Electrolyte Disorders in the Newborn

4

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4.1 Hyponatremia

Core Messages

- Hyponatremia typically results from a combination of arginine vasopressin excess plus free water intake**.**
- 3 % sodium chloride is the most effective therapy for treating hyponatremic encephalopathy.

Case Vignette

A 4-kg 2-week-old child is admitted to the hospital for severe bronchiolitis with hypoxia and tachypnea. The child is placed on parenteral fluids with 0.225 % sodium chloride (39 mEq/L) in 5 % dextrose in water at a rate of 16 mL/h. Twenty-four hours following admission, the child suffers a generalized tonic-clonic seizure. Biochemistries reveal serum sodium 122 mEq/L, potassium 4 mEq/L, blood urea nitrogen 2 mg/dL, creatinine 0.2 mg/dL, osmolality 238 mOsm/kg H_2O, urine osmolality 400 mOsm/kg H_2O, and urine sodium plus potassium concentration 90 mEq/L.

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4.1.1 Introduction

Hyponatremia is defined as a serum sodium level <135 mEq/L [1]. It is one of the most common electrolyte disorders encountered in the newborn in both the outpatient and inpatient setting. The cause is usually easily identified by history, but in many cases, it can be elusive. Hyponatremia has typically been viewed as relatively benign condition, but there is increasing evidence in both children and adults suggesting that hyponatremia is a serious condition [2]. Numerous studies in adults have revealed that even mild and asymptomatic hyponatremia is an independent predictor of mortality [3]. Studies in neonates have revealed that hyponatremia is an independent predictor of poor neuromotor outcome and has been associated with impaired neonatal growth and development, sensorineural hearing loss, cerebral palsy, and intracranial hemorrhages [4, 5]. The most serious complication of hyponatremia is that of hyponatremic encephalopathy. Increasing evidence has revealed that the majority of hyponatremic encephalopathy in children is iatrogenic and related to errors in parenteral fluid therapy [6].

4.1.2 Pathogenesis of Hyponatremia

Under normal circumstances, the human body can maintain plasma sodium levels within the normal range (135–145 mEq/L [135–145 mmol/L]), despite wide fluctuations in fluid intake. The

A.S. Chishti et al. (eds.), *Kidney and Urinary Tract Diseases in the Newborn*,
DOI 10.1007/978-3-642-39988-6_4, © Springer-Verlag Berlin Heidelberg 2014

Table 4.1 Causes of hyponatremia in the newborn

1. Water intoxication: improperly mixed infant formula
2. Gastrointestinal losses
(a) Diarrheal dehydration, congenital chloride diarrhea, intestinal fistulas
(b) Vomiting, pyloric stenosis, nasogastric suction
3. Skin losses: cystic fibrosis
4. Renal losses
(a) Salt-wasting nephropathy
(i) Bartter syndrome/Gitelman syndrome
(ii) Renal tubular acidosis/Fanconi syndrome
(iii) Nephronophthisis diuretics
(b) Mineralocorticoid deficiency
(i) Congenital adrenal hyperplasia
(ii) Bilateral adrenal hemorrhage
(c) Mineralocorticoid resistance
(i) Pseudohypoaldosteronism type 1
(ii) Obstructive uropathy
(iii) Pyelonephritis
(d) Diuretics
(e) Cerebral salt wasting
(f) Hyponatremic hypertensive syndrome
(g) Polyuric phase of acute kidney injury
5. Edematous states
(a) Heart failure
(b) Cirrhosis
(c) Nephrotic syndrome
6. Decrease peripheral vascular resistance
(a) Sepsis
(b) Hypothyroidism
7. Renal failure
(a) Acute
(b) Chronic
8. Non-hypovolemic states of ADH excess
(a) SIADH (Table 4.2)
(b) Postoperative state
(c) Nausea, vomiting
(d) Pain, stress
(e) Glucocorticoid deficiency
9. Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)

body's primary defense against developing hyponatremia is the kidney's ability to generate dilute urine and excrete free water. The primary reasons that children develop hyponatremia encompass underlying conditions that impair the kidney's ability to excrete free water (Table 4.1). Hyponatremia usually occurs in the setting of excess water intake, with or without sodium losses, in the presence of impaired free water excretion. The most common reason for impaired free water excretion is due to arginine vasopressin (AVP) excess. There are numerous hemodynamic and non-hemodynamic stimuli for AVP excess that place virtually all hospitalized patients at risk for developing hyponatremia. Common causes of AVP production are volume depletion, pain, stress, nausea, vomiting, pulmonary disorders, the postoperative state, central nervous system (CNS) disorders, edematous states, and narcotic use. Only under the most extreme circumstances can excess water intake or sodium loss alone lead to hyponatremia in the absence of impaired free water excretion.

4.1.3 Diagnostic Approach

Before embarking on an aggressive therapeutic regimen, it is vital to confirm that hyponatremia is in fact associated with hypoosmolality. Hyponatremia can be associated with either a normal or an elevated serum osmolality (Fig. 4.1). The most common reasons for this are hyperglycemia, severe hyperproteinemia, or hyperlipidemia [7]. Hyperglycemia results in hyperosmolality with a translocation of fluid from the intracellular space to the extracellular space, resulting in a 1.6 mEq/L fall in the serum sodium for every 100 mg/dL elevation in the serum glucose concentration above normal. Severe hyperlipidemia, hypercholesterolemia, hyperproteinemia, or radiocontrast can cause a displacement of plasma water, which will result in a decreased sodium concentration (pseudohyponatremia) with a normal serum osmolality. Serum sodiums are currently measured by either direct or indirect-reading ion-selective electrode potentiometry. The direct method will not result in pseudohyponatremia, as it measures the activity of sodium in the aqueous phase of serum only. The indirect method, on the other hand, can result in pseudohyponatremia as the specimen is diluted with a reagent prior to measurement. The indirect method is currently performed in approximately 60 % of chemistry labs in the United States; therefore,

