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Preventing neurological complications from dysnatremias in children

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Abstract Dysnatremias are among the most common electrolyte abnormalities encountered in hospitalized patients. In most cases, a dysnatremia results from improper fluid management. Dysnatremias can occasionally result in death or permanent neurological damage, a tragic complication that is usually preventable. In this manuscript, we discuss the epidemiology, pathogenesis and prevention and treatment of dysnatremias in children. We report on over 50 patients who have suffered death or neurological injury from hospital-acquired hyponatremia. The main factor contributing to hyponatremic encephalopathy in children is the routine use of hypotonic fluids in patients who have an impaired ability to excrete free-water, due to such causes as the postoperative state, volume depletion and pulmonary and central nervous system diseases. The appropriate use of 0.9% sodium chloride in parenteral fluids would likely prevent most cases of hospital-acquired hyponatremic encephalopathy. We report on 15 prospective studies in over 500 surgical patients that demonstrate that normal saline effectively prevents postoperative hyponatremia, and hypotonic fluids consistently result in a fall in serum sodium. Hyponatremic encephalopathy is a medical emergency that should be treated with hypertonic saline, and should never be managed with fluid restriction alone. Hospital-acquired hypernatremia occurs in patients who have restricted access to fluids in combination with ongoing free-water losses. Hypernatremia could largely be prevented by providing adequate free-water to patients who have

ongoing free-water losses or when mild hypernatremia ($\text{Na} > 145 \text{ mEq/l}$) develops. A group at high-risk for neurological damage from hypernatremia in the outpatient setting is that of the breastfed infant. Breastfed infants must be monitored closely for insufficient lactation and receive lactation support. Judicious use of infant formula supplementation may be called for until problems with lactation can be corrected.

Keywords Hypernatremia · Hyponatremia · Cerebral edema · Myelinolysis · Fluid therapy

Introduction

Dysnatremias are a common electrolyte abnormality in children in both the inpatient and outpatient settings. A serious complication of dysnatremias is brain injury. Brain injury is an especially tragic complication because in most cases it is a result of improper fluid management or inappropriate therapy. While there are numerous causes of dysnatremias in children, there are a few settings where the neurological sequelae are most common, and therefore could be prevented. Our goals are to point out the dangers of dysnatremias [1], outline the most important measures that can be instituted for prevention of dysnatremias [2] and discuss how to recognize and treat symptomatic dysnatremias [3].

Prevention and treatment of hyponatremic encephalopathy

Pathogenesis of hyponatremia

Hyponatremia, defined as a serum sodium $< 135 \text{ mEq/l}$, is a common disorder that occurs in both the inpatient and outpatient settings. The body's primary defense against developing hyponatremia is the kidney's ability to generate a dilute urine and excrete free-water. Rarely is excess ingestion of free-water alone the cause of hypona-

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Table 1 Disorders in impaired renal water excretion

1. Effective circulating volume depletion
a. Gastrointestinal losses: vomiting, diarrhea
b. Skin losses: cystic fibrosis
c. Renal losses: salt wasting nephropathy, diuretics, cerebral salt wasting, hypoaldosteronism
d. Edematous states: heart failure, cirrhosis, nephrosis, hypoalbuminemia
e. Decreased peripheral vascular resistance: sepsis, hypothyroid
2. Thiazide diuretics
3. Renal failure
a. Acute
b. Chronic
4. Non-hypovolemic states of ADH excess
a. Central nervous system disturbances: meningitis, encephalitis, brain tumors, head injury
b. Pulmonary disease: pneumonia, asthma, bronchiolitis
c. Cancer
d. Medications: cytoxan, vincristine, morphine, SSRIs, carbamazepine
e. Nausea, emesis, pain, stress
f. Postoperative state
g. Cortisol deficiency

tremia, as an adult with normal renal function can typically excrete over 15 l of free-water per day. It is also rare to develop hyponatremia from excess urinary sodium losses in the absence of free-water ingestion. In order for hyponatremia to develop it typically requires a relative excess of free-water in conjunction with an underlying condition that impairs the kidney's ability to excrete free-water (Table 1). Renal water handling is primarily under the control of arginine vasopressin (AVP), which is produced in the hypothalamus and released from the posterior pituitary. AVP release impairs water diuresis by increasing the permeability to water in the collecting tubule. There are osmotic, hemodynamic and non-hemodynamic stimuli for AVP release. In most cases of hyponatremia there is a stimulus for vasopressin production that results in impaired free-water excretion. The body will attempt to preserve the extracellular volume at the expense of the serum sodium; therefore, a hemodynamic stimulus for AVP production will override any inhibitory hypoosmolar effect of hyponatremia [1]. There are numerous stimuli for AVP production (Table 1) that occur in hospitalized patients that can make virtually any hospitalized patient at risk for hyponatremia.

Epidemiology of hyponatremic encephalopathy

Moderate hyponatremia, defined as a serum sodium <130 mEq/l, occurs in over 1% of hospitalized children

[2]. 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. Hyponatremic encephalopathy is a serious complication of hyponatremia that can result in death or permanent neurological injury. The true incidence of hyponatremic encephalopathy in hospitalized children is unknown as large prospective studies have not been done. A critical review of retrospective studies in children reveals that encephalopathy is a common complication of hyponatremia in both the inpatient and outpatient setting.

Over 50% of children with a serum sodium <125 mEq/l will develop hyponatremic encephalopathy (Table 2). Hospital-acquired hyponatremic encephalopathy is most often seen in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or in the postoperative period [3, 4, 5]. SIADH is caused by elevated ADH secretion in the absence of an osmotic or hypovolemic stimulus [6]. SIADH can occur because of a variety of illnesses, but most often occurs because of central nervous system (CNS) disorders, pulmonary disorders, malignancies and medications. Hyponatremia from SIADH is particularly dangerous in children with CNS injury such as encephalitis, as mild hyponatremia (sodium <135 mEq/l) has been associated with neurological deterioration and herniation [7, 8]. A common contributing factor in hospitalized children with SIADH who develop hyponatremic encephalopathy is the administration of hypotonic intravenous fluids.

