Monitoring fluid and electrolyte therapy in the newborn intensive care unit

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Fluid and electrolyte management is an important and challenging part of the management of any very premature or critically ill newborn. The newborn's ability to maintain fluid and electrolyte homeostasis in the face of the vagaries of extrauterine life is compromised by immature renal function.

The very premature neonate is at risk of excessive water loss and hypernatremia as the result of high insensible water loss, which is not subject to homeostatic control.

Management of fluid and electrolyte intake in premature infants is further complicated by diuresis and natriuresis in the first week of life, which result in an apparently physiologic contraction of the ECW (extracellular water) compartment, as well as shift of potassium from the ICW (intracellular water) to ECW compartments, which may result in life-threatening hyperkalemia.

With cord clamping, glucose and fat stores must be mobilized and gluconeogenesis stimulated in order to prevent hypoglycemia. For these reasons laboratory monitoring of fluid and electrolyte status is critical during this time.

Practical guidelines for monitoring fluid and electrolyte therapy based on gestational age and degree of illness are provided. Appropriate restraint and micromethod assays are necessary to minimize phlebotomy losses.

Reference ranges are provided where appropriate and their limitations are discussed.

Introduction

Fluid and electrolyte management is an important and challenging part of the management of any very premature or critically ill newborn. The transition from fetal to neonatal life is associated with major changes in water and electrolyte homeostasis.

Before birth, the fetus has a constant and readily available supply of water and electrolytes from the mother across the placenta and fetal water, and

electrolyte homeostasis is largely a function of maternal and placental homeostatic mechanisms.

After birth, the newborn must rapidly assume responsibility for fluid and electrolyte homeostasis with little ability to control intake and a diminished renal capacity to compensate for fluid and electrolyte perturbations, in an environment in which water and electrolyte losses are much more variable.

In preterm infants, there are major changes in total body fluid and electrolyte balance as well.

Thus, the goal of fluid and electrolyte therapy in the immediate postnatal period in preterm infants is not to maintain fluid and electrolyte balance, but to allow the appropriate changes to occur without detrimental perturbations in fluid and electrolyte status.

In critically ill infants, diseases and therapeutic interventions may impair their ability to maintain fluid and electrolyte homeostasis. Finally, relatively small absolute changes in total body water and electrolytes will result in relatively large percent changes in total body water and electrolytes in the neonate, especially in the smallest infants.

For these reasons, appropriate monitoring of fluid and electrolyte status is a cornerstone of management of the very premature or critically ill newborn. This discussion will be limited to the first week of life because this is the most dynamic period for body water and electrolytes.

Moreover, after the first several days of life, fluid and electrolyte management are part of nutritional management, which is beyond the scope of this review.

Background

Renal function. The newborn's ability to maintain fluid and electrolyte homeostasis in the face of the vagaries of extrauterine life is compromised by immature renal function. Glomerular filtration rate (GFR) varies directly with gestational age.

However, GFR is low even in the term infants, whether normalized to body weight or body surface area. This limits the ability of the newborn, especially the preterm newborn, to excrete water, sodium and potassium loads.

On the other hand, renal sodium losses are greater in preterm infants, but not term infants, under basal conditions due to reduced sodium reabsorptive capacity of the immature proximal tubule.

Finally, the ability of the newborn to conserve water is limited by lesser maximal capacity to concentrate their urine.

Evaluation of GFR in the newborn period is problematic. GFR cannot be extrapolated from the value of plasma creatinine, as is the case in older children and adults. First, plasma creatinine in cord blood largely reflects maternal renal function because creatinine equilibrates across the placenta.

Second, abrupt changes in the extracellular water (ECW) compartment volume and creatinine clearance after birth (as discussed below) preclude steady-state conditions in the first few days of life, which are required for GFR to be estimated from plasma creatinine concentration.

For these reasons, the appropriateness of renal function is better reflected in the rate of change in plasma creatinine concentration. In normal term infants, serum creatinine concentration declines exponentially in the first few days of life [1].