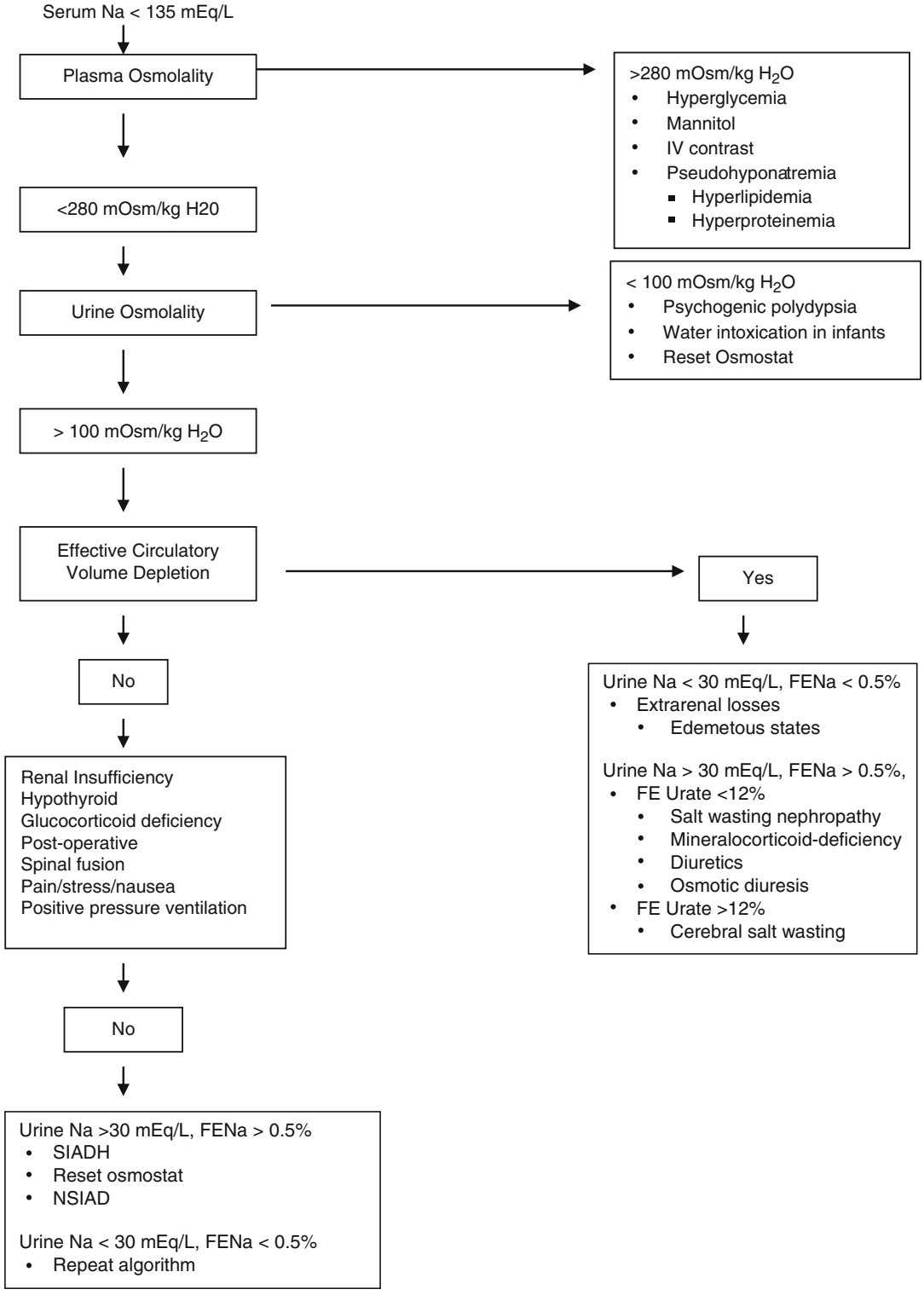

Fig. 4.1 Evaluation of hyponatremia

pseudohyponatremia remains an entity that clinicians need to be aware of. If hyponatremia is associated with hypoosmolality (true hyponatremia) and the history does not suggest an obvious cause, the next step is to measure the urinary osmolality to determine if there is an impaired ability to excrete free water (urine Osm > 100 mOsm/kg).

The information that is most useful in arriving at a correct diagnosis of hyponatremia is a detailed history of fluid balance, weight changes, medications (especially diuretics), and underlying medical illnesses. Hyponatremia is usually a multifactorial disorder, and a detailed history will identify sources of salt and water losses, free water ingestion, and underlying illnesses that cause a nonosmotic stimulus for vasopressin production. An assessment of the volume status on physical examination and the urinary electrolytes can be extremely helpful, but both can be misleading. In patients in whom hyponatremia is due to salt losses, such as diuretics, signs of volume depletion may be absent on physical examination, as the volume deficit may be nearly corrected due to oral intake of hypotonic fluids if the thirst mechanism is intact.

In general, a urinary sodium concentration <30 mEq/L and a fractional excretion of sodium (FENa) <0.5 % in adults are consistent with effective circulating volume depletion, while a urine sodium >30 mEq/L or a FENa >0.5 % is consistent with renal tubular dysfunction, use of diuretics, adrenal insufficiency, the syndrome of inappropriate antidiuretic hormone secretion (SIADH), or cerebral salt wasting [8]. The plasma uric acid and fraction excretion of urate (FE urate) can be helpful in distinguishing SIADH from other hyponatremic states associated with urinary sodium loss [9, 10]. SIADH virtually always associates with increase urate clearance with hypourecemia (serum uric acid <4 mg/dL) and an elevated FE urate (>12 %). There have been no studies to validating if these adult parameters for urine chemistries can be applied to the newborn with hyponatremia. Numerous factors can affect the urine chemistries, making interpretation difficult; therefore, the timing of the urinary measurements in relation to dosages of diuretics, intravenous fluid boluses, or fluid and sodium restriction is also important.

4.1.4 Prevention of Hospital-Acquired Hyponatremia

Hospital-acquired hyponatremia is of particular concern in the newborn as the standard of care in pediatrics has been to administer hypotonic fluids containing 0.2 % sodium chloride (34 mEq/L) as maintenance fluids [11]. The safety of this approach has never been established, and there have been numerous reports of death and permanent neurologic injury from hospital-acquired hyponatremic encephalopathy in children receiving hypotonic fluids [12]. Hospitalized children have numerous nonosmotic stimuli for vasopressin production that place them at risk for developing hyponatremia. Hyponatremia is especially dangerous in children with underlying CNS injury such as encephalitis, with mild hyponatremia (sodium >130 mEq/L) resulting in cerebral edema and even herniation [13, 14]. The most important measure that can be taken to prevent hyponatremia is to avoid using hypotonic fluids in children who have clear risks for nonosmotic AVP secretion and to initially administer isotonic saline, 0.9 % sodium chloride, unless otherwise clinically indicated [12, 15]. The serum sodium should be measured daily in any patient receiving continuous parenteral fluid and adjustments to the composition of intravenous fluids be made accordingly.