Postoperative hyponatremia is a serious problem in children; the majority of deaths resulting from hyponatremic encephalopathy have been reported in healthy children following routine surgical procedures [3, 4, 9]. Postoperative hyponatremia is caused by a combination of nonosmotic stimuli for ADH release, such as subclinical volume depletion, pain, nausea, stress, narcotics edema-forming conditions and the administration of hypotonic fluids. It is estimated that the mortality directly attributable to hyponatremic encephalopathy in children with postoperative hyponatremia (sodium <129 mEq/l) is 8% [3]. The most important factors resulting in postoperative hyponatremic encephalopathy are the failure to recognize the compromised ability of the patient to maintain free-water and the administration of hypotonic fluids.

Hyponatremic encephalopathy is also a concern in the outpatient setting [10, 11, 12]. It is primarily attributable to oral water intoxication in infants. Overall, 10% of children less than 2 years of age presenting to the emergency department with seizures are found to have hyponatremic encephalopathy (sodium <126 mEq/l) [10]. Of

Table 2 Incidence of hyponatremic encephalopathy in hospitalized children

Author	Reference no.	Inclusion criteria serum Na (mEq/l)	Incidence of hyponatremic encephalopathy (%)
Wattad et al. 1992	[2]	<125	53
Sarnaik et al. 1991	[5]	<125	60
Halberthal et al. 2001	[4]	<130 in 48 h	78

those children with no other recognized cause of seizures, the incidence of hyponatremic encephalopathy is 56% for children less than 2 years of age and 70% for children less than 6 months of age. Over 50% of patients with febrile seizures have hyponatremia, with the degree of hyponatremia being predictive of a repeat seizure during the same febrile period [13].

Prevention of hospital acquired-hyponatremic encephalopathy (avoid hypotonic maintenance parenteral fluids)

There is substantial evidence demonstrating that the routine administration of hypotonic fluids, as initially proposed by Holliday and Segar almost 50 years ago [14], can result in fatal hyponatremic encephalopathy [3, 4, 7, 8, 15, 16]. Holliday and Segar's initial recommendations primarily addressed the water needs for children in parenteral fluid therapy. The maintenance need for electrolytes was discussed in only one paragraph, where they surmised that the electrolyte composition of intravenous fluids should approximate that of human and cow milk. Holliday and Segar's paper was published in 1957 [14], the same year that Schwartz et al. described the first report of SIADH [17]. Since that time it has become apparent that there are numerous non-osmotic stimuli for ADH production in hospitalized children (Table 1), making the routine use of hypotonic fluids an unphysiologic and potentially dangerous therapy. In a recent report we pointed out the dangers of the routine use of hypotonic saline in maintenance parenteral fluids [9], as it has resulted in over 50 cases of death or neurological injury in children (Table 3). Other investigators, including Holliday, have since concurred that the administration of hypotonic parenteral fluids can result in dangerous hyponatremia [15, 16, 18, 19, 20, 21, 22]. Hanna et al. reported the incidence of hyponatremia to be 33% in infants transferred to the ICU with bronchiolitis, with 4% suffering hyponatremic encephalopathy. Hoorn et al. reported the incidence of acute hospital-acquired hyponatremia to be 10% in children presenting to the emergency department with a normal serum sodium. Five percent of these children went on to develop neurological sequelae. Hypotonic fluids were the main contributing factor for developing hyponatremia in both studies. In Table 3 we report on 3 additional children in western Pennsylvania who have suffered death or permanent neurological injury from hospital-acquired hyponatremia related to the administration of hypotonic fluids. A 3-week-old child was treated in a fashion that was recently recommended by Holliday [22], with a bolus of 0.9% NaCl followed by maintenance hypotonic fluids, while the other 2 received excessive hypotonic fluids as bolus therapy.

We have argued that administering isotonic saline in maintenance parental fluids is the most physiologic approach to preventing hospital-acquired hyponatremia [9]. Children requiring parenteral fluids should be considered to be at risk for developing hyponatremia, as the majority

will have a hemodynamic or non-hemodynamic stimulus for ADH production (Table 1), resulting in impaired free-water excretion. The administration of hypotonic fluids to a patient with impaired free-water excretion resulting from ADH excess will predictably result in hyponatremia. Prospective studies in over 500 postoperative children and adults have demonstrated that isotonic saline effectively prevents the development of hyponatremia and that hypotonic fluids consistently result in hyponatremia (Table 4). There is no rationale for administering hypotonic fluids unless there is a free-water deficit, hypernatremia or ongoing free-water losses, from such causes as diarrhea or a renal concentrating defect (Table 5). In fluid overload states such as nephrosis, cirrhosis, congestive heart failure or glomerulonephritis, both sodium and fluid restriction are of paramount importance to prevent hyponatremia and fluid overload. Even in fluid overload states, an argument could be made to use 0.9% sodium chloride at a greatly restricted volume, as excess free-water could contribute to hyponatremia.

Some have advocated fluid restriction as the preferred therapy to prevent hospital-acquired hyponatremia [21, 23]. While this approach may be effective, it is unphysiologic and potentially dangerous as it could perpetuate a state of subclinical volume depletion [24]. Most children who are admitted to the hospital in need of parenteral fluid, such as with pulmonary infections, central nervous system infection or gastrointestinal disease, have some degree of volume depletion (Table 5). In many cases this will be subclinical and difficult to assess on physical examination [25]. Fluid restriction would perpetuate such a state of volume depletion, which could be harmful. The administration of maintenance isotonic saline would both serve as an excellent volume expander and eliminate unnecessary free-water administration.

