - \text{observed sodium chloride})].$$

The authors also suggested a formula for the correction of metabolic alkalosis. Dose of arginine hydrochloride (mEq) = $[0.5 \text{ liters/kg} \times \text{body weight (kg)} \times (\text{observed sodium bicarbonate} - 24)]$. Administering one half of the calculated dose is suggested for correcting metabolic alkalosis.

Since Arginine Cl requires hepatic conversion for full activity, infants with hepatic dysfunction may require alternate therapy. Monitor for hyperkalemia especially when combined with other conditions or medications like potassium chloride and ACE inhibitors that can cause hyperkalemia.

(4) Role of acetazolamide: Acetazolamide causes excretion of bicarbonate and absorption of hydrogen ion and chloride in the proximal tubule. Acetazolamide, a carbonic anhydrase inhibitor has been found to be useful in the management of glaucoma, epilepsy, edema, intracranial hypertension, altitude sickness, etc in adults. Use of acetazolamide therapy has also been shown to improve metabolic alkalosis and hypochloremia in infants and children with chronic lung disease, congenital diaphragmatic hernia and congenital heart disease.92-94 Tam et al92 observed that, compared to baseline, mean serum bicarbonate and base excess were significantly lower and serum chloride were higher after 24 hours of acetazolamide therapy. Andrews et al95 also noted statistically significant differences in pH and bicarbonate levels with acetazolamide therapy in children. However, the use of acetazolamide in adults was associated with significant metabolic acidosis.96 Other side effects include GI discomfort, electrolyte disturbances—hyperchloraemia, hypokalaemia, hypernatremia. Currently there is no recommended dose and further studies are needed to standardize dose of acetazolamide for the management of metabolic alkalosis in infants and children.95

Summary
Chloride plays a vital role in several physiological functions in the body. Hypochloremia is associated with increased morbidity and mortality in adults and preterm infants as well. Due to possible role of hypochloremia in the morbidities associated with BPD such as nephrocalcinosis, hypochloremic alkalosis and poor growth, clinicians should be paying close attention to chloride levels to optimize the outcomes in preterm infants. Besides, the evidence suggests that hypochloremia may be associated with diuretic resistance, which makes maintaining chloride levels in the physiological range even more sense. Since sodium supplementation counters the renal absorption of calcium and lack of evidence for spironolactone role in diuretic therapy for BPD, alternative chloride supplements such as potassium or arginine chloride may need to be considered as the first line of therapy in the management of hypochloremia due to diuretic therapy.

Author Contributions
RKT: Review of the data and wrote a portion of the manuscript, compilation of data, and reference, review and submission of the manuscript in the required format; PA: conceive, design and wrote the portion of the manuscript that led to this submission, figure generation, review of the manuscript; SR: review of the data and wrote portion of the manuscript, review of the manuscript, and figure generation; ND: review of the data and wrote portion of the manuscript, review of the manuscript.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Renjithkumar Kalikkot Thekkeveedu https://orcid.org/0000-0003-3864-0911

References
1. Higgins RD, Jobe AH, Koso-Thomas M, et al. Bronchopulmonary dysplasia: executive summary of a workshop. J Pediatr. 2018;197:300-308.
2. Michael Z, Spyropoulos F, Ghanta S, Christou H. Bronchopulmonary dysplasia: an update of current pharmacologic therapies and new approaches. Clin Med Insights Pediatr. 2018;12:1179556518817322.
3. Bamat NA, Kirpalani H, Feudtner C, et al. Medication use in infants with severe bronchopulmonary dysplasia
admitted to United States children’s hospitals. J Perinatol. 2019;39:1291-1299.

4. Slaughter JL, Stenger MR, Reagan PB. Variation in the use of diuretic therapy for infants with bronchopulmonary dysplasia. Pediatrics. 2013;131:716-723.

5. Kao LC, Warburton D, Cheng MH, Cedeño C, Platzer AC, Keens TG. Effect of oral diuretics on pulmonary mechanics in infants with chronic bronchopulmonary dysplasia: results of a double-blind crossover sequential trial. Pediatrics. 1984;74:37-44.

6. Kao LC, Warburton D, Sargent CW, Platzer AC, Keens TG. Furosemide acutely decreases airways resistance in chronic bronchopulmonary dysplasia. J Pediatr. 1983;103:624-629.