4.1.5 Syndrome of Inappropriate Antidiuretic Hormone Production (SIADH)

SIADH is one of the most common causes of hyponatremia in the hospital setting and frequently leads to severe hyponatremia (plasma Na <120 mEq/L). It is caused by elevated AVP secretion in the absence of an osmotic or hypovolemic stimulus. SIADH can occur due to a variety of illnesses but most often occurs due to central nervous system disorders, pulmonary disorders, and

Table 4.2 Common causes of SIADH in the newborn

Central nervous system disorders	*Malignancies*
Infection: meningitis, encephalitis	Neuroblastoma
Neoplasms	Lymphomas
Vascular abnormalities	*Medications*
Hydrocephalus	Vincristine
Brain surgery	Intravenous Cytoxan
Head trauma	Carbamazepine
Intracranial hemorrhage or thrombosis	Oxcarbazepine
Pulmonary disorders	Narcotics
Pneumonia	Nonsteroidal anti-inflammatory drugs
Bronchiolitis	
Asthma	
Cystic fibrosis	
Positive-pressure ventilation	
Pneumothorax	

medications (Table 4.2) [16, 17]. Among the latter, the chemotherapeutic drugs vincristine and Cytoxan and the antiepileptic drug carbamazepine are especially common. SIADH is essentially a diagnosis of exclusion as can be seen from Fig. 4.1. Before SIADH can be diagnosed, diseases causing decreased effective circulating volume, renal impairment, adrenal insufficiency, and hypothyroidism must be excluded. Adrenal insufficiency can be difficult to rule out; therefore, cortisol level should be checked in a patient considered to have SIADH. The hallmarks of SIADH are as follows: mild volume expansion with low to normal plasma concentrations of creatinine, urea, uric acid, and potassium; impaired free water excretion with normal sodium excretion which reflects sodium intake; and hyponatremia which is relatively unresponsive to sodium administration in the absence of fluid restriction.

SIADH is usually of short duration and resolves with treatment of the underlying disorder and discontinuation of the offending medication. Fluid restriction is the cornerstone to therapy. However, fluid restriction results in slow correction of hyponatremia and is frequently impractical in infants who receive most of their nutrition as liquids. All intravenous fluids should be of a tonicity of at least normal saline, and if this does not correct the plasma sodium, 3 % sodium chloride may be given as needed. If a more rapid correction of hyponatremia is needed, the addition of a loop diuretic in combination with hypertonic saline is useful. Vasopressin 2 antagonists are new medications that are now FDA approved for the treatment SIADH in adults [18]. These drugs may have a role for treatment of SIADH in children.

4.1.6 Oral Water Intoxication in Infants

Water intoxication is one of the most common causes of symptomatic hyponatremia in healthy infants; 70 % of infants younger than 6 months of age who develop seizures that have no apparent cause are found to have hyponatremia due to water intoxication [19]. Most of these infants are living in poverty and develop water intoxication when caregivers either dilute formula inappropriately or supplement feedings with water [20]. Because an infant's caloric intake depends almost entirely on a liquid diet, hunger will drive the infant to accept a low-solute formula to the point of water intoxication. Infants typically present with generalized tonic-clonic seizures, respiratory insufficiency, and hypothermia. Affected infants may be managed with rapid and partial correction of hyponatremia via administration of hypertonic or normal saline [21]. The hyponatremia corrects rapidly due to a free water diuresis, and it corrects spontaneously in many infants after they resume normal feeding. With appropriate treatment, the prognosis generally is good without long-term neurologic sequelae.

4.1.7 Diuretics

Diuretics are a relatively common cause of hyponatremia in hospitalized children, with the potential for causing severe and symptomatic hyponatremia [22]. Hyponatremia is primarily seen with thiazide diuretics [23]. Thiazide diuretics can cause both acute and chronic hyponatremia, but typically hyponatremia develops in the

first few weeks following the initiation of therapy [24]. Thiazide diuretics frequently are employed to manage chronic lung disease or edema-forming states, and the effects of the diuretic are synergistic with other underlying disorders that cause hyponatremia. Excess water intake also is a major contributing factor to the development of hyponatremia among those receiving diuretics.

4.1.8 Hyponatremic Encephalopathy

A major consequence of hyponatremia is the influx of water into the intracellular space resulting in cellular swelling, which can lead to cerebral edema and encephalopathy [25]. The clinical manifestations of hyponatremia are primarily neurologic and related to cerebral edema caused by hypoosmolality. The symptoms of hyponatremic encephalopathy are quite variable between individuals with the only consistent symptoms being headache, nausea, vomiting, emesis, and weakness. As the cerebral edema worsens, patients then develop behavioral changes, and impaired response to verbal and tactile stimuli. Advanced symptoms are signs of cerebral herniation, with seizures, respiratory arrest, dilated pupils, and decorticate posturing. Headache, nausea, and vomiting are the most consistent symptoms of hyponatremic encephalopathy.

Newborns are at particularly high risk for developing hyponatremic encephalopathy due to their relatively larger brain to intracranial volume ratio as compared to adults [26]. A child's brain reaches adult size by 6 years of age, whereas the skull does not reach adult size until 16 years of age. Consequently, children have less room available in their rigid skulls for brain expansion and are likely to develop brain herniation from hyponatremia at higher serum sodium concentrations than adults. Other risks factors for developing hyponatremic encephalopathy are hypoxia and underlying central nervous system (CNS) disease [27]. Hypoxia impairs brain-cell-volume regulation and decreases cerebral perfusion [28]. Patient with underlying CNS disease are already at risk for intracranial hypertension and fall in serum sodium will exacerbate this.

4.1.8.1 Treatment of Hyponatremic Encephalopathy

Hyponatremic encephalopathy is a medical emergency that requires early recognition and treatment. The definitive therapy for treating hyponatremic encephalopathy is the administration of hypertonic saline (3 % NaCl, 513 mEq/L) [29]. Fluid restriction alone has no role in the management of symptomatic hyponatremia; 0.9 % NaCl is also inappropriate for the treatment of hyponatremic encephalopathy as it is not sufficiently hypertonic to induce the necessary reduction in cerebral edema central to the management of this condition. Once signs of encephalopathy are identified, prompt treatment is required in a monitored setting before imaging studies are performed. Endotracheal intubation and mechanical ventilation may be necessary to ensure appropriate gas exchange.