Interpretation of the rate of change in plasma creatinine concentration in preterm infants is complicated by the fact that with normal renal function the rate of decline is directly related to gestational age [2].

This is because GFR is directly related to gestational age and because renal tubular reabsorption of creatinine, which occurs uniquely in the newborn, varies inversely with maturity. In extremely premature infants, plasma creatinine concentration may remain unchanged or even increase slightly during the first week of life.

The plasma urea nitrogen concentration is a function of metabolic state, changes in ECW compartment volume and amount of protein intake, as well as GFR. Therefore, neither plasma urea nitrogen concentration nor plasma urea nitrogen-to-creatinine ratio adds significant additional information about renal function to that provided by plasma creatinine concentration.

Body water and sodium (Na). The newborn is at risk of excessive water loss and hypernatremia as the result of high evaporative water loss through the skin, insensible water loss (IWL), which is not subject to any sort of homeostatic control, as well as decreased capacity to concentrate the urine.

In general, IWL is inversely proportional to gestational and postnatal age and ambient humidity [3, 4]. However, IWL is difficult to predict because there is great variability among individual neonates, even when gestational and postnatal age and ambient humidity are taken into consideration.

In premature infants, management of fluid and electrolyte intake is further complicated by an abrupt and absolute decrease in total body water in the first few days after birth in premature infants.

This decrease is independent of the gradual changes in the proportion of body weight that is water and the changes in the proportions of total body water contributed by the ECW and intracellular water (ICW) compartments during development [5].

This decrease results in large part from contraction of the ECW compartment after birth [6-9]. The reason for this contraction is not well understood. However, relatively large increases in water and sodium intake are necessary to attenuate it [10] and even higher intakes are associated with increased morbidity [11, 12].

Thus, contraction of the ECW compartment (and, therefore, net water and sodium loss) is believed to be physiologically appropriate in the first week of life in preterm infants.

The excretion of water and sodium that occurs as the result of contraction of the ECW compartment in the first few days of life does not usually occur gradually. A characteristic pattern of fluid and electrolyte adaptation, which is largely independent of fluid and electrolyte intake, is observed in the first week of life in the majority of very premature newborns [13].

During the first day or two of life, urine output is low regardless of intake. Urinary sodium excretion is low. Low GFR limits the infant's ability to excrete water and electrolyte loads.

IWL will be the major route of water loss in very premature infants. During this time, under- or overestimation of IWL can lead to hypernatremic dehydration or water intoxication, respectively.

Subsequently, an abrupt increase in urine and urinary sodium output occurs regardless of water or sodium intake, as the result of abrupt increases in creatinine clearance and fractional excretion of sodium. Contraction of the ECW compartment occurs largely with this diuresis and natriuresis. Serum sodium concentration often rises sharply during this period.

Finally, as the ECW compartment stabilizes at an appropriately reduced volume, the neonate's ability to maintain fluid and electrolyte homeostasis improves, and urinary water and electrolyte excretion decreases and begins to vary appropriately with intake.

Potassium (K). In very premature infants, serum potassium concentration rises in the first 24 to 72 hours after birth, even in the absence of exogenous potassium intake and/or renal failure [14-16].

This increase is a result of a shift of potassium from the ICW to ECW space, in face of a limited capacity to secrete potassium (as the result of the low GFR during this time).

The magnitude of this shift correlates roughly with the degree of prematurity, but it does not seem to occur (or at least is not clinically significant) after 30 to 32 weeks of gestation [15].

The reason for and physiologic appropriateness of this shift is not known. However, it has been reported to result in hyperkalemia in 25 to 50 % of infants < 1000 g birth weight or < 28 weeks of gestation.

With the onset of diuresis and natriuresis, serum potassium concentration usually falls, as increased delivery of water and sodium to the distal nephron increases. In fact, hypokalemia commonly occurs after the onset of diuresis and natriuresis, even in infants who were previously hyperkalemic.

Glucose. With cord clamping, neonatal serum glucose concentration falls sharply over the first 60 to 90 minutes of life. Changes in counter-regulatory hormones and insulin result in mobilization of glucose and fat and stimulate gluconeogenesis.