7. Albersheim SG, Solimano AJ, Sharma AK, et al. Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. J Pediatr. 1989;115:615-620.

8. Segar JL. Neonatal diuretic therapy: furosemide, thiazides, and spironolactone. Clin Perinatol. 2012;39:209-220.

9. Stewart A, Brion LP, Ambrosio-Perez I. Diuretics acting on the distal renal tubule for preterm infants with or (developing) chronic lung disease: a practice looking for evidence. J Paediatr Child Health. 2020;56:1189-1193.

10. Baraton L, Ancel PY, Flamant C, Orsonneau JL, Darmaun D, Roze JC. Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. Pediatr. 2009;124:e655-e661.

11. Späth C, Sjöström ES, Ahlsson F, Ägren J, Domellöf M. Sodium supply influences plasma sodium concentration and the risks of hyper- and hyponatremia in extremely preterm infants. Pediatr Res. 2017;81:455-460.

12. Al-Dahhan J, Haycock GB, Chantler C, Stimmmer L. Sodium homeostasis in term and preterm neonates. I. Renal aspects. Arch Dis Child. 1983;58:335-342.

13. Kim YJ, Lee JA, Oh S, et al. Risk factors for late-onset hyponatremia and its influence on neonatal outcomes in preterm infants. J Korean Med Sci. 2015;30:456-462.

14. Hix JK, Silver S, Sterns RH. Diuretic-associated hyponatremia. Semin Nephrol. 2011;31:553-566.

15. Corneli HM, Gormley CJ, Baker RC. Hyponatremia and seizures presenting in the first two years of life. Pediatr Emerg Care. 1985;1:190-193.

16. Farrar HC, Chande VT, Fitzpatrick DF, Shema SJ. Hyponatremia as the cause of seizures in infants: a retrospective analysis of incidence, severity, and clinical predictors. Ann Emerg Med. 1995;26:42-48.

17. Fine BP, Ty A, Lestrangé N, Levine OR. Sodium deprivation growth failure in the rat: alterations in tissue composition and fluid spaces. J Nutr. 1987;117:1623-1628.

18. Al-Sofyani KA. Prevalence and clinical significance of hyponatremia in pediatric intensive care. J Pediatr Intensive Care. 2019;8:130-137.

19. Ertl T, Hadzisavvichiev K, Vincze O, Pytel J, Szabo I, Sulyok E. Hyponatremia and sensorineural hearing loss in preterm infants. Biomed. 2001;79:109-112.

20. Murphy DJ, Hope PL, Johnson A. Neonatal risk factors for cerebral palsy in very preterm babies: case-control study. BMJ. 1997;314:404-408.

21. Wattad A, Chiang ML, Hill LL. Hyponatremia in hospitalized children. Clin Pediatr (Phila). 1992;31:153-157.

22. Monnikendam CS, Mu TS, Aden JK, et al. Dysnatremia in extremely low birth weight infants is associated with multiple adverse outcomes. J Perinatol. 2019;39:842-847.

23. Abman SH, Rosenberg AA, Lum GM. Management of hyponatremia in infants with bronchopulmonary dysplasia. J Pediatr. 1988;113:789-790.

24. Mechanism and effects of manipulating chloride homeostasis in acute heart failure. https://clinicaltrials.gov/ct2/show/NCT03446651

25. Laudignon N, Ciampi A, Coupal L, Chemtob S, Aranda JY. Furosemide and ethacrynic acid: risk factors for the occurrence of serum electrolyte abnormalities and metabolic alkalosis in newborns and infants. Acta Paediatr Scand. 1989;78:133-135.

26. Laughon MM, Chantala K, Aliaga S, et al. Diuretic exposure in premature infants from 1997 to 2011. Am J Perinatol. 2015;32:49-56.

27. Pfortmueller CA, Uhlinger D, von Haeling S, Schebold JC. Serum chloride levels in critical illness-the hidden story. Intensive Care Med Exp. 2018;6:10.

28. Kotchen TA, Gallaher NH, Luke RG. Failure of NaHCO3 and KHCO3 to inhibit renin in the rat. Am J Physiol. 1987;261:1050-1056.