Children with suspected hyponatremic encephalopathy with either mild or advanced symptoms should receive 2 mL/kg of 3 % NaCl as a bolus over 10 min in order to rapidly reverse brain edema (Table 4.3). A single bolus of 3 % NaCl will result in at most a 2-mEq/L acute rise

Table 4.3 Treatment of symptomatic hyponatremia in the newborn

1. 2 cc/kg bolus of 3 % NaCl over 10 min
2. Repeat bolus 1–2 times as needed until symptoms improve Goal: 5–6 mEq/L increase in serum sodium in first 1–2 h
3. Recheck serum sodium following second bolus or Q 2 h
4. Hyponatremic encephalopathy is unlikely if no clinical improvement following an acute rise in serum sodium of 5–6 mEq/L
5. Stop further therapy with 3 % NaCl boluses when patient is either: (a) Symptom-free: awake, alert, responding to commands, resolution of headache and nausea (b) Acute rise in sodium of 10 mEq/L in if first 5 h
6. Correction in first 48 h should: (a) Not exceed 15–20 mEq/L (b) Avoid normo- or hypernatremia

in serum sodium. This dose might need to be repeated once or twice until symptoms subside, with the goal of correction being 5–6 mEq/L in the first 1–2 h. Children who have not had some neurologic response to three boluses of 3 % NaCl most likely do not have hyponatremic encephalopathy. To prevent complications arising from excessive therapy, 3 % NaCl should be discontinued when symptoms subside. The rate of correction should not exceed 20 mmol/L in the first 48 h, and correction should be to mildly hyponatremic values, avoiding normonatremia and hypernatremia in the first 48 h.

4.1.9 Risk Factors for Developing Cerebral Demyelination

Cerebral demyelination is a rare condition that has been primarily reported in adults with severe chronic hyponatremia (Na <115 mEq/L, >48 h) who have additional risk factors such as liver disease, severe malnutrition, hypokalemia, hypoxia, and a correction of serum sodium >25 mEq/L in the first 24–48 h of therapy [2]. In these high-risk patients, it is not clear that cerebral demyelination can be prevented even with careful correction of hyponatremia. Cerebral demyelination has not been reported in children with acute hospital-acquired hyponatremia, nor have neurologic complications been associated with the use of 3 % NaCl to treat children with hyponatremic encephalopathy. Cerebral demyelination is rarely reported in newborns as a newborn brain is not fully myelinated.

When symptomatic cerebral demyelination does follow the correction of hyponatremia, it typically follows a biphasic pattern. There is initially clinical improvement of the hyponatremic encephalopathy associated with correction of the serum sodium, which is followed by neurologic deterioration 2–7 days later. Cerebral demyelination can be both pontine and extrapontine. Classic features of pontine demyelination include mutism, dysarthria, spastic quadriplegia, pseudobulbar palsy, a pseudocoma with a "locked-in stare," and ataxia. The clinical features of extrapontine lesions are more varied, including behavior changes and movement disorders. Radiographic features of cerebral demyelination typically lag behind the clinical symptoms. Cerebral demyelination is best diagnosed on MRI approximately 14 days following correction. The classic radiographic findings on MRI are symmetrical lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted images. Some data suggest that cerebral demyelination can be detected earlier on MRI with diffusion-weighted imaging.

4.2 Hypernatremia

Core Messages

- The primary cause of hypernatremia is insufficient free water intake.
- Volume expansion with 0.9 % sodium chloride should precede the correction of hypernatremia if volume depletion is present.

Case Vignette

A 7-day-old female infant weighting 2.8 kg presents to the emergency department with a fever and lethargy. The child was born full term via a spontaneously vaginal delivery weighting 3.2 kg to a 22-year-old first-time mother who was exclusively breastfeeding the child. The postnatal course was complicated by neonatal jaundice which required 2 days of home phototherapy. The child is described as being a slow feeder, spending over 30 min on each breast. The child has been sleepy and fussy with a high-pitched cry. She has had two to three bowel movements a day and one diaper appeared to have pink urine. Biochemistries revealed a serum sodium 156 mEq/L, potassium 5.6 mEq/L, total carbon dioxide 12 mEq/L, blood urea nitrogen 40 mg/dL, and creatinine 0.8 mg/dL. Urine biochemistries reveal sodium <5 mEq/L, potassium 20 mEq/L, and osmolality 900 mOsm/kg/H_2O.

4.2.1 Introduction

Hypernatremia is defined as a serum sodium concentration >145 mEq/L. In both children and adults, hypernatremia is seen primarily in hospitals and occurs in individuals who have restricted access to water for a variety of reasons. Typically, affected patients are either debilitated by an acute or chronic illness, have neurologic impairment, or are at the extremes of age. Infants, especially those born preterm, are at particularly high risk for the development of hypernatremia because of their relatively small mass-to-surface area ratio and their dependency on a caretaker to administer fluids. Hypernatremia is particularly dangerous in the newborn as it can result in vascular complication. Diarrheal dehydration is an important cause of hypernatremia in the outpatient setting but is much less common than previously reported, presumably due to the advent of low-solute infant formulas and the increased use and availability of oral rehydration solutions.

A group at high risk for developing hypernatremia in the outpatient setting is that of the breastfed infant [30]. Breastfeeding-associated hypernatremia is on the rise. Over 15 % of mother-infant diads have difficulty establishing successful lactation during the first week postpartum. This is of particular concern for the primiparous infant. Reasons for lactation failure are multifactorial, including physiological factors which require 3–5 days for optimal breast milk production and mechanical factors resulting in a poor latch or insufficient time on the breast to stimulate optimal milk production. Hypernatremic dehydration results from a combination of insufficient lactation and increased breast milk sodium concentration. Hypernatremic dehydration can be difficult to diagnose as hypernatremic infants will have a better preserved extracellular volume.

4.2.2 Pathogenesis of Hypernatremia

The body has two defenses to protect against developing hypernatremia: the ability to produce a concentrated urine and a powerful thirst mechanism. AVP release occurs when the plasma osmolality exceeds 275–280 mOsm/kg and results in a maximally concentrated urine when the plasma osmolality exceeds 290–295 mOsm/kg. Thirst is the body's second line of defense but provides the ultimate protection against hypernatremia. If the thirst mechanism is intact and there is unrestricted access to free water, it is rare for someone to develop sustained hypernatremia from either excess sodium ingestion or a renal concentrating defect.