In most neonates, the resulting increase in endogenous glucose production results in an increase in and stabilization of plasma glucose concentration.

However, endogenous glucose production may be inadequate or unable to be sustained at an adequate rate with prematurity, with perinatal stress, with intrauterine growth retardation, in infants of diabetic mothers, and in infants who cannot be fed.

Exogenous glucose administration is then necessary to prevent hypoglycemia and conserve glycogen stores.

On the other hand, stress can result in marked hyperglycemia because of catecholamine-mediated mobilization of glycogen stores. Premature infants are also at increased risk of hyperglycemia with exogenous glucose infusion because of a sluggish insulin response to rising plasma glucose concentrations.

Thus, usual rates of glucose administration may, then, result in hyperglycemia with the attendant risks of hyperosmolality and osmotic diuresis.

Routine monitoring schedules (Table I)

From the discussion above, it is clear that the frequency of monitoring will depend on gestational age, postnatal age, and clinical condition. Monitoring must be frequent enough to avoid unrecognized perturbations in fluid and electrolyte status.

At the same time, the frequency of monitoring should be minimized as much as possible in order to avoid iatrogenic hypovolemia, anemia and blood transfusions. The monitoring guidelines presented are based on the author's experience with these considerations in mind.

Preanalytical considerations

The relatively small sample sizes required to minimize the decrement in the newborn's blood volume and the routes by which blood samples are obtained for analysis (predominantly skin puncture and indwelling catheters) make preanalytical considerations particularly important in the neonate.

Many of these considerations have been addressed previously on this site [17, 18]. Only one, often poorly understood, consideration will be discussed here.

Hyperlipemia is not uncommon in infants receiving intravenous lipid infusion as part of parenteral nutrition. This may result in fictitious hyponatremia; however, whether it does or not depends on the analytic method used to measure plasma sodium concentration.

Indirect ion-specific electrode analysis is typically used in large automated chemistry analyzers.

It involves dilution of the plasma sample with a large volume of diluent and, therefore, measures the concentration of sodium in the total plasma sample (plasma water and plasma solids, i.e. lipids and protein).

Hyperlipemia will result in relative less water (and thereby sodium) in a given volume of plasma, causing the reported plasma sodium concentration to be spuriously low.

This is also the case when serum sodium concentration is measured using flame photometry, which also requires

Gestational Age[1]	Analyte(s)	Monitoring schedule[2]
≤ 25 weeks	Na, K, Cl[3], tCO_2 (or HCO_3)[3,4]	By 8-12 h; then every 8-12 h until stable or trending towards reference range; then daily
	Glucose	Usually estimated frequently at point of care; values in the lower portion of the reference range estimated with dry-reagent test strips must be confirmed with a serum glucose concentration to reliably identify hypoglycemia[5]
	Creatinine	By 8-12 h; then daily
26-30 weeks	Na, K, CL, tCO_2 (or HCO_3)	By 12-24 h; then every 12-24 h until stable or trending towards reference range; then daily
	Glucose	As above
	Creatinine	Creatinine
30-34 weeks	Na, K, CL, tCO_2 (or HCO_3)	By 18-24 h, then daily. As above. By 18-24h, then only if renal insufficiency is anticipated or suspected
	Glucose	As above
	Creatinine	Creatinine
≥ 34 weeks on intravenous maintenance	Na, K, Cl, tCO_2 (or HCO_3)	At 18-24 h, then daily
	Glucose	As above
	Creatinine	At 18-24 h, then only if renal insufficiency is anticipated or suspected
≥ 34 weeks without intravenous maintenance	Na, K, Cl, CO_2 (or HCO_3)	Only as indicated by excessive weight loss or unusual water and electrolyte loss
	Glucose	As above, but only with risk factor or signs consistent with hypoglycemia
	Creatinine	Only if renal insufficiency is anticipated or suspected
1. Gestational age ranges are provided as approximations; the cutoffs are not intended to be rigid.		
2. Monitoring may need to be more frequent with renal dysfunction, unusual fluid and electrolyte losses, marked perturbations in fluid and electrolyte homeostasis, etc.		
3. Cl, Chloride; tCO_2, total carbon dioxide; HCO_3, bicarbonate		
4. Routine assessment of plasma Cl and total carbon dioxide (or bicarbonate) concentration provide little additional information, if acid-base status is being assessed with blood gases. The anion gap is of limited use in the evaluation of metabolic acidosis in the newborn, unless it is > two standard deviations above the mean (in which case positive predictive value is high, but sensitivity is low) or less than the mean (in which case negative predictive value is high, but specificity is low [21]. Furthermore, if the sample is obtained from a skin stick without prewarming, then the tCO_2 may be spuriously low. If organic acidosis is suspected, organic acid concentrations should be measured. This is now quite practical, because lactate will be the most common cause of organic acidosis by far in the newborn intensive care unit, and micromethod assay and point-of-care testing are available for this analyte.		
5. Other methods that involve very small sample volumes are available that offer accuracy and precision comparable with laboratory methods.		