Concerns have been raised that the administration of isotonic saline in maintenance parenteral fluids could result in additional complications not seen with hypotonic fluids, such as hypernatremia, acidosis or fluid overload [26]. Isotonic saline should not result in hypernatremia unless there is a renal concentrating defect, significant extrarenal renal free-water losses or prolonged fluid restriction (Table 5). In general, the kidney is able to generate free-water by excreting hypertonic urine, therefore providing sufficient free-water to replace insensible losses. It is also a misconception that the high chloride concentration in isotonic saline could result in acidosis. The pH of 0.9% sodium chloride in 5% dextrose in water is the same as that of 5% dextrose in water, pH 4. The acidosis reported with isotonic saline is a dilutional phenomenon resulting from rapid expansion of the extracellular volume [27]. This would not be expected with maintenance fluids. Isotonic saline should also not cause fluid overload, unless there is an impaired ability to excrete sodium, such as in an edematous state or acute glomerulonephritis (Table 5). In this situation fluid restriction would be required.

Excessive fluid administration is a risk factor for developing hyponatremia [15]. Many of the neurological

Table 3 Neurological injury due to hospital-acquired hyponatremia in children receiving hypotonic fluids. *D*₅ 5% dextrose; *ND* not disclosed

Author	Age (years)	Setting	Intravenous fluid	Sodium value (mEq/l)	Complication
Duke [99]	0.15	Meningitis	0.18% NaCl	137 to 131	Cerebral edema, dilated pupil
Jenkins [19]	ND	ND	Hypotonic	<130	2 deaths
Jackson [100]	1.5	Influenza	D ₅ water	120	Death, cerebral edema
	3	Meningitis	D ₅ water	128	Death, cerebral edema
Keating [12]	3	Dehydration	D ₅ water	133 to 114	Death, cerebral edema
	2	Hip surgery	Hypotonic	112	Death, cerebral edema
Gregorio [101]	4	Gastroenteritis	D ₅ 0.45% NaCl	136 to 118	Respiratory arrest, seizure, cerebral demyelination
Hoorn [15]	ND	ND	Hypotonic	142–128	Death, cerebral edema, cardiac arrest
Arieff [3]	3.5	Tonsillitis	Hypotonic	139 to 114	Quadriplegia
	5	Tonsillectomy		141 to 123	Death
	4	Tonsillectomy		139 to 115	Death
	15	Tonsillectomy		141 to 101	Death
	3.5	Tonsillectomy		138 to 121	Death
	12	Fracture setting		137 to 120	Mental retardation
	4	Fracture setting		139 to 118	Death
	3	Tonsillectomy		137 to 113	Death
	1.5	VP shunt		137 to 114	Vegetative
	9	Fracture setting		137 to 120	Vegetative
	15	Fracture setting		138 to 102	Vegetative
	4	Tonsillectomy		138 to 107	Death
	2	Orchiopexy		138 to 116	Death
	6	Nasal packing		138 to 119	Death
	12	Appendectomy		137 to 123	Death
	12	Pneumonia		134 to 116	Vegetative
Halberthal [4]	ND	ND	Hypotonic	<130	5 deaths, 1 neurological damage
Playfor [20]	1	Gastroenteritis	D ₄ 0.18% NaCl	137 to 120	Death, respiratory arrest, cerebral edema
Armour [102]	4	Renal transplant	Hypotonic	139 to 119	Death, respiratory arrest, cerebral edema
Eldredge [103]	5	Cerebral palsy, slit ventricles, heal cord repair	D ₅ 0.225% NaCl	127	Death, cardio-respiratory arrest
	8	Slit ventricles, spinal surgery	D ₅ 0.45% NaCl	129	Insertion of subdural bolt with eventual recovery
Paut [104]	ND	Postoperative	Hypotonic	118	Death
McRae [105]	10	Tonsillectomy	Hypotonic	115	Death, pulmonary edema, cerebral edema
	6	Tonsillectomy	D ₅ 0.2% NaCl	122	Death, respiratory arrest, cerebral edema
Hughes [106]	3	Spinal surgery	D ₄ 0.18% NaCl	118	Death, respiratory arrest, cerebral edema
Cowley [107]	ND	Spinal surgery	Hypotonic	118	Death, respiratory arrest, cerebral edema
McJunkin [7]	<15	LaCrosse encephalitis	D ₅ 0.45% NaCl	138 to 134	13 with neurological deterioration: 3 cerebral herniation, 6 status epilepticus, 1 coma
Moritz	0.06	Dehydration	D ₅ 0.225% NaCl	141 to 119	Cardio-respiratory arrest, cerebral edema, neurological devastation
	5	Tympanoplasty	Hypotonic	123	Cardiac arrest, cerebral edema, neurological devastation
	0.9	Gastroenteritis	D ₅ 0.3% NaCl	136 to 126	Death, cardio-respiratory arrest, cerebral edema

complications from hospital-acquired hyponatremia resulted from fluid administration well in excess of that recommended by Holliday and Segar (Table 3) [14]. Hyponatremia could develop even from the excess administration of isotonic saline if there is impaired urine dilution with a fixed urine osmolality of ≥ 500 mOsm/kg/ H_2O . This is of particular concern in the neurosurgical patient, who is at risk for cerebral salt wasting. It has been reported in postoperative neurosurgical patients that isotonic saline may not be sufficient prophylaxis against hyponatremia (Table 4) [28]. The administration of parenteral fluids should be considered an invasive procedure requiring close monitoring.

Clinical manifestation of hyponatremic encephalopathy

The symptoms of hyponatremic encephalopathy are quite variable among individuals with the only consistent symptoms being headache, nausea, vomiting, emesis and weakness [29]. As cerebral edema worsens, patients then develop behavioral changes and impaired response to verbal and tactile stimuli. Advanced symptoms are signs of cerebral herniation and include seizures, respiratory arrest, neurogenic pulmonary edema, dilated pupils and decorticate posturing. Arrhythmias have also been reported [30]. Not all patients have the usual progression in symptoms, and advanced symptoms can present suddenly.