4.2.3 Diagnosis

Hypernatremia is usually multifactorial and a systematic approach is required to determine the contributing factors (Fig. 4.2) [1]. A serum sodium, glucose, and osmolality must be evaluated. An elevated serum sodium is always associated with hyperosmolality and should be considered abnormal. In cases of significant hyperglycemia, the serum sodium will be depressed due to the associated translocation of fluids from the intracellular to extracellular space. Once the diagnosis of hypernatremia is established, a detailed history and review of fluid intake should be taken to determine if the patient has an intact thirst mechanism, has restricted access to fluids, or is not being provided adequate free water in intravenous fluids. If no apparent cause for hypernatremia is identified, then urine volume should be measured and compared to fluid intake, and the urine osmolality and electrolytes should be determined to assess if the renal concentrating ability is appropriate and to quantify the urinary free water losses. A less than maximally concentrated urine (<800 mOsm/kg) in the face of hypernatremia is a sign of a renal concentrating defect, as hypernatremia is a maximal stimulus for ADH release. In patients with hypernatremia, the following should be evaluated: gastrointestinal losses, urinary output, dermal losses from fever or burns, diet history (including tube feedings and breastfeeding), medication history (including diuretics), and sources of exogenous sodium. Salt poisoning should be suspected whenever the severity of hypernatremia, neurologic

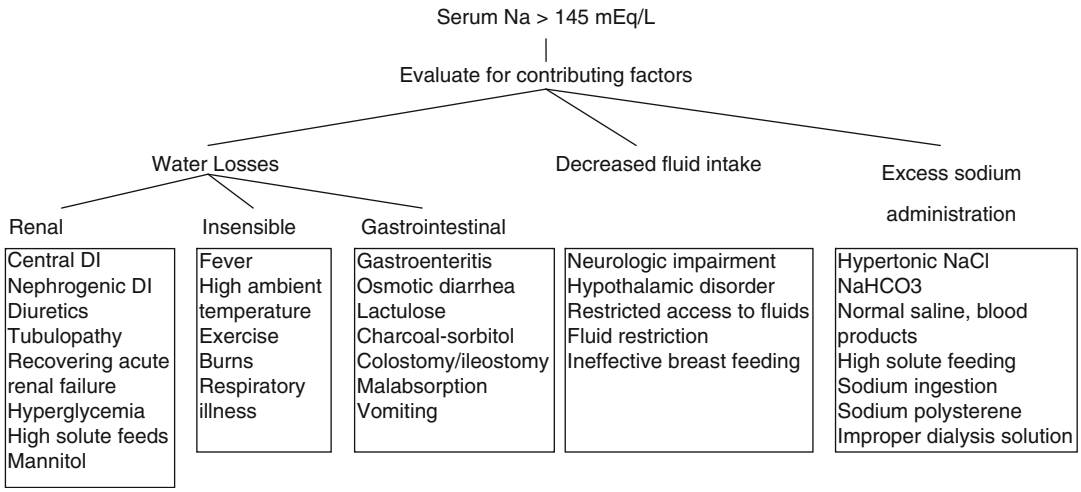

Fig. 4.2 Diagnostic approach to hypernatremia

manifestations, or hospital course does not correlate with the history of present illness. If this is suspected, a gastric sodium sample should be obtained as soon as possible, as a gastric sodium concentration greater than that of plasma is virtually diagnostic of salt poisoning.

4.2.4 Clinical Manifestations of Hypernatremia

Hypernatremia results in an efflux of fluid from the intracellular space to the extracellular space to maintain osmotic equilibrium. This leads to transient cerebral dehydration with cell shrinkage. Brain cell volume can decrease by as much as 10–15 % acutely but then quickly adapts. Within 1 h, the brain significantly increases its intracellular content of sodium and potassium, amino acids, and unmeasured organic substances called idiogenic osmoles. Within 1 week, the brain regains approximately 98 % of its water content [31]. If severe hypernatremia develops acutely, the brain may not be able to increase its intracellular solute sufficiently to preserve its volume, and the resulting cellular shrinkage can cause structural changes. Cerebral dehydration from hypernatremia can result in a physical separation of the brain from the meninges leading to a rupture of the delicate bridging veins and intracranial or intracerebral hemorrhages [32]. Venous sinus thrombosis leading to infarction can also develop. Acute hypernatremia has also been shown to cause cerebral demyelinating lesions in both animals and humans [33]. Patients with hepatic encephalopathy are at the highest risk for developing demyelinating lesions.

Children with hypernatremia are usually agitated and irritable but can progress to lethargy, listlessness, and coma [34]. On neurologic examination, they frequently have increased tone, nuchal rigidity, and brisk reflexes. Myoclonus, asterixis, and chorea can be present; tonic-clonic and absence seizures have been described. Hyperglycemia is a particularly common consequence of hypernatremia in children. Severe hypernatremia can also result in rhabdomyolysis. While earlier reports showed that hypocalcemia was associated with hypernatremia, this has not been found in more recent literature. In adults hypernatremia primarily manifests as central nervous system depression. Adults with hypernatremia are rarely alert, and most have confusion with abnormal speech and obtundation with stupor or coma. The degree of central nervous system depression appears to correlate with the severity of hypernatremia.

4.2.5 Treatment of Hypernatremia

The cornerstone of the management of hypernatremia is providing adequate free water to

correct the serum sodium. Hypernatremia is frequently accompanied by volume depletion. Fluid resuscitation with normal saline should be instituted to reestablish distal perfusion prior to any attempt to correct the free water deficit. Following initial volume expansion, the composition of parenteral fluid therapy largely depends on the etiology of the hypernatremia. Patients with sodium overload or a renal concentrating defect will require a more hypotonic fluid than patients with volume depletion and intact renal concentrating ability. Oral hydration should be instituted as soon as it can be safely tolerated. Plasma electrolytes should be checked every 2 h until the patient is neurologically stable.

A simple way of estimating the minimum amount of fluid necessary to correct the serum sodium is by the following equation:

$$\begin{aligned} &Free\,water\,deficit\,(mL) \\ &= 4\,mL \times lean\,body\,wt\,(kg) \\ &\times [desired\,change\,in\,serum\,Na\,mEq\,/\,\mathrm{L}] \end{aligned}$$

Larger amounts of fluid will be required depending on the fluid composition. To correct a 300 mL free water deficit, approximately 400 mL of 0.2 % sodium chloride in water or 600 mL of 0.45 % sodium chloride in water would be required, as they contain approximately 75 and 50 % free water, respectively. The calculated deficit does not account for insensible losses or ongoing urinary or gastrointestinal losses. Maintenance fluids, which include replacement of urine volume with hypotonic fluids, are given in addition to the deficit. Glucose-containing fluids should be limited as they can result in significant hyperglycemia.