29. Lorenz JN, Weihprecht H, Schnermann J, Skott O, Briggs JP. Renin release from isolated juxtaglomerular apparatus depends on macula densa chloride transport. Am J Physiol. 1991;260:F486-F493.

30. Sparks MA, Crowley SD, Gurlay SB, Mirsou M, Coffman TM. Classical renin-angiotensin system in kidney physiology. Compr Physiol. 2014;4:1201-1228.

31. Abman SH, Warady BA, Lum GM, Koops BL. Systemic hypertension in infants with bronchopulmonary dysplasia. J Pediatr. 1984;104:928-931.

32. Berend K, van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes? Eur J Intern Med. 2012;23:203-211.

33. Brix O, Thomsen B, Nuetten M, Hakala A, Pudas J, Giardina B. The chloride shift may facilitate oxygen loading and unloading to/from the hemoglobin from the brown bear (Ursus arctos L.). Comp Biochem Physiol B. 1990;95:865-868.

34. Krajewski ML, Rahgumath K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. Br J Surg. 2015;102:24-36.

35. Pfortmueller CA, Fleischmann E. Acetate-buffered crystalloid fluids: current knowledge, a systematic review. J Crit Care. 2016;35:96-104.
38. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg. 2012;255:821-829.

39. Rein JL, Coca SG: “I don’t get no respect”: the role of chloride in acute kidney injury. Am J Physiol Renal Physiol. 2019;316:F587-F605.

40. Grodin JL, Simon J, Hachamovitch R, et al. Prognostic role of serum chloride levels in acute decompensated heart failure. J Am Coll Cardiol. 2015;66:659-666.

41. Grodin JL, Verbrugge FH, Ellis SG, Mullens W, Testani JM, Tang WH. Importance of abnormal chloride homeostasis in stable chronic heart failure. Circ Heart Fail. 2016;9:e002453.

42. Testani JM, Hanberg JS, Arroyo JP, et al. Hypochloremia is strongly and independently associated with mortality in patients with chronic heart failure. Eur J Heart Fail. 2016;18:660-668.

43. Bei HZ, You SJ, Zheng D, et al. Prognostic role of hypochloremia in acute ischemic stroke patients. Acta Neurol Scand. 2017;136:672-679.

44. Jarboe TM, Penman RW, Luke RG. Ventilatory failure due to metabolic alkalosis. Chest. 1972;61:618-635.

45. Tuller MA, Mehdi F. Compensatory hypoventilation and hypercapnia in primary metabolic alkalosis. Report of three cases. Am J Med. 1971;50:281-290.

46. Alexander JK, West JR, Wood JA, Richards DW. Analysis of the respiratory response to carbon dioxide inhalation in varying clinical states of hypercapnia, anoxia, and acid-base derangement. J Clin Invest. 1955;34:511-532.

47. Hanberg JS, Rao V, Ter Maaten JM, et al. Hypochloremia and diuretic resistance in heart failure: mechanistic insights. Circ Heart Fail 2016;9:10.1161/CIRCHEARTFAILURE.116.003180 e003180.

48. Perlman JM, Moore V, Siegel MJ, Dawson J. Is chloride depletion an important contributing cause of death in infants with bronchopulmonary dysplasia? Pediatrics. 1986;77:212-216.

49. Overstreet DW, Jackson JC, van Belle G, Truog WE. Estimation of mortality risk in chronically ventilated infants with bronchopulmonary dysplasia. Pediatrics. 1991;88:1153-1160.

50. Iacobelli S, Kermorvant-Duchemin E, Bonsante F, Lapillonne A, Gouyon JB. Chloride balance in pre-term infants during the first week of life. Int J Pediatri. 2012;2012:931597.

51. Dartois LL, Levek C, Grover TR, Murphy ME, Ross EL. Diuretic use and subsequent electrolyte supplementation in a level IV neonatal intensive care unit. J Pediatri Pharmacol Ther. 2020;25:124-130.

52. Seifert JL, Chang HY. Disorders of acid-base balance: new perspectives. Kidney Dis (Basel). 2017;2:170-186.

53. Bar A, Cies J, Stapleton K, Tauber D, Chopra A, Shore PM. Acetazolamide therapy for metabolic alkalosis in critically ill pediatric patients. Pediatr Crit Care Med. 2015;16:e34-e40.