Table 4 Relationship between postoperative fluid composition and change in serum sodium. 0.9% NaCl=[Na] 154 mEq/l. RL Ringer's lactate [Na] 131 mEq/l. Hartmann's 131 Hartmann' solution [Na] 131 mEq/l. Plasmalyte 148 [Na] 148 mEq/l. NA not available

Age group	Authors	Surgical procedure	n	Fluid composition	Preop. Na mEq/l	Postop. Na mEq/l
Adult	Steele 1997 [108]	Gynecological	22	RL intraop., 0.9% NaCl postop.	140±0.5	136±0.5
Adult	Bomberger 1986 [109]	Aortic	102	RL	138±0.7	137.9±0.7
			80	0.45% NaCl	138±0.5	133.5±1.1
Adult	Scheingraber 1997 [27]	Gynecological	12	0.9% NaCl	140±1.8	141.9±2
			12	RL	140±1.8	137.8±1.4
Adult	Tindall 1981 [110]	Vagotomy	6	0.9% NaCl	140±0.86	139.4±0.78
			6	D ₅ W	140±0.86	131.8±0.7
Adult	Stillstrom 1987 [111]	Cholecystectomy	9	RL	141±0.8	138±0.7
			9	0.45% NaCl	140±0.7	137±6.7
			9	D ₅ W	138±0.6	134±1.1
Adult	McFarlane 1994 [112]	Hepatobiliary	15	0.9% NaCl	141±3.1	142±1.3
			15	Plasmalyte 148	139±3.4	139.6±1.8
Adult	Wilkes 2001 [113]	Elective (general)	24	0.9% NaCl	141±3.1	142±1.3
			23	Hartmann's 131	137.8±2.7	137±2.7
Adult	Waters 2001 [114]	Aortic	33	0.9% NaCl	141±3	143±4
			33	RL	142±3	139±3
Adult	Takil 2002 [115]	Spinal	15	0.9% NaCl	140±2	143±3
			15	RL	142±3	136±4
Adult	Boldt 2002 [116]	Abdominal (cancer)	21	0.9% NaCl	134±3	135±4
			21	RL	136±2	133±3
Pediatric	Burrows 1983 [117]	Spinal	4	RL	138±2.7	135±1.9
			20	0.45 or 0.22% NaCl	138±1.7	131±2.8
Pediatric	Brazel 1996 [118]	Spinal	5	Hartmann's 131	141±2.8	138.1±1.9
			7	0.3 or 0.18% NaCl	139.5±1.9	129.5±3.7
Pediatric	Judd 1990 [119]	Tonsillectomy	6	0.9% NaCl	140*	141.2±1.2
Pediatric	Levine 1999 [28]	Cranial vault	10	0.9% NaCl	NA	132.3±2.45
Pediatric	Cowley 1988 [107]	Spinal	8	0.45% NaCl	140.6±1.1	132.7±1.6

* Standard deviation not available

Risk factors for developing hyponatremic encephalopathy *Hypoxia*

Age

Children under 16 years of age are at increased risk for developing hyponatremic encephalopathy due to their relatively larger brain to intracranial volume ratio as compared with adults [3, 31]. 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 [32, 33]. 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. The average serum sodium in children with hyponatremic encephalopathy is 120 mEq/l [5, 34], while that in adults is 111 mEq/l [5, 34, 35, 36]. Animal data also suggest that prepubertal children may have impaired ability to regulate brain cell volume due to diminished cellular sodium extrusion related to lower testosterone levels [31]. Children will have a high morbidity from symptomatic hyponatremia unless appropriate therapy is instituted early [3, 4, 7, 8, 9].

Hypoxia is a major risk factor for the development of hyponatremic encephalopathy. The occurrence of a hypoxic event such as respiratory insufficiency is a major factor militating against survival without permanent brain damage in patients with hyponatremia [37]. The combination of systemic hypoxia and hyponatremia is more deleterious than is either factor alone because hypoxia impairs the ability of the brain to adapt to hyponatremia, leading to a vicious cycle of worsening hyponatremic encephalopathy [38]: hyponatremia in turn leads to a decrement of both cerebral blood flow and arterial oxygen content [39]. Patients with symptomatic hyponatremia can develop hypoxia by one of at least two different mechanisms: neurogenic pulmonary edema or hypercapnic respiratory failure [39]. Respiratory failure can be of very sudden onset in patients with symptomatic hyponatremia [37, 40]. Prompt recognition of neurogenic pulmonary edema and treatment with hypertonic saline are imperative, as failure to treat is almost always fatal [40]. The majority of neurological morbidity seen in patients with hyponatremia has occurred in patients who have had a respiratory arrest as a feature of hyponatremic encephalopathy [3, 35, 36, 37, 41]. Recent data have shown that