The rate of correction of hypernatremia is largely dependent on the severity of the hypernatremia and the etiology. Due to the brain's relative inability to extrude unmeasured organic substances called idiogenic osmoles, rapid correction of hypernatremia can lead to cerebral edema. While there are no definitive studies that document the optimal rate of correction that can be undertaken without developing cerebral edema, empirical data have shown that unless symptoms of hypernatremic encephalopathy are present, a rate of correction not exceeding 1 mEq/h or 15 mEq/24 h is reasonable [35]. In severe hypernatremia (>170 mEq/L), serum sodium should not be corrected to below 150 mEq/L in the first 48–72 h. Seizures occurring during the correction of hypernatremia are not uncommon in children but may be a sign of cerebral edema. Hypotonic fluid infusion should be ceased and hypertonic saline should be administered when signs of cerebral edema occur during the correction of hypernatremia is suspected. Seizures associated with the correction of hyponatremia are usually self-limited and not a sign of long-term neurologic sequelae. Patients with acute hypernatremia, corrected by the oral route, can tolerate a more rapid rate of correction with a much lower incidence of seizures. The type of therapy is largely dependent on the etiology of the hypernatremia and should be tailored to the pathophysiologic events involved in each patient (Table 4.4).

4.2.6 Potassium Homeostasis

Potassium is the most abundant cation in the body, with 98 % of potassium residing intracellular and 2 % extracellular. It is the ratio of intracellular to extracellular potassium concentration that determines the resting membrane

Table 4.4 Management of hypernatremia

Etiology	Treatment[a]
(A) Sodium and water loss Gastroenteritis	0.45 % Sodium chloride in 5 % dextrose in water
(B) Primary water loss Ineffective breastfeeding	0.2–0.45 % Sodium chloride in 5 % dextrose in water
(C) Nephrogenic diabetes insipidus	0.1 % Sodium chloride in 2.5 % dextrose in water (acute management)
(D) Central diabetes insipidus	Desmopressin acetate
(E) Sodium overload	5 % Dextrose in water Diuretics or dialysis may be needed

[a]Avoid 5 % dextrose in water if hyperglycemia is present

potential; therefore, the body must maintain the extracellular potassium concentration in a fairly narrow range of 3.5–5.5 mEq/L to prevent neurologic and conduction disturbances. Potassium can be consumed in large quantities in the diet and is absorbed rapidly in the gastrointestinal tract. The serum potassium is acutely regulated by a transcellular shift of potassium from extracellular to intracellular by the release of insulin and β-adrenergic catecholamines. The long-term regulation of potassium is via urinary excretion which is primarily regulated by aldosterone release. The serum potassium does not reflect the total body potassium content, as disorders in serum potassium may be due to acute intracellular shift or more chronic potassium depletion or overload. Chronic perturbations in serum potassium are better tolerated than acute changes, as the gradient in intracellular to extracellular potassium will be less severe. Chronic states of hyperkalemia generally reflect a disorder in renal function or mineralocorticoid activity, and hypokalemia represents total body potassium depletion.

4.3 Hypokalemia

Core Messages

- Hypokalemia does not cause significant arrhythmias unless there is significant underlying cardiac disease or digoxin use.
- Excessive correction of hypokalemia can result in dangerous hyperkalemia.

Case Vignette

A 3-week-old infant is evaluated for poor weight gain. The child was born at 36 weeks' gestation with a weight of 2.6 kg and a history of maternal polyhydramnios. At approximately 20 days of age, the child developed frequent bowel movements, non-bilious emesis, and abdominal distention. Upon presentation the child weights 2.5 kg. Serum electrolytes reveal a sodium of 132 mEq/L, potassium 2.6 mEq/L, chloride 94 mEq/L, and total carbon dioxide 35 mEq/L.

4.3.1 Clinical Effects of Hypokalemia

Hypokalemia, defined as a serum potassium <3.6 mEq/L, is a common electrolyte abnormality occurring in hospitalized patients [36]. Mild hypokalemia, potassium 3–3.5 mEq/L, is usually asymptomatic. Hypokalemia does not cause significant arrhythmias, other than U waves, unless there is underlying cardiac disease or digoxin use, where even mild hypokalemia can contribute to arrhythmias. Serum potassium <3.0 mEq/L can lead to weakness, myopathy, constipation, and intestinal ileus, while a serum potassium <2.5 mEq/L can cause rhabdomyolysis and ascending paralysis. When hypokalemia develops, the underlying cause should be addressed and corrected as hypokalemia is associated with increased morbidity and mortality in both children and adults.

4.3.2 Causes of Hypokalemia (Table 4.5)

Hypokalemia is not particularly common in the newborn. One of the most common causes of potassium depletion is from the use of loop or thiazide diuretics [37]. Diuretics are frequently used in the neonate with respiratory distress syndrome or bronchopulmonary dysplasia, but there is little evidence to support their use [38]. Loop and thiazide diuretics increase sodium delivery to the collecting duct. This leads to maximal sodium reabsorption in these segments and facilitates potassium excretion. Chronic diuretic use may be associated with effective circulating volume depletion which further stimulates the renin-angiotensin-aldosterone pathway, increasing urinary potassium losses. Hyperchloremic metabolic

Table 4.5 Causes of hypokalemia

1. Inadequate intake
2. Urinary losses
(a) Diuretics
(b) Salt-wasting nephropathy
(i) Fanconi syndrome
(c) Osmotic diuresis
(i) Uncontrolled diabetes
(d) Transport disorder
(i) Bartter and Gitelman syndromes
(e) Mineralocorticoid excess
(f) Magnesium depletion
(i) Amphotericin B
(g) Alkalosis
(h) Non-reabsorbable anions (penicillins)
3. Extrarenal losses
(a) Vomiting
(b) Diarrhea
(c) Malabsorption
(d) Tumors
(e) Dialysis
4. Transcellular shifts
(a) ß$_2$-Adrenergic agents
(b) Insulin
(c) Theophylline
(d) Hyperthyroidism
(e) Hypokalemic periodic paralysis

alkalosis, which is a frequent complication of diuretics, contributes to hypokalemia by impairing chloride-linked sodium reabsorption, thereby increasing distal tubule sodium reabsorption and potassium excretion. Hypomagnesemia, which is a common complication of diuretic therapy, promotes urinary potassium losses by unknown mechanisms. The combination of loop plus thiazide diuretics can lead to profound hypokalemia.

Other disorders leading to hypokalemia are conditions which lead to gastrointestinal losses, transcellular shifts in potassium, or mineralocorticoid excess. Potassium is primarily excreted in the stool by the colonic epithelium; therefore, any process that results in diarrhea can cause large potassium losses. Intestinal losses from an ileostomy or upper gastrointestinal losses from vomiting or nasogastric do not contain significant amounts of potassium. Hyperchloremic alkalosis induced by emesis can cause hypokalemia by increasing urinary potassium losses. ß$_2$-adrenergics, theophylline, and insulin can cause hypokalemia by causing a transcellular shift in potassium. There are numerous medical conditions that are associated with increased mineralocorticoid production or activity that can cause hypokalemia, especially in conjunction with diuretics, such as seen with renovascular hypertension.