54. Tanios BY, Oram MO, Noujeim C, et al. Carbonic anhydrase inhibitors in patients with respiratory failure and metabolic alkalosis: a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2018;22:275.

55. Heinly MM, Wassner SJ. The effect of isolated chloride depletion on growth and protein turnover in young rats. Pediatr Nephrol. 1994;8:555-560.

56. Tuchman S, Asico LD, Escano C, Bobb DA, Ray PE. Development of an animal model of nephrocalcinosis via selective dietary sodium and chloride depletion. Pediatr Res. 2013;73:194-200.

57. Rodriguez-Soriano J, Vallo A, Castillo G, Oliveros R, Cea JM, Balzategui MJ. Biochemical features of dietary chloride deficiency syndrome: a comparative study of 30 cases. J Pediatriatr. 1983;103:209-214.

58. Linshaw MA, Harrison HL, Gruskin AB, et al. Hypochloremic alkalosis in infants associated with soy protein formula. J Pediatriatr. 1980;96:635-640.

59. Grossman H, Duggan E, McCamman S, Welcher E, Hellerstein S. The dietary chloride deficiency syndrome. Pediatrics. 1980;66:366-374.

60. Willoughby A, Moss HA, Hubbard VS, et al. Developmental outcome in children exposed to chloride-deficient formula. Pediatrics. 1987;79:851-857.

61. Malloy MH, Graubard B, Moss H, et al. Hypochloremic metabolic alkalosis from ingestion of a chloride-deficient infant formula: outcome 9 and 10 years later. Pediatrics. 1991;87:811-822.

62. Hoorn EJ, Ellison DH. Diuretic resistance. Am J Kidney Dis. 2017;69:136-142.

63. Doering A, Jenkins CA, Storrow AB, et al. Markers of diuretic resistance in emergency department patients with acute heart failure. Int J Emerg Med. 2017;10:17.

64. Ter Maaten JM, Damman K, Hanberg JS, et al. Hypochloremia, diuretic resistance, and outcome in patients with acute heart failure. Circ Heart Fail. 2016;9:e003109.

65. Sierra CM, Hernandez EA, Parbuoni KA. Use of arginine hydrochloride in the treatment of metabolic alkalosis or hypochloremia in pediatric patients. J Pediatri Pharmacol Ther. 2018;23:111-118.

66. Bragulat E, de la Sierra A, Antonio MT, Coca A. Endothelial dysfunction in salt-sensitive essential hypertension. Hypertension. 2001;37:444-448.

67. Bagrov AY, Lakatta EG. The dietary sodium-blood pressure plot “stiffens”. Hypertension. 2004;44:22-24.

68. Boddi M, Poggesi L, Coppo M, et al. Human vascular renin-angiotensin system and its functional changes in relation to different sodium intakes. Hypertension. 1998;31:836-842.

69. Sehgal A, Malikivi A, Paul E, Tan K, Menahem S. Systemic arterial stiffness in infants with bronchopulmonary dysplasia: potential cause of systemic hypertension. J Pediatriatr. 2016;36:564-569.

70. Alagappan A, Malloy MH. Systemic hypertension in very low-birth weight infants with bronchopulmonary dysplasia: incidence and risk factors. Am J Pediatriatr. 1998;15:3-8.

71. Anderson AH, Warady BA, Daily DK, Johnson JA, Thomas MK. Systemic hypertension in infants with
severe bronchopulmonary dysplasia: associated clinical factors. *Am J Perinatol.* 1993;10:190-193.

72. Bancalari E, Wilson-Costello D, Iben SC. Management of infants with bronchopulmonary dysplasia in North America. *Early Hum Dev.* 2005;81:171-179.

73. Wells TG. The pharmacology and therapeutics of diuretics in the pediatric patient. *Pediatr Clin North Am.* 1990;37:463-504.

74. Hoffman DJ, Gerdes JS, Abbasi S. Pulmonary function and electrolyte balance following spironolactone treatment in preterm infants with chronic lung disease: a double-blind, placebo-controlled, randomized trial. *J Perinatol.* 2000;20:41-45.

75. Ellison DH, Loffing J. Thiazide effects and adverse effects: insights from molecular genetics. *Hypertension.* 2009;54:196-202.