TABLE I. Guidelines for monitoring fluid and electrolyte therapy in the neonatal intensive care unit. (Modified from Lorenz JM. Assessing fluid and electrolyte status in the newborn. Clin Chem 1997; 43: 205-10, with permission).

sample dilution. The same measurement error will occur with any electrolyte analyzed in diluted plasma, but it is clinically significant only for sodium.

Hyperlipemia can be avoided by discontinuing the intravenous lipid infusion for several hours before obtaining the plasma sample for analysis, but this is often impractical. Direct ion-specific electrode analysis, which is typically employed in blood gas analyzers and point-of-contact instruments, measures electrical activity in plasma water (which is the physiologically relevant measure) in undiluted whole-blood or plasma samples.

Plasma electrical activity is then converted to plasma concentration by a fixed ion-specific multiplier, which is independent of plasma solids. The result, therefore, is unaffected by variations in the amount of solids in plasma.

See Holbek et al for a particularly lucid explanation of this issue [19].

Analytical considerations

Blood sample volume. The most important determinant of the blood volume transfused is the volume of blood taken for laboratory testing. Blood volume is 80 mL/kg body weight in term newborns and 100 mL/kg in preterm newborns.

Blood transfusion may be required when > 10-15 % of total blood volume is withdrawn over two to three days. Thus, the availability of micromethod assays is mandatory in centers regularly caring for newborns - even healthy full-term newborns.

It is also critical for the smallest newborns, who require the most frequent testing, that phlebotomists, nurses and physicians be knowledgeable about the minimum volume of sample required for an analysis or combination of analyses and that analytes should be grouped so that sample volume is minimized.

It is also prudent to record and track the volume of blood removed, at least in very small infants.
Turnaround time. All analyses in Table I should routinely be available 24 hours per day, seven days per week with an intralaboratory turnaround time of two hours. STAT analyses should be available with an intralaboratory turnaround time of 30 minutes.

Analytical error. In the United States, the federal government has specified total allowable analytical error that a proficiency testing value may have (**Table II**) [20]. Total analytical error is composed of intralaboratory imprecision and interlaboratory inaccuracy.

Clinicians should be knowledgeable at least about the precision of analyte measurements used in their own center, so that the significance of changes in values over time can be appropriately interpreted.

Reference ranges (Table III)

Reference ranges specific to newborns by gestational age and postnatal age have been published.

However, with the exception of the upper limit of potassium concentration and the lower limit of glucose concentration (see **Table III**), they have been determined on the basis of the statistical distribution of values within "healthy" newborns.

CLIA proficiency testing requirements [20]
Sodium ± 4 mmol/L
Potassium ± 0.5 mmol/L
Chloride ± 5 %
Glucose ± 0.3 mmol/L (± 6 mg/dL) or 10 %
Creatinine ± 25 mmol/L (± 0.3 mg/dL) or 15 % (whichever is greater)

TABLE II

This is problematic for newborns; first, because these vary with intake, which is prescribed by the caretaker and not for the most part moderated by the infant. Second, being born prematurely is not "healthy".