4.3.3 Bartter Syndrome

Bartter syndrome is rare but important cause of hypokalemia in the newborn [39]. Bartter syndrome is a heterogenous disorder characterized by defects in distal tubular sodium and chloride reabsorption occurring in the thick ascending limb of the loop of Henle with secondary hyperreninemia and hyperaldosteronism. To date there are five different types of Bartter syndrome. These conditions generally have clinical features similar to that of being on a loop diuretic with hypercalciuria being a prominent feature. A severe form of Bartter syndrome that occurs in the newborn is referred to as antenatal Bartter syndrome or hyperprostaglandin E syndrome. Antenatal Bartter syndrome is associated with maternal polyhydramnios, preterm birth, intrauterine and postnatal polyuria, recurrent vomiting, failure to thrive, growth retardation, and severe bouts of dehydration.

4.3.4 Treatment of Hypokalemia

The treatment of hypokalemia is controversial as excess potassium supplementation, especially via the intravenous route, can cause dangerous hyperkalemia [40]. Hypokalemia is generally asymptomatic, and therapy should aim for a slow correction over a period of days, preferably by the enteral route as potassium chloride in two to three divided doses. In cases of cardiac arrhythmias, severe myopathies, paralysis, or severe hypokalemia (potassium <2 mEq/L), aggressive intravenous administration of potassium is indicated. Potassium should be given as potassium chloride, as there is generally an accompanying

chloride deficit. Potassium should not be infused faster than 0.5 mEq/kg/h. The infusion should be stopped every 2–3 h to reassess the serum potassium. A parenteral fluid potassium concentration >60 mEq/L should not be administered through a peripheral intravenous line as it can cause sclerosis of the vein, and potassium infiltration can cause tissue necrosis. Magnesium depletion should be corrected as hypomagnesemia promotes urinary potassium losses. Potassium-sparing diuretics can be helpful to curtail urinary potassium losses.

4.4 Hyperkalemia

Core Messages

- Hyperkalemia can result in fatal cardiac arrhythmias.
- Exchange resins are ineffective and dangerous in the treatment of non-oliguric hyperkalemia of the premature infant.

Case Vignette

A preterm infant is admitted to the neonatal intensive care unit. The child was born at 26 weeks' gestation with a birth weight of 900 g with an Apgar score of 5 at 5 min. The child is intubated and ventilated and is given surfactant. The child did not receive antenatal dexamethasone. The child is placed on intravenous fluids without potassium. At 18 h of life, the child is noted to have peaked T waves on the monitor with a widening QRS. STAT biochemistries reveal a nonhemolyzed potassium of 7.4 mEq/L with a serum sodium of 136 mEq/L, carbon dioxide of 18 mEq/L, and serum creatinine of 0.8 mg/dL. Urine output is normal at 3 mL/kg/h.

4.4.1 Newborns at Risk for Hyperkalemia (Table 4.6)

Hyperkalemia is defined as serum potassium >6 mEq/L in newborns and >5 mEq/L in children outside of the newborn period. The preterm neonate is at particularly high risk for developing hyperkalemia. Hyperkalemia is common during the first few days after birth in premature infants

Table 4.6 Causes of hyperkalemia

1. Factitious
(a) Hemolysis
(b) Thrombocytosis (platelets >1,000,000/mm^3)
(c) Leukocytosis (white blood cell count >100,000/mm^3)
(d) Repeated fist clenching with tourniquet in place
2. Non-oliguric hyperkalemia of the premature infant
3. Impaired potassium excretion
(a) Renal insufficiency or failure
(b) Mineralocorticoid deficiency
(i) Hereditary enzyme deficiencies
(ii) Addison's disease
(iii) Hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis)
(iv) Heparin-induced inhibition of aldosterone synthesis
(c) Pseudohypoaldosteronism
(i) Hereditary
(ii) Pyelonephritis
4. Medications
(a) Potassium-sparing diuretics
(b) ACE inhibitors
(c) Angiotensin receptor blockers
(d) NSAIDs
(e) Cyclosporine/tacrolimus
(f) Trimethoprim
(g) Pentamidine
5. Impaired potassium entry into cells
(a) Insulin deficiency or resistance
(b) Hyperchloremic metabolic acidosis
(c) Hypertonicity (uncontrolled diabetes)
(d) Massive tissue breakdown (rhabdomyolysis)
(e) Familial hyperkalemic periodic paralysis
(f) Medications
(i) B-blockers
(ii) Digoxin (at toxic levels)
(iii) Succinylcholine
(iv) Arginine
(v) Lysine
6. Excess potassium administration
(a) Total parenteral nutrition
(b) Potassium supplements
(c) Diet or enteral feeds
(d) RBC transfusion
(e) Penicillin G potassium

with a gestational age <28 weeks. This condition is termed non-oliguric hyperkalemia of the premature infant, which is defined as a serum potassium >7 mEq/L during the first 72 h of life in the presence of normal urinary output >1 mL/kg/h [41]. Neonatal hyperkalemia can result in cardiac arrhythmias and has resulted in sudden death. Non-oliguric hyperkalemia results from a transcellular shift of potassium into the extracellular space and spontaneously resolves after the first few days of life. Hyperkalemia in the older newborn typically results from either excess potassium intake, decreased potassium excretion, or a transcellular shift of potassium from the intracellular to extracellular space. There are usually multiple factors contributing to hyperkalemia; therefore, a detailed evaluation of potassium intake, renal function, and medication history is mandatory.

Pseudohyperkalemia is a common cause of hyperkalemia in the newborn resulting from cell breakdown following venipuncture or capillary sampling [42]. A common setting for serious hyperkalemia in the children is oliguric acute renal failure, such as seen in urinary tract obstruction from posterior urethral valves. Mineralocorticoid deficiency and resistance are also important causes of severe hyperkalemia in the newborn. Severe hyperkalemia can develop in infants with pyelonephritis due to transient pseudohypoaldosteronism with the associated features of hyponatremia, acidosis, and elevated plasma renin activity and aldosterone [43]. A rare but serious form of hyperkalemia in the newborn is that of pseudohypoaldosteronism type 1 (PHA-1) [44]. PHA-1 results from mutations in the mineralocorticoid receptor. It results in severe hyperkalemia in the first week of life with salt loss, acidosis, and elevated aldosterone levels. It requires lifelong sodium supplementation and dietary potassium restriction. Hyperkalemia from acute and chronic kidney disease or from massive tissue breakdown from rhabdomyolysis or tumor lysis syndrome is much less common in newborn than in the older child. Hyperkalemia from hyperchloremic metabolic acidosis is relatively common in children and results from a transcellular shift in potassium. Serum potassium rises on average 0.6 mEq/L (0.24–1.7 mEq/L) for every 0.1 unit fall in pH. An elevated anion gap acidosis has little or no effect on serum potassium.