Table 5 Adjusting maintenance parenteral fluids for disease states

Isotonic saline (0.9% sodium chloride)	Fluid restriction	Hypotonic fluids
<p>Effective circulating volume depletion</p> <ul style="list-style-type: none"> ● Dehydration ● Salt wasting nephropathy <ul style="list-style-type: none"> ○ Bartter syndrome ○ Adrenal insufficiency ● Decreased peripheral vascular resistance <ul style="list-style-type: none"> ○ Sepsis ○ Hypothyroid <p>Non-hypovolemic states of ADH excess</p> <ul style="list-style-type: none"> ● Central nervous system disturbances <ul style="list-style-type: none"> ○ Meningitis ○ Encephalitis ○ Brain tumors ○ Head injury ● Pulmonary disease <ul style="list-style-type: none"> ○ Pneumonia ○ Asthma ○ Bronchiolitis ● Cancer ● Medications <ul style="list-style-type: none"> ○ Cytosin ○ Vincristine ○ Narcotics ○ Carbamazepine ○ SSRIs ● Nausea, emesis, pain, stress ● Postoperative state ● Glucocorticoid deficiency 	<p>Edematous states</p> <ul style="list-style-type: none"> ● Congestive heart failure ● Nephrosis ● Cirrhosis ● Hypoalbuminemia <p>Renal insufficiency</p> <ul style="list-style-type: none"> ● Acute glomerulonephritis ● Acute tubular necrosis ● End stage renal disease 	<p>Free-water deficit</p> <ul style="list-style-type: none"> ● Hyponatremia <p>Renal concentrating defect</p> <ul style="list-style-type: none"> ● Congenital nephrogenic diabetes insipidus ● Sick cell disease ● Obstructive uropathy ● Reflux nephropathy ● Renal dysplasia ● Nephronophthisis ● Tubulo-interstitial nephritis <p>Extra-renal free-water losses</p> <ul style="list-style-type: none"> ● Burns ● Premature neonates ● Fever ● Infectious diarrhea

hypoxia is the strongest predictor of mortality in patients with symptomatic hyponatremia [42].

Therapy of hyponatremic encephalopathy

In general, correction with hypertonic saline is unnecessary and potentially harmful if there are no neurological manifestations of hyponatremia. Symptomatic hyponatremia, on the other hand, is a medical emergency. Once signs of encephalopathy are identified prompt treatment is required in a monitored setting, even before imaging studies are performed. The airway should be secured; endotracheal intubation and mechanical ventilation may be necessary. Symptomatic hyponatremia should never be treated with fluid restriction alone. If symptomatic hyponatremia is recognized and treated promptly, prior to developing a hypoxic event, the neurological outcome is good [5, 36, 41, 43].

Patients with symptomatic hyponatremia should be treated with hypertonic saline (3%, 513 mEq/l) using an infusion pump. The rate of infusion should raise the plasma sodium by about 1 mEq/l per hour until either (1) the patient is alert and seizure free, (2) the plasma sodium has increased by 20 mEq/l or (3) a serum sodium of about 125–130 mEq/l has been achieved, whichever occurs first [5, 41, 43, 44, 45, 46, 47, 48, 49]. If the patient is actively seizing or with impending respiratory arrest the serum

sodium can be raised by as much as 4–8 mEq/l in the first hour or until the seizure activity ceases [48]. Prospective studies have demonstrated that the optimal rate of correction of symptomatic hyponatremia is approximately 15–20 mEq in 48 h, as patients with correction of hyponatremia in this range have a much lower mortality and an improved neurological outcome compare to those with a correction of less than 10 mEq in 48 h [36, 41]. Assuming that total body water comprises 50% of total body weight, 1 ml/kg of three percent sodium chloride will raise the plasma sodium by about 1 mEq/l. In some cases furosemide can also be used to prevent pulmonary congestion and to increase the rate of serum sodium correction.

Risk factors for developing cerebral demyelination

Cerebral demyelination is a rare complication that has been associated with symptomatic hyponatremia [50]. Animal data have demonstrated that correction of hyponatremia by >25 mEq/l in 24 h is associated with cerebral demyelination [51, 52]. This has resulted in a mistaken belief that a rapid rate of correction is likely to result in cerebral demyelination [53]. In fact, studies have shown that the rate of correction has little to do with the development of cerebral demyelinating lesions, and that lesions seen in hyponatremic patients are more closely associated with other comorbid factors or the magnitude of correc-

Table 6 Risk factors for developing cerebral demyelination in hyponatremic patients

Risk factor
1. Development of hypernatremia
2. Increase in serum sodium exceeding 25 mmol/l in 48 h
3. Hypoxemia
4. Severe liver disease
5. Alcoholism
6. Cancer
7. Severe burns
8. Malnutrition
9. Hypokalemia
10. Diabetes
11. Renal failure

tion in serum sodium (Table Table 6) [41, 52, 54, 55, 56]. In one prospective study it was observed that hyponatremic patients who develop demyelinating lesions had either (1) been made hypernatremic inadvertently, (2) had their plasma sodium levels corrected by greater than 25 mmol/l in 48 h, (3) suffered a hypoxic event or (4) had severe liver disease [41]. Some data have suggested that azotemia may decrease the risk of developing cerebral demyelination [57].

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 neurological deterioration 2 to 7 days later [37, 58]. 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 [59]. 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 symptomatology [60]. Cerebral demyelination is best diagnosed on MRI approximately 14 days following correction [61]. The classic radiographic findings on MRI are symmetrical lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted images [62]. Some data suggest that cerebral demyelination can be detected earlier on MRI with diffusion-weighted imaging [60].

The outcome of cerebral demyelination is not as severe as was previously believed [63]. Cerebral demyelination has been found to be an incidental finding on neuroimaging and at autopsy in patients with chronic illnesses [64]. In most reported cases of cerebral demyelination attributed to dysnatremias, long-term follow-up has demonstrated improvement in neurological symptoms and regression of radiographic findings [58, 63]. The primary cause of brain damage in patients with hyponatremia is not cerebral demyelination, but cerebral edema and herniation [35, 36, 65]. Most brain damage occurs in untreated patients and is not a consequence of therapy; therefore, patients with symptomatic hyponatremia need prompt therapy.