Therefore, values that are not statistically unusual (e.g. hypernatremia in extremely premature infants) may not be without adverse effects. On the other hand, as for any reference range based on statistical distributions, values out of the range (e.g. moderately elevated plasma glucose concentrations in stressed or preterm infants receiving endogenous glucose) may not have serious consequences or be indicative of pathology. Reference ranges in **Table III** are intended as approximate guidelines.

Analyte	Plasma concentrations[1]	
	SI units	Conventional units
Sodium[2]	135-145 mmol/L	135-145 mEq/L
Potassium[3]	3.6-6.7 mmol/L	3.6-6.7 mEq/L
Chloride[2]	101-111 mmol/L	101-111 mEq/L
Total carbon dioxide[2]	23-28 mmol/L[4]	24-28 mEq/L[4]
Bicarbonate[2]	22-27 mmol/L[4]	22-27 mmol/L[4]
Glucose	2.65-8.3 mmol/L	47-150 mg/dl
Creatinine	Not applicable[6]	Not applicable[6]

1. Although these analytes are often measured in serum, reference ranges for most are available only in plasma. However, with the exception of potassium (see footnote 3), concentrations of analytes in serum and plasma are similar.
2. Ranges given are for adults; there is no reason to believe, however, that these are not the physiologically optimal ranges to maintain in the newborn. Values outside these ranges are common in the premature newborns with normal water and electrolyte homeostatic capacity and no unusual fluid and electrolyte losses; therefore, values outside these ranges are not necessarily indicative of homeostatic mechanism pathology or abnormal fluid and electrolyte losses.
3. Serum potassium concentration [14]. During whole-blood clotting, platelets release potassium into serum; therefore, plasma potassium concentration in adults is typically 0.2-0.3 mmol/L lower in plasma than in serum.
4. With partial pressure of carbon dioxide 5.4 kPa (40 mmHg); varies directly with the partial pressure of carbon dioxide in the absence of any perturbation in metabolic acid-base status; lower values are the rule in the immediate postnatal period after normal labor (because of lactic acidosis) and in preterm infants after the first few days of life (because of decreased renal acid secretory capacity) in the absence of pathology.
5. There is no general agreement on the definition of hypoglycemia. In fact, the value that is clinically significant may vary depending upon the availability of alternative fuels for brain metabolism and associate comorbidities, e.g. polycythemia, asphyxia, hypocapnia. However, physiologic responses and poorer mental and motor development have been observed among infants who had plasma glucose concentrations of 2.6 mmol/L [22].
6. Initially a function of maternal plasma creatinine concentration, then varies with gestational and postnatal age. Rudd *et al* [2] reported reference ranges for plasma creatinine concentration measured using a modification of the Jaffe reaction for infants 25-42 weeks of gestational age in 4-week groupings at 2, 7, 14, 21 and 28 days of age. However, values have been reported to be 50 % lower with automated enzymatic methods with which there is less interference by bilirubin, ketoacids and cephalosporins [23].

TABLE III. Reference ranges (Modified from Lorenz JM. Assessing fluid and electrolyte status. Clin Chem 1997; 43: 205-10, with permission.)

Summary

The first week of life is a very dynamic period for body water and electrolytes during which the risk of perturbations of body water and electrolytes is great. Laboratory monitoring of fluid and electrolyte status is critical during this time.

Monitoring must be frequent enough to insure that perturbations in fluid and electrolyte status are recognized before they become critical, but no more than necessary to minimize iatrogenic hypovolemia, anemia and blood transfusions.

Micromethod assays and knowledge of minimum sample volumes required for analyses are also mandatory to minimize phlebotomy losses. Guidelines regarding the frequency of laboratory monitoring based on gestational age and clinical condition can be useful, especially for less experienced clinicians.

It is important to be aware of potential preanalytical sources of error to avoid being misled by spurious values.

Finally, clinicians should be aware of the degree of imprecision in the measurement of each analyte in their own laboratories, in order to not misinterpret changes in analyte concentrations of the magnitude of these imprecisions as true trends.

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