4.4.2 Clinical Effects of Hyperkalemia

The ratio of intracellular to extracellular potassium is the major determinant of the resting membrane potential [42]. Hyperkalemia decreases resting membrane potential facilitating depolarization and impairing repolarization. The symptoms of mild to moderate hyperkalemia are usually asymptomatic; however, the first presenting symptom may be a fatal cardiac arrhythmia. Clinical manifestations that can result from membrane potential effects in striated muscle include weakness, paresthesias, and ascending paralysis. Ascending paralysis is usually seen in patients with chronic renal insufficiency when the serum potassium exceeds 7.5 mEq/L.

The effects of potassium on cardiac conduction are the most worrisome features (Table 4.7). Hyperkalemia interferes with atrioventricular and intraventricular conduction pathways leading to arrhythmias. The risks of arrhythmias usually correlate with the degree of hyperkalemia,

Table 4.7 Electrographic manifestations of hyperkalemia

Serum potassium level	Expected ECG abnormality
Mild hyperkalemia 5.5–6.5 mEq/L	Tall, tent-shaped ("peaked") T waves with narrow base, best seen in precordial leads (lead II)
Moderate hyperkalemia 6.5–8.0 mEq/L	Peaked T waves Prolonged PR interval Decreased amplitude of P waves Widening of QRS complex
Severe hyperkalemia >8.0 mEq/L	Absence of P wave Intraventricular blocks, fascicular blocks, bundle branch blocks, QRS axis shift Progressive widening of the QRS complex resulting in bizarre QRS morphology Eventual "sine-wave" pattern (sinoventricular rhythm), ventricular fibrillation, asystole

Table 4.8 Emergency management of hyperkalemia

1. Evaluation
(a) Confirm that potassium value is venous and nonhemolyzed
(b) Place patient on cardiac monitor (lead II) and obtain ECG
2. Conduction abnormalities
(a) Calcium gluconate (10 %) 100 mg/kg/dose (1 mL/kg/dose) over 3–5 min. Works immediately with a 15–30-min duration. Can be repeated in 15 min
3. Serum potassium >6.5 mEq/L
(a) Move potassium into cells:
(i) Regular insulin 0.1 U/kg with 25 % glucose 2 mL/kg over 30 min. Onset is 10–20 min with a duration of 2–3 h
(ii) Albuterol nebulization 0.5 % 0.25 mg/kg/dose over 10 min. Onset of action 20–30 min, duration 2–3 h. Can be used in conjunction with insulin and glucose
(iii) Sodium bicarbonate 1 mEq/kg, only if hyperchloremic metabolic acidosis, onset of action is 1–3 h
(b) Remove potassium from body:
(i) Loop diuretic
(ii) Hemodialysis or peritoneal dialysis
(iii) Fludrocortisone

but arrhythmias are more likely to occur with rapid increases in serum potassium then with gradual increases. The most consistent ECG finding of hyperkalemia is increased T waves followed by widening of the QRS complex. There is no clear cutoff where arrhythmias will develop, but patients with serum potassium >6.0 mEq/L should be considered at risk for arrhythmias, and patients with levels exceeding 6.5 mEq/L or electrocardiographic features should receive immediate treatment.

4.4.3 Treatment of Hyperkalemia

The treatment of hyperkalemia largely depends on both the etiology and severity of hyperkalemia [42]. The presence of ECG changes or serum potassium exceeding 6.5 mEq/L requires immediate therapy (Table 4.8). Calcium can reverse cardiac conduction abnormalities and should be administered if ECG changes or present. Calcium must be administered through a properly function intravenous line as extravasation can cause tissue necrosis. This is of particular concern in the term and preterm infant where reliable vascular access can be difficult to establish. The acute management of hyperkalemia involves shifting potassium intracellularly. The administration of insulin and glucose is the most reliable first-line therapy for the treatment of hyperkalemia. β_2-adrenergic agent such as albuterol has been used successfully both intravenously and nebulized in the treatment of hyperkalemia. These agents both lower serum potassium by 0.6–1 mEq/L within 30 min and have an additive effect when use together. Insulin is effective in all patients but has the disadvantage of potentially causing hypoglycemia and requiring vascular access, which can be difficult to establish in small children. Albuterol's main advantage is that it can be administered quickly and repeatedly without the need for vascular access with minimal side effects. The main disadvantage of albuterol is that it is ineffective in 10–20 % of patients. Both insulin and albuterol lower the serum potassium for 2–3 h, while additional therapies can be instituted to remove potassium from the body. Sodium bicarbonate has recently lost favor in the acute management of hyperkalemia as it is relatively ineffective in the absence of severe acidosis, has a delayed onset of action of 1 h, and can cause fluid overload and hypernatremia.

Following the acute lowering of serum potassium by causing an intracellular shift in potassium, the next objective is to remove potassium from the body via urine, stool, or dialytic therapies. The preferred method of removing potassium from the body is via urinary losses, and measures should be undertaken to improve urinary flow. Prerenal causes of acute renal failure should be promptly treated with volume expansion, obstructive causes should be corrected, and urinary flow should be optimized with diuretics. When potassium removal via urinary losses is not possible, then an exchange transfusion or dialysis may be indicated. Sodium polystyrene (Kayexalate) is an exchange resin which has been used for the treatment of hyperkalemia. Kayexalate removes 0.5–1.0 mEq of potassium

in exchange for 2–3 mEq of sodium. The primary site of potassium removal is the colon; therefore, the gastric administration of Kayexalate can take 6 h for potassium removal, while a retention enema can work in hours. Kayexalate is unpalatable, and to quickly deliver any significant volume to a child will likely require nasogastric administration or a retention enema. Kayexalate can have serious intestinal complications, particularly in the preterm infant [45]. There have been multiple reports of bowel necrosis, intestinal perforation, bowel impaction, and intestinal bezoars. Kayexalate has not been found to be effective in the treatment of non-oliguric hyperkalemia and has been associated with a high mortality. Kayexalate should not be used for the treatment of non-oliguric hyperkalemia in the premature infant and is best avoided in the term newborn. Hemodialysis is a rapid and effective means of potassium removal when there is a severe renal impairment and an acutely rising serum potassium.

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