Patients with hyponatremia due to water intoxication, diarrheal dehydration, thiazide diuretics or dDAVP are at high risk for overcorrection of hyponatremia and require extreme care and monitoring. In these illnesses, once volume depletion is corrected or when the offending medication is discontinued, there will be a reversal of the urine osmolality from concentrated to dilute, resulting in a free-water diuresis with a potentially rapid overcorrection of hyponatremia if saline-containing fluids are administered. This will not typically occur in SIADH, as this is a saline-resistant hyponatremia. To prevent an overcorrection of hyponatremia, hypotonic fluids and possibly even dDAVP may have to be given. It has also been demonstrated that where there is an overcorrection of hyponatremia, a therapeutic re-lowering can ameliorate the symptoms of cerebral demyelination [66]. Children with symptomatic hyponatremia should have close neurological follow up for the first few months as neurological sequelae can be subtle and a delayed phenomenon.

Case illustrations (beware of formulas)

It is tempting to rely on formulas to aid in correcting the serum sodium in dysnatremias. Unfortunately, these equations either assume that the body is a closed system [67] or require the assistance of a programmable calculator [68]. Equations that assume the body is a closed system and do not account for renal water handling are physiologically incorrect and can result in either an overcorrection or an under-correction in serum sodium. There are two groups of patients in which closed system equations that do not take into account urinary losses will result in a significant miscalculation. The first group is patients who will have a natriuresis associated with volume expansion. Examples would be SIADH, postoperative states and cerebral salt wasting. In this situation, closed-system equations will underestimate the change in serum sodium. The second group is patients who will have a reverse urine osmolality or free-water diuresis following volume expansion with saline. Examples would be patients with psychogenic polydipsia, discontinuation of dDAVP, water intoxication (primarily in infants) and diarrheal dehydration. These patients require special care, as saline administration can result in a brisk free-water diuresis and, consequently, overcorrection of hyponatremia, which leads to brain damage. It must be emphasized that any formula that does not take into account the urinary response will be inaccurate and should only be used as a rough guide to aid in therapy. Below are illustrative cases of hyponatremic encephalopathy.

Case 1: SIADH

A 10-kg 1-year-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 in 5% dextrose in water at a rate of 40 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 0.3 mg/dl, osmolality 238 mOsm/kg H₂O, urine osmolality 400 mOsm/kg H₂O and urine sodium plus potassium concentration 90 mEq/l.

This child has developed hyponatremic encephalopathy due to the administration of hypotonic fluid in the setting of SIADH associated with pulmonary disease. An acute elevation in serum sodium is required as the child is actively seizing. Assuming that total body water is 50% of body weight, 1 ml/kg of 3% sodium chloride will increase the serum sodium by 1 mEq/l in a closed system. Over 1 h, 5 ml/kg (50 ml) of 3% sodium chloride is administered to increase the serum sodium by 5 mEq/l. Following the infusion the serum sodium is 126 mEq/l, slightly lower than predicted due to urinary sodium losses, and seizures have abated. The patient is then fluid restricted with 20 ml/h of 0.9% sodium chloride in 10% dextrose in water and slowly corrects over the next 48 h.

Case 2: cerebral salt wasting

A 10-kg 1-year-old child is admitted for surgical removal of an astrocytoma. Postoperatively, this child is placed on 0.9% sodium chloride in 5% dextrose in water at a rate of 40 ml/h as prophylaxis against hyponatremia. Twenty-four hours following surgery, the child's level of alertness has decreased, and is having dry heaves. The child is in negative fluid balance by 400 ml with a 0.5 kg weight loss and is tachycardic. Serum biochemistries reveal serum sodium 123 mEq/l, potassium 4 mEq, blood urea nitrogen 10 mEq/l, creatinine 0.3 mg/dl, osmolality 240 mOsm/kg H₂O, urine osmolality 600 mOsm/kg H₂O and urine sodium plus potassium concentration 250 mEq/l.

Despite prophylaxis with normal saline, this child developed severe hyponatremia from a hypertonic urine from cerebral salt wasting. The child is symptomatic, but is not actively seizing and without respiratory compromise; therefore, a rate of correction of 1 mEq/l/h would be a safe initial rate of correction until neurological symptoms improve. The child is given two 200 ml boluses of 0.9% sodium chloride to correct the volume deficit. Continuous parenteral fluids consist of 30 ml/h of 3% sodium chloride (513 mEq/l) and 30 ml/h of 0.9% sodium chloride in 10% dextrose in water. This would result in an average sodium concentration for both fluids combined of 333 mEq/l. Assuming ongoing urinary losses of 60 ml/h, the serum sodium would correct by about 1 mEq/h, far less than the 3 mEq/h predicted by a closed-system equation. The rate of infusion of saline and 3% sodium chloride would be further adjusted to match urine output and control the rate of correction of serum sodium.

Case 3: thiazide diuretic

A 3-kg 5-month-old infant, born pre-term, is evaluated in the emergency department for lethargy and irritability. The child is on hydrochlorothiazide for bronchopulmonary dysplasia and is fed Neocate infant formula. Lab work is obtained and the child is bolused with 20 ml/kg of 0.9% sodium chloride. Biochemistries reveal serum sodium 105 mEq/l, potassium 3.2 mEq/l, total CO₂ 30 mEq/l, blood urea nitrogen 8 mg/dl, creatinine 0.2 mg/dl and osmolality 205 mOsm/kg H₂O. Urine biochemistries are subsequently obtained, which reveal urine sodium less than 10 mEq/l, potassium 15 mEq/l and urine osmolality 100 mOsm/kg H₂O. Repeat serum chemistries reveal serum sodium of 111 mEq/l, and the child is more alert.

Infant formula has a low electrolyte concentration and can result in profound hyponatremia when infants are on a thiazide diuretic, which causes urinary electrolyte losses in excess of intake. The child is mildly symptomatic because this is a chronic hyponatremia developing over weeks. Following volume expansion with 0.9% sodium chloride, the child is experiencing a free-water diuresis and may develop a rapid and extreme correction if 0.9 or 3% sodium chloride is administered. The safest approach would be to administer 0.225% sodium chloride with 30 mEq/l potassium chloride at a rate of 12 ml/h and discontinue the diuretic. As soon as the child is more alert, parenteral fluid should be discontinued and oral feeds resumed. The correction in serum sodium should be limited to no more than 25 mEq/48 h. If the rate of correction is too rapid the fluid sodium composition may need to be changed to 0.115% sodium chloride or therapeutic relowering with the addition of dDAVP may be necessary.