76. Liamis G, Mitrogianni Z, Liberopoulos EN, Tsimihodimos V, Elisaf M. Electrolyte disturbances in patients with hyponatremia. *Intern Med.* 2007;46:685-690.

77. Tiwari S, Packer RK, Hu X, Sugimura Y, Verbalis JG, Ecelbarger CA. Increased renal alpha-ENaC and NCC abundance and elevated blood pressure are independent of hyperaldosteronism in vasopressin escape. *Am J Physiol Renal Physiol.* 2006;291:F49-F57.

78. Buck ML. Clinical experience with spironolactone in pediatrics. *Ann Pharmacother.* 2005;39:823-828.

79. Moffett BS, Haworth TE, Wang Y, Afonso N, Checchia PA. Spironolactone effect on potassium supplementation in paediatric cardiac intensive care patients. *J Clin Pharm Ther.* 2017;42:433-437.

80. Hobbins SM, Fowler RS, Rowe RD, Korey AG. Spironolactone therapy in infants with congestive heart failure secondary to congenital heart disease. *Arch Dis Child.* 1981;56:934-938.

81. Aperia A, Broberger O, Herin P, Zetterström R. Sodium excretion in relation to sodium intake and aldosterone excretion in newborn pre-term and full-term infants. *Acta Paediatr Scand.* 1979;68:813-817.

82. Spitzer A. The role of the kidney in sodium homeostasis during maturation. *Kidney Int.* 1982;21:539-545.

83. Osorio AV, Alon US. The relationship between urinary calcium, sodium, and potassium excretion and the role of potassium in treating idiopathic hypercalciuria. *Pediatrics.* 1997;100:675-681.

84. Frassetto LA, Nash E, Morris RC Jr, Sebastian A. Comparative effects of potassium chloride and bicarbonate on thiazide-induced reduction in urinary calcium excretion. *Kidney Int.* 2000;58:748-752.

85. Mok NS, Tong CK, Yuen HC. Concomitant-acquired Long QT and Brugada syndromes associated with indapamide-induced hypokalemia and hyponatremia. *Pacing Clin Electrophysiol.* 2008;31:772-775.

86. Fichman MP, Vorherr H, Kleeman CR, Telfer N. Diuretic-induced hyponatremia. *Ann Intern Med.* 1971;75:853-863.

87. Nguyen MK, Kurtz I. Determinants of plasma water sodium concentration as reflected in the Edelman equation: role of osmotic and Gibbs-Donnan equilibrium. *Am J Physiol Renal Physiol.* 2004;286:F828-F837.

88. Brunette MG, Mailloux J, Lajeunesse D. Calcium transport through the luminal membrane of the distal tubule. I. Interrelationship with sodium. *Kidney Int.* 1992;41:281-288.

89. Brickman AS, Massry SG, Coburn JW. Changes in serum and urinary calcium during treatment with hydrochlorothiazide: studies on mechanisms. *J Clin Invest.* 1972;51:945-954.

90. Campfield T, Braden G, Flynn-Valone P, Powell S. Effect of diuretics on urinary oxalate, calcium, and sodium excretion in very low birth weight infants. *Pediatrics.* 1997;99:814-818.

91. Martin WJ, Matzke GR. Treating severe metabolic alkalosis. *Clin Pharm.* 1982;1:42-48.

92. Tam B, Chhay A, Yen L, et al. Acetazolamide for the management of chronic metabolic alkalosis in neonates and infants. *Am J Ther.* 2014;21:477-481.

93. Moffett BS, Moffett TI, Dickerson HA. Acetazolamide therapy for hypochloremic metabolic alkalosis in pediatric patients with heart disease. *Am J Ther.* 2007;14:331-335.

94. López C, Alcaraz AJ, Toledo B, Cortejoso L, Gil-Ruiz MA. Acetazolamide therapy for metabolic alkalosis in pediatric intensive care patients. *Pediatr Crit Care Med.* 2016;17:e551-e558.

95. Andrews MG, Johnson PN, Lammers EM, Harrison DL, Miller JL. Acetazolamide in critically ill neonates and children with metabolic alkalosis. *Ann Pharmacother.* 2013;47:1130-1135.

96. Heller I, Halevy J, Cohen S, Theodor E. Significant metabolic acidosis induced by acetazolamide. Not a rare complication. *Arch Intern Med.* 1985;145:1815-1817.