Case 4: dDAVP administration

A 50-kg, 16-year-old female with a history of cleft lip and palate is to undergo maxillofacial surgery. Preoperative evaluation reveals Von Willebrand's disease. Perioperatively, she is administered dDAVP and postoperatively 0.45% sodium chloride in 5% dextrose at a rate of 90 ml/h and dDAVP. She begins to complain of a severe headache, followed by nausea, which does not respond to antiemetics. The intravenous fluid rate is then increased to 140 ml/h. She then develops confusion and combativeness, followed by obtundation and urinary incontinence. A CAT scan reveals cerebral edema. Serum biochemistries are then obtained that reveal sodium 118 mEq/l, potassium 4 mEq/l, blood urea nitrogen 4 mg/dl, creatinine 0.7 mg/dl, osmolality 233 mOsm/kg H₂O, urine osmolality 500 mOsm/kg H₂O and urine sodium plus potassium 200 mEq/l.

This adolescent has hyponatremia from the exogenous administration of dDAVP in conjunction with hypotonic fluids. She is symptomatic with cerebral edema and could have an impending respiratory arrest. Over 1 h, 8 ml/kg (400 ml) of 3% sodium chloride are administered, with an

anticipated rise of no more than 8 mEq/l as she is excreting a hypertonic urine. Following the infusion of hypertonic saline her serum sodium is 123 mEq/l, and her symptoms have much improved. The dDAVP is continued, as withdrawal would result in excessive correction from a free-water diuresis. To complete a slow correction, 0.9% sodium chloride in 10% dextrose in water is administered at 40 ml/h.

Prevention of hypernatremia (morbidity and mortality)

Pathogenesis

Hypernatremia is defined as a serum sodium greater than 145 mEq/l. The body has two defenses to protect against developing hypernatremia: the ability to produce a concentrated urine and a powerful thirst mechanism. ADH release occurs when the plasma osmolality exceeds 275–280 mosmol/kg/H₂O and results in a maximally concentrated urine when the plasma osmolality exceeds 290–295 mosmol/kg/H₂O. 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.

Epidemiology of hypernatremia

Hypernatremia is primarily a hospital-acquired condition occurring in children of all ages who have restricted access to fluids. Moderate hypernatremia, serum sodium greater than 150 mEq/l, occurs in over 1% of hospitalized patients [69]. The majority of children with hypernatremia are debilitated by an acute or chronic illness, have neurological impairment, are critically ill or are born premature [69]. Hypernatremia in the intensive care setting is a particularly common problem as patients are usually either intubated or moribund, and frequently are fluid restricted, receive large amounts of sodium as blood products and/or have renal concentrating defects from diuretics or renal dysfunction [69]. The majority of hypernatremia results from the failure to administer sufficient free-water to patients who are unable to care for themselves and have restricted access to fluids [69].

A group at high risk for developing hypernatremia in the outpatient setting is that of the breastfed infant [70]. Breastfeeding-associated hypernatremia is on the rise [71]. Over 15% of mother-infant diads have difficulty establishing successful lactation during the 1st week post partum [72]. This is of particular concern for the primiparous infant. Reasons for lactation failure are multifactorial, including physiological factors that 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 [70]. Hyper-

natremic dehydration results from a combination of insufficient lactation and increased breast milk sodium concentration [73]. Hypernatremic dehydration can be difficult to diagnose as hypernatremic infants will have a better preserved extracellular volume [74]. Diarrheal dehydration is also 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.

Morbidity and mortality

Anatomical changes and brain adaptation

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 [44]. Within 1 h the brain can significantly increase 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. 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 [75, 76] and venous sinus thrombosis leading to infarction [77]. Acute hypernatremia has also been shown to cause cerebral demyelinating lesions in both animals and humans [44, 78, 79, 80]. Patients with hepatic encephalopathy are at the highest risk for developing demyelinating lesions [81].

Clinical manifestations and mortality

Children with hypernatremia are usually agitated and irritable, but can progress to lethargy, listlessness and coma [82]. On neurological 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 [83]. While earlier reports showed that hypocalcemia was associated with hypernatremia, this has not been found in more recent literature [69].

Hypernatremia is associated with a mortality rate of 15% in children; this rate is estimated to be 15 times higher than the age-matched mortality in hospitalized children without hypernatremia [69]. The high mortality is unexplained. Most of the deaths are not directly related

to central nervous system pathology and appear to be independent of the severity of hypernatremia. Recent studies have noted that patients who develop hypernatremia following hospitalization and patients with a delay in treatment have the highest mortality [69, 84, 85]. Approximately 40% of the deaths in children with hypernatremia occurred while patients were still hypernatremic [69].

A subset of patients that have a particularly high morbidity and mortality are infants with hypernatremic dehydration [86] and patients with end-stage liver disease [81, 87]. Most of the current deaths or neurological damage directly attributable to hypernatremia have resulted from vascular thrombosis and intracranial hemorrhages in infants with hypernatremic dehydration in general [88], and breastfeeding-associated hypernatremia in particular [89]. Patients with end-stage liver disease are particularly susceptible to additional brain injury from hypernatremia and at high risk for developing cerebral demyelination [50, 78].

Prevention of hypernatremia

Pediatricians face new challenges in preventing hypernatremia in children. Hypernatremia is primarily a hospital-acquired condition that affects children with restricted access to fluids in combination with ongoing free-water losses via the urine or gastrointestinal tract. Large amounts of sodium-containing fluids such as blood products or sodium bicarbonate administration can also be contributing factors. Mild hypernatremia (serum Na >145 mEq/l) is the first sign that inadequate free-water is being administered to maintain body water homeostasis and that fluid therapy must be adjusted. Increased free-water will need to be administered by either increasing the volume of fluid administration and/or decreasing the sodium content in perenteral fluids. This will largely depend on the volume and composition of ongoing losses. Mild hypernatremia should not be considered a benign occurrence, and should be a signal to the physician to reassess fluid therapy. All patients who have restricted access to enteral fluids should have fluid balance and serum biochemistries monitored daily.

In order to prevent hypernatremia in the breast fed infant, it is imperative that nursing mothers be provided adequate lactation support and that the American Academy of Pediatrics guidelines be followed, including a weight check within 3 to 5 days of age [90]. Breastfed infants with greater than 7% weight loss or jaundice should be evaluated for hypernatremic dehydration, and aggressive lactation support should be provided. Infant formula should be used judiciously to support the infant until problems with lactation are corrected.

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; therefore fluid resuscitation with normal saline or colloid should be instituted prior to correcting 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, which assumes the total body water to be 50% of body weight:

$$\text{Free - water deficit (ml)} = 4 \text{ ml} \times \text{lean body weight (kg)} \\ \times [\text{Desired change in serum Na mEq/L}] \quad (1)$$

Larger amounts of fluid will be required depending on the fluid composition. To correct a 3-l free-water deficit, approximately 4 l of 0.225% sodium chloride in water or 6 l 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 replacement.

The rate of correction of hypernatremia is largely dependent on the severity of the hypernatremia and the etiology. Because of the brain's relative inability to extrude unmeasured organic substances called idiogenic osmoles, rapid correction of hypernatremia can lead to cerebral edema [44]. Surprisingly, there are few reports of death or serious neurological morbidity in humans resulting from rapid correction of hypernatremia. In the case of mass accidental salt poisoning, there are reports of infants with serum sodium greater than 200 mEq/l who were corrected by as much as 120 mEq in 24 h without adverse neurological sequelae [91]. 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 [92, 93, 94]. In severe hypernatremia (>170 mEq/l), serum sodium should not be corrected to below 150 mEq/l in the first 48–72 h [93]. Seizures occurring during the correction of hypernatremia are not uncommon in children, and may be a sign of cerebral edema [95, 96, 97]. They can usually be managed by slowing the rate of correction or by giving hypertonic saline to increase the serum sodium a few milliequiva-

lents. Seizures are usually self-limited and not a sign of long-term neurological sequelae [92, 93]. Patients with acute hyponatremia, corrected by the oral route, can tolerate a more rapid rate of correction with a much lower incidence of seizures [95, 98]. The type of therapy is largely dependent on the etiology of the hyponatremia and should be tailored to the pathophysiologic events of each patient.

Case illustrations

Case 1: gastroenteritis

A 7-kg, 6-month-old child with vomiting and diarrhea for 3 days presents to the emergency department and appears 10% dehydrated. Biochemistries reveal 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 800 mOsm/kg/H₂O.

This child has an estimated volume deficit of approximately 700 ml with a composition of approximately 0.9% NaCl (154 mEq/l). In order to correct the serum sodium by 10 mEq/l in 24 h, a minimum of 280 ml of electrolyte free-water ($4 \text{ ml} \times 7 \text{ kg} \times 10 \text{ mEq/l} = 280 \text{ ml}$) would have to be administered. The child should initially be bolused with 50 ml/kg (350 ml) of normal saline. This would leave the remaining deficit of 350 ml of isotonic fluid to be corrected over 24 h. Maintenance fluids of 700 ml for the next 24 h in addition to 350 ml of deficit therapy would result in a total volume of 1,050 ml or 44 ml/h; 0.45% NaCl in 5% dextrose in water would provide 575 ml of free-water and 575 ml of isotonic fluid. This would be adequate therapy to correct both the volume deficit and free-water deficit and to provide for urinary losses.

Case 2: nephrogenic diabetes insipidus

A 20-kg, 5-year-old child with nephrogenic diabetes insipidus has contracted a stomach flu and has not been able to keep down fluids for the past 12 h. He presents to the emergency department markedly dehydrated with sunken eyes, doughy skin and documented 2-kg weight loss. Serum biochemistries reveal serum sodium 172 mEq/l, potassium 4.5 mEq/l, blood urea nitrogen 20 mg/dl and creatinine 0.6 mg/dl. Urine biochemistries reveal sodium 25 mEq/l, potassium 15 mEq/l and osmolality 100 mOsm/kg/H₂O. On further history his mother reports that the child usually drinks between 4 and 5 l of fluids a day.

This child's fluid deficit is primarily free-water. To correct the serum sodium back to normal value of 140 mEq/l would require approximately 2.5 l of free-water ($4 \text{ ml} \times 20 \text{ kg} \times 30 \text{ mEq/l}$). Unfortunately, bolus therapy with free-water will result in too rapid a fall in serum sodium. The child will initially have to be bolused with 40 ml/kg of 0.9 NaCl in order to restore the extra-

cellular volume. Further fluid therapy would require maintenance fluids, which for him are about 4,000 ml/day plus free-water deficit to lower the serum sodium by 10 mEq/24 h, which is 800 ml ($4 \text{ ml} \times 20 \text{ kg} \times 10 \text{ mEq/l}$) to give total 24 h volume of 4,800 ml or 200 ml/h. In order to lower the sodium the composition of fluid will need to be more hypotonic than his urine; 0.115% NaCl (Na 19 mEq/l) in 2.5% dextrose in water with 10 mEq of KCl per liter would be appropriate to start with. A higher dextrose concentration could result in hyperglycemia given the high rate of fluid administration. Biochemistries would have to be monitored hourly initially as response to therapy can be unpredictable based on the urinary response. As soon as the child can keep down oral fluids, parenteral fluids should be tapered off.

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